ISBN: 978-9-6128-599-8

ESTD: 1984

Two-Days International Conference on

"Critical Infrastructure & Sustainable Development"

22nd & 23rd March 2024

Proceeding of

IC-CISD-2024

organised by

Department of Civil Engineering

K. D. K. College of Engineering, Nagpur

(An Autonomous Institute)

In Association with

- American Society of Civil Engineers, Indian Section (ASCE-IS)
- Department of Civil Engineering, University of Peradeniya, Sri Lanka
- Institution of Engineers India, Nagpur Local Centre (IEI-NLC)
- Indian Concrete Institute, Nagpur chapter (ICI-NC)
- Indian water works association, Nagpur Centre (IWWA-NC)
- Association of Consulting Civil Engineers, Nagpur Centre (ACCE-NC)
- Institute For Educational Research & Publication, Chennai (IFERP)

Editor: Dr. Valsson Varghese

Co-Editor: Prof. M. N. Umare

Structural Health Monitoring Using Non-Destructive Testing

Sivva Hemanth Sai[1], M. Sai Kiran[2], K. Mokshitha[3]
[1]Asst. professor, [2]B. Tech scholars,[1,2] Dept of Civil Engineering, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana.

ABSTRACT:

A Civil engineering structure provides space for livelihood in domestic, residential, commercial regularly. This is especially used in civil, structural, constructional engineering and it is used for large structures, long spans and nuclear reactors etc. Structural health monitoring aims assess to behaviour of structures and evaluate the performance of the material. Health monitoring structures consists of sensors, wireless technology, transmission data, electric power and internal connection. Non-Destructive testing methods are used to evaluate the strength and performance of the concrete structures. Structural health monitoring is necessary to ensure the safety, reliability, and longevity of civil engineering structures, as well as to optimize maintenance and repair processes, reduce costs, and enhance overall infrastructure resilience. It plays a crucial role in safeguarding public safety and the efficient operation of critical infrastructure systems. This project also deals with the Non-destructive testing of a Reinforced Concrete structure with an age of 30 days after curing using rebound hammer.

Keywords: Structural health monitoring, Rebound hammer, Strength, Non-Destructive Methods

Critical Study on The Current Status of Sustainable And Affordable Housing

Sagar Kamlakar Gurmule[1], Dr. Pallavi Bisen[2]
[1]PG Student M.Tech (Structural Engineering), [2]Assistant Professor, Department of Civil Engineering,[1,2]K.D.K. College of Engineering, Nagpur, Maharashtra,India

ABSTRACT:

This research delves into the analysis of affordable and sustainable housing in India. Although the combination of cost and sustainability might seem contradictory, it's crucial for ensuring the long-term durability of projects. The main objective of this thesis is to examine existing policies through case studies from the literature, shedding light on their implementation globally. Despite India's significant progress in the 'Housing for All Mission 2022,' there is still more work needed. The regulations governing affordable housing have laid the groundwork for a smoother process involving various stakeholders at different stages. In India, a global ecosystem is required to provide vocational training along with affordable housing. The government launched the PMAY (U) schemes in 2015, aiming to address housing shortages in urban areas. However, the implementation of these schemes often takes time, causing cost estimates to expand, impacting financially vulnerable EWS categories. To address this, the research examines current policies and their global execution through literature review case studies. It also explores construction techniques, emphasizing the use of low-cost and sustainable building materials to reduce construction costs and benefit recipients both aesthetically and economically. The paper further compares construction costs between low-cost and conventional buildings using Stadpro and Revit software.

Keywords: Low-cost housing, affordable housing, low-cost building material, various housing scheme's, cost effective, sustainable, construction techniques, stadpro and revit software

Determining Bearing Capacity of Soil Samples in Laboratory Assessment of Ghatkesar Mandal

Meti Karthik Kumar Reddy[1], Aili Hari Prasad[2], E Shekar[2]
[1]Assistant Professor,' [2]B.Tech Scholar,[1,2]Department of Civil Engineering, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana

ABSTRACT:

Soil is considered by the engineer as a complex material produced by weathering of the solid rock. Soil is the most important material which is in use for construction of civil engineering structures. Amongst all parameters, the bearing capacity of soil to support the load coming over its unit area is very Important. There are various methods for calculation of bearing capacity of soil put forth by v a r i o u s scientists. Principal factors that Influence ultimate bearing capacities are type of soil, width of foundation, soil weight in shear zone and surcharge. Structural rigidity and the contact stress distribution do not greatly influence bearing capacity. Bearing capacity analysis assumes a uniform contact pressure between the foundation and underlying soil. With other factors unchanged the type of failure of soil, depth of foundation, and effect of water table also governs the bearing capacity of soil. The present paper deals with the study of effect o f t h e shape of footing on bearing capacity of soil. In general, other factors remaining constant, bearing capacity of soil goes on increasing as depth or width of foundation increases. The comparison of bearing capacity of soil with methods of analysis given by Terzaghi and IS code method is carried out for different shapes i.e., strip, square, circular and rectangle. In case of local shear failure, amongst different shapes of footing the bearing capacity of strip footing is found to be lowest in comparison with square, circular and rectangular shaped footings. Bearing capacity is crucial in construction, determining a soil's ability to support structural loads. This abstract explores factors influencing soil bearing capacity, methods of analysis, and implications for safe and efficient foundation design.

Keywords: Bearing Capacity, Soil Parameters, Strip Footing, Depth of Foundation

Effect of Construction And Demolition Waste As Coarse Aggregate And Coconut Shell As Fine Aggregate in Concrete

Anadi Haldar, Rina Mohurle, Divya Kaushal, Jayesh Tembhare, Akash Bachar, Sajal Rokde.
[1,2,3,4,5,6.] Students,Tulsiramji Gaikwad Patil College of engineering and technology Nagpur, India

ABSTRACT:

Coconut shell is one of the most prevalent agricultural solid wastes in several tropical countries. Construction and Demolition (C@D) waste are generated during the creation of structures or building or when renewing or demolishing a current structure. Coconut shell as a replacement for fine aggregate at 10%,20% and 30% by weight respectively. Construction and Demolition waste as a replacement for coarse aggregate at 20%, 30%, 40%, 50%, 60% by weight respectively. Size of aggregate 20-25mm, and size of fine aggregate 4-5mm. Concrete ratio of Mix proportion 1:1.52:3.56:0.5, 1 part of cement 1, 2 part of fine aggregate 1.52, 3 part of coarse aggregate 3.56, 4 part of water 0.5.

Keywords: Coconut shell waste, Construction and Demolition waste, Use in concrete, Cost.

K. D. K. College of Engineering, Nagpur

Estd.1984

(An Autonomus Institute)

Department of Civil Engineering

(NBA and NAAC accredited)

in association with

American Society of Civil Engineers, Indian Section (ASCE - IS)

Indian Concrete Institute Nagpur Centre

The Institute of Engineers (India) – Nagpur Centre

Association of Consulting Civil Engineers, (ACCE)- Nagpur Centre

Indian Water Works Association (IWWA)-Nagpur Centre

Department of Civil Engineering, University of Peradeniya, Sri Lanka

Institute for Engineering Research & Publication, Chennai (IFERP)

CERTIFICATE OF APPRECIATION

This is to certify that

***Sivva Hemanth Sai,* Assistant Professor,**

Dept of Civil Engineering, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana.

has participate in Two-Days International Conference on *"Critical Infrastructure & Sustainable Development"* (IC-CISD-2024) (22-23 March 2024)", organized by Department of Civil Engineering, K. D. K. College of Engineering, Nagpur. He / She has presented a paper in the conference on "Structural Health Monitoring Using Non-Destructive Testing"

Er. R. B. Satpathy CEO, IFERP	*Dr. Sarang. Paranjape* Chairman ACCE&NC	*Er. Ravindra J Ringshia* President, ASCE&ISWR	*Dr. O. N.Mukharjee* Chairman IWWA- NC	*Er. H. D. Chandewar* Chairman, ICI (NC)	*Er. Satish Raipure* Chairman, IEI-NLC	*Dr. Ranjith Dissanayake* Sr. Prof. Uni, of Peradeniya President, Institution of EngineersSri Lanka	*Dr. A. M. Badar* Conference Chair (IC-CISD) Vice-Principal, KDKCE	*Dr. Valsson Varghese* Convener (IC-CISD) Principal, KDKCE

K. D. K. College of Engineering, Nagpur

Estd.1984

(An Autonomus Institute)

Department of Civil Engineering

(NBA and NAAC accredited)

in association with

American Society of Civil Engineers, Indian Section (ASCE - IS)

Indian Concrete Institute Nagpur Centre

The Institute of Engineers (India) – Nagpur Centre

Association of Consulting Civil Engineers, (ACCE)- Nagpur Centre

Indian Water Works Association (IWWA)-Nagpur Centre

Department of Civil Engineering, University of Peradeniya, Sri Lanka

Institute for Engineering Research & Publication, Chennai (IFERP)

CERTIFICATE OF APPRECIATION

This is to certify that

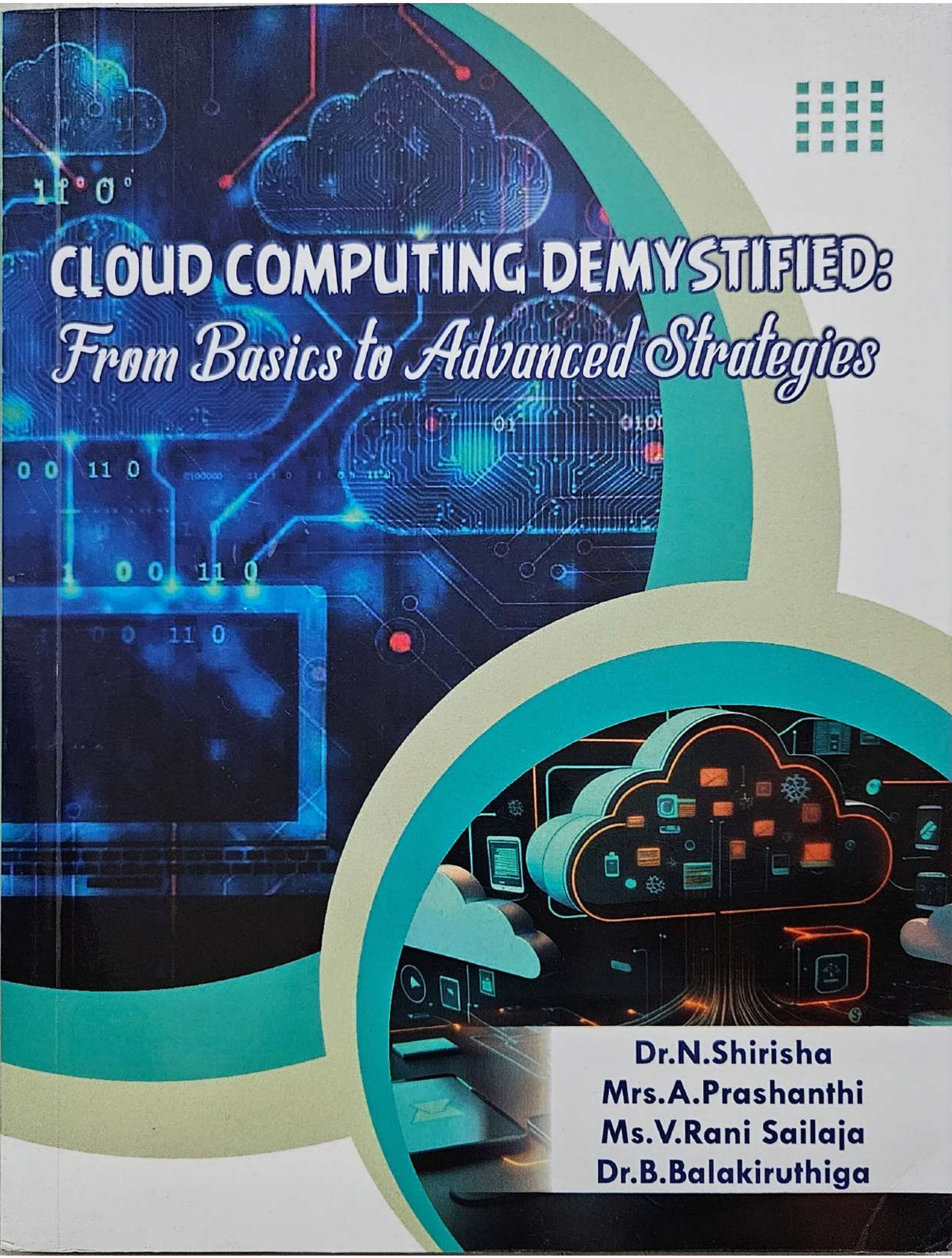
Meti Karthik Kumar Reddy, *Assistant Professor,*

Department of Civil Engineering, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana

has participate in Two-Days International Conference on *"Critical Infrastructure & Sustainable Development"* (IC-CISD-2024) (22-23 March 2024)", organized by Department of Civil Engineering, K. D. K. College of Engineering, Nagpur. He / She has presented a paper in the conference on "Determining Bearing Capacity of Soil Samples in Laboratory Assessment of Ghatkesar Mandal"

Er. R. B. Satpathy CEO, IFERP	*Dr. Sarang. Paranjape* Chairman ACCENC	*Er. Ravindra J Ringshia* President, ASCEISWR	*Dr. O. N.Mukharjee* Chairman IWWA- NC	*Er. H. D. Chandewar* Chairman, ICI (NC)	*Er. Satish Raipure* Chairman, IEI-NLC	*Dr. Ranjith Dissanayake* Sr. Prof. Uni, of Peradeniya President, Institution of EngineersSri Lanka	*Dr. A. M. Badar* Conference Chair (IC-CISD) Vice-Principal, KDKCE	*Dr. Valsson Varghese* Convener (IC-CISD) Principal, KDKCE

CLOUD COMPUTING DEMYSTIFIED:
From Basics to Advanced Strategies



Dr.N.Shirisha
Mrs.A.Prashanthi
Ms.V.Rani Sailaja
Dr.B.Balakiruthiga

CLOUD COMPUTING DEMYSTIFIED:
FROM BASICS TO ADVANCED STRATEGIES

Authors
Dr. K. Shailaja
Associate Professor
Department of Computer Science and Engineering, MLR Institute of Technology, Hyderabad, Telangana, India.

Mrs. A. Prashanthi
Assistant Professor
Department of Computer Science and Engineering
Malla Reddy Education Society's Group of Institutions, Hyderabad, Telangana, India.

Mr. V. Rani Sailaja
Assistant Professor
Department of Computer Science and Engineering
Malla Reddy Group of Institutions, Hyderabad, Telangana, India.

Dr. S. BALAKRUTHIGA
Assistant Professor
Department of Computer Science and Engineering
Karpagam Academy of Research and Education (KARE), Viruthunagar, Tamilnadu

WELL TECH INTERNATIONAL
PUBLISHING HOUSE
INDIA

About the Authors

Dr.N.Shirisha working as Associate Professor, Computer Science and Engineering Department at MLR Institute of Technology, Hyderabad, Telangana, India. She received the B.TECH degree in Computer Science and Engineering from Malla Reddy Institute of Technology and sciences, Hyderabad in 2009. In 2012, received the M.Tech degree in Software Engineering from DRK Institute of Science & Technology, Hyderabad. In 2021, received the Ph.D. degree in Faculty of Computer Science & Engineering from KLU, Vijayawada, Andhra Pradesh, India. She has 13 years of experience in teaching and 1.5 years in research, she published around 20 publications in International/National journals and 10 publications in conferences. Five Patents in data mining and big data analytics. Research interest includes data mining, Information Security, Network Security, Big data Analytics and Machine Learning. She is Active member in Professional Societies and Member of ISTE, IAENG, AIMER.

Mrs.A.Prashanthi working as Assistant Professor, Computer Science and Engineering Department at Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana, India. She received the B.Tech degree in Computer Science and Engineering from Sri Kottam Tulasi Reddy Memorial College of Engineering, Mahabubnagar in 2007. In 2010, received the M.Tech degree in Computer Science and Engineering from Vardhaman College of Engineering, Shamshabad in 2010. In 2017, Registered for Ph.D Programme in Department of Computer Science and Engineering from Osmania University, Hyderabad, Telangana, India. She has 13 years of experience in teaching, over 8 Research Papers in International Journals and 5 Conferences in Reputed Management. She has guided 10 UG scholars. Research Interest includes Information Security, Network Security, Machine Learning and Cloud Computing. She is Very Active in Professional Societies and Member of IEEE, CSI, IAENG, CSTA, IET.

Ms.V.Rani Sailaja working as Assistant Professor, Computer Science and Engineering Department at Nalla Narasimha Reddy Group of Institutions, Hyderabad, Telangana, India. She received B.Tech degree in Computer Science and Engineering from Sri Venkateshwara Engineering College, Suryapet in 2004. In 2012, received the M.Tech degree in Computer Science and Engineering from Bharat Institute of Engineering and Technology, Hyderabad. She has 5.2 years of experience in teaching and 1.2 years in Digital Marketing. She published 2 publications in international journals. Research interest includes Cloud Computing, Data Mining, Information Security, Artificial Intelligence, Big Data Analytics and Machine Learning. She got certified as Oracle Certified Associate (OCA) from Oracle University, California in 2007, March.

Dr.B.Balakiruthiga was working as an Assistant Professor in Department of Computer Science and Engineering at Kalasalingam Academy of Research and Education (KARE), Virudhunagar, Tamilnadu. At present she is working in Department of Networking and Communications under School of Computing at SRM Institute of Engineering and Technology since November 2022. Totally she has 12 years of teaching experience. She has completed her Bachelor of Engineering in Computer Science and Engineering from Maharaja Engineering College, Anna University, Chennai, Tamilnadu, India in 2009 and received her Master of Technology in Network Engineering from KARE, Virudhunagar, Tamilnadu, India in 2011. Her research interest includes Network Routing, Data Center Networks and Software Defined Networks. Contact her at balakirb@srmist.edu.in

ISBN 978-81-965459-2-5

9 788196 545925

WIPH Publishers

INTELLECTUAL PROPERTY INDIA
PATENTS | DESIGNS | TRADE MARKS
GEOGRAPHICAL INDICATIONS

सत्यमेव जयते

ORIGINAL
क्रम सं/ Serial No. : 157711

पेटेंट कार्यालय, भारत सरकार | The Patent Office, Government Of India

डिजाइन के पंजीकरण का प्रमाण पत्र | Certificate of Registration of Design

डिजाइन सं. / Design No. : 397731-001

तारीख / Date : 17/10/2023

पारस्परिकता तारीख / Reciprocity Date* :

देश / Country :

प्रमाणित किया जाता है कि संलग्न प्रति में वर्णित डिजाइन जो *NOVEL PRESYMPTOMATIC BREAST CANCER DETECTION DEVICE* से संबंधित है, का पंजीकरण, श्रेणी 24-02 में 1.Dr. Naga Raju Hari Manikyam 2. Dr. M. Thangamani 3.Dr. Nalini Kanta Sahoo 4.S. Savitha के नाम में उपर्युक्त संख्या और तारीख में कर लिया गया है।

Certified that the design of which a copy is annexed hereto has been registered as of the number and date given above in class 24-02 in respect of the application of such design to *NOVEL PRESYMPTOMATIC BREAST CANCER DETECTION DEVICE* in the name of 1.Dr. Naga Raju Hari Manikyam 2. Dr. M. Thangamani 3.Dr. Nalini Kanta Sahoo 4.S. Savitha.

डिजाइन अधिनियम, 2000 तथा डिजाइन नियम, 2001 के अध्यधीन प्रावधानों के अनुसरण में।

In pursuance of and subject to the provisions of the Designs Act, 2000 and the Designs Rules, 2001.

जारी करने की तिथि :
Date of Issue : 21/02/2024

उन्नत की ओर

महानियंत्रक पेटेंट, डिजाइन और व्यापार चिह्न
Controller General of Patents, Designs and Trade Marks

*पारस्परिकता तारीख (यदि कोई हो) जिसकी अनुमति दी गई है तथा देश का नाम। डिजाइन का स्वत्वाधिकार पंजीकरण की तारीख से दस वर्षों के लिए होगा जिसका विस्तार, अधिनियम एवं नियम के निबंधनों के अधीन, पाँच वर्षों की अतिरिक्त अवधि के लिए किया जा सकेगा। इस प्रमाण पत्र का उपयोग विधिक कार्यवाहियों अथवा विदेश में पंजीकरण प्राप्त करने के लिए नहीं हो सकता है।

The reciprocity date (if any) which has been allowed and the name of the country. Copyright in the design will subsist for ten years from the date of Registration, and may under the terms of the Act and Rules, be extended for a further period of five years. This Certificate is not for use in legal proceedings or for obtaining registration abroad.

7

Heart Failure Detection Through SMOTE for Augmentation and Machine Learning Approach for Classification

G. Kiran Kumar[1]*, Anila M.[1], Naga Raju Hari Manikyam[2], Venkata Nagaraju Thatha[3], R. Vijaya Kumar Reddy[4] and Krishna Reddy Papana[5]

[1]*Department of Computer Science and Engineering, Chaitanya Bharathi Institute of Technology, Hyderabad, India*
[2]*Dept. of Computer Science and Engineering, Nalla Narasimha Reddy Group of Institutions, Hyderabad*
[3]*Department of Information Technology, MLR Institute of Technology, Hyderabad*
[4]*Department of CSE, Koneru Lakshmaiah Education Foundation, Vaddeswaram, AP, India*
[5]*Department of ECE, Dhanekula Institute of Engineering and Technology-Vijayawada Andhra Pradesh, India*

Abstract

Chronic heart failure poses a significant global health challenge, necessitating innovative strategies for early detection and management. While pharmaceutical interventions are crucial, there's a growing recognition of the additional benefits of exercise in addressing this condition. In this study, we employ the Synthetic Minority Over-sampling Technique (SMOTE) to augment our dataset. We utilize a range of machine learning algorithms, including XG Boost, k-Nearest Neighbors (KNN), Adaboost, and Support Vector Machines (SVM), to enhance the model's effectiveness in early heart failure detection. Through rigorous validation via cross-validation techniques, this research underscores its paramount significance in the medical field. By improving our ability to detect heart failure at its early stages, this study has the potential to save lives by enabling timely interventions. This research highlights the promising role of machine learning in advancing healthcare and emphasizes the critical importance of early detection and

**Corresponding author*: ganipalli.kiran@gmail.com

R. Nidhya, Manish Kumar, S. Karthik, Rishabh Anand and S. Balamurgan (eds.) Smart Factories for Industry 5.0 Transformation, (123–134) © 2024 Scrivener Publishing LLC

intervention in managing this pervasive global health issue. Chronic heart failure necessitates multifaceted solutions, and this study represents a significant step forward in the pursuit of enhanced detection and management. By integrating machine learning techniques and recognizing the role of exercise in therapy, this study offers a comprehensive approach to address this pressing health concern. It paves the way for a more proactive and effective response to chronic heart failure on a global scale.

***Keywords*:** Synthetic minority over-sampling technique, machine learning algorithms, heart failure, cross-validation, healthcare

7.1 Introduction

Heart failure stands as a significant global health challenge, characterized by the heart's inefficiency in pumping blood, leading to debilitating symptoms and complications. Reports from the World Health Organization (WHO) underscore its pervasive impact on millions worldwide, with its prevalence escalating, particularly in aging populations [1]. The burden extends beyond individual health, burdening healthcare systems with increased hospitalizations, soaring costs, and diminished quality of life. The condition's high mortality rate underscores the urgency of early detection and effective management [1]. Recognizing the complementary role of exercise alongside pharmaceutical interventions, this study endeavors to enhance heart failure detection using machine learning techniques [2]. By leveraging patient health parameter data, we employ nine machine learning algorithms and introduce the innovative Principal Component Heart Failure (PCHF) feature engineering technique [2]. In a related study, heart rate variability (HRV) emerges as a valuable method for detecting and assessing congestive heart failure (CHF) [3]. Leveraging multi-fractal detrended fluctuation analysis (MFDFA), this study quantifies the complexity of HRV to discern differences between healthy individuals and those with CHF [3]. In another realm, Point-of-Care (PoC) measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) holds promise in HF diagnosis and management [4]. Serial measurements of NT-proBNP, reflecting cardiac wall stretch, offer insights into HF progression and intervention efficacy [4]. Further, the intersection of oncology and cardiology underscores the need for early detection of cardiotoxicity in cancer patients to prevent heart failure [5]. Integrating genetic and Electronic Health Record (EHR) data, machine learning models aim to identify patients at high risk of treatment-related heart failure [5].

In clinical practice, accurate arrhythmia detection remains crucial, driving exploration into deep neural networks' potential [6]. Recurrent and residual architectures show promise in classifying ECG recordings, aiding in timely diagnosis and management [6]. As heart failure rates rise among diverse populations, early detection becomes paramount in averting associated risks [7]. Machine learning models, leveraging patient data, offer a valuable approach in assessing heart failure risk, particularly in individuals with predisposing factors such as diabetes [8]. In summary, these studies collectively underscore the multifaceted efforts to improve heart failure detection, diagnosis, and management using innovative techniques and data-driven approaches. Through advancements in machine learning, cardiac health can be better monitored, leading to earlier interventions and improved patient outcomes.

7.2 Literature Survey

M. Gjoreski and colleagues [9] have achieved promising results in chronic heart failure (CHF) detection by combining classic Machine Learning (ML) and end-to-end Deep Learning (DL) techniques. Their approach demonstrated an impressive aggregated accuracy of 92.9%, surpassing the recent PhysoNet challenge's baseline method by a significant margin. Furthermore, they identified 15 expert features for distinguishing between CHF phases with an accuracy of 93.2%, highlighting the versatility of their model. These findings suggest the potential for more accessible CHF patient identification and the development of home-based monitoring solutions, which could potentially reduce hospitalizations and improve CHF management.

W. Ning and colleagues [10] introduced a highly effective automatic congestive heart failure (CHF) detection model, utilizing a hybrid deep learning approach involving a convolutional neural network (CNN) and a recursive neural network (RNN). Their model achieved outstanding accuracy, sensitivity, and specificity for 5-minute ECG signal analysis, surpassing previous research efforts and demonstrating potential as a valuable clinical tool for CHF patient detection.

L. Zou, Z. Huang, and their team [11] demonstrated the robustness of their model by outperforming state-of-the-art methods in both centralized and decentralized learning settings. With accuracies of 89.83% and 87.54%, respectively, their federated framework shows promise for improving CHF detection without compromising data security.

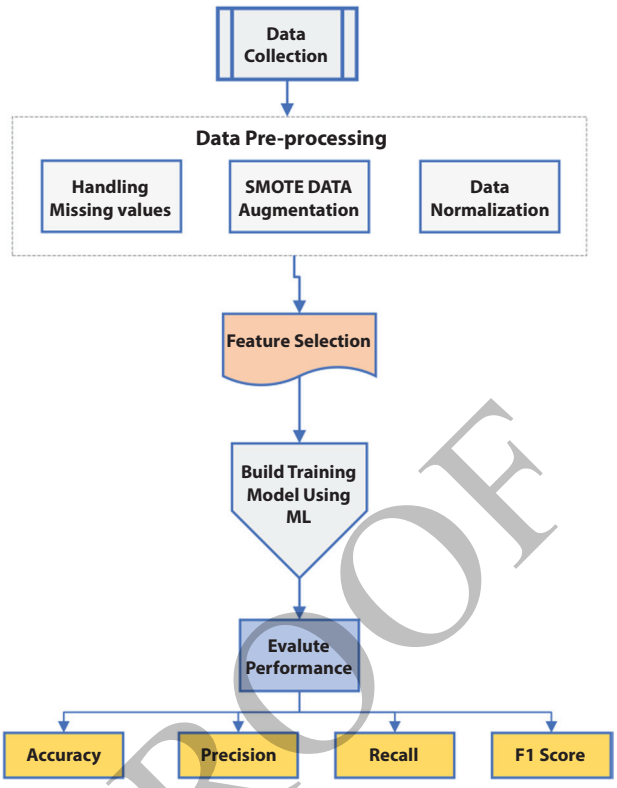
S. Mehrang and colleagues [12] explored the potential of smartphone-based mechanocardiography (sMCG) for detecting atrial fibrillation (AFib) and acute decompensated heart failure (ADHF) in hospitalized cardiac patients. Their supervised machine learning approach yielded remarkable results, with high area under the ROC curve values for AFib and ADHF detection.

E. Prabhakararao *et al.* [13] developed a model, DA-DRRNet, for congestive heart failure (CHF) detection in ECG data. Their model achieved impressive accuracy at both the beat-level and 24-hour record-level diagnosis, offering transparency in CHF identification. M. Morshed and colleagues [14] presented a deep learning network for directly detecting heart-valve-related diseases (HVDs) from phonocardiogram (PCG) signals. Their model significantly improved accuracy and performance, showcasing competitiveness in HVD detection. A. Bhardwaj and team [15] achieved a significant advancement in the early detection of valvular heart diseases (VHD) using phonocardiogram (PCG) signals. Their method demonstrated remarkable classification accuracy, particularly in binary classification tasks. J. Botros and colleagues [16] proposed a model for efficient and accessible HF diagnosis, achieving exceptional performance on both unbalanced and balanced datasets. These results underscore the potential of their model as a reliable diagnostic tool for HF, with implications for early detection and improved patient outcomes.

7.3 Proposed Methodology

Heart failure detection incorporates the Synthetic Minority Over-sampling Technique (SMOTE) for data augmentation, alongside a machine learning classification ~~strategy.~~ A variety of algorithms, such as logistic regression, decision trees, random forests, support vector machines, and neural networks, are utilized in this process. SMOTE tackles class imbalance by generating synthetic instances of the minority class, thereby enhancing the model's capability to identify heart failure cases. The objective of the SMOTE approach is to refine the segmentation of the minority class, ensuring that the machine learning model encounters a more balanced representation of both positive and negative instances. Consequently, this enhances the overall robustness and accuracy of the heart failure detection system.

Data Collection: The initial step in heart failure detection entails thorough data collection, gathering diverse patient-related variables such as demographic details, medical history, and lifestyle factors to construct a



Q4 **Figure 7.1** Proposed methodology for heart failure prediction.

comprehensive dataset. This dataset aims to provide a representative sample for training and testing the machine learning model. Additionally, integrating the Synthetic Minority Over-sampling Technique (SMOTE) helps address potential class imbalances by generating synthetic instances of the minority class, thus contributing to a more balanced dataset.

Data Pre-processing: Following data collection, the dataset undergoes meticulous pre-processing to ensure its suitability for machine learning algorithms. This step involves handling missing or erroneous data, normalizing numerical features, and encoding categorical variables. The inclusion of SMOTE during this phase assists in mitigating the effects of class imbalance by artificially expanding the representation of the minority class. The pre-processed dataset is then partitioned into training and testing sets to facilitate model evaluation and validation.

Feature Extraction: Feature extraction is crucial for refining the dataset to optimize model performance. This process entails selecting relevant

variables and leveraging SMOTE to augment the representation of the minority class. By enhancing the segmentation of the minority class, feature extraction ensures that the machine learning model encounters a more balanced distribution of both positive and negative instances. This improves the model's ability to accurately recognize and classify heart failure cases.

Classification: The final phase involves applying various machine learning classification algorithms, such as logistic regression, decision trees, random forests, support vector machines, and neural networks. The model is trained using the pre-processed and augmented dataset, with hyperparameters adjusted to optimize performance. Subsequently, the model's accuracy, precision, recall, and other relevant metrics are evaluated using the testing set. The integration of SMOTE, from data pre-processing to feature extraction, enhances the robustness and accuracy of the heart failure detection system by addressing class imbalances and improving the model's overall generalizability.

7.4 Results and Discussion

The performance metrics of several machine learning algorithms, namely KNN, Random Forest, SVM, Decision Tree, AdaBoost, and XGBoost, were evaluated for predicting a specific outcome. Notably, XGBoost emerged as the top-performing model, exhibiting impressive values across precision, recall, F1-score, and accuracy metrics, indicating its superior predictive capability. While Random Forest, SVM, and AdaBoost also showcased commendable performance, XGBoost stood out as the most robust algorithm for this particular task. Its high precision and recall values highlight its effectiveness in accurately identifying both positive and negative instances, rendering it a reliable choice for precise predictions. These results offer valuable insights into selecting the most suitable model, especially in scenarios where precision and recall hold significant importance, emphasizing the necessity of comprehensive consideration of algorithm performance.

Figure 7.2 illustrates the evaluation of classification models, which entails comparing predicted labels to true labels using a confusion matrix. This matrix outlines True Positives (correct positive predictions), True Negatives (correct negative predictions), False Positives (incorrect positive predictions), and False Negatives (incorrect negative predictions). Precision, computed as TP / (TP + FP), assesses the accuracy of positive

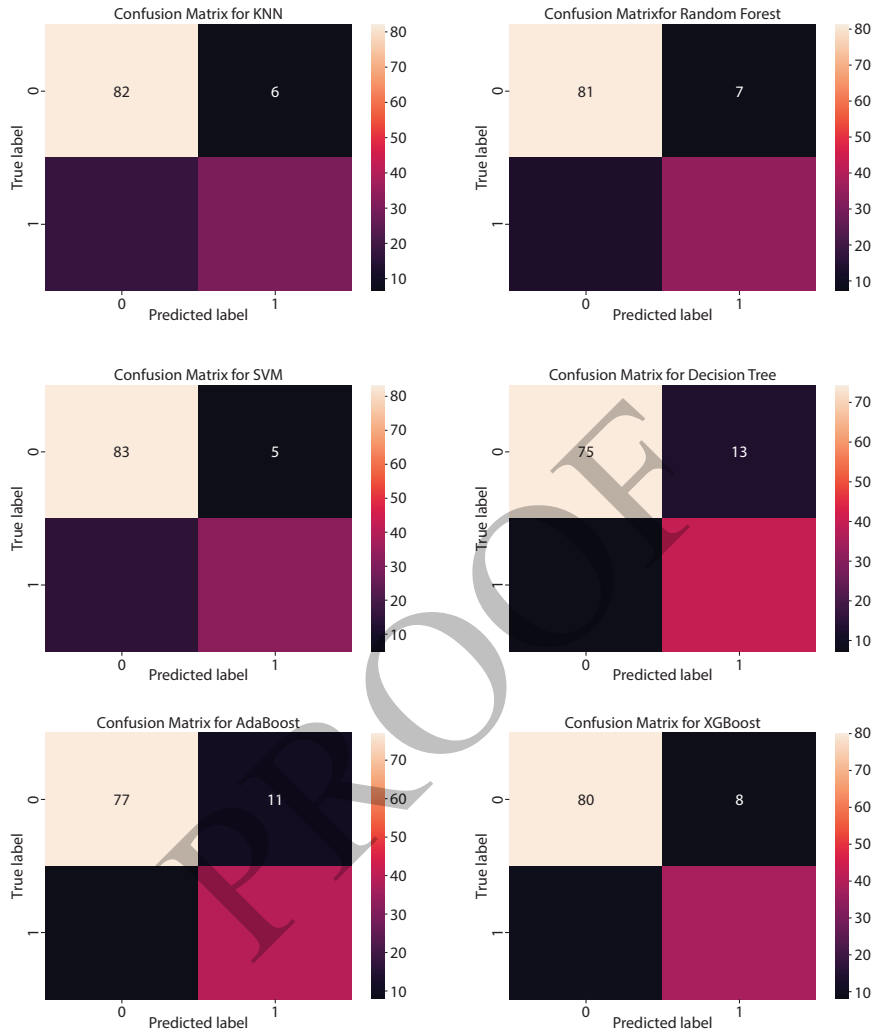


Figure 7.2 Confusion matrix for existing machine learning algorithms.

predictions, while Recall (Sensitivity) evaluates the model's capability to capture all positive instances (TP / (TP + FN)). F1-score, striking a balance between precision and recall, serves as a comprehensive metric. Analyzing predicted versus true labels in a confusion matrix provides a nuanced understanding of a model's performance, considering not only overall accuracy but also the specificities of correct and incorrect predictions. This aids in model refinement and selection based on particular requirements.

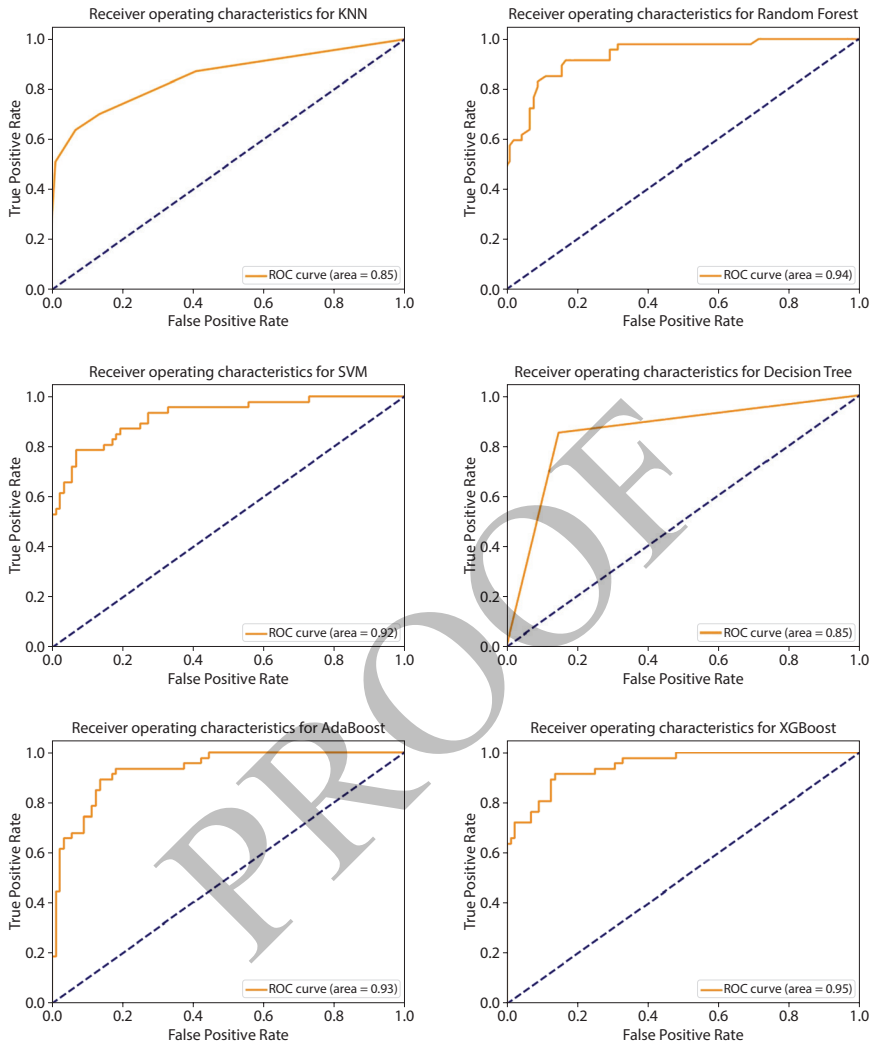


Figure 7.3 ROC curve for existing machine learning algorithms.

In Figure 7.3, the Receiver Operating Characteristic (ROC) curve serves as a graphical depiction of a binary classification model's performance across different threshold settings. It plots the True Positive Rate (Sensitivity or Recall) against the False Positive Rate, showcasing how the model performs at different classification thresholds. The area under the ROC curve (AUC-ROC) quantifies the model's capability to differentiate between positive and negative instances, with higher AUC values indicating better performance. The ROC curve offers valuable insights by

visualizing the trade-off between sensitivity and specificity, enabling the selection of an optimal threshold tailored to specific task requirements. A model with an ROC curve closely following the top-left corner signifies excellent performance, while a curve along the diagonal line indicates no discriminatory power. Overall, the ROC curve serves as a crucial tool for assessing and comparing classification models' discriminatory ability, providing valuable insights into their effectiveness across varying decision thresholds.

Table 7.1 presents the performance metrics, including precision, recall, F1-score, and accuracy, for various machine learning algorithms—KNN, Random Forest, SVM, Decision Tree, AdaBoost, and XGBoost—in predicting a specific outcome. Notably, XGBoost stands out with remarkable precision, recall, F1-score, and accuracy values of 0.974, 0.926, 0.909,

Table 7.1 Performance analysis for heart failure model.

Algorithm	Accuracy	Precision	Recall	F1 score
KNN	0.82963	0.833333	0.638298	0.722892
Random Forest	0.851852	0.829268	0.723404	0.772727
SVM	0.851852	0.864865	0.680851	0.761905
Decision Tree	0.851852	0.754717	0.851064	0.8
AdaBoost	0.859259	0.78	0.829787	0.804124
XGBoost	0.974074	0.926087	0.908511	0.917204

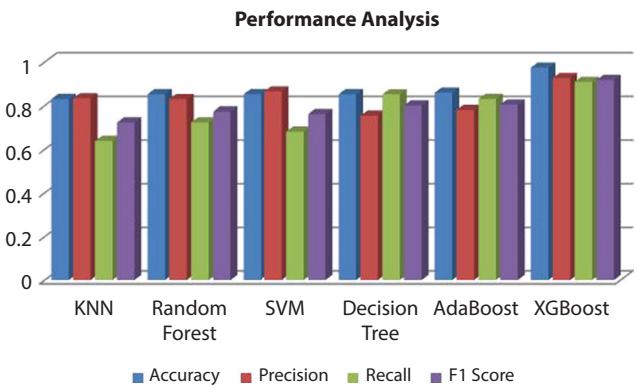


Figure 7.4 Performance analysis.

and 0.917, respectively, showcasing its robust predictive capability. This indicates that XGBoost surpasses other models in terms of performance. While Random Forest, SVM, and AdaBoost also demonstrate commendable performance, their metrics are slightly lower compared to XGBoost. The results underscore XGBoost's reliability in achieving high precision and recall simultaneously, which are essential for accurate predictions in the given scenario. Consequently, these findings inform the selection of an appropriate model, emphasizing XGBoost's effectiveness, particularly in situations where both precision and recall hold significant importance.

7.5 Conclusion

In summary, this study introduces an innovative approach to address the global health challenge of chronic heart failure by integrating machine learning and exercise therapy. Through the utilization of SMOTE for dataset augmentation and a diverse array of machine learning algorithms, the research demonstrates a robust methodology for early detection. The inclusion of cross-validation techniques adds rigor to the validation process, highlighting the significance of the findings in the medical field. By improving our capacity to detect heart failure at its onset, this study holds the potential to save lives through timely interventions. Furthermore, the proposed model underscores the promising role of machine learning in healthcare and underscores the critical importance of early detection and intervention in managing this widespread health issue. With a comprehensive approach encompassing pharmaceutical interventions, exercise therapy, and advanced machine learning techniques, this method represents a significant advancement in the pursuit of better detection and management of chronic heart failure globally, offering a proactive and effective strategy to address this pressing health concern.

References

1. Athalye, G., Sarde, A., Badgujar, M., Gaikwad, V., Sondkar, S., Hybrid Gradient Boost based Heart Failure Prediction System. *2023 International Conference on Emerging Smart Computing and Informatics (ESCI)*, Pune, India, pp. 1–6, 2023, doi: 10.1109/ESCI56872.2023.10099903.
2. Qadri, A.M., Raza, A., Munir, K., Almutairi, M.S., Effective Feature Engineering Technique for Heart Disease Prediction With Machine Learning. *IEEE Access*, 11, 56214–56224, 2023, doi: 10.1109/ACCESS.2023.3281484.

3. Li, S., Multifractal Detrended Fluctuation Analysis of Congestive Heart Failure Disease Based on Constructed Heartbeat Sequence. *IEEE Access*, 8, 205244–205249, 2020, doi: 10.1109/ACCESS.2020.3037080.
4. Li, Y., Wang, X., Tang, Q., Qian, Z., Unsupervised Learning Based Heart Failure Detection Using ECG Signal. *2023 International Conference on Data Science and Network Security (ICDSNS)*, Tiptur, India, pp. 1–5, 2023, doi: 10.1109/ICDSNS58469.2023.10244978.
5. Yu, Z., *et al*., Identify Cancer Patients at Risk for Heart Failure using Electronic Health Record and Genetic Data. *2022 IEEE 10th International Conference on Healthcare Informatics (ICHI)*, Rochester, MN, USA, pp. 138–142, 2022, doi: 10.1109/ICHI54592.2022.00032.
6. Singh, S., Animesh, Penzel, T., Classification and Detection of Heart Rhythm Irregularities using Machine Learning. *2020 First International Conference on Power, Control and Computing Technologies (ICPC2T)*, Raipur, India, pp. 438–442, 2020, doi: 10.1109/ICPC2T48082.2020.9071495.
7. Sarswat, A., Harshita, Tarushi, Bansal, P., Malik, K., Analysis of heart failure survival rates in middle-aged and older people using machine learning model. *2023 13th International Conference on Cloud Computing, Data Science & Engineering (Confluence)*, Noida, India, pp. i–viii, 2023, doi: 10.1109/Confluence56041.2023.10048807.
8. Gahane, A. and Kotadi, C., An Analytical Review of Heart Failure Detection based on IoT and Machine Learning. *2022 Second International Conference on Artificial Intelligence and Smart Energy (ICAIS)*, Coimbatore, India, pp. 1308–1314, 2022, doi: 10.1109/ICAIS53314.2022.9742913.
9. Gjoreski, M., Gradišek, A., Budna, B., Gams, M., Poglajen, G., Machine Learning and End-to-End Deep Learning for the Detection of Chronic Heart Failure From Heart Sounds. *IEEE Access*, 8, 20313–20324, 2020, doi: 10.1109/ACCESS.2020.2968900.
10. Ning, W., Li, S., Wei, D., Guo, L.Z., Chen, H., Automatic Detection of Congestive Heart Failure Based on a Hybrid Deep Learning Algorithm in the Internet of Medical Things. *IEEE Internet Things J.*, 8, 16, 12550–12558, Aug. 15, 2021, doi: 10.1109/JIOT.2020.3023105.
11. Zou, L., Huang, Z., Yu, X., Zheng, J., Liu, A., Lei, M., Automatic Detection of Congestive Heart Failure Based on Multiscale Residual UNet++: From Centralized Learning to Federated Learning. *IEEE Trans. Instrum. Meas.*, 72, 1–13, 2023. Art no. 4001013, doi: 10.1109/TIM.2022.3227955.
12. Mehrang, S., *et al.*, Classification of Atrial Fibrillation and Acute Decompensated Heart Failure Using Smartphone Mechanocardiography: A Multilabel Learning Approach. *IEEE Sens. J.*, 20, 14, 7957–7968, July 15, 2020, doi: 10.1109/JSEN.2020.2981334.
13. Prabhakararao, E. and Dandapat, S., Congestive Heart Failure Detection From ECG Signals Using Deep Residual Neural Network. *IEEE Trans. Syst. Man Cybern.: Syst.*, 53, 5, 3008–3018, May 2023, doi: 10.1109/TSMC.2022.3221843.

14. Morshed, M. and Fattah, S.A., SAR-CardioNet: A Network for Heart Valve Disease Detection From PCG Signal Based on Split-Self Attention With Residual Paths. *IEEE Sens. J.*, 23, 17, 19553–19560, Sept. 1, 2023, doi: 10.1109/JSEN.2023.3289109.
15. Bhardwaj, A., Singh, S., Joshi, D., Explainable Deep Convolutional Neural Network for Valvular Heart Diseases Classification Using PCG Signals. *IEEE Trans. Instrum. Meas.*, 72, 1–15, 2023. Art no. 2514215, doi: 10.1109/TIM.2023.3274174.
16. Botros, J., Mourad-Chehade, F., Laplanche, D., Detection of Heart Failure Using a Convolutional Neural Network via ECG Signals. *2022 15th International Congress on Image and Signal Processing, BioMedical Engineering and Informatics (CISP-BMEI)*, Beijing, China, pp. 1–5, 2022, doi: 10.1109/CISP-BMEI56279.2022.9980118.

Answer all Queries (Q) in the margin of the text. When requested, provide missing intext reference citation as well as intext reference for figure/table. Please annotate the PDF and read the whole chapter again carefully. Careful proofing is key to optimal output.

Author Queries

Q1 Please note that author job title was removed per Scrivener style.

Q2 Please provide country for affiliations 2 and 3.

Q3 Short running title was provided. Kindly check if OK. If not, please provide short running title with a maximum of 45 characters (including spaces) per Scrivener guideline.

Q4 Please provide missing call-out/citation of Figures 7.1 and 7.4 in the main text (Example: Figure 7.1 shows the evidence of.....). Note that figure citations should be cited sequentially.

Network Security: Strategies for Robust and Resilient Security

Dr. N. Shirisha
Mrs. A. Prashanthi | Mrs. K. Jayasri
Mrs. Nandikante Shravani

About the Authors

Dr.N.Shirisha working as Associate Professor, Computer Science and Engineering Department at MLR Institute of Technology, Hyderabad, Telangana, India. She received the B.TECH degree in Computer Science and Engineering from Malla Reddy Institute of Technology and sciences, Hyderabad in 2009. In 2012, received the M.Tech degree in Software Engineering from DRK Institute of Science & Technology, Hyderabad. In 2021, received the Ph.D. degree in Faculty of Computer Science & Engineering from KLU, Vijayawada, Andhra Pradesh, India. She has 13 years of experience in teaching and 1.5 years in research, she published around 20 publications in International/National journals and 10 publications in conferences. Five Patents in data mining and big data analytics. Research interest includes data mining, Information Security, Network Security, Big data Analytics and Machine Learning. She is Active member in Professional Societies and Member of ISTE, IAENG, AIMER.

Mrs.A.Prashanthi working as Assistant Professor, Computer Science and Engineering Department at Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana, India. She received the B.Tech degree in Computer Science and Engineering from Sri Kottam Tulasi Reddy Memorial College of Engineering, Mahabubnagar in 2007. In 2010, received the M.Tech degree in Computer Science and Engineering from Vardhaman College of Engineering, Shamshabad in 2010. In 2017, Registered for Ph.D Programme in Department of Computer Science and Engineering from Osmania University, Hyderabad, Telangana, India. She has 13 years of experience in teaching, over 8 Research Papers in International Journals and 5 Conferences in Reputed Management. She has guided 10 UG scholars. Research Interest includes Information Security, Network Security, Machine Learning and Cloud Computing. She is Very Active in Professional Societies and Member of IEEE, CSI, IAENG, CSTA, IET.

Mrs.K.Jayasri working as Assistant Professor, Computer Science and Engineering Department at Nalla Narasimha Reddy Educational Society's Group of Institutions, Hyderabad, Telangana, India. She received the B.TECH degree in Computer Science and Engineering from Lenora College of Engineering and Technology, Rampachodavaram, E.G.Dist in 2007. In 2012, received the M.Tech degree in Software Engineering from Jawaharlal Nehru Technological University, Hyderabad. She has 11 years of experience in teaching. She published many publications in International/National journals and conferences. She got many Certifications from CISCO, NPTEL.

Mrs.Nandikante Shravani working as an Assistant Professor, Computer Science and Engineering Department at Nalla Narasimha Reddy Educational Society's Group of Institutions, Hyderabad, Telangana, India. She received the B.TECH& M.Tech degree in Computer Science & Engineering from Jawaharlal Nehru Technological University, Hyderabad. She has 5 years of experience in teaching with research interest in IOT, Machine Learning, Networks. She published many publications in International/ National journals and conferences. She got many Certifications from CISCO, NPTEL.

ICAP PUBLISHERS
DO-CONTINENTAL ACADEMIC PUBLISHERS

INDO-CONTINENTAL ACADEMIC PUBLISHERS
A MSME REGISTERED COMPANY | ISO 9001:2015 CERTIFIED
INDIA

ISBN 978-81-955203-3-5
9 788196 520335

ABOUT THE AUTHORS

Dr.R.Priya working as a Professor in the Department of Physics, R.M.D. Engineering College, Kavaraipettai. She has about 26 years of teaching experience. She received her M.Sc., in Physics, M.Phil. in Theoretical Physics and Ph.D. in Physics from University of Madras, Chennai, Tamil Nadu State. She has published 24 research papers in Scopus/WoS indexed Journals and presented many research papers at various National/International conferences including one at Singapore. She is an active Researcher and her areas of research include Growth and Characterization of NLO and Ferroelectric Crystals, Nanomaterials and in general Material Science. She is a life member in ISTE, IACG, IAPT and Member in MRS-Singapore. She is recipient of the prestigious AICTE-Lilavati Award for the year 2021-2022 with second runner-up position.

Dr.Rashmi Trivedi is working as a Professor in the Department of Humanity and Sciences (Chemistry) in NNRESGI, HYDERABAD. She did Ph.D. in Chemistry from Devi Ahilya Vishva Vidyalaya, Indore (M.P.) in the year of 2000 & holds an M.Sc. degree in Chemistry, securing the 8th position in the University (Devi Ahilya Vishva Vidyalaya, Indore, M.P.) Merit list in 1995 post-graduation examination. She has 27 years of teaching experience & published paper in reputed National & International journals. Dr.Trivedi is author of two books and also holds a patent in her name. She is a life member of ISTE, Research Journal of Chemistry & Environment and International Association of Engineers (IAENG). She delivered lecture in National level seminar as resource person & also act as an instrumental judge for National level oral & poster presentation competitions. She organized National-level webinars, guest lecturers & Poster presentation competitions Successfully.

Dr.T.Kranthi Kumar working as an Assistant Professor in the Department of Chemistry, Sreenidhi Institute of Science and Technology, has about 14 years of teaching experience. He received Ph.D. degree in Organic Chemistry from Mewar University, Rajasthan state. He has published 14 research papers in refereed National, International journals and 6 research papers in the proceedings of various international conferences. He has received best paper awards for his research papers at International conferences. His areas of research include Hetero cyclic compounds, Nano materials, Renewable energy systems.

Mr.Gaurav Singh is an Assistant Professor in the Department of Chemistry at CMR Technical Campus, located in Kandlakoya, Medchal Road, Hyderabad. With a teaching experience of 14 years, he holds MSc (Chemistry) and M.Tech (Nanotechnology) degrees. Currently, he is pursuing a Ph.D. in Chemistry from CIT Kokrajhar, Assam. His research focuses on the advanced synthesis of nanocatalysts for transesterification of oil into biodiesel, utilizing Response Surface Methodology and Machine Learning Tools. Additionally, he has expertise in fabricating piezoelectric thin films through RF/DC Magnetron sputtering and synthesizing nanomaterials (such as CNTs, Graphene, and Quantum Dots) for various applications, particularly in the field of electronics. Mr. Gaurav Singh has successfully obtained grants from MSME and has published six research papers in international peer-reviewed journals. Mr. Gaurav Singh has published three books and holds five Indian patents to his credit. Furthermore, he has actively participated in over 40 international and national conferences, workshops, and Faculty Development Programs (FDPs). Notably, Mr. Gaurav Singh organized a National Conference in 2015, which received funding from DRDO.

Infinite Research
Registered under MSME
Government of India
https://www.infinite-research.org
info@infiniteresearch.org
infiniteresearchorg@gmail.com
+91 7995871450, +91 8919552865

ISBN 978-81-964504-3-2

9 788196 504632

NANOMATERIALS

NANOMATERIALS

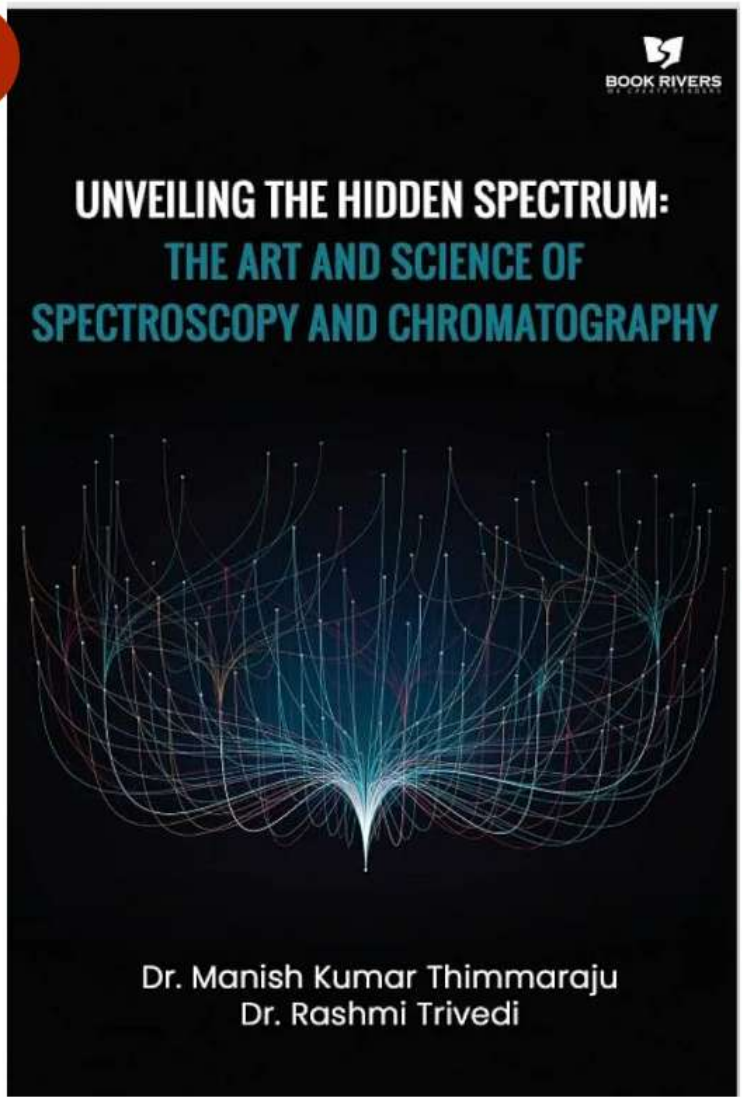
Dr. R. Priya
Dr. Rashmi Trivedi
Dr. T. Kranthi Kumar
Mr. Gaurav Singh

Infinite Research
A Research Hub

SPECTRUM The Art and Science of Spectroscopy and Chromatography

22 November 2023
ISBN-13: 978-9358421927 **ISBN-10:** 9358421924

5% off



A MINI-REVIEW ON BENZIMIDAZOLE DERIVATIVES: A PHARMACOPHORE AGENT

Abstract

Nowadays, benzimidazole is an essential class of N-heterocyclic compounds. Benzimidazole that consists of six-member benzene ring system combined with five-member imidazole ring compound systems. Benzimidazole central part molecules go on with the essential center of attention among the accessible heterocyclic compounds for the reason that of more than a few pharmacological and medicinally vital properties. The biologically significant benzimidazoles accomplish the center of attention owing to their stability, stupendous bioavailability, and broad range of biological capability. The current examination on benzimidazole derivatives reveals and talks about the biological activities of benzimidazole derivatives extensively experienced as pharmacological agents.

Keywords: Benzimidazoles, Biological activity, Pharmacological agent, Medicinal chemistry, Anti-cancer, Anti-bacteria.

Authors

Cheruku Shruthi
Department of Chemistry
Kommuri Pratap Institute of Technology
Hyderabad, Telangana, India.

P. Sudha
Department of Chemistry
Nalla Narasimha Reddy Education Society's group of Institution
Hyderabad, Telangana, India.

G. B. Dharma Rao
Department of Chemistry
Kommuri Pratap Institute of Technology
Hyderabad, Telangana, India.
gbdharmarao@gmail.com

I. INTRODUCTION

Heterocyclic molecules experienced for the majority of exceptional and assorted range of organic molecules. A remarkable extent of heterocyclic molecules has been synthesized up to paramount position. Heterocyclic molecules are quickly growing in quantity owing to extensive synthetic research and moreover their superior biological activity. Such heterocyclic compounds have a widespread choice of exercises in the field of medicinal chemistry. Biologically, dyestuff, sanitizers, electronics, corrosion inhibitors, optics, antioxidants, pharmacology, material sciences and copolymer synthesis are supplementary well-known applications.[1] Heterocyclic center nucleus imparts a important function in medicinal chemistry and provides as a very important central part for the move forward of a diversity of recently bare heterocyclic compounds and their analogues.

Benzimidazole is a bicyclic compound molecule in which aromatic benzene ring system combined with 4- and 5- position of the imidazole ring system and it furthermore known as benzoglyoxaline. Imidazole ring molecule seizes two nitrogen atoms at non-adjacent site in five member ring system. During 1950, when 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole was established as a central part of the molecule of vitamin B12 as shown Figure-1,[2] curiosity have been engendered to enlarge prospective pharmacological agent with benzimidazole as a crucial core nucleus.[3]

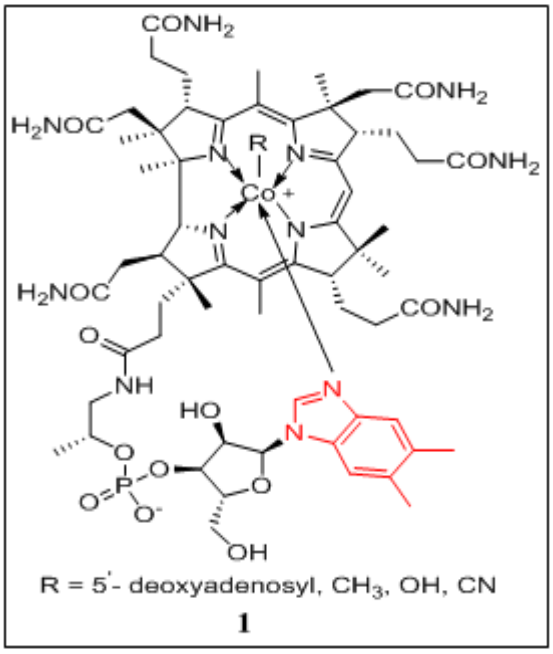


Figure 1: Vitamin B12 Enclosing Benzimidazole as a Central Part.

Benzimidazole molecule is an enormously principal and vital unit in drug development and its analogues are used because a considerable class of medicinally important compounds in the field of pioneering drug improvement. Some of benzimidazole derivatives disclose momentous biological consideration against several viruses, and have effective anti parasitic agents, antimicrobial agents, anti tumor agents, and inhibitors of the hepatitis C virus RNA polymerase. Benzimidazole derivativs as a veterinary drug are as well mostly experienced for anticipation and dealing of parasitic infections in aquaculture and

agriculture. Furthermore, a small number of them also used as pre- or post-harvest fungicides for the control of a widespread variety of fungi, which influence field crops, gathered fruit and vegetables. [4] Extension of benzimidazole central part in diverse group of pharmacological agents such as antiviral, antimicrobial, antihypertensive, anticancer, antiparasitic, and CNS stimulant in addition to antidepressants has ended it useful for the progression of various therapeutic agents. [5]

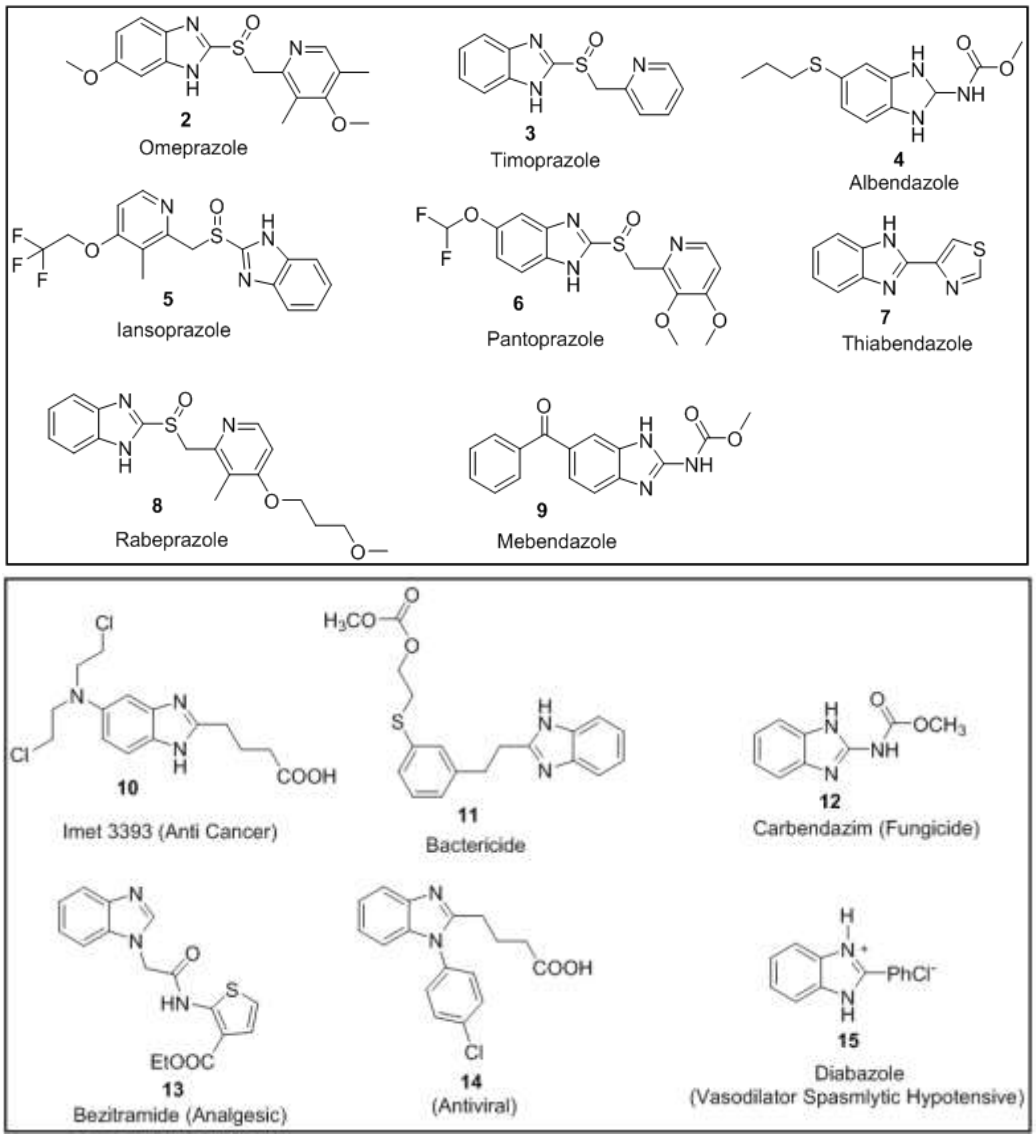
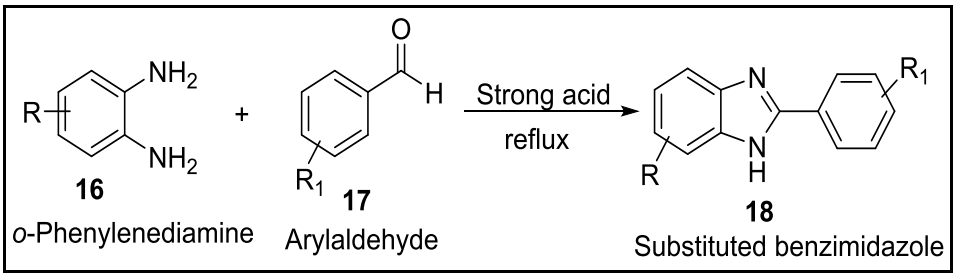


Figure 2: Bioactive Molecules Containing Benzimidazole Molecule as a Core Unit.

Chemistry and estimation of a variety of benzimidazole with substituttion analogues experienced the development of albendazole, omeprazole, rabeprazole, lansoprazole, timoprazole, pantoprazole, thiabendazole, mebendazole are broadly used anthelmintic FDA standard drugs which are commercially accessible in present market existing benzimidazole central unit in their moiety as described in Figure-2.[6] Such a considerable benzimidazole central unit was synthesized by reacting *o*-Phenylenediamine (OPDA) with carbonyl compounds, beneath strong acidic conditions (Scheme-1) which was frequently used synthetic protocol to synthesize benzimidazole analogue.[7]



Scheme 1: Traditional Synthesis of Benzimidazole Analogues.

II. TAUTOMERISM IN BENZIMIDAZOLE

Organic isomer derivatives that rapidly interconverted by a chemical reaction known as tautomerization. The outcomes of this reaction in the formal transformation of a hydrogen atom or proton, accompanied by a exchange of a single bond and adjacent double bond.[8] The perception of tautomerizations is called tautomerism.[8] The numbering of the benzimidazole ring system is described in Figure-3 even though benzimidazole as possessing the proton at N1 there essentially exhibit a rapid exchange flanked by the –NH- and =N- nitrogen atoms, and form two tautomers, **19** and **20**, might be strained for the benzimidazole molecule.[3]

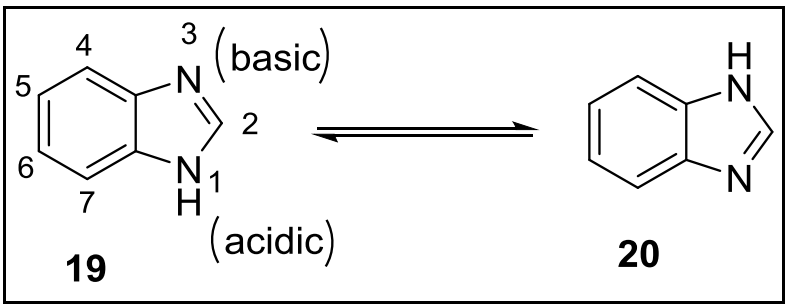


Figure 3: Existence of Tautomerism in Benzimidazole Molecule.

III. PHARMACOLOGICAL ACTIVITIES OF BENZIMIDAZOLE DERIVATIVES

Based on the resource of extensive rang literature assessment analysis benzimidazole derivatives demonstrates a wide range of pharmacological activities [9] as shown in Figure-4. Based on the pharmacologically bio-active compounds which include benzimidazole as central part, the synthetic and industrial chemist paying additional attentiveness on the synthesis of benzimidazole analogues to boost up its pharmacological activity. In the chapter we were paying attention on the pharmacological activity of benzimidazole derivatives.

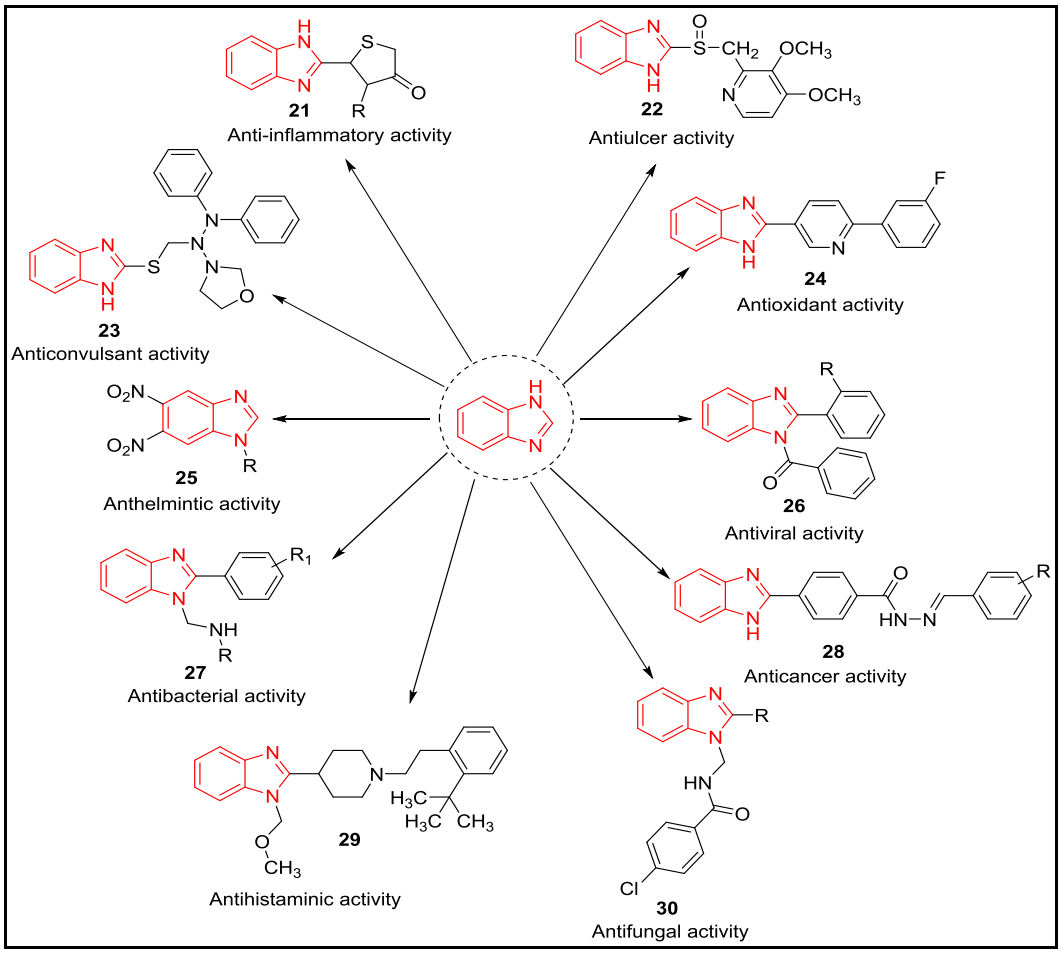
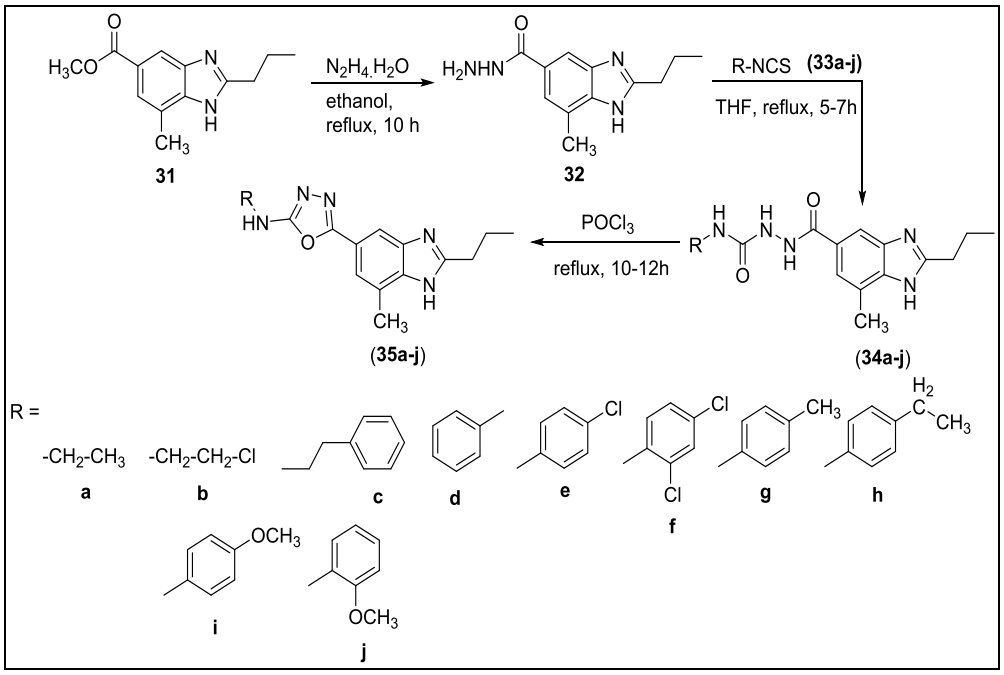


Figure 4: Significant Pharmacological Active Compounds which Enclose Benzimidazole Central Part.

R. Katikireddy *et. al* described the synthesis of benzimidazole hybrid with oxadiazol-2-*N*-alkyl/aryl amines[10] as prescribed in Scheme-2. Initially, methylester (**31**) react with hydrazine hydrate under reflux condition to form acid hydrazide (**32**). The acid hydrazide further react with different alkyl/aryl isocyanates (**33**) in THF to obtained the semicarbazide derivatives (**34**) followed by the cyclodehydration with $POCl_3$ to attained the title compound benzimidazole hybrid with oxadiazol-2-*N*-alkyl/aryl amines (**35**). All the synthesized compounds are examined for in-vitro anticancer activity by employing MTT colorimetric assay averse to the human cancer cell lines in comparison of Doxorubicin as authenticate standard drug. Among all the synthesized compounds **35f** was set up to be the most successful anticancer agent with IC_{50} values of 4.68 ± 0.04, 4.16 ± 0.02, 5.40 ± 0.08 mM against the HeLa, MCF-7, and A549 cell lines correspondingly and **35a**, **35d**, **35g**, **35i** and **35j** exhibit the less effective to human cancer cell lines than Doxorubicin.



Scheme 2: Synthesis of Benzimidazole Hybrid with Oxadiazol-2-*N*-Alkyl/Aryl Amines Derivatives.

S. E-S. Saeed *et. al* reported the synthesis and characterization of benzimidazole derivatives based on lanthanum mixed ligand complexes [12]. At first, 2-aminomethylbenzimidazole dihydrochloride was reacted with salicylaldehyde to attain the 2-(1H-benzimidazol-2-ylmethyliminomethyl) phenol as a ligand. The metal complex was synthesized in two steps. In first step Lanthanum (III) chloride was react with 2-(1H-benzimidazol-2-ylmethyliminomethyl) phenol ligand (**36**) to form the main (benzimidazole Schiff Base) complex (**37**) [La (L) Cl_2 (H_2O_2)]. The main complex was further treated with ammonia, furfural (Fur) and salicylaldehyde (Sal) as a secondary ligand to furnish the [La(L)Cl_2(NH_3)] (**38**), [La(L)Cl(Fur)] (**39**), or [La(L)Cl(Sal)] (**40**) complexes respectively as shown in Figure-5.

All the synthesized complex compounds are tested against the HCT116 cell line cytotoxicity and it was found that Compound (**36**) (HL) showed IC_{50} at 27 µg/ml, complex (**38**) [La (L) Cl_2(NH_3)] showed IC_{50} at 34.6 µg/ml, Complex (**39**) [La(L)Cl(Fur)] showed IC_{50} at 63 µg/ml, complex (**37**) [La (L) Cl_2(H_2O_2)]showed IC_{50} at 75 µg/ml, and complex (**40**) [La (L) Cl(Sal)] showed the lowest HCT116 cell line cytotoxicity at 92 µg/ml when compared with sulphorhodamine-B (SRB) as standard drug.

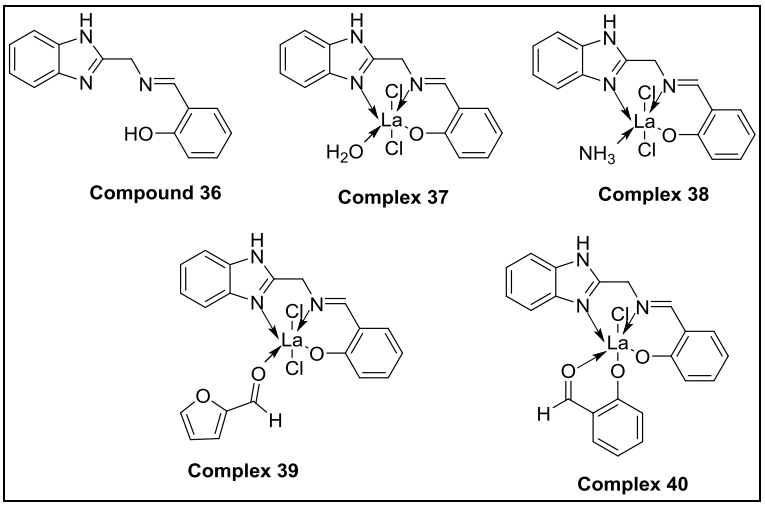
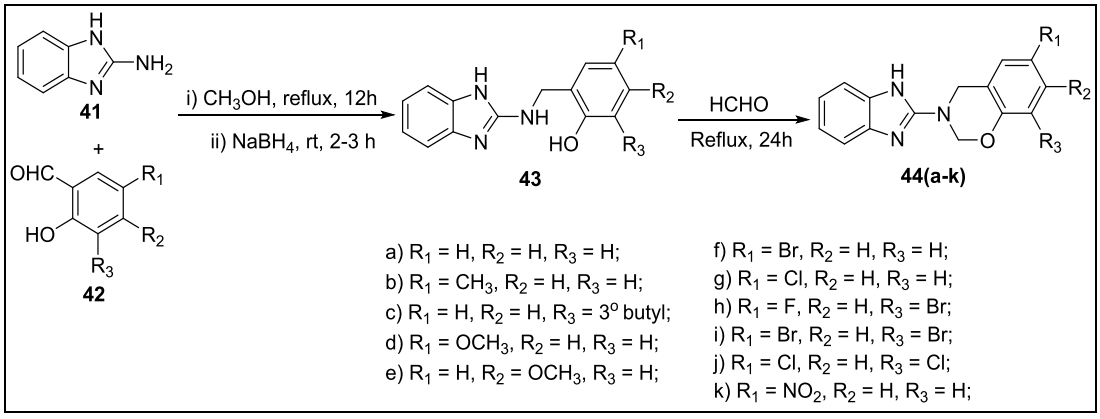


Figure 5: Compound (**36**) (HL), Complex (**37**) [La (L) $Cl_2(H_2O_2)$], Complex (**38**) [La (L) $Cl_2(NH_3)$, Complex (**39**) [La(L)Cl(Fur), and Complex (**40**) [La (L) Cl(Sal)].

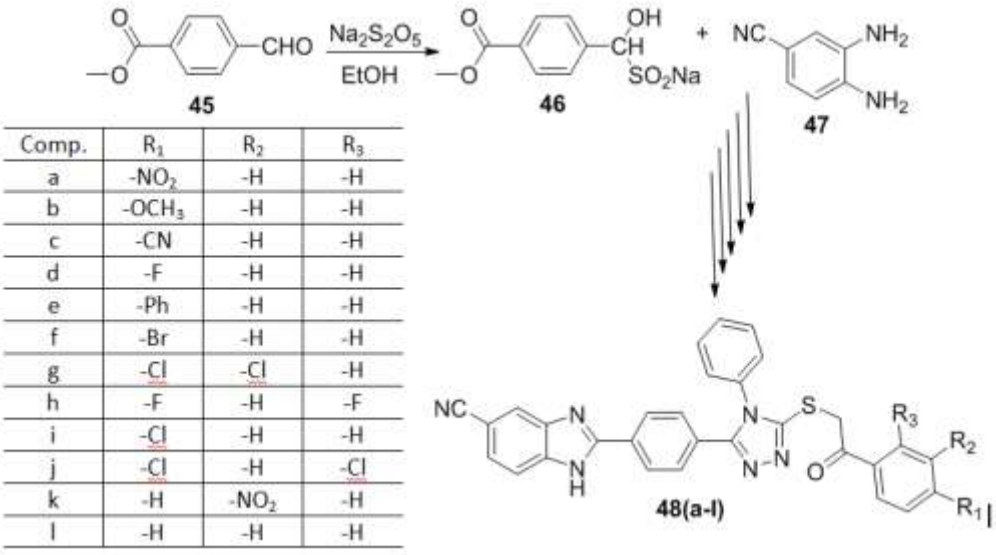
G. Srinivas *et.al* [13] described the synthesis of 3,4-dihydro-2H-benzo[e] [1, 3] oxazines tethered benzimidazole derivatives using benzimidazol-2-amine (**41**) reacted with different 2-hydroxybenzaldehydes (**42**) by the addition of $NaBH_4$ to attained the intermediate (**43**) followed by the addition of formaldehyde to furnish the target compound 3,4-dihydro-2H-benzo[e] [1, 3] oxazines tethered benzimidazole (**44a-k**) as shown in Scheme-3. The entire synthesized target derivatives were studies for the anticancer activity in view of breast cancer cell lines (MCF-7) with reference of Doxorubicin drug. Compound **44e** exhibit exceptional activity against cell lines MCF-7 with IC_{50} values of 8.60 ± 0.75, compare to the authenticate drug Doxorubicin IC_{50} value of 9.11±0.54 against MCF-7 cell line. Compounds **44i** also signified superior activity with an IC_{50} value of 9.85±0.69 µM on par with Doxorubicin against MCF-7 cells. Left over synthesized derivatives **44a**, **44b**, **44c**, **44d**, **44f**, **44g**, **44h**, **44j** and **44k** existing the excellent to reasonable activity in view of MCF-7 cell lines.



Scheme 3: Synthesis of 3,4-dihydro-2H-benzo[e] [1, 3] Oxazines Tethered Benzimidazole Derivatives.

E. Guzel *et.al* [14] reported the synthesis of benzimidazole-1,2,4-triazole derivatives in six steps as shown in Scheme-4. Initially, methyl 4-formylbenzoate (**45**) was react with

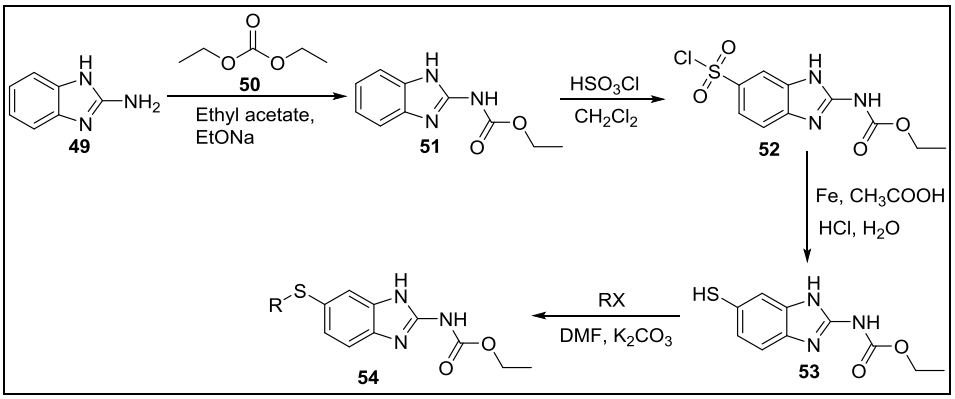
sodium metabisulfite to furnish the sodium metabisulfite (**46**) followed by the condensation reaction of 5-cyano-1,2-phenylenedi amine (**47**) to obtained the methyl 4-(5-cyano-1H-benz[d]imidazole-2- yl)benzoate intermediate. The intermediate further react with hydrazine hydrate to attain the 4-(5-cyano-1H-benz[d]imidazol-2-yl)benzohydrazide intermediate followed by the reaction phenyl isothiocyanate, NaOH in ethanol and 2-bromoacetophenone to achieve the final title compound benzimidazole-1,2,4-triazole derivatives (**48a-l**). All the synthesized derivatives were screened for their in vitro antifungal activity counter to *C. albicans, C. glabrata, C. krusei, and C. parapsilopsis. The compounds* **48b**, **48i**, and **48j** exhibited the excellent antifungal activity with their MIC values of 0.97 μg/mL compared with voriconazole and fluconazole.



Comp.	R_1	R_2	R_3
a	$-NO_2$	-H	-H
b	$-OCH_3$	-H	-H
c	-CN	-H	-H
d	-F	-H	-H
e	-Ph	-H	-H
f	-Br	-H	-H
g	-Cl	-Cl	-H
h	-F	-H	-F
i	-Cl	-H	-H
j	-Cl	-H	-Cl
k	-H	$-NO_2$	-H
l	-H	-H	-H

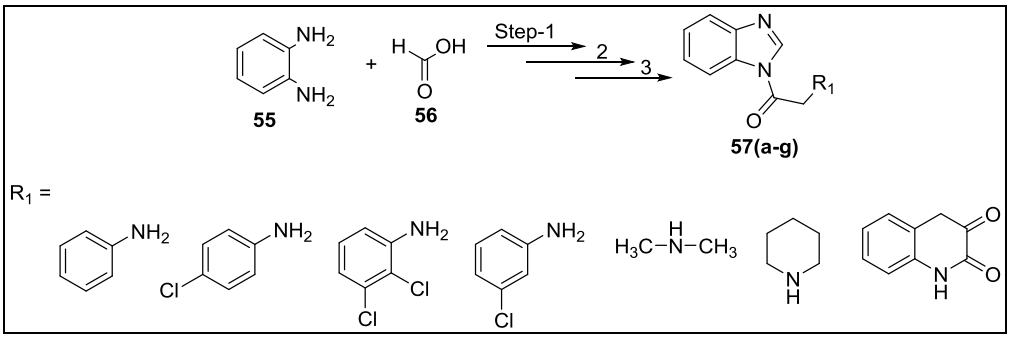
Scheme 4: Synthesis of Benzimidazole-1,2,4-triazole Derivatives.

Lei Yang reported the design and synthesis of new-fangled benzimidazole compounds including thioether and carbamate moieties.[15] Initially, benzimidazole (**49**) react with diethyl carbonate (**50**) to form a intermediate (**51**) and it is further react with sulfonic acid to obtained the intermediate (**52**) and again intermediate **52** stirred in mixture of HCl and CH_3COOH with Fe to obtained the intermediate **53**. Finally the title compound (**54**) was obtained by the reaction of intermediate **53** with K_2CO_3 and RX in DMF as described in Scheme-5. The whole synthesized analogues were tested for antifungal activity *aganist C. mandshurica, T. cucumeris, B. cinerea, V. daliae, P. infestans,* and *G. zeae* at 50μg/mL. Among all the compounds E11 and E15 exhibit the superior vitro antifungal activity against *V. daliae*, than albendazole and E11 perform immense in vitro antifungal activity against *P. infestans* (75%) to albendazole (61%).



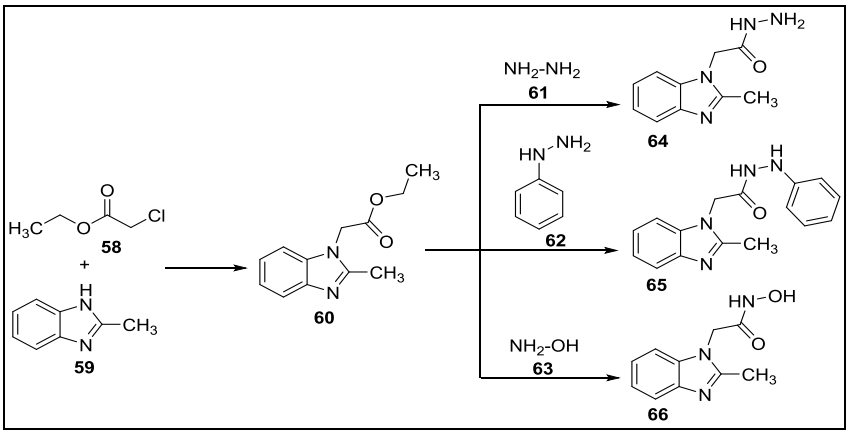
Scheme 5: Synthesis of Benzimidazole Analogues including thioether and Carbamate Moieties

Ali *et.al* addressed [16] the three step synthesis of 1-(1H-benzimidazol-1- yl)-2-(substituted) ethanone derivatives as shown in Scheme-6. In step-1 *O*-phenylene diamine (**55**) react with formic acid (**56**) to get benzimidazole and is react with chloro-acetyl chloride to obtain 1-(1H-benzimidazol-1-yl)-2-chloroetanone in step-2. Finally, in step-3 the 1-(1H-benzimidazol-1- yl)-2-chloroetanone compound is treated with chloroform to attained the title product 1-(1H-benzimidazol-1-yl)-2-(substituted) ethanone derivatives (**57**). Among all the synthesized compounds **57b, 57e** and **57g** exhibit the potential In-vitro anti-inflammatory activity using tetracycline as reference drug.



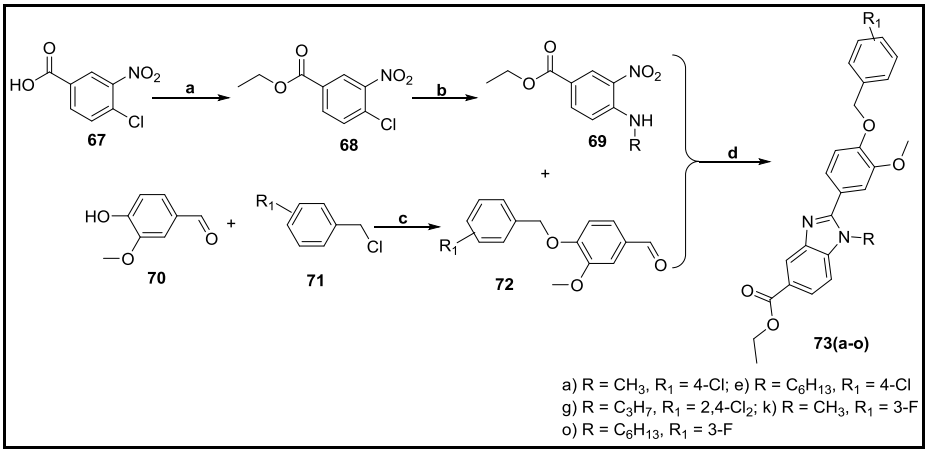
Scheme 6: Synthesis of 1-(1H-benzimidazol-1- yl)-2-(substituted) Ethanone Derivatives.

A.K. Maharana *et.al* reported the synthesis of new benzimidazole derivatives as mentioned in Scheme-7.[17] Ethylchloroacetate (**58**) in acetone is reacted with 2-methylbenzomidazole (**59**) in acetone to obtained the 2-methyl-benzimidazol with acetate group (**60**). The title compounds are synthesized by the addition of hydrazine hydrate (**61**), phenyl hydrazine (**62**) and hydroxylamine (**63**) to the (2-methyl-1H-benzimidazol-1-yl) acetate (**60**) to achieved the following desired compounds 2-(2-methyl-1H-benzimidazol-1-yl) acetohydrazide (**64**), 2-methyl-benzimidazole along with N-phenylacetohydrazide (**65**) and 2-methyl-benzimidazole along with N-hydroxy-acetamide (**66**) respectively. The synthesized benzimidazole derivatives were examined for anti-inflammatory activity make use of Carrageenan-Induced hind paw edema assay with ibuprofen as standard in rats and found that MBNHYD exhibited the good anti-inflammatory activity in contrast to standard drug.



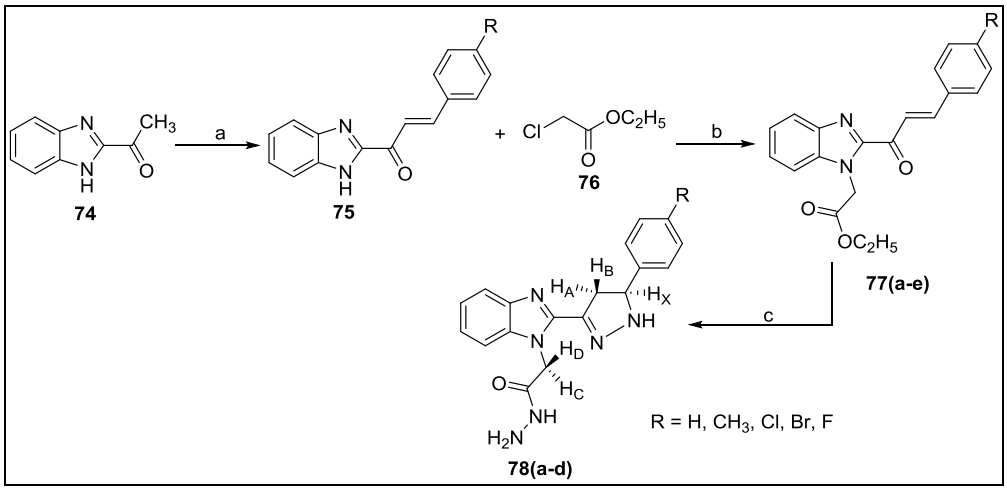
Scheme 7: Synthesis of Target Benzimidazole Derivatives.

R. Sathyanarayana *et al.*[18] synthesized the novel benzimidazole derivatives (**73a–o**) as shown in Scheme-8. The esterification of 4-chloro-3-nitrobenzoic acid (**67**) was carried out by a catalytic amount of conc. H_2SO_4 under reflux condition to produce the intermediate (**68**), subsequently reaction with 1°-amines bearing diverse alkyl group in existence of base like triethylamine to produce the intermediate (**69**). On the other hand, the derivatives of 4-(benzyloxy)-3-methoxybenzaldehyde (**72**) was synthesized by the reaction of benzyl chlorides analogues (**71**) with vanillin (**70**) by means of catalytic amount of K_2CO_3 as a base in DMF under refluxing condition for 3 h and the yield of the target products are 80-95%.
The desired products are synthesized by the reaction of intermediate **69** and **72** which are present in DMSO using reducing agent like $Na_2S_2O_4$ (sodium dithionite) formed the substituted benzimidazole analogues (**73a–o**). The synthesized compounds were studied for anti-infammatory activity by protein denaturation of bovine serum albumin. Based on in vitro anti-infammatory activity, synthesized benzimidazole derivatives **73a**, **73e**, **73g**, **73k** and **73o** were assessed for their in vivo antiinfammatory activity at 50 mg/kg dose level by examining the carrageenan–induced paw edema assay exhibited excellent anti-infammatory activity 77.50%, 75.25%, 43.35%, 72.11%, 70.10% respectively while examined to standard drug indomethacin which exhibit 74.02% inhibition.



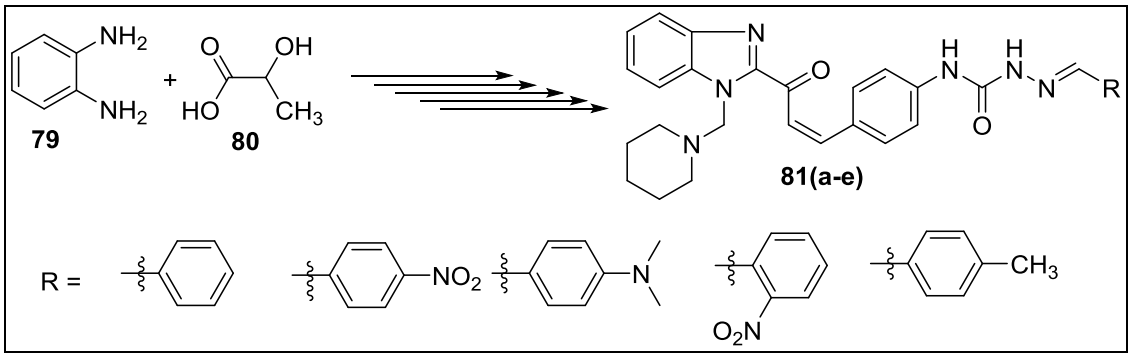
Scheme 8: Synthesis of Substituted Benzimidazole Derivatives (**73a–o**). Reagents and conditions: a) H_2SO_4, dry ethanol, 16 h; b) n-alkylamine, triethylamine, room temperature; c) K_2CO_3, DMF, 3 h; d) substituted benzyloxybenzaldehydes, sodium dithionite, 90°C, 3 h.

G. K. Padhy *et. al* [19] discussed the synthesis of novel benzimidazole-pyrazoline hybrid compounds as shown in the Scheme-9. Initially, the 2-acetylbenzimidazole (**74**) was synthesized by the reaction of lactic acid with *o*-phenylenediamine and it is reacted with arylaldehyde to attain the chalcone (**75**) synthon intermediate. The intermediate was further treated with ethyl chloroacetate (**76**) to obtain the substituted benzimidazole chalocone esters (**77a-e**). Finally, benzimidazole chalcone ester react with hydrazine hydrate to furnish the target acid hydrazides of benzimidazole linked pyrazolines (**78a-d**) compounds. The whole derivatives of synthesized compounds are examined for their antibacterial activity in comparison with ciprofloxacin as authenticate standard drug. Among all synthesized compounds **5a** exhibit the potential antibacterial activity of 62.5 µg mL^{-1} against S.aureus.



Scheme 9: Synthesis of Benzimidazole-pyrazoline hybrid Compounds. Reagents and Conditions: a) Ar-CHO, 10% NaOH, EtOH, stir; b) dry acetone, K_2CO_3, reflux; c) $NH_2.NH_2.H_2O$, alcohol, reflux.

M. Selvakumaran *et.al* addressed the synthesis of new-fangled benzimidazole linked piperidine analogues as shown in Scheme-10. *O-Phenylenediamine* (**79**) react with lactic acid (**80**) to form 1-(1H-benzimidazol-2-yl) ethanol followed by the treatment of $K_2Cr_2O_7$ and H_2SO_4 to produce 1-(1H-benzimidazol-2-yl)ethanone intermediate. In the consequent step, using Mannich base reaction the intermediate was treated with piperidine and formaldehyde to attain 1-(1-(piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)ethanone. The target molecules 1-(4-sub stitutedbenzylidene)-4-(4-(3-oxo-3-(1-(piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)prop-1-enyl)phenyl)semicarbazide (**81a-e)** were synthesized by the reaction of 1-(1-(piperidin-1-ylmethyl)-1H-benzimidazol-2-yl)ethanone with 4-amino benzaldehyde, sodium cyanate, hydrazine hydrate, and various aromatic aldehydes in different reaction conditions.[20] The all synthesized compounds were evaluated for their antibacterial activity. Among all the synthesized compounds, **81b, 81d** and **81e** exhibit the excellent antibacterial activity against *Bacillus subtilis*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa* bacteria in comparsion with standard drug Ciprofloxacin.



Scheme 10: Synthesis of Benzimidazole Linked Piperidine Derivatives.

IV. CONCLUSION

In summary, benzimidazole analogues have paying a remarkable reflection for the reason that of their adaptable experience in the medicinal chemistry. In this chapter, we have converse a diversity of benzimidazole analogues comprehensively used in the field of medicinal chemistry and used as guide molecules in drug modernization studies. This chapter can authenticate to be unbelievably obliging for chemists or research scholars in the advancement of novel methodologies for the vast synthesis of biologically and medicinally active novel benzimidazoles derivatives and large-scale production of biologically active novel benzimidazole derivatives.

V. CONFLICT OF INTEREST

The authors state no conflict of interest, financial or else.

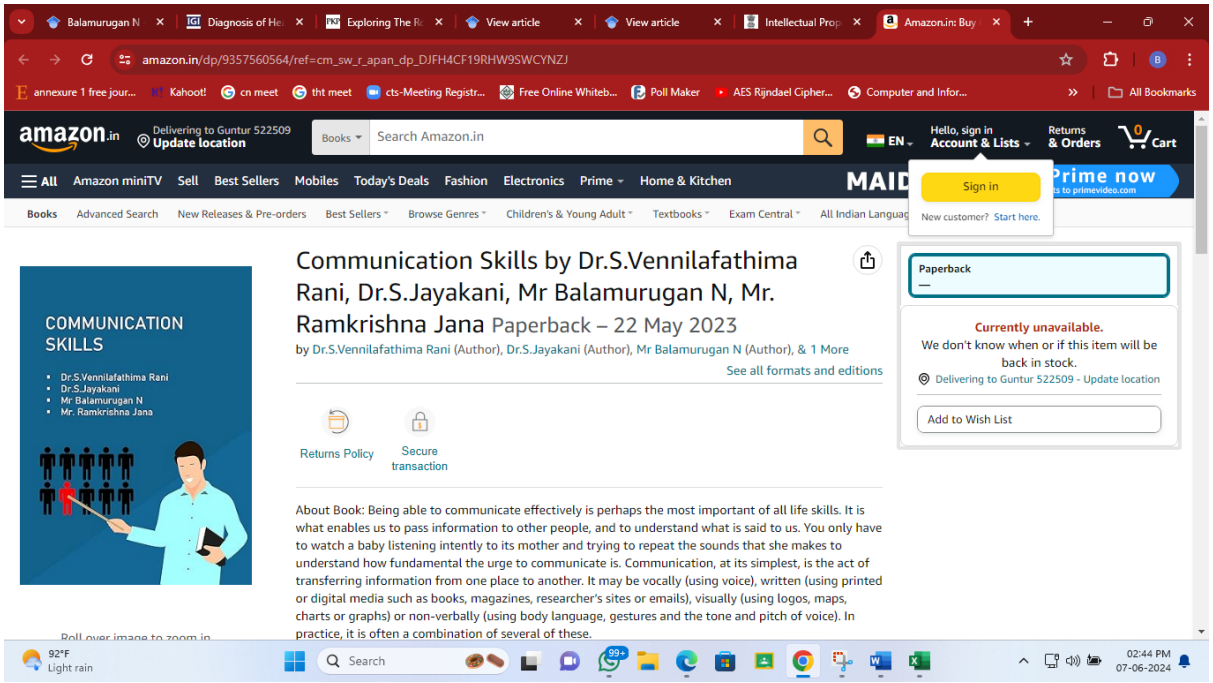
VI. ACKNOWLEDGEMENT

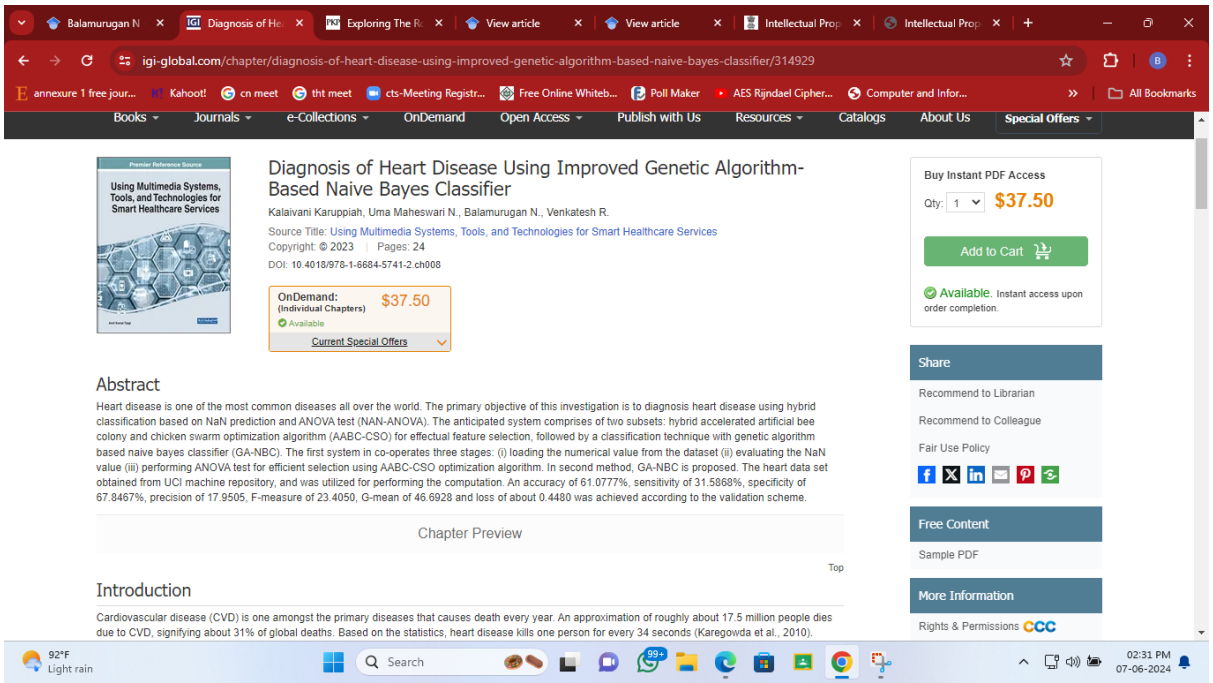
Ch. Shruthi and G. B. Dharma Rao express their sincere gratefulness to the Principal and KPRIT management, Hyderabad, India and P. Sudha conveys her special thanks to the management of NNRG, Hyderabad for providing the amenities to write and propose this chapter for the publication.

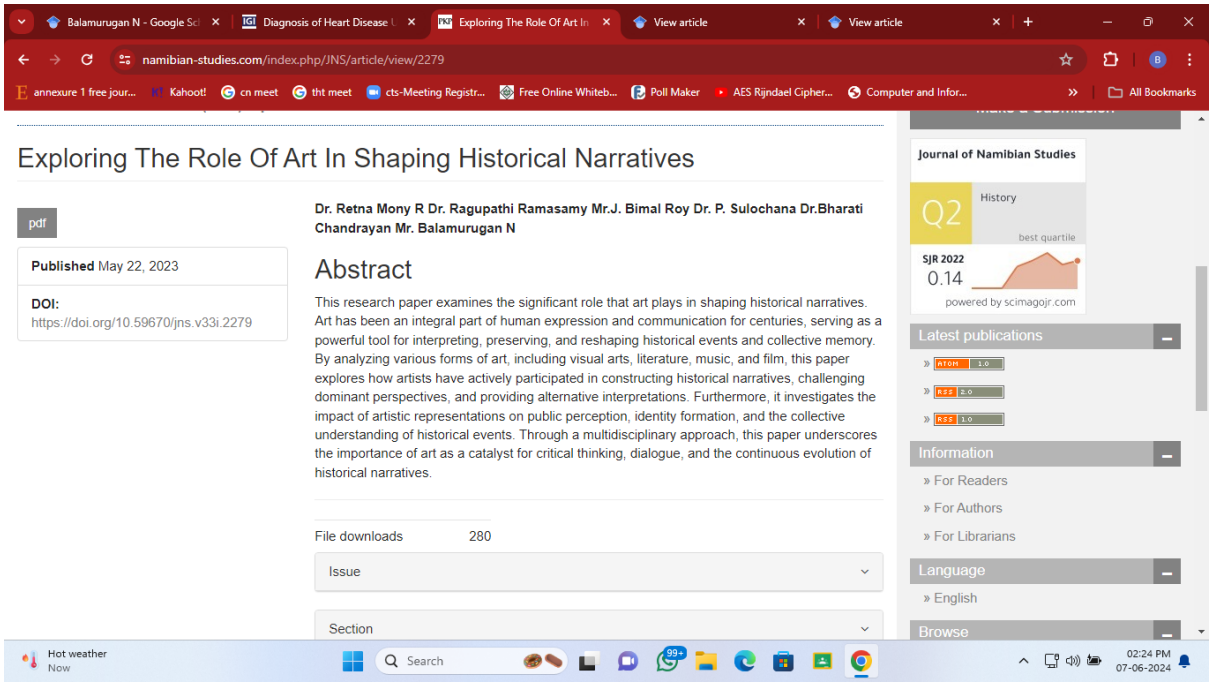
REFERENCES

[1] Qadir T, Amin A, Sharma PK, Jeelani I, Abe H. A Review on Medicinally Important Heterocyclic Compounds. The open Medicinal Chemistry Journal. 2022; 16:1-34.
[2] Bonnett, R. The Chemistry of the Vitamin B12 Group. Chemical Review. 1963; 63(6):573–605.
[3] Townsend LB, Wise DS. The synthesis and chemistry of certain anthelmintic benzimidazoles. Parasitology Today. 1990; 6(4):107-112.
[4] Isasi SB, Quezada C, Pessoa H, Morello A, Kogan MJ, Lueje AA. Determination znd characterization of new benzomidazoles with activity against Trypanosoma cruzi by UV spectroscopy and HPCL. Biorganic & Medicinal Chemistry. 2008; 16(16):7622-7630.
[5] Salahuddin, Shaharyar M, Mazumdera A. Benzimidazoles: A biologically active compounds. Arabian Journal of Chemistry, 2017; 10(S1):S157-S173.
[6] Singh N, Pandurangan A, Rana K, Anand P, Ahamad A, Tiwari, AK. Benzimidazole: A short review of their antimicrobial activities. International Current Pharmaceutical Journal. 2012; 1(5):119-127.
[7] Nannapaneni DT, Gupta AVSSS, Reddy Ml, Sarva RCh. Synthesis, Characterization, and Biological Evaluation of Benzimidazole Derivatives as Potential Anxiolytics. J Young Pharm. 2010; 2(3):273-279.

[8] Su F, Sun Z, Su W, Liang X. NMR investigation and theoretical calculations on the tautomerism of benzimidazole compounds. Journal of Molecular Structure. 2018; 1173:690-696.
[9] Arora SS, Babbar R. A Comprehensive Review on Therapeutic Potential of Benzimidazole: A Miracle Scaffold. Journal of Pharmaceutical Technology. Research and Management. 2020; 8(1):23-29.
[10] Katikireddy R, Srinivas M, Ramu K, Murali Krishna MPS, Durgaiah G, Reddy YN. Synthesis, anticancer activity and molecular docking studies of hybrid benzimidazole-1,3,4-oxadiazol-2-N-alkyl/aryl amines. Polycyclic Aromatic Compounds, 2022; 42(9):5855-5869.
[11] Saeed S E-S, Alhakimi AN. Synthesis, characterization of Lanthanum mixed ligand complexes based on benzimidazole derivative and the effect of the added ligand on the antimicrobial, and anticancer activities. Journal of Natural Sciences and Mathematics, 2022; 15: 35-53.
[12] Srinivas G, Raghu D, Veerabhadraiah M, Vishnu T, Namratha V. Design, synthesis of benzimidazole tethered 3,4 dihydro 2H benzo[e] [1, 3] oxazines as anticancer agents, Molecular Diversity, 2023; https://doi.org/10.1007/s11030-023-10661-3.
[13] Guzel E, Cevik UA, Evren AE, Bostanci HE, Gul UD, Kayis U, Ozkay Y, Kaplancikli ZA. Synthesis of benzimidazole-1,2,4-triazole derivatives as potential antifungal agents targeting 14α-demethylase. ACS Omega, 2023; 8: 4369-4384.
[14] Lei Yang. Design, synthesis, and antifungal activity of novel benzimidazole derivatives bearing thioether and carbamate moieties. Journal of Chemistry, 2022; Article ID 8646557: 1-4.
[15] Ali A, Vasanthi R, Tiwari Y, Ahmad TDS, Zambare YB, Deokule TA, Hechhu R, Chandha M. Synthesis of some novel benzimidazole derivatives as potential therapeutic agents. European Chemical Bulletin, 2023; 12(si6): 4235-4246.
[16] Moharana AK, Dash RN, Mahanandia NC, Subudhi BB. Synthesis of anti-inflammatory activity evaluation of some benzimidazole derivatives. Pharmaceutical Chemistry Journal, 2022; 56(8):1070-1074.
[17] Sathyanarayana R, Poojary B, Srinivasa SM, Merugumolu VK, Chandrashekarappa RB, Rangappa S. In vitro, in vivo and in silico driven identification of novel benzimidazole derivatives as anticancer and anti infammatory agents", Journal of the Iranian Chemical Society. 2021; 19:1301-1317.
[18] Padhy GK, Rath D, Bhukta P, Kumar LA, Sethy K, Panda J, Raul SK, Behera AK. Synthesis of noval benzimidazole-pyrazoline hybrid molecules as antibacterial and anticancer agent. Journal of Pharmaceutical Negative Results, 2023; 14(1): 521-526.
[19] Selvakumaran M, Predhanekar MI, Kubaib A, Visagaperumal D. Novel Benzimidazole linked piperidine derivatives screened for antibacterial and antioxidant properties with Density Functional and Molecular Mechanic tools. Results in Chemistry, 2023; 5:100765.


Balamurugan N
Diagnosis of He
Exploring The R
View article
View article
Intellectual Prop
Amazon.in: Buy
amazon.in/dp/9357560564/ref=cm_sw_r_apan_dp_DJFH4CF19RHW9SWCYNZJ
annexure 1 free jour...
Kahoot!
cn meet
tht meet
cts-Meeting Registr...
Free Online Whiteb...
Poll Maker
AES Rijndael Cipher...
Computer and Infor...
All Bookmarks
amazon.in
Delivering to Guntur 522509
Update location
Books
Search Amazon.in
EN
Hello, sign in
Account & Lists
Returns
& Orders
Cart
All
Amazon miniTV
Sell
Best Sellers
Mobiles
Today's Deals
Fashion
Electronics
Prime
Home & Kitchen
Sign in
New customer? Start here.
Books
Advanced Search
New Releases & Pre-orders
Best Sellers
Browse Genres
Children's & Young Adult
Textbooks
Exam Central
COMMUNICATION SKILLS
Dr.S.Vennilafathima Rani
Dr.S.Jayakani
Mr Balamurugan N
Mr. Ramkrishna Jana
Communication Skills by Dr.S.Vennilafathima Rani, Dr.S.Jayakani, Mr Balamurugan N, Mr. Ramkrishna Jana Paperback – 22 May 2023
by Dr.S.Vennilafathima Rani (Author), Dr.S.Jayakani (Author), Mr Balamurugan N (Author), & 1 More
See all formats and editions
Returns Policy
Secure transaction
About Book: Being able to communicate effectively is perhaps the most important of all life skills. It is what enables us to pass information to other people, and to understand what is said to us. You only have to watch a baby listening intently to its mother and trying to repeat the sounds that she makes to understand how fundamental the urge to communicate is. Communication, at its simplest, is the act of transferring information from one place to another. It may be vocally (using voice), written (using printed or digital media such as books, magazines, researcher's sites or emails), visually (using logos, maps, charts or graphs) or non-verbally (using body language, gestures and the tone and pitch of voice). In practice, it is often a combination of several of these.
Paperback
Currently unavailable.
We don't know when or if this item will be back in stock.
Delivering to Guntur 522509 - Update location
Add to Wish List
92°F
Light rain
Search
02:44 PM
07-06-2024


Balamurugan N
Diagnosis of He
Exploring The R
View article
View article
Intellectual Prop
Intellectual Prop
igi-global.com/chapter/diagnosis-of-heart-disease-using-improved-genetic-algorithm-based-naive-bayes-classifier/314929
annexure 1 free jour...
Kahoot!
cn meet
tht meet
cts-Meeting Registr...
Free Online Whiteb...
Poll Maker
AES Rijndael Cipher...
Computer and Infor...
All Bookmarks
Books
Journals
e-Collections
OnDemand
Open Access
Publish with Us
Resources
Catalogs
About Us
Special Offers
Using Multimedia Systems, Tools, and Technologies for Smart Healthcare Services
Diagnosis of Heart Disease Using Improved Genetic Algorithm-Based Naive Bayes Classifier
Kalaivani Karuppiah, Uma Maheswari N., Balamurugan N., Venkatesh R.
Source Title: Using Multimedia Systems, Tools, and Technologies for Smart Healthcare Services
Copyright: © 2023 | Pages: 24
DOI: 10.4018/978-1-6684-5741-2.ch008
OnDemand: (Individual Chapters) $37.50
Available
Current Special Offers
Buy Instant PDF Access
Qty: 1 $37.50
Add to Cart
Available. Instant access upon order completion.
Share
Recommend to Librarian
Recommend to Colleague
Fair Use Policy
Free Content
Sample PDF
More Information
Rights & Permissions
Abstract
Heart disease is one of the most common diseases all over the world. The primary objective of this investigation is to diagnosis heart disease using hybrid classification based on NaN prediction and ANOVA test (NAN-ANOVA). The anticipated system comprises of two subsets: hybrid accelerated artificial bee colony and chicken swarm optimization algorithm (AABC-CSO) for effectual feature selection, followed by a classification technique with genetic algorithm based naive bayes classifier (GA-NBC). The first system in co-operates three stages: (i) loading the numerical value from the dataset (ii) evaluating the NaN value (iii) performing ANOVA test for efficient selection using AABC-CSO optimization algorithm. In second method, GA-NBC is proposed. The heart data set obtained from UCI machine repository, and was utilized for performing the computation. An accuracy of 61.0777%, sensitivity of 31.5868%, specificity of 67.8467%, precision of 17.9505, F-measure of 23.4050, G-mean of 46.6928 and loss of about 0.4480 was achieved according to the validation scheme.
Chapter Preview
Top
Introduction
Cardiovascular disease (CVD) is one amongst the primary diseases that causes death every year. An approximation of roughly about 17.5 million people dies due to CVD, signifying about 31% of global deaths. Based on the statistics, heart disease kills one person for every 34 seconds (Karegowda et al., 2010).
92°F
Light rain
Search
02:31 PM
07-06-2024


Balamurugan N - Google Sc
Diagnosis of Heart Disease
Exploring The Role Of Art In
View article
View article
namibian-studies.com/index.php/JNS/article/view/2279
annexure 1 free jour...
Kahoot!
cn meet
tht meet
cts-Meeting Registr...
Free Online Whiteb...
Poll Maker
AES Rijndael Cipher...
Computer and Infor...
All Bookmarks
Exploring The Role Of Art In Shaping Historical Narratives
pdf
Published May 22, 2023
DOI:
https://doi.org/10.59670/jns.v33i.2279
Dr. Retna Mony R Dr. Ragupathi Ramasamy Mr.J. Bimal Roy Dr. P. Sulochana Dr.Bharati Chandrayan Mr. Balamurugan N
Abstract
This research paper examines the significant role that art plays in shaping historical narratives. Art has been an integral part of human expression and communication for centuries, serving as a powerful tool for interpreting, preserving, and reshaping historical events and collective memory. By analyzing various forms of art, including visual arts, literature, music, and film, this paper explores how artists have actively participated in constructing historical narratives, challenging dominant perspectives, and providing alternative interpretations. Furthermore, it investigates the impact of artistic representations on public perception, identity formation, and the collective understanding of historical events. Through a multidisciplinary approach, this paper underscores the importance of art as a catalyst for critical thinking, dialogue, and the continuous evolution of historical narratives.
File downloads 280
Issue
Section
Journal of Namibian Studies
Q2
History
best quartile
SJR 2022
0.14
powered by scimagojr.com
Latest publications
Information
» For Readers
» For Authors
» For Librarians
Language
» English
Browse
Hot weather
Now
Search
02:24 PM
07-06-2024

About Authors

Ms. Manjula R., M.Sc (Mathematics), is an Assistant Professor with 14 years of teaching experience. She authored 4 paper publications and presented and participated in various national and international conferences.

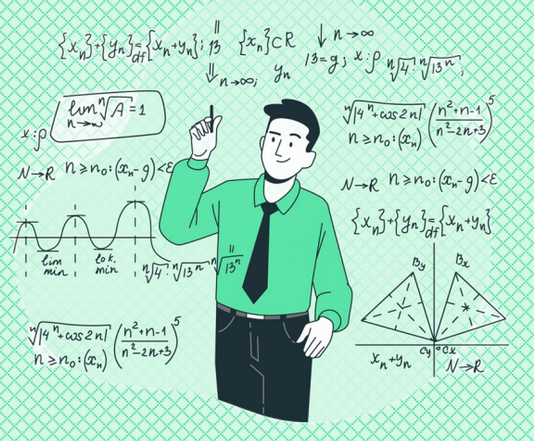
Ms. Varalaxmi K., M.Sc (Mathematics), is an Assistant Professor with 15 years of teaching experience. She authored 4 paper publications and presented and participated in various national and international conferences. She also has a membership in ISTE.

Ms. Suresh T., M.Sc (Mathematics) & B.Ed, is an Assistant Professor and Head (Mathematics) with 16 years of teaching experience. He authored a few paper publications and presented and participated in various national and international conferences.

Ms. Rajitha J., M.Sc (Mathematics), is an Assistant Professor with 14 years of teaching experience. She authored a few paper publications and presented and participated in various national and international conferences.

About Book

This Book of Number Theory is a captivating exploration of one of the oldest branches of mathematics. From its ancient origins to modern-day breakthroughs, this book uncovers the patterns, properties, and relationships that lie at the heart of numbers. It delves into topics such as divisibility, prime numbers, modular arithmetic, Diophantine equations, prime number distribution, and sieve methods. With its comprehensive coverage and engaging explanations, The Book of Number Theory reveals the beauty and significance of this fascinating mathematical discipline.



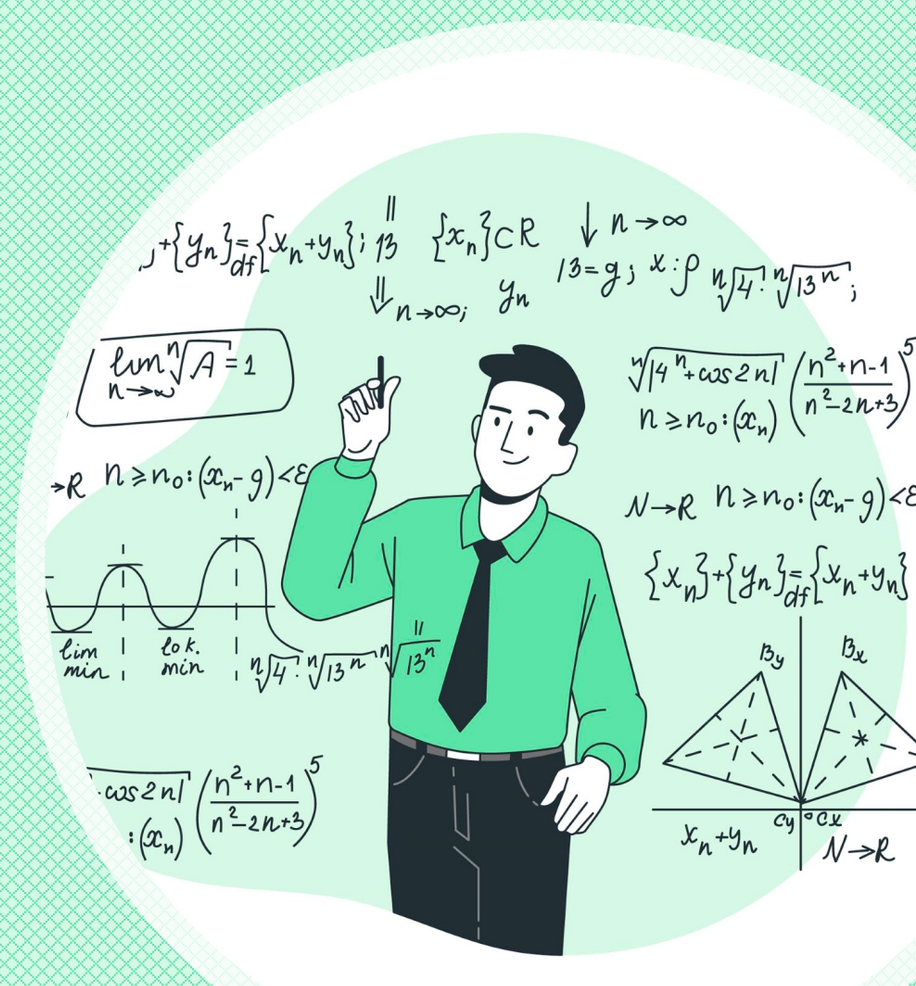
9 781312 346895

Number Theory

Manjula R., Varalaxmi K., Sureh T., Rajitha J.

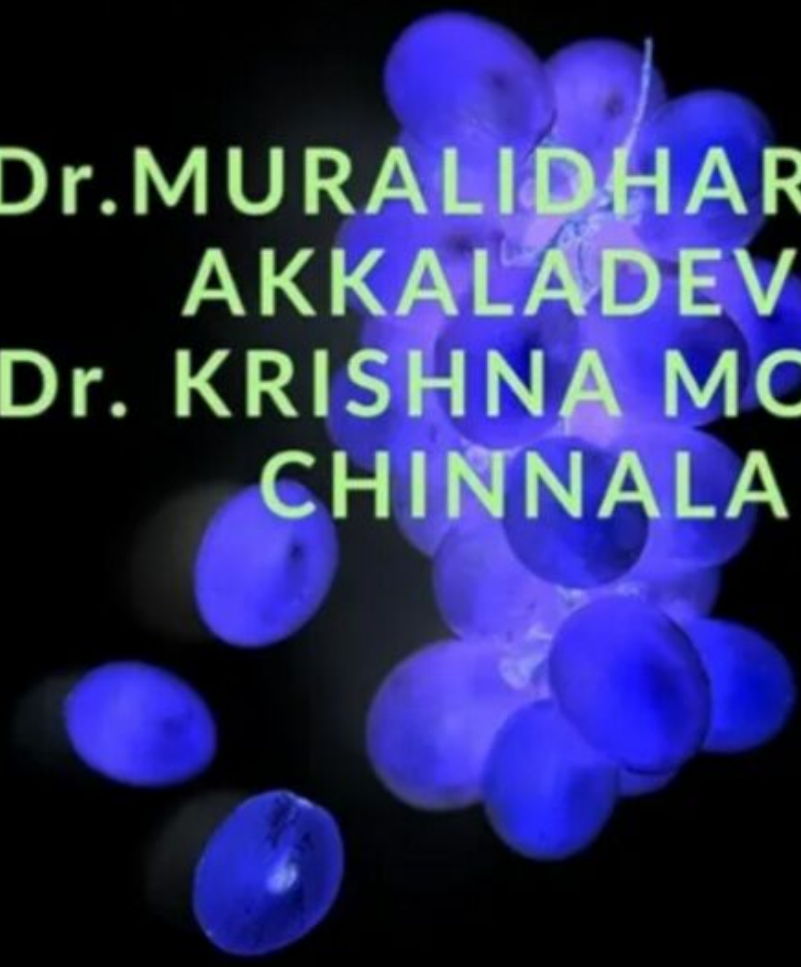
NUMBER THEORY

Manjula R., Varalaxmi K.,
Suresh T., Rajitha J.



Essentials of Clinical Toxicology

Dr.MURALIDHAR RAO AKKALADEVI
Dr. KRISHNA MOHAN CHINNALA



ADVANCED PHARMACOTHERAPEUTICS AND DISEASE MANAGEMENT

Prof. Krishna Mohan Chinnala
Dr. Muralidhar Rao Akkaladevi

Engineering Materials

Sabu Thomas
Poushali Das
Sayan Ganguly *Editors*

Quantum Dots Based Nanocomposites

Design, Fabrication and Emerging Applications

Springer

Metadata of the chapter that will be visualized in SpringerLink

Book Title	Quantum Dots Based Nanocomposites	
Series Title		
Chapter Title	Discovery and History of Quantum Dots	
Copyright Year	2024	
Copyright HolderName	The Author(s), under exclusive license to Springer Nature Switzerland AG	
Author	Family Name	**Reddy**
	Particle	
	Given Name	**Konatham Teja Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmacy
	Organization	University College of Technology, Osmania University
	Address	Amberpet, Hyderabad, Telangana, 500007, India
	Email	
Author	Family Name	**Madhavi Latha**
	Particle	
	Given Name	**B.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Chemistry, School of Pharmacy
	Organization	Nalla Narasimha Reddy Education Society's Group of Institution
	Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
	Email	
Author	Family Name	**Gupta**
	Particle	
	Given Name	**Jeetendra Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Institute of Pharmaceutical Research
	Organization	GLA University Mathura
	Address	Bharthia, Uttar Pradesh, India
	Email	
Author	Family Name	**Chaitanya**
	Particle	
	Given Name	**A.**
	Prefix	
	Suffix	

	Role	
	Division	
	Organization	Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution
	Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
	Email	
Author	Family Name	**Srinivasa Babu**
	Particle	
	Given Name	**P.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutics
	Organization	Vignan Pharmacy College
	Address	Vadlamudi, Guntur, Andhra Pradesh, 522213, India
	Email	
Author	Family Name	**G.**
	Particle	
	Given Name	**Vamseekrishna.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Analysis
	Organization	NRI College of Pharmacy
	Address	Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh, 521212, India
	Email	
Author	Family Name	**Manikanta**
	Particle	
	Given Name	**Yeluguri**
	Prefix	
	Suffix	
	Role	
	Division	School of Pharmaceutical Sciences
	Organization	Velsinstitute of Science Technology and Advanced Studies (VISTAS)
	Address	Pallavaram, Tamilnadu, 600117, India
	Email	
Corresponding Author	Family Name	**Sahithi**
	Particle	
	Given Name	**Alapati**
	Prefix	
	Suffix	
	Role	
	Division	
	Organization	Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution

Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
Email	sahithi.a@pharma.nnrg.edu.in

Abstract

Quantum dots are a type of semiconducting material that possesses distinctive electronic and optical characteristics at the nanoscale level. As a result, they have found extensive utility in a diverse array of scientific and technological domains. The present chapter provides a historical account of quantum dots, beginning with their initial discovery in the 1980s and extending to contemporary times. The chapter provides an overview of the different techniques employed in the synthesis and fabrication of quantum dots, which include colloidal synthesis, vapor-phase synthesis, and epitaxial growth. The text delineates the various categories of quantum dots, including core-shell and alloyed quantum dots, and elucidates how their characteristics can be adjusted to cater to particular use cases. Moreover, the chapter explores the diverse implementations of quantum dots in domains such as photovoltaic technology, illumination, medical visualisation, and quantum information processing. The text also addresses the potential hazards linked to quantum dots, such as apprehensions regarding toxicity and ecological consequences.

Discovery and History of Quantum Dots

Konatham Teja Kumar Reddy, B. Madhavi Latha, Jeetendra Kumar Gupta, A. Chaitanya, P. Srinivasa Babu, Vamseekrishna. G., Yeluguri Manikanta, and Alapati Sahithi

Abstract Quantum dots are a type of semiconducting material that possesses distinctive electronic and optical characteristics at the nanoscale level. As a result, they have found extensive utility in a diverse array of scientific and technological domains. The present chapter provides a historical account of quantum dots, beginning with their initial discovery in the 1980s and extending to contemporary times. The chapter provides an overview of the different techniques employed in the synthesis and fabrication of quantum dots, which include colloidal synthesis, vapor-phase synthesis, and epitaxial growth. The text delineates the various categories of quantum dots, including core-shell and alloyed quantum dots, and elucidates how their characteristics can be adjusted to cater to particular use cases. Moreover, the chapter explores the diverse implementations of quantum dots in domains such as

K. T. K. Reddy
Department of Pharmacy, University College of Technology, Osmania University, Amberpet, Hyderabad, Telangana 500007, India

B. Madhavi Latha
Department of Pharmaceutical Chemistry, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution, Chowdariguda, Ghatkesar, Ranga Reddy 500088, India

J. K. Gupta
Institute of Pharmaceutical Research, GLA University Mathura, Bharthia, Uttar Pradesh, India

A. Chaitanya · A. Sahithi (✉)
Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution, Chowdariguda, Ghatkesar, Ranga Reddy 500088, India
e-mail: sahithi.a@pharma.nnrg.edu.in

P. Srinivasa Babu
Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, Andhra Pradesh 522213, India

Vamseekrishna. G.
Department of Pharmaceutical Analysis, NRI College of Pharmacy, Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh 521212, India

Y. Manikanta
School of Pharmaceutical Sciences, Velsinstitute of Science Technology and Advanced Studies (VISTAS), Pallavaram, Tamilnadu 600117, India

T. Sabu et al. (eds.), *Quantum Dots Based Nanocomposites*, Engineering Materials,
https://doi.org/10.1007/978-3-031-54779-9_2

photovoltaic technology, illumination, medical visualisation, and quantum information processing. The text also addresses the potential hazards linked to quantum dots, such as apprehensions regarding toxicity and ecological consequences.

1 Introduction

1.1 What Are Quantum Dots?

Quantum dots are incredibly small nanocrystals with sizes in the region of a few nanometers that are formed of semiconducting materials. They can be compared to synthetic atoms because of the distinct electrical and optical characteristics they display that are not present in their bulk counterparts [1]. Due to their tiny size, which causes the material's electrical characteristics to become quantized, quantum dots have peculiar properties [2]. Particularly, the quantization of the electronic energy levels occurs when a quantum dot is created and its electrons are constrained within a constrained area of space [3]. Due to this, discrete energy levels are created, and these levels are governed by the quantum dot's size, composition, and shape [4]. These energy levels are known as the "quantum confinement effect," and they give birth to a variety of intriguing features that may be tweaked and controlled by altering the quantum dot's size and make-up [5]. Optoelectronics is one of the most promising fields in which quantum dots can be used. In example, photovoltaic cells and highly efficient light-emitting diodes (LEDs) can be produced using quantum dots [6–8]. The colour of the light emitted by the LED may be precisely modified due to the controllable quantum dot size [9, 10]. Quantum dots can also be employed as down-converters to boost solar cells' efficiency by expanding the quantity of light that can be absorbed. Biomedicine is a promising area for using quantum dots. Quantum dots are fluorescent probes that can be utilised for imaging and disease diagnostics [11–13]. Due to their tiny size, quantum dots can enter cells and tissues and produce high-resolution photographs of biological structures. Quantum dots can also be functionalized with particular targeting molecules to bind to certain cells or tissues with a specific preference, enabling tailored drug administration [14]. Quantum dots are an exciting area of study that could revolutionise a variety of industries, including optoelectronics, healthcare, and energy [15–22]. Due to their special qualities, such as the quantum confinement effect, quantum dots are highly adaptable materials that can be tweaked and controlled to fit various needs [23]. They will therefore probably continue to play a significant role in many fields of science and technology going forward.

The distinctive characteristics and potential uses of quantum dots render them significant in both technological and research domains [24]. Nanoparticles of semiconductors can be accurately designed to exhibit distinct electronic and optical characteristics, rendering them advantageous in various domains such as optoelectronics,

biomedicine, and energy [14]. Quantum dots possess the potential to yield light-emitting diodes (LEDs) and photovoltaic cells with exceptional efficiency in the field of optoelectronics. Quantum dots possess the potential to enhance colour accuracy and diminish power consumption in displays and lighting applications due to their capability to emit light at highly specific wavelengths [25]. Furthermore, quantum dots possess the potential to serve as down-converters, thereby enhancing the efficacy of photovoltaic cells through the amplification of light absorption [26]. Quantum dots have been identified as potential fluorescent probes for imaging and diagnosis of diverse diseases in the field of biomedicine [27]. The diminutive dimensions of quantum dots facilitate their infiltration into tissues and cells, thereby affording high-fidelity visual representations of biological structures [28–30]. Furthermore, quantum dots possess the ability to be functionalized with particular targeting molecules, which can facilitate the selective binding to specific cells or tissues. This feature allows for the possibility of targeted drug delivery [16, 20, 31]. Quantum dots possess the potential to enhance the efficacy of solar cells by augmenting the extent of light absorption in the field of energy. Researchers have the ability to produce materials that can absorb light across a wide range of wavelengths by adjusting the size and composition of quantum dots [32]. Quantum dots hold significant importance in the realm of fundamental research in physics and materials science, in addition to their specific applications [33]. Quantum dots can be employed by researchers to investigate the conduct of electrons within a restricted area, thereby facilitating an enhanced comprehension of quantum mechanics and the emergence of novel materials and technologies [34]. Quantum dots possess distinctive characteristics and hold significant potential for utilisation in diverse domains, rendering them crucial in both technological and research contexts [35]. Nanoparticles possess the capability to bring about a significant transformation in domains such as optoelectronics, biomedicine, and energy. It is highly probable that they will persist in playing a crucial role in various fields of science and technology in the forthcoming years.

1.2 Early History of Quantum Dots

The inception of quantum dots can be traced back to the early 1980s, when the Russian physicist Alexei Ekimov and the American physicist Louis E. Brus conducted groundbreaking research in this field. In the year 1982, Ekimov made a discovery regarding small semiconductor crystals that were referred to as “zero-dimensional” entities. These crystals displayed quantum confinement effects that were not observable in bulk semiconductors [36]. In 1983, Brus made independent discoveries that yielded similar effects and subsequently introduced the term “quantum dots” to refer to these minute nanocrystals. The research conducted by Brus was centred on the optical characteristics of said materials, demonstrating that they discharged light at distinct wavelengths which were contingent on their dimensions. During the decades of 1980s and 1990s, scholars conducted further investigations on the characteristics of quantum dots and devised novel approaches for their synthesis and

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

manipulation. In 1994, a group of researchers from Bell Labs conducted a demonstration that showcased the potential of quantum dots in the development of light-emitting diodes (LEDs) with superior efficiency. This breakthrough discovery paved the way for novel applications in the field of optoelectronics. Subsequent to that time, scholars have achieved noteworthy progress in the production and analysis of quantum dots, resulting in novel implementations in the domains of biomedicine, energy, and other related areas [2]. Quantum dots represent a burgeoning field of study that is currently experiencing rapid growth, owing to their numerous potential applications and substantial commercial appeal [37–39].

Quantum mechanics underpins quantum confinement effects in quantum dots. Knowing electron behaviour in quantum dots requires knowing the wave-particle duality of matter and energy quantization in restricted systems. Electrons travel freely in a three-dimensional lattice structure in bulk semiconductor materials. Electrons can occupy any energy level in these continuous materials. However, nanoscale semiconductor materials restrict electron movement in all three dimensions. Electron energy levels are quantized by confinement, depending on the quantum dot's size and shape [40]. Quantized energy levels in quantum dots provide them unique features not found in bulk semiconductors. Quantum dots produce light at specified wavelengths depending on their size and shape, hence their emission spectra are crisp and narrow. Quantum dots are potential for LEDs and solar cells due to their emission spectrum tenability [41, 42]. The effective mass approximation and k-p approach are used to calculate quantum dot electron energy levels and wave functions. These models take into account quantum confinement, semiconductor crystal structure, and composition. Quantum physics predicts that electron energy levels become quantized in restricted systems, which underlies quantum confinement effects in quantum dots [17, 43, 44]. Quantization of energy levels in quantum dots produces unique electrical and optical features that have many uses in science and technology [45, 46].

The investigation of size-dependent properties of nanocrystals was initiated in the 1980s through early experimental studies. The phenomenon of the shift in absorption and emission spectra towards higher energies was observed by researchers in certain semiconductor nanocrystals, as the size of the nanocrystals decreased. The observed blue-shift in the spectra has been ascribed to the quantum confinement effect, which emerges from the confinement of electrons and holes within a limited volume of the nanocrystal [47]. The phenomenon in question leads to the quantization of energy levels of both electrons and holes, thereby causing alterations in the optical and electronic characteristics of the nanocrystals that are dependent on their size [48]. The initial investigations initiated a novel area of inquiry regarding the characteristics and prospective uses of nanocrystals. Apart from the blue-shifted absorption and emission spectra, the scholars also noted alterations in various characteristics of nanocrystals, including their magnetic behaviour and conductivity, which were dependent on their size. As particle size decreases in certain materials, such as gold and silver, the melting point exhibits a corresponding decrease [49]. The observed phenomenon, commonly referred to as "melting point depression", can be attributed to the heightened surface area-to-volume ratio of the particles. This characteristic renders the particles more vulnerable to surface melting and thermal

fluctuations [50]. Size-dependent properties of nanocrystals have been investigated, including their mechanical characteristics, such as hardness and ductility, as well as their catalytic activity in chemical reactions. The impact of the morphology and constitution of nanocrystals on their characteristics, as well as their interplay with other substances and biological systems, has been examined by scholars. In general, the initial experimental investigations concerning the size-dependent characteristics of nanocrystals have initiated a novel area of inquiry into the attributes and prospective uses of materials at the nanoscale. Currently, the investigation of nanocrystals and other nanomaterials is a swiftly expanding field of study with numerous potential applications in domains such as electronics, energy, biomedicine, and other related fields.

1.3 First Synthesis of Quantum Dots

Louis E. Brus and his team accomplished the initial prosperous amalgamation of quantum dots in 1984. The researchers employed solution-phase methodologies to produce colloidal quantum dots composed of semiconductors, specifically CdSe, CdTe, and CdS [51]. The process of synthesis entailed the introduction of precursors, namely cadmium and selenium, into a heated solution of a coordinating solvent, such as tri-n-octylphosphine oxide (TOPO) and trioctylphosphine (TOP). Subsequent to the reaction, a coordinating ligand, namely hexadecylamine (HDA), was introduced to serve as a capping agent with the purpose of regulating the dimensions and morphology of the quantum dots [52]. The quantum dots obtained exhibited a high degree of uniformity in size, superior quantum efficiency, and a robust luminescent property, rendering them a desirable candidate for a diverse array of applications. The triumph of this particular method of synthesis has paved the way for further exploration into the synthesis and characteristics of colloidal quantum dots. Currently, solution-phase synthesis is a frequently employed technique for the production of quantum dots, with numerous modifications and advancements implemented over time to enhance regulation of the quantum dots' size, shape, and characteristics. Brief explanation of the synthesis technique.

2 Key Contributions from Early Researchers

The initial investigators of quantum dots made significant advancements that facilitated their current utilisation in various domains. The identification of the quantum confinement effect stands out as a significant contribution. During the initial years of the 1980s, Alexei Ekimov and Louis E. Brus conducted research and made observations that revealed the absorption and emission spectra of specific semiconductor nanocrystals underwent a shift towards higher energies with a decrease in the size of the nanocrystals. The observed blue-shifted spectra can be explained by the quantum

confinement effect, which is a result of the confinement of electrons and holes within a limited volume of the nanocrystal. The phenomenon under consideration leads to the quantization of energy levels of both electrons and holes thereby causing alterations in the optical and electronic characteristics of the nanocrystals that are dependent on their size. The development of synthetic methods for quantum dots was deemed a significant contribution. The synthesis of colloidal quantum dots through solution-phase techniques was pioneered by Louis E. Brus and R. Murray. The techniques employed in this study entailed the introduction of precursor substances into a coordinating solvent, succeeded by the incorporation of a capping agent to regulate the dimensions and morphology of the quantum dots. The quantum dots that were produced exhibited a limited range of sizes, a high quantum yield, and robust luminescence, rendering them appealing for utilisation in a diverse array of applications. In the initial stages of research, quantum dots were subjected to diverse methodologies to determine their properties [53]. The optical properties of quantum dots were investigated using absorption and emission spectroscopy, while their structural properties were examined through X-ray diffraction and transmission electron microscopy. The researchers additionally examined the impacts of dimensions, morphology, and constitution on the characteristics of quantum dots. Early researchers have demonstrated the potential applications of quantum dots in various fields. The distinct optical and electronic characteristics of quantum dots were demonstrated by Paul Alivisatos and Moungi Bawendi, which could be utilised for various purposes including optoelectronics, sensing, and biolabeling [54]. The research conducted by the authors established the fundamental principles for the emergence of quantum dots as a distinct area of study, and facilitated their integration into a diverse array of contemporary applications. In brief the finds can be uttered like these:

- The quantum confinement effect was initially observed by early researchers. This phenomenon causes the energy levels of electrons and holes in a nanocrystal to become quantized. Consequently, the optical and electronic properties of the nanocrystal undergo size-dependent changes [55].
- The researchers additionally devised synthetic procedures for quantum dots through solution-phase methodologies, yielding nanocrystals characterised by a limited size range, elevated quantum efficiency, and robust luminescence.
- Quantum dots were characterised by early researchers through a range of techniques such as absorption and emission spectroscopy, X-ray diffraction, and transmission electron microscopy.
- The researchers conducted an investigation into the impact of quantum dot size, shape, and composition on their respective properties.
- The initial researchers exhibited the potential uses of quantum dots in domains such as optoelectronics, sensing, and biolabeling, thereby establishing the groundwork for their current utilisation in a diverse array of applications.

3 Advancements in Quantum Dot Synthesis

Various techniques have been devised for the production of quantum dots, each possessing unique merits and drawbacks. Several frequently employed techniques include:

1. The colloidal synthesis method is a commonly employed technique for the production of quantum dots in a liquid medium. The present technique involves the dissolution of precursors in a suitable solvent, subsequent to which a reducing agent and stabilising agent are introduced. Quantum dots are generated via a process of nucleation and growth.
2. The sol-gel synthesis technique entails the chemical reactions of hydrolysis and condensation of metal alkoxides in a solution, resulting in the formation of a substance with a gel-like consistency. Subsequently, the gel is subjected to a drying process and subsequently exposed to heat in order to generate the quantum dots.
3. The process of chemical vapour deposition entails the application of a slender layer of a precursor substance onto a substrate, succeeded by the reaction of the precursor with a reactant in the gas phase, resulting in the formation of quantum dots.
4. The electrochemical synthesis technique entails the deposition of metal ions onto a substrate while a reducing agent is present, resulting in the formation of quantum dots.
5. The process of plasma synthesis entails the utilisation of a plasma discharge to produce exceedingly reactive species that can interact with precursor gases, resulting in the formation of quantum dots.
6. The process of laser ablation entails utilising a laser beam to ablate a solid target, thereby producing plasma that can interact with a gas-phase reactant to create quantum dots.

Each of the aforementioned techniques possesses unique benefits and drawbacks with respect to regulating the dimensions, morphology, and chemical makeup of the quantum dots, as well as their potential for expansion and consistency in results. The selection of the appropriate technique is contingent upon the particular usage scenario and the intended characteristics of the quantum dots.

4 Discussion of the Role of Surface Chemistry in Quantum Dot Synthesis

Quantum dots are semiconductor materials at the nanoscale level that possess distinctive electronic and optical characteristics, rendering them exceedingly appealing for utilisation in various domains, including but not limited to biological imaging, optoelectronics, and energy. The process of synthesising quantum dots is intricate and

demands meticulous regulation of the nanocrystals' size, shape, and composition. The significance of surface chemistry in quantum dot synthesis cannot be overstated, as it has a profound impact on the growth kinetics, stability, and properties of the nanocrystals [56]. The manipulation of the surface chemistry of quantum dots can be achieved through the incorporation of ligands or surface coatings during the process of synthesis. The ligands exhibit an interaction with the surface of the quantum dots, thereby influencing their size, shape, and properties. Ligands serve multiple pivotal functions in the process of quantum dot fabrication [57]. Primarily, they function as capping agents that impede the agglomeration of quantum dots, which is a pivotal element in regulating the dimensions of the nanocrystals. The presence of ligands induces steric hindrance among the quantum dots, thereby constraining their capacity to approach one another and coalesce into aggregates. The growth kinetics of nanocrystals can be influenced by ligands, which have the ability to modulate the surface energy of quantum dots. The quantum dot's surface energy plays a crucial role in determining its propensity to accept atoms or molecules during the growth process, thereby influencing its size and morphology [58]. The modulation of surface energy through the use of ligands can effectively decelerate the rate of nanocrystal growth, ultimately resulting in the production of smaller and more homogenous particles. In addition, it should be noted that ligands have the potential to modify the surface charge of quantum dots, thereby affecting their stability and interactions with chemical or biological surroundings [4, 59–61]. The determination of nanoparticle stability in a solution is reliant on the crucial factor of surface charge. The manipulation of surface charge by ligands can establish a protective enclosure around quantum dots, thereby impeding their aggregation or interaction with other molecules present in the solution. The selection of ligands employed in the process of synthesis plays a crucial role in determining the surface chemistry of quantum dots [62]. This, in turn, has a significant impact on their properties and potential applications. Hydrophilic ligands, such as carboxylic acids or amines, can generate a water-soluble surface, which facilitates the utilisation of quantum dots in biological imaging and sensing applications. In contrast, ligands that exhibit hydrophobic properties have the ability to augment the stability of quantum dots in solvents that lack polarity, thereby conferring utility in optoelectronic domains.

Over the years, there have been notable developments in the production of quantum dots. Presented below is a concise summary of some of the principal progressions.

The initial methods of synthesising quantum dots involved colloidal synthesis and were accomplished in the early 1990s. Subsequently, additional methodologies, including sol-gel synthesis and chemical vapour deposition, were also established. The technique of size-tunable synthesis was developed by researchers in the late 1990s, which enabled accurate manipulation of the size of quantum dots. The aforementioned outcome was attained via alterations in the reaction parameters, including but not limited to adjustments in temperature, duration, and concentration of the precursor substances [63]. The development of high-quality synthesis methods in the early 2000s resulted in significant progress in the production of quantum dots with superior optical and electronic properties, as reported by researchers. The

aforementioned outcome was attained through the utilisation of materials with high levels of purity and the optimisation of synthesis conditions to reduce the occurrence of defects [64]. The development of quantum dots has garnered increasing attention in recent times, with a focus on utilising novel materials like perovskites and metal-organic frameworks. The aforementioned materials possess distinctive benefits, including elevated quantum yields and adjustable bandgaps [65]. The escalating demand for quantum dots across diverse applications has prompted a concentration on the advancement of large-scale synthesis techniques. Recent developments in this field encompass the implementation of continuous flow synthesis and microwave-assisted synthesis techniques.

5 Properties of Quantum Dots

The optical properties of quantum dots are dependent on their size, shape, and composition, which give rise to their distinctive characteristics. The quantization of energy levels arises due to the confinement of electrons and holes within a small volume in quantum dots, resulting in size-dependent properties. As the dimensions of the quantum dot decrease, the energy levels exhibit greater discreteness, leading to an increase in the bandgap and a corresponding shift in the absorption and emission spectra towards higher energies [66]. The phenomenon being referred to is commonly recognised as the quantum confinement effect. The surface area-to-volume ratio of a quantum dot is influenced by its size, which in turn affects its reactivity and stability, as well as its bandgap.

The properties of quantum dots can be significantly influenced by their shape [67–70]. Quantum dots that are anisotropic in nature, such as nanorods or nanowires, demonstrate absorption and emission spectra that are dependent on polarisation. This is attributed to the alignment of the dipoles along the longitudinal axis of the particle [71]. The electronic structure and optical properties of a quantum dot can be altered by its shape, resulting in modifications to its energy levels. Quantum dots possessing faceted geometries may manifest distinct surface terminations, thereby influencing their surface chemistry and stability.

The properties of a quantum dot can be significantly influenced by its composition, particularly its chemical makeup. The determination of the bandgap of a quantum dot is contingent upon the disparity in energy levels between the conduction and valence bands, a factor that is subject to the quantum dot's size and composition [72]. Cadmium-based quantum dots are known to demonstrate a greater bandgap in comparison to lead-based quantum dots of equivalent size. The chemical composition of a quantum dot can have a significant impact on its surface chemistry, thereby influencing its stability and reactivity.

The optical characteristics of quantum dots have garnered significant attention owing to their potential utility in diverse domains [73]. Quantum dots possess a narrow emission spectra and high quantum yields, rendering them suitable for deployment as fluorescent probes. Furthermore, the tunability of quantum dots' emission

spectra can be achieved through alterations in their size, shape, and composition, rendering them remarkably versatile [74]. Quantum dots possess the capability to be deliberately designed to emit at particular wavelengths within the visible or near-infrared spectrum, thereby rendering them advantageous for employment in imaging and sensing applications.

To summarise, the characteristics of quantum dots are significantly influenced by their dimensions, morphology, and chemical makeup. Comprehending the aforementioned characteristics holds paramount significance in customising quantum dots for particular uses in domains such as optoelectronics, biomedicine, and energy transformation. Furthermore, current investigations within the discipline are concentrated on enhancing the stability and quantum yield of quantum dots, while also delving into novel applications for these distinctive nanomaterials.

6 Overview of the Application of Quantum Dots in Various Fields

Semiconductor nanoparticles known as quantum dots possess distinctive electronic and optical characteristics that render them highly advantageous instruments across a range of disciplines. Nanocrystals are commonly composed of materials like cadmium selenide, cadmium telluride, and indium arsenide, and exhibit a size distribution ranging from a few to several hundred nanometers. The field of optoelectronics has witnessed a significant utilisation of quantum dots. Quantum dots possess distinctive optical characteristics owing to their high surface-to-volume ratio, which is attributed to their diminutive size. Particularly, they possess the ability to produce light at exact wavelengths, rendering them suitable for implementation in superior quality screens, light-emitting diodes, and photovoltaic cells. The capacity of emitting light in various hues, coupled with their elevated luminosity, renders them advantageous in the context of illuminative purposes. Quantum dots have the potential to serve as a labelling tool for biological molecules and cells in the field of biological imaging, thereby facilitating their visualisation and monitoring. Compared to conventional organic dyes, they present various benefits, including enhanced luminosity, improved resistance to photodegradation, and narrower emission spectra. Moreover, the diminutive dimensions of quantum dots render them capable of infiltrating tissues to a significant extent, thereby rendering them well-suited for deployment in the realm of in vivo imaging. The utilisation of quantum dots in the domain of energy production is currently under investigation. Quantum dots have the ability to absorb a wider spectrum of light wavelengths in comparison to conventional solar cells, thereby enhancing their capacity to transform solar energy into electrical energy. Furthermore, quantum dots exhibit promising prospects for utilisation in energy storage systems, including batteries and supercapacitors. Quantum dots are currently under investigation in the realm of information technology due to their potential to serve as qubits, which are fundamental units in the construction of quantum computers.

The utilisation of quantum dots is applicable in the advancement of memory and data storage devices that possess high-speed and high-capacity capabilities. Quantum dots exhibit potential for utilisation in sensing and detection applications. These devices have the capability to function as sensors for detecting alterations in environmental factors such as temperature, pressure, and others. Furthermore, they have the capability to detect and distinguish diverse categories of molecules such as biomolecules, contaminants, and explosives. Quantum dots exhibit distinctive electronic and optical characteristics that render them highly favourable for diverse applications spanning multiple domains. Anticipated progress in research endeavours is poised to yield noteworthy breakthroughs in the utilisation and creation of these nanoparticles across domains encompassing energy, healthcare, and information technology.

7 Quantum Dot Technology

The distinct characteristics exhibited by quantum dots have resulted in their utilisation across a diverse array of technological domains (Fig. 1). The principal implementations of quantum dots are as follows.

Quantum dots have found extensive application in the realm of display technology, particularly in LED backlit displays. The utilisation of these elements results in the

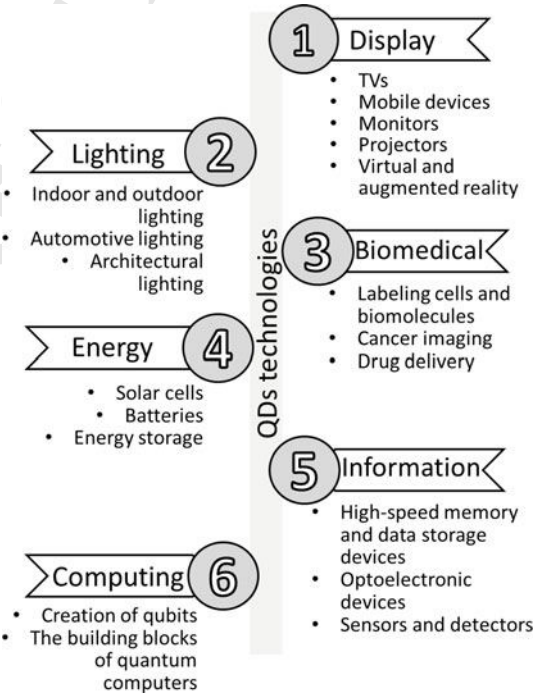


Fig. 1 Various types of applications of QDs nanoparticles

generation of hues that are more pronounced, accompanied by an elevated degree of luminosity and differentiation [75]. Conventional LED displays typically employ white LEDs in conjunction with colour filters to generate diverse hues; however, this approach may lead to energy dissipation and a reduced range of colours. In contrast, displays utilising quantum dots employ blue light emitting diodes (LEDs) in conjunction with quantum dots that generate red and green light upon being stimulated by the blue light source. The outcome of this is an expanded range of colours and a display that consumes less energy.

Quantum dots exhibit distinctive optical characteristics that render them valuable for medical imaging purposes. Fluorescent tags can be utilised for the purpose of identifying and tracking particular cells or molecules within the human body. Quantum dots possess the ability to be tailored to emit light at precise wavelengths, rendering them highly suitable for imaging purposes that necessitate superior resolution and sensitivity [76]. Furthermore, they are currently under development as contrast agents to facilitate more accurate imaging of neoplasms and other anomalous tissues.

The utilisation of quantum dots is being explored as a means of enhancing the efficacy of solar cells through the capture of a wider range of light wavelengths, which can subsequently be converted into electrical energy [77]. Solar cells conventionally comprise crystalline silicon and possess a limited capacity to absorb light wavelengths. The incorporation of quantum dots into the solar cell enables the capture of a wider range of light wavelengths, thereby facilitating the conversion of light energy into electrical energy [49]. The utilisation of quantum dots in conjunction with other materials has the potential to yield multi-junction solar cells that exhibit superior levels of efficiency.

Quantum dots have the potential to serve as qubits within quantum computing frameworks. Qubits serve as the fundamental units of quantum computers and possess the ability to exist in numerous states concurrently, thereby facilitating expedited processing as compared to conventional computers. Quantum dots exhibit extended coherence times and are amenable to facile manipulation, rendering them a propitious substrate for constructing quantum computers on a macroscopic scale.

Quantum dots are currently being utilised in the development of energy-efficient lighting solutions that offer superior quality [16, 49, 69]. Light-emitting diodes (LEDs) have the potential to serve as a substitute for conventional fluorescent or incandescent bulbs, as they are capable of emitting light with a broader spectrum of colours and a greater luminosity. Quantum dot lighting possesses the added benefit of enhanced energy efficiency, thereby resulting in considerable cost reductions in the long run.

Quantum dots are currently under development for various biotechnology purposes such as drug delivery, biomolecule detection, and disease diagnosis. Nanoparticles possess the capability to selectively target particular cells or molecules, thereby rendering them a potent instrument in the realm of nanomedicine. Quantum dots possess the capability of being tailored to selectively bind with particular proteins or nucleic acids, thereby enabling their application in the detection of biomolecules or diagnosis of diseases.

In general, quantum dots exhibit a broad spectrum of potential applications across diverse domains, and continued scientific inquiry and innovation is anticipated to yield further compelling utilities in the times ahead. Quantum dots possess distinctive characteristics that render them highly adaptable and multifaceted, thereby positioning them as a technology with considerable potential for diverse applications.

The field of optoelectronics has shown interest in utilising quantum dots due to their distinctive optical characteristics. Quantum dots exhibit a quantized energy spectrum owing to their diminutive size, resulting in the emission of light at distinct wavelengths. The aforementioned characteristic renders them highly suitable for utilisation in light-emitting diodes and laser devices, wherein meticulous regulation of the emanated wavelengths holds paramount significance. Quantum dots exhibit a broad absorption spectrum, enabling them to capture light across a diverse range of wavelengths. The aforementioned characteristic holds practical significance in down-conversion scenarios, wherein photons with high energy levels are transformed into photons with lower energy levels that can be assimilated by conventional semiconductor materials, such as silicon.

Furthermore, quantum dot light-emitting diodes (QLEDs) possess the capability to offer superior visual displays featuring an extensive range of colours. Quantum dots have the capability to emit light across a diverse range of colours, encompassing those within the visible spectrum. Quantum dot light-emitting diodes (LEDs) exhibit high efficiency and are capable of generating vivid and intense hues, rendering them a compelling substitute for conventional LEDs in lighting and display contexts.

Quantum dots have been identified as a potential material for advanced solar cells owing to their distinctive characteristics. Quantum dots possess a significant benefit in their ability to effectively absorb light across a wide spectrum of wavelengths. This implies that the light-capturing capacity of conventional semiconductor materials, such as silicon, is restricted to a limited range of wavelengths, whereas the aforementioned materials can capture a broader spectrum of light. Furthermore, quantum dots possess the capability to function as down-converting layers. This feature facilitates the enhancement of the light-capturing capacity of conventional silicon solar cells by transforming high-energy photons into lower-energy photons that can be assimilated by silicon.

Quantum dots possess the capability to enhance the efficacy of solar cells by enabling them to apprehend light in the infrared segment of the spectrum, which is beyond the reach of silicon-based solar cells. The reason for this is that quantum dots can be customised to possess a band gap that can be adjusted to the targeted wavelength spectrum. The integration of quantum dots into photovoltaic cells is being investigated by scholars as a means of enhancing their efficacy and diminishing the expense of solar power.

The utilisation of quantum dots as qubits, which are the fundamental units of quantum computers, is a viable option in the field of quantum computing. The utilisation of the spin of an electron in a quantum dot as a qubit and the exploitation of the quantum properties of these systems for the purpose of executing quantum computations can be achieved. The scalability of quantum dots and their compatibility with current semiconductor manufacturing processes make them a promising

technology. This implies that they possess the capability of being manufactured in significant quantities and incorporated into pre-existing electronic apparatus.

Nevertheless, there are still obstacles to be overcome with regards to preserving the consistency of the qubits for extended durations. The reason for the susceptibility of qubits to decoherence is attributed to the high sensitivity of quantum dots to their surrounding environment, whereby any form of noise or fluctuations can result in the loss of coherence. Scholars are currently engaged in the development of methodologies aimed at regulating the ambient conditions surrounding quantum dots, with the objective of mitigating the deleterious effects of noise on their operational efficacy.

The distinctive optical characteristics of quantum dots render them a desirable option for application in the fields of biotechnology and medical imaging. Fluorescent probes have the potential to serve as tracking agents for cellular or molecular movements within biological systems. Quantum dots exhibit exceptional stability and emit bright and persistent light, rendering them a highly suitable option for various imaging applications. Moreover, quantum dots have the potential to serve as contrast agents in medical imaging, offering superior resolution and heightened sensitivity in comparison to conventional imaging techniques.

Quantum dots possess potential for utilisation in drug delivery and therapeutic applications. Due to their diminutive dimensions, nanoparticles possess the ability to infiltrate cells and tissues. Additionally, their surface can be modified with targeting molecules, thereby enabling the transportation of therapeutic agents or drugs to precise cells or tissues.

Quantum dots exhibit potential applications in diverse fields including catalysis, sensing, and data storage performance in various chemical reactions. The electronic and optical properties of nanoparticles, which are dependent on their size, have been found to have a significant impact on their catalytic activity. As a result, they have been employed as catalysts in a variety of chemical reactions.

8 Commercialization of Quantum Dots

The inception of quantum dots' commercialization dates back to the latter part of the 1990s. Subsequently, there has been a notable surge in their manufacturing and utilisation. Quantum dots are extensively utilised in display technology as a primary application, facilitating the creation of energy-efficient and high-quality displays. Quantum dots have been employed in medical imaging due to their ability to selectively bind to particular tissues and produce more precise images compared to conventional imaging methods. Quantum dots have recently gained traction in the realm of quantum computing as a potential application, serving as fundamental units or qubits for quantum computers. The potential application of quantum dots in solar cells is currently under investigation, with the aim of enhancing the efficiency of the cells and decreasing the expenses associated with solar energy production. The commercialization of quantum dots has encountered various obstacles, such as the exorbitant

expenses associated with their manufacturing and apprehensions regarding their plausible toxicity. Notwithstanding the challenges, scholars and enterprises are endeavouring to surmount them by devising novel production techniques and investigating measures to enhance the safety of quantum dots for human utilisation.

The process of commercialising quantum dots has been in progress for a number of years, and it is anticipated that the quantum dots market will experience substantial growth in the near future. Several prominent corporations are engaged in the process of commercialising quantum dots.

1. Nanosys is a prominent enterprise that specialises in the advancement and monetization of quantum dots. The corporation provides a variety of display technology products, such as quantum dot films, LED backlights, and colour conversion layers.
2. QD Vision is a prominent enterprise that specialises in the advancement and dissemination of quantum dots. The corporation provides quantum dot merchandise that caters to display technology, lighting, and biomedical applications.
3. Samsung is a significant participant in the market for quantum dot displays. The QLED (Quantum Dot LED) technology employed by the company is utilised in its premium-grade televisions and monitors.
4. LG is a significant participant in the quantum dot display industry. The NanoCell TVs manufactured by the company utilise quantum dot technology to augment colour precision and luminosity.
5. Quantum Materials Corp is a corporation that specialises in the research, development, and manufacturing of quantum dots for a wide range of applications, including but not limited to display, lighting, solar cells, and biomedical imaging.
6. Crystalplex Corporation is a specialised enterprise that focuses on the advancement of quantum dots for the purpose of biomedical imaging and diagnostics.
7. NN-Labs is a corporation that specialises in the production of top-notch quantum dots for various purposes such as LED illumination, display technology, and biomedical imaging.
8. Ocean NanoTech is a commercial enterprise that specialises in the manufacture and distribution of quantum dots, which are utilised in various fields such as imaging, diagnostics, and sensing.
9. Quantum Solutions is a corporation that specialises in the production of top-tier quantum dots utilised in various applications, including but not limited to solar cells, LED lighting, and display technology.

Other leading companies are also in market which is depicted in Table 1.

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Table 1 Different companies those are working in quantum dots and their focus on the market

Company	Industry	Focus
IBM	Computing	Quantum computing
Google	Computing	Quantum computing
Microsoft	Computing	Quantum computing
Rigetti Computing	Computing	Quantum computing
IonQ	Computing	Quantum computing
Honeywell	Computing	Quantum computing
PsiQuantum	Computing	Quantum computing
Cambridge Quantum Computing	Computing	Quantum computing
Zapata Computing	Computing	Quantum software
Xanadu	Computing	Quantum computing and photonics
Q-CTRL	Computing	Quantum control
Atom Computing	Computing	Neutral atom quantum computing
D-Wave Systems	Computing	Quantum computing (quantum annealing)
Airbus	Aerospace	Quantum computing, communication and sensing
Lockheed Martin	Aerospace	Quantum computing, communication and sensing
Honeywell Quantum Solutions	Aerospace	Quantum computing, communication and sensing
Qrypt	Cybersecurity	Quantum key distribution
ID Quantique	Cybersecurity	Quantum key distribution
Crypta Labs	Cybersecurity	Quantum random number generators
Toshiba	Electronics	Quantum communication and encryption
Alibaba Group	Cloud services	Quantum computing
Amazon Web Services	Cloud services	Quantum computing
IBM Q Network	Network	Collaborative quantum computing
QuTech	Academic/research	Quantum computing
Max Planck Institute	Academic/research	Quantum computing, communication and sensing
University of Oxford	Academic/research	Quantum computing
University of Waterloo	Academic/research	Quantum computing
Harvard Quantum Initiative	Academic/research	Quantum computing
Nanosys	Materials science	Quantum dot films for display technology
QD Vision	Materials science	Quantum dots for display technology and lighting

(continued)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Table 1 (continued)

Company	Industry	Focus
Quantum Materials Corp	Materials science	Quantum dots for display technology, solar cells, and biomedical imaging
NN-Labs	Materials science	Quantum dots for led lighting, display technology, and biomedical imaging
Ocean NanoTech	Materials science	Quantum dots for biomedical imaging, diagnostics, and sensing
Crystalplex Corporation	Biotechnology	Quantum dots for biomedical imaging and diagnostics

9 Challenges and Opportunities in the Commercialization of Quantum Dots

Quantum dots exhibit several characteristics that render them a highly favourable material for a diverse array of applications, such as optoelectronics, biotechnology, and energy harvesting. Notwithstanding, there exist a number of obstacles and prospects that necessitate resolution in order to effectively bring quantum dots to market.

Challenges:

The commercialization potential of quantum dots is limited due to the relatively high production cost of producing high-quality ones. The elevated expense can be attributed to the intricate process of synthesis, utilisation of costly initial components, and the requirement for specialised equipment. The presence of heavy metals, such as cadmium, in certain quantum dots has raised concerns regarding their potential toxicity during production and use. The development of non-toxic and biocompatible quantum dots is imperative for their effective utilisation in biomedical applications. The long-term stability of quantum dots is limited due to their susceptibility to degradation, which ultimately impacts their performance. The cause of this instability can be attributed to various factors, including exposure to light, oxygen, and temperature fluctuations. This presents a notable obstacle that must be overcome in order to facilitate the commercialization of these products.

Opportunities:

Quantum dots exhibit distinctive optical characteristics that render them advantageous for various optoelectronic applications, including but not limited to display technology, lighting, and solar cells. Quantum dot displays exhibit superior colour gamut, colour accuracy, and energy efficiency in comparison to conventional LCD displays. The field of biotechnology has shown great potential in utilising quantum dots as effective instruments for biomedical imaging and drug delivery. Quantum dots possess high luminosity and stability, and their emission characteristics can be adjusted to precise wavelengths, rendering them valuable for visualising particular

biological structures and functions. Quantum dots possess the capability to absorb light across a broad spectrum of wavelengths, rendering them a viable option for solar energy harvesting. These can be utilised to augment the efficacy of photovoltaic cells, and to fabricate novel substances for energy retention.

To summarise, the commercialization of quantum dots encounters various obstacles such as high production expenses, apprehensions regarding toxicity, and durability. Quantum dots have emerged as a promising material for a diverse array of applications, including optoelectronics, biotechnology, and energy harvesting, presenting significant opportunities in these fields. The realisation of the complete potential of quantum dots in the future will necessitate the resolution of challenges and the development of novel applications.

10 Future of Quantum Dots

The particular optical, electrical, and physical characteristics of quantum dots render them a propitious domain of investigation. Quantum dots are utilised in optoelectronics for various purposes, including but not limited to display technology, lighting, and solar cells. Ongoing research endeavours are focused on enhancing the performance and efficiency of quantum dot displays, exploring novel lighting technologies, and optimising the efficacy of solar cells. Quantum dots exhibit promising potential in the realm of biomedical applications, specifically in the areas of drug delivery and imaging. Scholars are currently exploring methods to enhance the biocompatibility of quantum dots and mitigate their toxicity. Additionally, they are devising novel imaging techniques and targeting strategies for drug administration. Quantum dots exhibit promise in the realm of quantum computing owing to their capacity to confine and manoeuvre individual electrons. Scholars are currently investigating potential applications of quantum dots in the development of qubits, which serve as the fundamental building blocks of quantum information, with the aim of enhancing the efficacy of quantum computing platforms. Quantum dots have potential applications in energy storage, including but not limited to batteries and capacitors. Ongoing research endeavours are focused on the development of novel materials and devices for the purpose of energy storage, utilising quantum dots. Quantum dots exhibit potential applications in the realm of environmental monitoring and remediation, including the detection of pollutants and the augmentation of water purification processes. Ongoing research endeavours are focused on the development of novel sensing and treatment technologies utilising quantum dots. In recent decades, scholars have achieved notable advancements in comprehending the conduct of quantum dots and devising novel techniques for their amalgamation and integration into apparatus. The following discourse outlines potential advancements and future trajectories in the realm of quantum dot research and its practical applications. Quantum dot sensors have been employed for the detection of minute variations in temperature, pressure, and magnetic fields. Currently, scholars are investigating the potential of quantum dots as biosensors for the identification of biomolecules, including proteins and DNA.

The potential applications of these biosensors encompass medical diagnostics and drug discovery. The utilisation of quantum dots in solar cells has been shown to increase their efficacy by augmenting light absorption and subsequent conversion into electrical energy. Scientists are currently engaged in enhancing the reliability and expandability of solar cells that are based on quantum dots, with the aim of rendering them feasible for commercial purposes. The utilisation of quantum dots as qubits in quantum computing is a promising avenue for exploration. Quantum dots are being investigated by researchers as a potential foundation for constructing quantum computers that exhibit greater stability and scalability in comparison to alternative qubit configurations. Quantum dot-based light-emitting diodes (LEDs) have been developed as a promising solution for efficient and adjustable lighting and display applications. Scholars are currently engaged in enhancing the effectiveness and chromatic accuracy of light-emitting diodes that utilise quantum dots, with the aim of rendering them comparable to conventional LEDs. Quantum dots have the potential to serve as memory devices in electronic systems. Quantum dots are being investigated by scholars as a potential non-volatile memory storage alternative that can be downsized to dimensions smaller than those of existing memory technologies. To attain these advancements and fully exploit the capabilities of quantum dots, it is imperative for researchers to enhance their comprehension of the fundamental physics of quantum dots and devise novel techniques for their synthesis and integration into devices. Furthermore, the progression of fabrication and manufacturing methodologies will play a crucial role in the expansion of quantum dot-centered devices for commercial purposes.

11 Conclusion

The potential application of quantum dots in solid-state lighting, specifically in LED lights, is a noteworthy impact. The utilisation of quantum dots as colour conversion agents enables the generation of white light that exhibits superior energy efficiency and colour rendering characteristics in comparison to conventional lighting sources.

Quantum dots are currently being investigated in the realm of biology and medicine due to their potential applications in targeted drug delivery and gene therapy. Biological molecules can be applied as a coating to enable targeted delivery of drugs or genes to affected cells or tissues, thereby minimising the risk of unintended impacts. Quantum dots possess the capability to transform the domain of quantum cryptography by facilitating the creation and transmission of secure quantum keys for data encryption. Similar to other nascent technologies, quantum dots present certain potential hazards, including apprehensions regarding toxicity and ecological consequences. Scholars are currently investigating methods to tackle these issues and guarantee the secure and ethical advancement of quantum dot technology. To conclude, quantum dots represent an intriguing and auspicious realm of investigation that harbours the possibility of transforming diverse domains of science and technology. Due to their distinctive characteristics and adaptability, they are deemed

indispensable instruments for scientists and professionals who are engaged in the advancement of novel applications and technologies.

References

1. Bacon, M., Bradley, S.J., Nann, T.: Graphene quantum dots. Part. Part. Syst. Charact. **31**(4), 415–428 (2014)
2. Ganguly, S., et al.: Advancement in science and technology of carbon dot-polymer hybrid composites: a review. Funct. Compos. Struct. **1**(2), 022001 (2019)
3. Mansur, H.S.: Quantum dots and nanocomposites. Wiley Interdisc. Rev. Nanomed. Nanobiotechnol. **2**(2), 113–129 (2010)
4. Das, P., et al.: Heteroatom doped photoluminescent carbon dots for sensitive detection of acetone in human fluids. Sens. Actuators, B Chem. **266**, 583–593 (2018)
5. Semonin, O.E., Luther, J.M., Beard, M.C.: Quantum dots for next-generation photovoltaics. Mater. Today **15**(11), 508–515 (2012)
6. Bozyigit, D., Yarema, O., Wood, V.: Origins of low quantum efficiencies in quantum dot LEDs. Adv. Func. Mater. **23**(24), 3024–3029 (2013)
7. Latief, U., et al.: Luminescent Manganese/Europium doped ZnS quantum dots: tunable emission and their application as fluorescent sensor. J. Alloy. Compd. **910**, 164889 (2022)
8. Mukherjee, C., et al.: Layered T full adder using quantum-dot cellular automata. In: 2015 IEEE International Conference on Electronics, Computing and Communication Technologies (CONECCT). IEEE (2015)
9. Piloto, A.M.L., et al.: Cellulose-based hydrogel on quantum dots with molecularly imprinted polymers for the detection of CA19-9 protein cancer biomarker. Microchim. Acta **189**(4), 134 (2022)
10. Ahmed, S.R., et al.: Target specific aptamer-induced self-assembly of fluorescent graphene quantum dots on palladium nanoparticles for sensitive detection of tetracycline in raw milk. Food Chem. **346**, 128893 (2021)
11. Sol-Fernández, D., et al.: Digging on the application of novel rod-like particles of polydopamine-CdTe quantum dots for photohermal cancer therapy (2021)
12. Reimann, S.M., Manninen, M.: Electronic structure of quantum dots. Rev. Mod. Phys. **74**(4), 1283 (2002)
13. Kouwenhoven, L.P., Austing, D., Tarucha, S.: Few-electron quantum dots. Rep. Prog. Phys. **64**(6), 701 (2001)
14. Bailey, R.E., Smith, A.M., Nie, S.: Quantum dots in biology and medicine. Phys. E **25**(1), 1–12 (2004)
15. Bonilla, J.C., et al.: Applications of quantum dots in food science and biology. Trends Food Sci. Technol. **53**, 75–89 (2016)
16. Das, P., et al.: Carbon dot biopolymer-based flexible functional films for antioxidant and food monitoring applications. ACS Appl. Polym. Mater. **4**(12), 9323–9340 (2022)
17. Das, P., et al.: Tailor made magnetic nanolights: fabrication to cancer theranostics applications. Nanosc. Adv. **3**(24), 6762–6796 (2021)
18. Das, P., et al.: Carbon-dots-initiated photopolymerization: an in situ synthetic approach for MXene/poly (norepinephrine)/copper hybrid and its application for mitigating water pollution. ACS Appl. Mater. Interfaces **13**(26), 31038–31050 (2021)
19. Rajabzadeh, A.R., et al.: Magnetic Quantum Dots for Bioimaging. CRC Press (2023)
20. Das, P., et al.: Waste-derived sustainable fluorescent nanocarbon-coated breathable functional fabric for antioxidant and antimicrobial applications. ACS Appl. Mater. Interfaces (2023)
21. Das, P., et al.: MXene/0D nanocomposite architectures: design, properties and emerging applications. Mater. Today Nano **24**, 100428 (2023)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

22. Das, P., et al.: Naturally derived carbon dots in situ confined self-healing and breathable hydrogel monolith for anomalous diffusion-driven phytomedicine release. ACS Appl. Bio Mater. **5**(12), 5617–5633 (2022)
23. Das, P., et al.: One-step synthesis of fluorescent carbon dots for bio-labeling assay. In: Macromolecular Symposia. Wiley Online Library (2018)
24. Jamieson, T., et al.: Biological applications of quantum dots. Biomaterials **28**(31), 4717–4732 (2007)
25. Jelinek, R.: Carbon Quantum Dots, pp. 29–46. Carbon quantum dots. Springer International Publishing, Cham (2017)
26. Lent, C.S., Tougaw, P.D.: A device architecture for computing with quantum dots. Proc. IEEE **85**(4), 541–557 (1997)
27. Van Dam, J.A., et al.: Supercurrent reversal in quantum dots. Nature **442**(7103), 667–670 (2006)
28. Parak, W.J., Pellegrino, T., Plank, C.: Labelling of cells with quantum dots. Nanotechnology **16**(2), R9 (2005)
29. Shiohara, A., et al.: On the cyto-toxicity caused by quantum dots. Microbiol. Immunol. **48**(9), 669–675 (2004)
30. Güçlü, A.D., et al.: Graphene Quantum Dots. Springer (2014)
31. Das, P., et al.: Carbon dots for heavy-metal sensing, pH-sensitive cargo delivery, and antibacterial applications. ACS Appl. Nano Mater. **3**(12), 11777–11790 (2020)
32. Tian, P., et al.: Graphene quantum dots from chemistry to applications. Mater. Today Chem. **10**, 221–258 (2018)
33. Smith, A.M., Nie, S.: Next-generation quantum dots. Nat. Biotechnol. **27**(8), 732–733 (2009)
34. Bimberg, D., Pohl, U.W.: Quantum dots: promises and accomplishments. Mater. Today **14**(9), 388–397 (2011)
35. Das, P., et al.: Dual doped biocompatible multicolor luminescent carbon dots for bio labeling, UV-active marker and fluorescent polymer composite. Luminescence **33**(6), 1136–1145 (2018)
36. Bawendi, M.G., Steigerwald, M.L., Brus, L.E.: The quantum mechanics of larger semiconductor clusters ("quantum dots"). Annu. Rev. Phys. Chem. **41**(1), 477–496 (1990)
37. Ganguly, S., et al.: Microwave-synthesized polysaccharide-derived carbon dots as therapeutic cargoes and toughening agents for elastomeric gels. ACS Appl. Mater. Interfaces **12**(46), 51940–51951 (2020)
38. Ganguly, S., et al.: Microwave assisted green synthesis of Zwitterionic photolumenescent N-doped carbon dots: an efficient 'on-off' chemosensor for tracer Cr (+ 6) considering the inner filter effect and nano drug-delivery vector. Colloids Surf. A **579**, 123604 (2019)
39. Saravanan, A., et al.: Green synthesis of multifunctional carbon dots with antibacterial activities. Nanomaterials **11**(2), 369 (2021)
40. Dai, X., et al.: Solution-processed, high-performance light-emitting diodes based on quantum dots. Nature **515**(7525), 96–99 (2014)
41. Ganguly, S., et al.: Strongly blue-luminescent N-doped carbogenic dots as a tracer metal sensing probe in aqueous medium and its potential activity towards in situ Ag-nanoparticle synthesis. Sens. Actuators, B Chem. **252**, 735–746 (2017)
42. Liu, Z., et al.: Micro-light-emitting diodes with quantum dots in display technology. Light Sci. Appl. **9**(1), 83 (2020)
43. Sun, Q., et al.: Bright, multicoloured light-emitting diodes based on quantum dots. Nat. Photon. **1**(12), 717–722 (2007)
44. Das, P., et al.: Graphene based emergent nanolights: a short review on the synthesis, properties and application. Res. Chem. Intermed. **45**, 3823–3853 (2019)
45. Ahmed, S.R., et al.: Graphdiyne quantum dots for H2O2 and dopamine detection. ACS Appl. Nano Mater. **6**(10), 8434–8443 (2023)
46. Maity, P.P., et al.: Capra cartilage-derived peptide delivery via carbon nano-dots for cartilage regeneration. Front. Bioeng. Biotechnol. **11** (2023)
47. Zhao, G., et al.: Orbital mixing between colloidal quantum dots and surface-bound molecules. J. Phys. Chem. Lett. **13**(51), 11892–11898 (2022)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

48. Xu, Q., et al.: Recent progress of quantum dots for energy storage applications. Carbon Neutrality **1**(1), 13 (2022)
49. Abdellatif, A.A., et al.: Biomedical applications of quantum dots: overview, challenges, and clinical potential. Int. J. Nanomed. 1951–1970 (2022)
50. Rainò, G., et al.: Ultra-narrow room-temperature emission from single CsPbBr 3 perovskite quantum dots. Nat. Commun. **13**(1), 2587 (2022)
51. Efros, A.L., Brus, L.E.: Nanocrystal quantum dots: from discovery to modern development. ACS Nano **15**(4), 6192–6210 (2021)
52. Raja, A., et al.: Energy transfer from quantum dots to graphene and MoS2: the role of absorption and screening in two-dimensional materials. Nano Lett. **16**(4), 2328–2333 (2016)
53. Shirasaki, Y., et al.: Emergence of colloidal quantum-dot light-emitting technologies. Nat. Photon. **7**(1), 13–23 (2013)
54. Somers, R.C., Bawendi, M.G., Nocera, D.G.: CdSe nanocrystal based chem-/bio-sensors. Chem. Soc. Rev. **36**(4), 579–591 (2007)
55. Ramalingam, G., et al.: Quantum Confinement. IntechOpen (2020)
56. Hines, D.A., Kamat, P.V.: Recent advances in quantum dot surface chemistry. ACS Appl. Mater. Interfaces **6**(5), 3041–3057 (2014)
57. Kilina, S.V., Tamukong, P.K., Kilin, D.S.: Surface chemistry of semiconducting quantum dots: theoretical perspectives. Acc. Chem. Res. **49**(10), 2127–2135 (2016)
58. Bilan, R., et al.: Quantum dot surface chemistry and functionalization for cell targeting and imaging. Bioconjug. Chem. **26**(4), 609–624 (2015)
59. Ganguly, S., et al.: Sonochemical green reduction to prepare Ag nanoparticles decorated graphene sheets for catalytic performance and antibacterial application. Ultrason. Sonochem. **39**, 577–588 (2017)
60. Das, P., et al.: Surface quaternized nanosensor as a one-arrow-two-hawks approach for fluorescence turn “on–off–on” bifunctional sensing and antibacterial activity. New J. Chem. **43**(16), 6205–6219 (2019)
61. Ganguly, S., Margel, S.: Bioimaging probes based on magneto-fluorescent nanoparticles. Pharmaceutics **15**(2), 686 (2023)
62. Devi, S., et al.: Quantum dots: an emerging approach for cancer therapy. Front. Mater. **8**, 798440 (2022)
63. Bukowski, T.J., Simmons, J.H.: Quantum dot research: current state and future prospects. Crit. Rev. Solid State Mater. Sci. **27**(3–4), 119–142 (2002)
64. Coe-Sullivan, S.: Quantum dot developments. Nat. Photonics **3**(6), 315–316 (2009)
65. Winnik, F.M., Maysinger, D.: Quantum dot cytotoxicity and ways to reduce it. Acc. Chem. Res. **46**(3), 672–680 (2013)
66. Lim, S.Y., Shen, W., Gao, Z.: Carbon quantum dots and their applications. Chem. Soc. Rev. **44**(1), 362–381 (2015)
67. Ganguly, S., Margel, S.: Fluorescent quantum dots-based hydrogels: Synthesis, Fabrication and multimodal biosensing. Talanta Open 100243 (2023)
68. Ganguly, S.: Reinforcement mechanisms of quantum dot-polymer composites. In: Quantum Dots and Polymer Nanocomposites, pp. 151–169. CRC Press (2022)
69. Ganguly, S.: 13 Challenges prospects of and magnetic future quantum dots. Magnetic Quantum Dots for Bioimaging 269 (2023)
70. Das, P., et al.: Converting waste Allium sativum peel to nitrogen and sulphur co-doped photoluminescence carbon dots for solar conversion, cell labeling, and photobleaching diligences: a path from discarded waste to value-added products. J. Photochem. Photobiol. B. **197**, 111545 (2019)
71. Jang, E., Jang, H.: Quantum dot light-emitting diodes. Chem. Rev. **123**(8), 4663–4692 (2023)
72. Liu, S.-F., et al.: 3D nanoprinting of semiconductor quantum dots by photoexcitation-induced chemical bonding. Science **377**(6610), 1112–1116 (2022)
73. Wu, X.-G., et al.: Industry outlook of perovskite quantum dots for display applications. Nat. Nanotechnol. **17**(8), 813–816 (2022)

74. Karagianni, A., et al.: Application of carbon-based quantum dots in photodynamic therapy. Carbon **203**, 273–310 (2023)
75. Manikandan, V., Lee, N.Y.: Green synthesis of carbon quantum dots and their environmental applications. Environ. Res. **212**, 113283 (2022)
76. Kaur, A., et al.: Nanocomposites of carbon quantum dots and graphene quantum dots: environmental applications as sensors. Chemosensors **10**(9), 367 (2022)
77. Deng, S., et al.: Rational design of $ZnMn_2O_4$ quantum dots in a carbon framework for durable aqueous zinc-ion batteries. Angew. Chem. **134**(12), e202115877 (2022)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Author Queries

Chapter 2

Query Refs.	Details Required	Author's response
AQ1	Please check and confirm if the author names and initials are correct.	
AQ2	Please confirm if the section headings identified are correct.	

Metadata of the chapter that will be visualized in SpringerLink

Book Title	Quantum Dots Based Nanocomposites	
Series Title		
Chapter Title	Discovery and History of Quantum Dots	
Copyright Year	2024	
Copyright HolderName	The Author(s), under exclusive license to Springer Nature Switzerland AG	
Author	Family Name	**Reddy**
	Particle	
	Given Name	**Konatham Teja Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmacy
	Organization	University College of Technology, Osmania University
	Address	Amberpet, Hyderabad, Telangana, 500007, India
	Email	
Author	Family Name	**Madhavi Latha**
	Particle	
	Given Name	**B.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Chemistry, School of Pharmacy
	Organization	Nalla Narasimha Reddy Education Society's Group of Institution
	Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
	Email	
Author	Family Name	**Gupta**
	Particle	
	Given Name	**Jeetendra Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Institute of Pharmaceutical Research
	Organization	GLA University Mathura
	Address	Bharthia, Uttar Pradesh, India
	Email	
Author	Family Name	**Chaitanya**
	Particle	
	Given Name	**A.**
	Prefix	
	Suffix	

	Role	
	Division	
	Organization	Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution
	Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
	Email	
Author	Family Name	**Srinivasa Babu**
	Particle	
	Given Name	**P.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutics
	Organization	Vignan Pharmacy College
	Address	Vadlamudi, Guntur, Andhra Pradesh, 522213, India
	Email	
Author	Family Name	**G.**
	Particle	
	Given Name	**Vamseekrishna.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Analysis
	Organization	NRI College of Pharmacy
	Address	Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh, 521212, India
	Email	
Author	Family Name	**Manikanta**
	Particle	
	Given Name	**Yeluguri**
	Prefix	
	Suffix	
	Role	
	Division	School of Pharmaceutical Sciences
	Organization	Velsinstitute of Science Technology and Advanced Studies (VISTAS)
	Address	Pallavaram, Tamilnadu, 600117, India
	Email	
Corresponding Author	Family Name	**Sahithi**
	Particle	
	Given Name	**Alapati**
	Prefix	
	Suffix	
	Role	
	Division	
	Organization	Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution

Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
Email	sahithi.a@pharma.nnrg.edu.in

Abstract

Quantum dots are a type of semiconducting material that possesses distinctive electronic and optical characteristics at the nanoscale level. As a result, they have found extensive utility in a diverse array of scientific and technological domains. The present chapter provides a historical account of quantum dots, beginning with their initial discovery in the 1980s and extending to contemporary times. The chapter provides an overview of the different techniques employed in the synthesis and fabrication of quantum dots, which include colloidal synthesis, vapor-phase synthesis, and epitaxial growth. The text delineates the various categories of quantum dots, including core-shell and alloyed quantum dots, and elucidates how their characteristics can be adjusted to cater to particular use cases. Moreover, the chapter explores the diverse implementations of quantum dots in domains such as photovoltaic technology, illumination, medical visualisation, and quantum information processing. The text also addresses the potential hazards linked to quantum dots, such as apprehensions regarding toxicity and ecological consequences.

Discovery and History of Quantum Dots

Konatham Teja Kumar Reddy, B. Madhavi Latha, Jeetendra Kumar Gupta, A. Chaitanya, P. Srinivasa Babu, Vamseekrishna. G., Yeluguri Manikanta, and Alapati Sahithi

Abstract Quantum dots are a type of semiconducting material that possesses distinctive electronic and optical characteristics at the nanoscale level. As a result, they have found extensive utility in a diverse array of scientific and technological domains. The present chapter provides a historical account of quantum dots, beginning with their initial discovery in the 1980s and extending to contemporary times. The chapter provides an overview of the different techniques employed in the synthesis and fabrication of quantum dots, which include colloidal synthesis, vapor-phase synthesis, and epitaxial growth. The text delineates the various categories of quantum dots, including core-shell and alloyed quantum dots, and elucidates how their characteristics can be adjusted to cater to particular use cases. Moreover, the chapter explores the diverse implementations of quantum dots in domains such as

K. T. K. Reddy
Department of Pharmacy, University College of Technology, Osmania University, Amberpet, Hyderabad, Telangana 500007, India

B. Madhavi Latha
Department of Pharmaceutical Chemistry, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution, Chowdariguda, Ghatkesar, Ranga Reddy 500088, India

J. K. Gupta
Institute of Pharmaceutical Research, GLA University Mathura, Bharthia, Uttar Pradesh, India

A. Chaitanya · A. Sahithi (✉)
Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution, Chowdariguda, Ghatkesar, Ranga Reddy 500088, India
e-mail: sahithi.a@pharma.nnrg.edu.in

P. Srinivasa Babu
Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, Andhra Pradesh 522213, India

Vamseekrishna. G.
Department of Pharmaceutical Analysis, NRI College of Pharmacy, Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh 521212, India

Y. Manikanta
School of Pharmaceutical Sciences, Velsinstitute of Science Technology and Advanced Studies (VISTAS), Pallavaram, Tamilnadu 600117, India

T. Sabu et al. (eds.), *Quantum Dots Based Nanocomposites*, Engineering Materials,
https://doi.org/10.1007/978-3-031-54779-9_2

photovoltaic technology, illumination, medical visualisation, and quantum information processing. The text also addresses the potential hazards linked to quantum dots, such as apprehensions regarding toxicity and ecological consequences.

1 Introduction

1.1 What Are Quantum Dots?

Quantum dots are incredibly small nanocrystals with sizes in the region of a few nanometers that are formed of semiconducting materials. They can be compared to synthetic atoms because of the distinct electrical and optical characteristics they display that are not present in their bulk counterparts [1]. Due to their tiny size, which causes the material's electrical characteristics to become quantized, quantum dots have peculiar properties [2]. Particularly, the quantization of the electronic energy levels occurs when a quantum dot is created and its electrons are constrained within a constrained area of space [3]. Due to this, discrete energy levels are created, and these levels are governed by the quantum dot's size, composition, and shape [4]. These energy levels are known as the "quantum confinement effect," and they give birth to a variety of intriguing features that may be tweaked and controlled by altering the quantum dot's size and make-up [5]. Optoelectronics is one of the most promising fields in which quantum dots can be used. In example, photovoltaic cells and highly efficient light-emitting diodes (LEDs) can be produced using quantum dots [6–8]. The colour of the light emitted by the LED may be precisely modified due to the controllable quantum dot size [9, 10]. Quantum dots can also be employed as down-converters to boost solar cells' efficiency by expanding the quantity of light that can be absorbed. Biomedicine is a promising area for using quantum dots. Quantum dots are fluorescent probes that can be utilised for imaging and disease diagnostics [11–13]. Due to their tiny size, quantum dots can enter cells and tissues and produce high-resolution photographs of biological structures. Quantum dots can also be functionalized with particular targeting molecules to bind to certain cells or tissues with a specific preference, enabling tailored drug administration [14]. Quantum dots are an exciting area of study that could revolutionise a variety of industries, including optoelectronics, healthcare, and energy [15–22]. Due to their special qualities, such as the quantum confinement effect, quantum dots are highly adaptable materials that can be tweaked and controlled to fit various needs [23]. They will therefore probably continue to play a significant role in many fields of science and technology going forward.

The distinctive characteristics and potential uses of quantum dots render them significant in both technological and research domains [24]. Nanoparticles of semiconductors can be accurately designed to exhibit distinct electronic and optical characteristics, rendering them advantageous in various domains such as optoelectronics,

biomedicine, and energy [14]. Quantum dots possess the potential to yield light-emitting diodes (LEDs) and photovoltaic cells with exceptional efficiency in the field of optoelectronics. Quantum dots possess the potential to enhance colour accuracy and diminish power consumption in displays and lighting applications due to their capability to emit light at highly specific wavelengths [25]. Furthermore, quantum dots possess the potential to serve as down-converters, thereby enhancing the efficacy of photovoltaic cells through the amplification of light absorption [26]. Quantum dots have been identified as potential fluorescent probes for imaging and diagnosis of diverse diseases in the field of biomedicine [27]. The diminutive dimensions of quantum dots facilitate their infiltration into tissues and cells, thereby affording high-fidelity visual representations of biological structures [28–30]. Furthermore, quantum dots possess the ability to be functionalized with particular targeting molecules, which can facilitate the selective binding to specific cells or tissues. This feature allows for the possibility of targeted drug delivery [16, 20, 31]. Quantum dots possess the potential to enhance the efficacy of solar cells by augmenting the extent of light absorption in the field of energy. Researchers have the ability to produce materials that can absorb light across a wide range of wavelengths by adjusting the size and composition of quantum dots [32]. Quantum dots hold significant importance in the realm of fundamental research in physics and materials science, in addition to their specific applications [33]. Quantum dots can be employed by researchers to investigate the conduct of electrons within a restricted area, thereby facilitating an enhanced comprehension of quantum mechanics and the emergence of novel materials and technologies [34]. Quantum dots possess distinctive characteristics and hold significant potential for utilisation in diverse domains, rendering them crucial in both technological and research contexts [35]. Nanoparticles possess the capability to bring about a significant transformation in domains such as optoelectronics, biomedicine, and energy. It is highly probable that they will persist in playing a crucial role in various fields of science and technology in the forthcoming years.

1.2 Early History of Quantum Dots

The inception of quantum dots can be traced back to the early 1980s, when the Russian physicist Alexei Ekimov and the American physicist Louis E. Brus conducted groundbreaking research in this field. In the year 1982, Ekimov made a discovery regarding small semiconductor crystals that were referred to as “zero-dimensional” entities. These crystals displayed quantum confinement effects that were not observable in bulk semiconductors [36]. In 1983, Brus made independent discoveries that yielded similar effects and subsequently introduced the term “quantum dots” to refer to these minute nanocrystals. The research conducted by Brus was centred on the optical characteristics of said materials, demonstrating that they discharged light at distinct wavelengths which were contingent on their dimensions. During the decades of 1980s and 1990s, scholars conducted further investigations on the characteristics of quantum dots and devised novel approaches for their synthesis and

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

manipulation. In 1994, a group of researchers from Bell Labs conducted a demonstration that showcased the potential of quantum dots in the development of light-emitting diodes (LEDs) with superior efficiency. This breakthrough discovery paved the way for novel applications in the field of optoelectronics. Subsequent to that time, scholars have achieved noteworthy progress in the production and analysis of quantum dots, resulting in novel implementations in the domains of biomedicine, energy, and other related areas [2]. Quantum dots represent a burgeoning field of study that is currently experiencing rapid growth, owing to their numerous potential applications and substantial commercial appeal [37–39].

Quantum mechanics underpins quantum confinement effects in quantum dots. Knowing electron behaviour in quantum dots requires knowing the wave-particle duality of matter and energy quantization in restricted systems. Electrons travel freely in a three-dimensional lattice structure in bulk semiconductor materials. Electrons can occupy any energy level in these continuous materials. However, nanoscale semiconductor materials restrict electron movement in all three dimensions. Electron energy levels are quantized by confinement, depending on the quantum dot's size and shape [40]. Quantized energy levels in quantum dots provide them unique features not found in bulk semiconductors. Quantum dots produce light at specified wavelengths depending on their size and shape, hence their emission spectra are crisp and narrow. Quantum dots are potential for LEDs and solar cells due to their emission spectrum tenability [41, 42]. The effective mass approximation and k-p approach are used to calculate quantum dot electron energy levels and wave functions. These models take into account quantum confinement, semiconductor crystal structure, and composition. Quantum physics predicts that electron energy levels become quantized in restricted systems, which underlies quantum confinement effects in quantum dots [17, 43, 44]. Quantization of energy levels in quantum dots produces unique electrical and optical features that have many uses in science and technology [45, 46].

The investigation of size-dependent properties of nanocrystals was initiated in the 1980s through early experimental studies. The phenomenon of the shift in absorption and emission spectra towards higher energies was observed by researchers in certain semiconductor nanocrystals, as the size of the nanocrystals decreased. The observed blue-shift in the spectra has been ascribed to the quantum confinement effect, which emerges from the confinement of electrons and holes within a limited volume of the nanocrystal [47]. The phenomenon in question leads to the quantization of energy levels of both electrons and holes, thereby causing alterations in the optical and electronic characteristics of the nanocrystals that are dependent on their size [48]. The initial investigations initiated a novel area of inquiry regarding the characteristics and prospective uses of nanocrystals. Apart from the blue-shifted absorption and emission spectra, the scholars also noted alterations in various characteristics of nanocrystals, including their magnetic behaviour and conductivity, which were dependent on their size. As particle size decreases in certain materials, such as gold and silver, the melting point exhibits a corresponding decrease [49]. The observed phenomenon, commonly referred to as "melting point depression", can be attributed to the heightened surface area-to-volume ratio of the particles. This characteristic renders the particles more vulnerable to surface melting and thermal

fluctuations [50]. Size-dependent properties of nanocrystals have been investigated, including their mechanical characteristics, such as hardness and ductility, as well as their catalytic activity in chemical reactions. The impact of the morphology and constitution of nanocrystals on their characteristics, as well as their interplay with other substances and biological systems, has been examined by scholars. In general, the initial experimental investigations concerning the size-dependent characteristics of nanocrystals have initiated a novel area of inquiry into the attributes and prospective uses of materials at the nanoscale. Currently, the investigation of nanocrystals and other nanomaterials is a swiftly expanding field of study with numerous potential applications in domains such as electronics, energy, biomedicine, and other related fields.

1.3 First Synthesis of Quantum Dots

Louis E. Brus and his team accomplished the initial prosperous amalgamation of quantum dots in 1984. The researchers employed solution-phase methodologies to produce colloidal quantum dots composed of semiconductors, specifically CdSe, CdTe, and CdS [51]. The process of synthesis entailed the introduction of precursors, namely cadmium and selenium, into a heated solution of a coordinating solvent, such as tri-n-octylphosphine oxide (TOPO) and trioctylphosphine (TOP). Subsequent to the reaction, a coordinating ligand, namely hexadecylamine (HDA), was introduced to serve as a capping agent with the purpose of regulating the dimensions and morphology of the quantum dots [52]. The quantum dots obtained exhibited a high degree of uniformity in size, superior quantum efficiency, and a robust luminescent property, rendering them a desirable candidate for a diverse array of applications. The triumph of this particular method of synthesis has paved the way for further exploration into the synthesis and characteristics of colloidal quantum dots. Currently, solution-phase synthesis is a frequently employed technique for the production of quantum dots, with numerous modifications and advancements implemented over time to enhance regulation of the quantum dots' size, shape, and characteristics. Brief explanation of the synthesis technique.

2 Key Contributions from Early Researchers

The initial investigators of quantum dots made significant advancements that facilitated their current utilisation in various domains. The identification of the quantum confinement effect stands out as a significant contribution. During the initial years of the 1980s, Alexei Ekimov and Louis E. Brus conducted research and made observations that revealed the absorption and emission spectra of specific semiconductor nanocrystals underwent a shift towards higher energies with a decrease in the size of the nanocrystals. The observed blue-shifted spectra can be explained by the quantum

confinement effect, which is a result of the confinement of electrons and holes within a limited volume of the nanocrystal. The phenomenon under consideration leads to the quantization of energy levels of both electrons and holes thereby causing alterations in the optical and electronic characteristics of the nanocrystals that are dependent on their size. The development of synthetic methods for quantum dots was deemed a significant contribution. The synthesis of colloidal quantum dots through solution-phase techniques was pioneered by Louis E. Brus and R. Murray. The techniques employed in this study entailed the introduction of precursor substances into a coordinating solvent, succeeded by the incorporation of a capping agent to regulate the dimensions and morphology of the quantum dots. The quantum dots that were produced exhibited a limited range of sizes, a high quantum yield, and robust luminescence, rendering them appealing for utilisation in a diverse array of applications. In the initial stages of research, quantum dots were subjected to diverse methodologies to determine their properties [53]. The optical properties of quantum dots were investigated using absorption and emission spectroscopy, while their structural properties were examined through X-ray diffraction and transmission electron microscopy. The researchers additionally examined the impacts of dimensions, morphology, and constitution on the characteristics of quantum dots. Early researchers have demonstrated the potential applications of quantum dots in various fields. The distinct optical and electronic characteristics of quantum dots were demonstrated by Paul Alivisatos and Moungi Bawendi, which could be utilised for various purposes including optoelectronics, sensing, and biolabeling [54]. The research conducted by the authors established the fundamental principles for the emergence of quantum dots as a distinct area of study, and facilitated their integration into a diverse array of contemporary applications. In brief the finds can be uttered like these:

- The quantum confinement effect was initially observed by early researchers. This phenomenon causes the energy levels of electrons and holes in a nanocrystal to become quantized. Consequently, the optical and electronic properties of the nanocrystal undergo size-dependent changes [55].
- The researchers additionally devised synthetic procedures for quantum dots through solution-phase methodologies, yielding nanocrystals characterised by a limited size range, elevated quantum efficiency, and robust luminescence.
- Quantum dots were characterised by early researchers through a range of techniques such as absorption and emission spectroscopy, X-ray diffraction, and transmission electron microscopy.
- The researchers conducted an investigation into the impact of quantum dot size, shape, and composition on their respective properties.
- The initial researchers exhibited the potential uses of quantum dots in domains such as optoelectronics, sensing, and biolabeling, thereby establishing the groundwork for their current utilisation in a diverse array of applications.

3 Advancements in Quantum Dot Synthesis

Various techniques have been devised for the production of quantum dots, each possessing unique merits and drawbacks. Several frequently employed techniques include:

1. The colloidal synthesis method is a commonly employed technique for the production of quantum dots in a liquid medium. The present technique involves the dissolution of precursors in a suitable solvent, subsequent to which a reducing agent and stabilising agent are introduced. Quantum dots are generated via a process of nucleation and growth.
2. The sol-gel synthesis technique entails the chemical reactions of hydrolysis and condensation of metal alkoxides in a solution, resulting in the formation of a substance with a gel-like consistency. Subsequently, the gel is subjected to a drying process and subsequently exposed to heat in order to generate the quantum dots.
3. The process of chemical vapour deposition entails the application of a slender layer of a precursor substance onto a substrate, succeeded by the reaction of the precursor with a reactant in the gas phase, resulting in the formation of quantum dots.
4. The electrochemical synthesis technique entails the deposition of metal ions onto a substrate while a reducing agent is present, resulting in the formation of quantum dots.
5. The process of plasma synthesis entails the utilisation of a plasma discharge to produce exceedingly reactive species that can interact with precursor gases, resulting in the formation of quantum dots.
6. The process of laser ablation entails utilising a laser beam to ablate a solid target, thereby producing plasma that can interact with a gas-phase reactant to create quantum dots.

Each of the aforementioned techniques possesses unique benefits and drawbacks with respect to regulating the dimensions, morphology, and chemical makeup of the quantum dots, as well as their potential for expansion and consistency in results. The selection of the appropriate technique is contingent upon the particular usage scenario and the intended characteristics of the quantum dots.

4 Discussion of the Role of Surface Chemistry in Quantum Dot Synthesis

Quantum dots are semiconductor materials at the nanoscale level that possess distinctive electronic and optical characteristics, rendering them exceedingly appealing for utilisation in various domains, including but not limited to biological imaging, optoelectronics, and energy. The process of synthesising quantum dots is intricate and

demands meticulous regulation of the nanocrystals' size, shape, and composition. The significance of surface chemistry in quantum dot synthesis cannot be overstated, as it has a profound impact on the growth kinetics, stability, and properties of the nanocrystals [56]. The manipulation of the surface chemistry of quantum dots can be achieved through the incorporation of ligands or surface coatings during the process of synthesis. The ligands exhibit an interaction with the surface of the quantum dots, thereby influencing their size, shape, and properties. Ligands serve multiple pivotal functions in the process of quantum dot fabrication [57]. Primarily, they function as capping agents that impede the agglomeration of quantum dots, which is a pivotal element in regulating the dimensions of the nanocrystals. The presence of ligands induces steric hindrance among the quantum dots, thereby constraining their capacity to approach one another and coalesce into aggregates. The growth kinetics of nanocrystals can be influenced by ligands, which have the ability to modulate the surface energy of quantum dots. The quantum dot's surface energy plays a crucial role in determining its propensity to accept atoms or molecules during the growth process, thereby influencing its size and morphology [58]. The modulation of surface energy through the use of ligands can effectively decelerate the rate of nanocrystal growth, ultimately resulting in the production of smaller and more homogenous particles. In addition, it should be noted that ligands have the potential to modify the surface charge of quantum dots, thereby affecting their stability and interactions with chemical or biological surroundings [4, 59–61]. The determination of nanoparticle stability in a solution is reliant on the crucial factor of surface charge. The manipulation of surface charge by ligands can establish a protective enclosure around quantum dots, thereby impeding their aggregation or interaction with other molecules present in the solution. The selection of ligands employed in the process of synthesis plays a crucial role in determining the surface chemistry of quantum dots [62]. This, in turn, has a significant impact on their properties and potential applications. Hydrophilic ligands, such as carboxylic acids or amines, can generate a water-soluble surface, which facilitates the utilisation of quantum dots in biological imaging and sensing applications. In contrast, ligands that exhibit hydrophobic properties have the ability to augment the stability of quantum dots in solvents that lack polarity, thereby conferring utility in optoelectronic domains.

Over the years, there have been notable developments in the production of quantum dots. Presented below is a concise summary of some of the principal progressions.

The initial methods of synthesising quantum dots involved colloidal synthesis and were accomplished in the early 1990s. Subsequently, additional methodologies, including sol-gel synthesis and chemical vapour deposition, were also established. The technique of size-tunable synthesis was developed by researchers in the late 1990s, which enabled accurate manipulation of the size of quantum dots. The aforementioned outcome was attained via alterations in the reaction parameters, including but not limited to adjustments in temperature, duration, and concentration of the precursor substances [63]. The development of high-quality synthesis methods in the early 2000s resulted in significant progress in the production of quantum dots with superior optical and electronic properties, as reported by researchers. The

aforementioned outcome was attained through the utilisation of materials with high levels of purity and the optimisation of synthesis conditions to reduce the occurrence of defects [64]. The development of quantum dots has garnered increasing attention in recent times, with a focus on utilising novel materials like perovskites and metal-organic frameworks. The aforementioned materials possess distinctive benefits, including elevated quantum yields and adjustable bandgaps [65]. The escalating demand for quantum dots across diverse applications has prompted a concentration on the advancement of large-scale synthesis techniques. Recent developments in this field encompass the implementation of continuous flow synthesis and microwave-assisted synthesis techniques.

5 Properties of Quantum Dots

The optical properties of quantum dots are dependent on their size, shape, and composition, which give rise to their distinctive characteristics. The quantization of energy levels arises due to the confinement of electrons and holes within a small volume in quantum dots, resulting in size-dependent properties. As the dimensions of the quantum dot decrease, the energy levels exhibit greater discreteness, leading to an increase in the bandgap and a corresponding shift in the absorption and emission spectra towards higher energies [66]. The phenomenon being referred to is commonly recognised as the quantum confinement effect. The surface area-to-volume ratio of a quantum dot is influenced by its size, which in turn affects its reactivity and stability, as well as its bandgap.

The properties of quantum dots can be significantly influenced by their shape [67–70]. Quantum dots that are anisotropic in nature, such as nanorods or nanowires, demonstrate absorption and emission spectra that are dependent on polarisation. This is attributed to the alignment of the dipoles along the longitudinal axis of the particle [71]. The electronic structure and optical properties of a quantum dot can be altered by its shape, resulting in modifications to its energy levels. Quantum dots possessing faceted geometries may manifest distinct surface terminations, thereby influencing their surface chemistry and stability.

The properties of a quantum dot can be significantly influenced by its composition, particularly its chemical makeup. The determination of the bandgap of a quantum dot is contingent upon the disparity in energy levels between the conduction and valence bands, a factor that is subject to the quantum dot's size and composition [72]. Cadmium-based quantum dots are known to demonstrate a greater bandgap in comparison to lead-based quantum dots of equivalent size. The chemical composition of a quantum dot can have a significant impact on its surface chemistry, thereby influencing its stability and reactivity.

The optical characteristics of quantum dots have garnered significant attention owing to their potential utility in diverse domains [73]. Quantum dots possess a narrow emission spectra and high quantum yields, rendering them suitable for deployment as fluorescent probes. Furthermore, the tunability of quantum dots' emission

spectra can be achieved through alterations in their size, shape, and composition, rendering them remarkably versatile [74]. Quantum dots possess the capability to be deliberately designed to emit at particular wavelengths within the visible or near-infrared spectrum, thereby rendering them advantageous for employment in imaging and sensing applications.

To summarise, the characteristics of quantum dots are significantly influenced by their dimensions, morphology, and chemical makeup. Comprehending the aforementioned characteristics holds paramount significance in customising quantum dots for particular uses in domains such as optoelectronics, biomedicine, and energy transformation. Furthermore, current investigations within the discipline are concentrated on enhancing the stability and quantum yield of quantum dots, while also delving into novel applications for these distinctive nanomaterials.

6 Overview of the Application of Quantum Dots in Various Fields

Semiconductor nanoparticles known as quantum dots possess distinctive electronic and optical characteristics that render them highly advantageous instruments across a range of disciplines. Nanocrystals are commonly composed of materials like cadmium selenide, cadmium telluride, and indium arsenide, and exhibit a size distribution ranging from a few to several hundred nanometers. The field of optoelectronics has witnessed a significant utilisation of quantum dots. Quantum dots possess distinctive optical characteristics owing to their high surface-to-volume ratio, which is attributed to their diminutive size. Particularly, they possess the ability to produce light at exact wavelengths, rendering them suitable for implementation in superior quality screens, light-emitting diodes, and photovoltaic cells. The capacity of emitting light in various hues, coupled with their elevated luminosity, renders them advantageous in the context of illuminative purposes. Quantum dots have the potential to serve as a labelling tool for biological molecules and cells in the field of biological imaging, thereby facilitating their visualisation and monitoring. Compared to conventional organic dyes, they present various benefits, including enhanced luminosity, improved resistance to photodegradation, and narrower emission spectra. Moreover, the diminutive dimensions of quantum dots render them capable of infiltrating tissues to a significant extent, thereby rendering them well-suited for deployment in the realm of in vivo imaging. The utilisation of quantum dots in the domain of energy production is currently under investigation. Quantum dots have the ability to absorb a wider spectrum of light wavelengths in comparison to conventional solar cells, thereby enhancing their capacity to transform solar energy into electrical energy. Furthermore, quantum dots exhibit promising prospects for utilisation in energy storage systems, including batteries and supercapacitors. Quantum dots are currently under investigation in the realm of information technology due to their potential to serve as qubits, which are fundamental units in the construction of quantum computers.

The utilisation of quantum dots is applicable in the advancement of memory and data storage devices that possess high-speed and high-capacity capabilities. Quantum dots exhibit potential for utilisation in sensing and detection applications. These devices have the capability to function as sensors for detecting alterations in environmental factors such as temperature, pressure, and others. Furthermore, they have the capability to detect and distinguish diverse categories of molecules such as biomolecules, contaminants, and explosives. Quantum dots exhibit distinctive electronic and optical characteristics that render them highly favourable for diverse applications spanning multiple domains. Anticipated progress in research endeavours is poised to yield noteworthy breakthroughs in the utilisation and creation of these nanoparticles across domains encompassing energy, healthcare, and information technology.

7 Quantum Dot Technology

The distinct characteristics exhibited by quantum dots have resulted in their utilisation across a diverse array of technological domains (Fig. 1). The principal implementations of quantum dots are as follows.

Quantum dots have found extensive application in the realm of display technology, particularly in LED backlit displays. The utilisation of these elements results in the

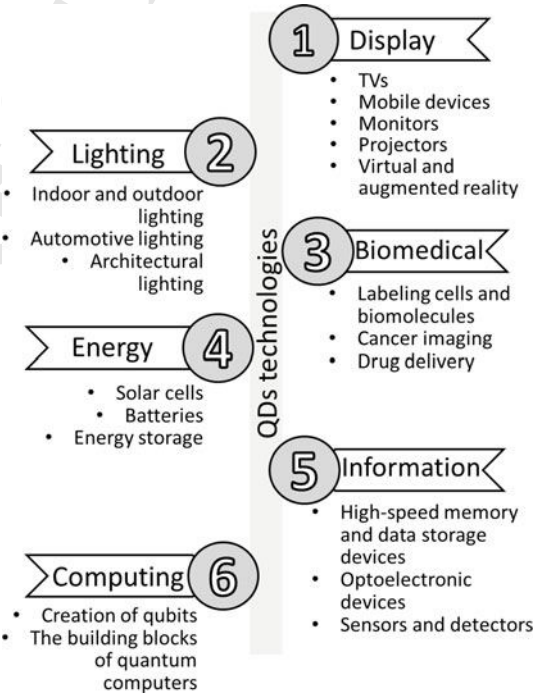


Fig. 1 Various types of applications of QDs nanoparticles

generation of hues that are more pronounced, accompanied by an elevated degree of luminosity and differentiation [75]. Conventional LED displays typically employ white LEDs in conjunction with colour filters to generate diverse hues; however, this approach may lead to energy dissipation and a reduced range of colours. In contrast, displays utilising quantum dots employ blue light emitting diodes (LEDs) in conjunction with quantum dots that generate red and green light upon being stimulated by the blue light source. The outcome of this is an expanded range of colours and a display that consumes less energy.

Quantum dots exhibit distinctive optical characteristics that render them valuable for medical imaging purposes. Fluorescent tags can be utilised for the purpose of identifying and tracking particular cells or molecules within the human body. Quantum dots possess the ability to be tailored to emit light at precise wavelengths, rendering them highly suitable for imaging purposes that necessitate superior resolution and sensitivity [76]. Furthermore, they are currently under development as contrast agents to facilitate more accurate imaging of neoplasms and other anomalous tissues.

The utilisation of quantum dots is being explored as a means of enhancing the efficacy of solar cells through the capture of a wider range of light wavelengths, which can subsequently be converted into electrical energy [77]. Solar cells conventionally comprise crystalline silicon and possess a limited capacity to absorb light wavelengths. The incorporation of quantum dots into the solar cell enables the capture of a wider range of light wavelengths, thereby facilitating the conversion of light energy into electrical energy [49]. The utilisation of quantum dots in conjunction with other materials has the potential to yield multi-junction solar cells that exhibit superior levels of efficiency.

Quantum dots have the potential to serve as qubits within quantum computing frameworks. Qubits serve as the fundamental units of quantum computers and possess the ability to exist in numerous states concurrently, thereby facilitating expedited processing as compared to conventional computers. Quantum dots exhibit extended coherence times and are amenable to facile manipulation, rendering them a propitious substrate for constructing quantum computers on a macroscopic scale.

Quantum dots are currently being utilised in the development of energy-efficient lighting solutions that offer superior quality [16, 49, 69]. Light-emitting diodes (LEDs) have the potential to serve as a substitute for conventional fluorescent or incandescent bulbs, as they are capable of emitting light with a broader spectrum of colours and a greater luminosity. Quantum dot lighting possesses the added benefit of enhanced energy efficiency, thereby resulting in considerable cost reductions in the long run.

Quantum dots are currently under development for various biotechnology purposes such as drug delivery, biomolecule detection, and disease diagnosis. Nanoparticles possess the capability to selectively target particular cells or molecules, thereby rendering them a potent instrument in the realm of nanomedicine. Quantum dots possess the capability of being tailored to selectively bind with particular proteins or nucleic acids, thereby enabling their application in the detection of biomolecules or diagnosis of diseases.

In general, quantum dots exhibit a broad spectrum of potential applications across diverse domains, and continued scientific inquiry and innovation is anticipated to yield further compelling utilities in the times ahead. Quantum dots possess distinctive characteristics that render them highly adaptable and multifaceted, thereby positioning them as a technology with considerable potential for diverse applications.

The field of optoelectronics has shown interest in utilising quantum dots due to their distinctive optical characteristics. Quantum dots exhibit a quantized energy spectrum owing to their diminutive size, resulting in the emission of light at distinct wavelengths. The aforementioned characteristic renders them highly suitable for utilisation in light-emitting diodes and laser devices, wherein meticulous regulation of the emanated wavelengths holds paramount significance. Quantum dots exhibit a broad absorption spectrum, enabling them to capture light across a diverse range of wavelengths. The aforementioned characteristic holds practical significance in down-conversion scenarios, wherein photons with high energy levels are transformed into photons with lower energy levels that can be assimilated by conventional semiconductor materials, such as silicon.

Furthermore, quantum dot light-emitting diodes (QLEDs) possess the capability to offer superior visual displays featuring an extensive range of colours. Quantum dots have the capability to emit light across a diverse range of colours, encompassing those within the visible spectrum. Quantum dot light-emitting diodes (LEDs) exhibit high efficiency and are capable of generating vivid and intense hues, rendering them a compelling substitute for conventional LEDs in lighting and display contexts.

Quantum dots have been identified as a potential material for advanced solar cells owing to their distinctive characteristics. Quantum dots possess a significant benefit in their ability to effectively absorb light across a wide spectrum of wavelengths. This implies that the light-capturing capacity of conventional semiconductor materials, such as silicon, is restricted to a limited range of wavelengths, whereas the aforementioned materials can capture a broader spectrum of light. Furthermore, quantum dots possess the capability to function as down-converting layers. This feature facilitates the enhancement of the light-capturing capacity of conventional silicon solar cells by transforming high-energy photons into lower-energy photons that can be assimilated by silicon.

Quantum dots possess the capability to enhance the efficacy of solar cells by enabling them to apprehend light in the infrared segment of the spectrum, which is beyond the reach of silicon-based solar cells. The reason for this is that quantum dots can be customised to possess a band gap that can be adjusted to the targeted wavelength spectrum. The integration of quantum dots into photovoltaic cells is being investigated by scholars as a means of enhancing their efficacy and diminishing the expense of solar power.

The utilisation of quantum dots as qubits, which are the fundamental units of quantum computers, is a viable option in the field of quantum computing. The utilisation of the spin of an electron in a quantum dot as a qubit and the exploitation of the quantum properties of these systems for the purpose of executing quantum computations can be achieved. The scalability of quantum dots and their compatibility with current semiconductor manufacturing processes make them a promising

technology. This implies that they possess the capability of being manufactured in significant quantities and incorporated into pre-existing electronic apparatus.

Nevertheless, there are still obstacles to be overcome with regards to preserving the consistency of the qubits for extended durations. The reason for the susceptibility of qubits to decoherence is attributed to the high sensitivity of quantum dots to their surrounding environment, whereby any form of noise or fluctuations can result in the loss of coherence. Scholars are currently engaged in the development of methodologies aimed at regulating the ambient conditions surrounding quantum dots, with the objective of mitigating the deleterious effects of noise on their operational efficacy.

The distinctive optical characteristics of quantum dots render them a desirable option for application in the fields of biotechnology and medical imaging. Fluorescent probes have the potential to serve as tracking agents for cellular or molecular movements within biological systems. Quantum dots exhibit exceptional stability and emit bright and persistent light, rendering them a highly suitable option for various imaging applications. Moreover, quantum dots have the potential to serve as contrast agents in medical imaging, offering superior resolution and heightened sensitivity in comparison to conventional imaging techniques.

Quantum dots possess potential for utilisation in drug delivery and therapeutic applications. Due to their diminutive dimensions, nanoparticles possess the ability to infiltrate cells and tissues. Additionally, their surface can be modified with targeting molecules, thereby enabling the transportation of therapeutic agents or drugs to precise cells or tissues.

Quantum dots exhibit potential applications in diverse fields including catalysis, sensing, and data storage performance in various chemical reactions. The electronic and optical properties of nanoparticles, which are dependent on their size, have been found to have a significant impact on their catalytic activity. As a result, they have been employed as catalysts in a variety of chemical reactions.

8 Commercialization of Quantum Dots

The inception of quantum dots' commercialization dates back to the latter part of the 1990s. Subsequently, there has been a notable surge in their manufacturing and utilisation. Quantum dots are extensively utilised in display technology as a primary application, facilitating the creation of energy-efficient and high-quality displays. Quantum dots have been employed in medical imaging due to their ability to selectively bind to particular tissues and produce more precise images compared to conventional imaging methods. Quantum dots have recently gained traction in the realm of quantum computing as a potential application, serving as fundamental units or qubits for quantum computers. The potential application of quantum dots in solar cells is currently under investigation, with the aim of enhancing the efficiency of the cells and decreasing the expenses associated with solar energy production. The commercialization of quantum dots has encountered various obstacles, such as the exorbitant

expenses associated with their manufacturing and apprehensions regarding their plausible toxicity. Notwithstanding the challenges, scholars and enterprises are endeavouring to surmount them by devising novel production techniques and investigating measures to enhance the safety of quantum dots for human utilisation.

The process of commercialising quantum dots has been in progress for a number of years, and it is anticipated that the quantum dots market will experience substantial growth in the near future. Several prominent corporations are engaged in the process of commercialising quantum dots.

1. Nanosys is a prominent enterprise that specialises in the advancement and monetization of quantum dots. The corporation provides a variety of display technology products, such as quantum dot films, LED backlights, and colour conversion layers.
2. QD Vision is a prominent enterprise that specialises in the advancement and dissemination of quantum dots. The corporation provides quantum dot merchandise that caters to display technology, lighting, and biomedical applications.
3. Samsung is a significant participant in the market for quantum dot displays. The QLED (Quantum Dot LED) technology employed by the company is utilised in its premium-grade televisions and monitors.
4. LG is a significant participant in the quantum dot display industry. The NanoCell TVs manufactured by the company utilise quantum dot technology to augment colour precision and luminosity.
5. Quantum Materials Corp is a corporation that specialises in the research, development, and manufacturing of quantum dots for a wide range of applications, including but not limited to display, lighting, solar cells, and biomedical imaging.
6. Crystalplex Corporation is a specialised enterprise that focuses on the advancement of quantum dots for the purpose of biomedical imaging and diagnostics.
7. NN-Labs is a corporation that specialises in the production of top-notch quantum dots for various purposes such as LED illumination, display technology, and biomedical imaging.
8. Ocean NanoTech is a commercial enterprise that specialises in the manufacture and distribution of quantum dots, which are utilised in various fields such as imaging, diagnostics, and sensing.
9. Quantum Solutions is a corporation that specialises in the production of top-tier quantum dots utilised in various applications, including but not limited to solar cells, LED lighting, and display technology.

Other leading companies are also in market which is depicted in Table 1.

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Table 1 Different companies those are working in quantum dots and their focus on the market

Company	Industry	Focus
IBM	Computing	Quantum computing
Google	Computing	Quantum computing
Microsoft	Computing	Quantum computing
Rigetti Computing	Computing	Quantum computing
IonQ	Computing	Quantum computing
Honeywell	Computing	Quantum computing
PsiQuantum	Computing	Quantum computing
Cambridge Quantum Computing	Computing	Quantum computing
Zapata Computing	Computing	Quantum software
Xanadu	Computing	Quantum computing and photonics
Q-CTRL	Computing	Quantum control
Atom Computing	Computing	Neutral atom quantum computing
D-Wave Systems	Computing	Quantum computing (quantum annealing)
Airbus	Aerospace	Quantum computing, communication and sensing
Lockheed Martin	Aerospace	Quantum computing, communication and sensing
Honeywell Quantum Solutions	Aerospace	Quantum computing, communication and sensing
Qrypt	Cybersecurity	Quantum key distribution
ID Quantique	Cybersecurity	Quantum key distribution
Crypta Labs	Cybersecurity	Quantum random number generators
Toshiba	Electronics	Quantum communication and encryption
Alibaba Group	Cloud services	Quantum computing
Amazon Web Services	Cloud services	Quantum computing
IBM Q Network	Network	Collaborative quantum computing
QuTech	Academic/research	Quantum computing
Max Planck Institute	Academic/research	Quantum computing, communication and sensing
University of Oxford	Academic/research	Quantum computing
University of Waterloo	Academic/research	Quantum computing
Harvard Quantum Initiative	Academic/research	Quantum computing
Nanosys	Materials science	Quantum dot films for display technology
QD Vision	Materials science	Quantum dots for display technology and lighting

(continued)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Table 1 (continued)

Company	Industry	Focus
Quantum Materials Corp	Materials science	Quantum dots for display technology, solar cells, and biomedical imaging
NN-Labs	Materials science	Quantum dots for led lighting, display technology, and biomedical imaging
Ocean NanoTech	Materials science	Quantum dots for biomedical imaging, diagnostics, and sensing
Crystalplex Corporation	Biotechnology	Quantum dots for biomedical imaging and diagnostics

9 Challenges and Opportunities in the Commercialization of Quantum Dots

Quantum dots exhibit several characteristics that render them a highly favourable material for a diverse array of applications, such as optoelectronics, biotechnology, and energy harvesting. Notwithstanding, there exist a number of obstacles and prospects that necessitate resolution in order to effectively bring quantum dots to market.

Challenges:

The commercialization potential of quantum dots is limited due to the relatively high production cost of producing high-quality ones. The elevated expense can be attributed to the intricate process of synthesis, utilisation of costly initial components, and the requirement for specialised equipment. The presence of heavy metals, such as cadmium, in certain quantum dots has raised concerns regarding their potential toxicity during production and use. The development of non-toxic and biocompatible quantum dots is imperative for their effective utilisation in biomedical applications. The long-term stability of quantum dots is limited due to their susceptibility to degradation, which ultimately impacts their performance. The cause of this instability can be attributed to various factors, including exposure to light, oxygen, and temperature fluctuations. This presents a notable obstacle that must be overcome in order to facilitate the commercialization of these products.

Opportunities:

Quantum dots exhibit distinctive optical characteristics that render them advantageous for various optoelectronic applications, including but not limited to display technology, lighting, and solar cells. Quantum dot displays exhibit superior colour gamut, colour accuracy, and energy efficiency in comparison to conventional LCD displays. The field of biotechnology has shown great potential in utilising quantum dots as effective instruments for biomedical imaging and drug delivery. Quantum dots possess high luminosity and stability, and their emission characteristics can be adjusted to precise wavelengths, rendering them valuable for visualising particular

biological structures and functions. Quantum dots possess the capability to absorb light across a broad spectrum of wavelengths, rendering them a viable option for solar energy harvesting. These can be utilised to augment the efficacy of photovoltaic cells, and to fabricate novel substances for energy retention.

To summarise, the commercialization of quantum dots encounters various obstacles such as high production expenses, apprehensions regarding toxicity, and durability. Quantum dots have emerged as a promising material for a diverse array of applications, including optoelectronics, biotechnology, and energy harvesting, presenting significant opportunities in these fields. The realisation of the complete potential of quantum dots in the future will necessitate the resolution of challenges and the development of novel applications.

10 Future of Quantum Dots

The particular optical, electrical, and physical characteristics of quantum dots render them a propitious domain of investigation. Quantum dots are utilised in optoelectronics for various purposes, including but not limited to display technology, lighting, and solar cells. Ongoing research endeavours are focused on enhancing the performance and efficiency of quantum dot displays, exploring novel lighting technologies, and optimising the efficacy of solar cells. Quantum dots exhibit promising potential in the realm of biomedical applications, specifically in the areas of drug delivery and imaging. Scholars are currently exploring methods to enhance the biocompatibility of quantum dots and mitigate their toxicity. Additionally, they are devising novel imaging techniques and targeting strategies for drug administration. Quantum dots exhibit promise in the realm of quantum computing owing to their capacity to confine and manoeuvre individual electrons. Scholars are currently investigating potential applications of quantum dots in the development of qubits, which serve as the fundamental building blocks of quantum information, with the aim of enhancing the efficacy of quantum computing platforms. Quantum dots have potential applications in energy storage, including but not limited to batteries and capacitors. Ongoing research endeavours are focused on the development of novel materials and devices for the purpose of energy storage, utilising quantum dots. Quantum dots exhibit potential applications in the realm of environmental monitoring and remediation, including the detection of pollutants and the augmentation of water purification processes. Ongoing research endeavours are focused on the development of novel sensing and treatment technologies utilising quantum dots. In recent decades, scholars have achieved notable advancements in comprehending the conduct of quantum dots and devising novel techniques for their amalgamation and integration into apparatus. The following discourse outlines potential advancements and future trajectories in the realm of quantum dot research and its practical applications. Quantum dot sensors have been employed for the detection of minute variations in temperature, pressure, and magnetic fields. Currently, scholars are investigating the potential of quantum dots as biosensors for the identification of biomolecules, including proteins and DNA.

The potential applications of these biosensors encompass medical diagnostics and drug discovery. The utilisation of quantum dots in solar cells has been shown to increase their efficacy by augmenting light absorption and subsequent conversion into electrical energy. Scientists are currently engaged in enhancing the reliability and expandability of solar cells that are based on quantum dots, with the aim of rendering them feasible for commercial purposes. The utilisation of quantum dots as qubits in quantum computing is a promising avenue for exploration. Quantum dots are being investigated by researchers as a potential foundation for constructing quantum computers that exhibit greater stability and scalability in comparison to alternative qubit configurations. Quantum dot-based light-emitting diodes (LEDs) have been developed as a promising solution for efficient and adjustable lighting and display applications. Scholars are currently engaged in enhancing the effectiveness and chromatic accuracy of light-emitting diodes that utilise quantum dots, with the aim of rendering them comparable to conventional LEDs. Quantum dots have the potential to serve as memory devices in electronic systems. Quantum dots are being investigated by scholars as a potential non-volatile memory storage alternative that can be downsized to dimensions smaller than those of existing memory technologies. To attain these advancements and fully exploit the capabilities of quantum dots, it is imperative for researchers to enhance their comprehension of the fundamental physics of quantum dots and devise novel techniques for their synthesis and integration into devices. Furthermore, the progression of fabrication and manufacturing methodologies will play a crucial role in the expansion of quantum dot-centered devices for commercial purposes.

11 Conclusion

The potential application of quantum dots in solid-state lighting, specifically in LED lights, is a noteworthy impact. The utilisation of quantum dots as colour conversion agents enables the generation of white light that exhibits superior energy efficiency and colour rendering characteristics in comparison to conventional lighting sources.

Quantum dots are currently being investigated in the realm of biology and medicine due to their potential applications in targeted drug delivery and gene therapy. Biological molecules can be applied as a coating to enable targeted delivery of drugs or genes to affected cells or tissues, thereby minimising the risk of unintended impacts. Quantum dots possess the capability to transform the domain of quantum cryptography by facilitating the creation and transmission of secure quantum keys for data encryption. Similar to other nascent technologies, quantum dots present certain potential hazards, including apprehensions regarding toxicity and ecological consequences. Scholars are currently investigating methods to tackle these issues and guarantee the secure and ethical advancement of quantum dot technology. To conclude, quantum dots represent an intriguing and auspicious realm of investigation that harbours the possibility of transforming diverse domains of science and technology. Due to their distinctive characteristics and adaptability, they are deemed

indispensable instruments for scientists and professionals who are engaged in the advancement of novel applications and technologies.

References

1. Bacon, M., Bradley, S.J., Nann, T.: Graphene quantum dots. Part. Part. Syst. Charact. **31**(4), 415–428 (2014)
2. Ganguly, S., et al.: Advancement in science and technology of carbon dot-polymer hybrid composites: a review. Funct. Compos. Struct. **1**(2), 022001 (2019)
3. Mansur, H.S.: Quantum dots and nanocomposites. Wiley Interdisc. Rev. Nanomed. Nanobiotechnol. **2**(2), 113–129 (2010)
4. Das, P., et al.: Heteroatom doped photoluminescent carbon dots for sensitive detection of acetone in human fluids. Sens. Actuators, B Chem. **266**, 583–593 (2018)
5. Semonin, O.E., Luther, J.M., Beard, M.C.: Quantum dots for next-generation photovoltaics. Mater. Today **15**(11), 508–515 (2012)
6. Bozyigit, D., Yarema, O., Wood, V.: Origins of low quantum efficiencies in quantum dot LEDs. Adv. Func. Mater. **23**(24), 3024–3029 (2013)
7. Latief, U., et al.: Luminescent Manganese/Europium doped ZnS quantum dots: tunable emission and their application as fluorescent sensor. J. Alloy. Compd. **910**, 164889 (2022)
8. Mukherjee, C., et al.: Layered T full adder using quantum-dot cellular automata. In: 2015 IEEE International Conference on Electronics, Computing and Communication Technologies (CONECCT). IEEE (2015)
9. Piloto, A.M.L., et al.: Cellulose-based hydrogel on quantum dots with molecularly imprinted polymers for the detection of CA19-9 protein cancer biomarker. Microchim. Acta **189**(4), 134 (2022)
10. Ahmed, S.R., et al.: Target specific aptamer-induced self-assembly of fluorescent graphene quantum dots on palladium nanoparticles for sensitive detection of tetracycline in raw milk. Food Chem. **346**, 128893 (2021)
11. Sol-Fernández, D., et al.: Digging on the application of novel rod-like particles of polydopamine-CdTe quantum dots for photohermal cancer therapy (2021)
12. Reimann, S.M., Manninen, M.: Electronic structure of quantum dots. Rev. Mod. Phys. **74**(4), 1283 (2002)
13. Kouwenhoven, L.P., Austing, D., Tarucha, S.: Few-electron quantum dots. Rep. Prog. Phys. **64**(6), 701 (2001)
14. Bailey, R.E., Smith, A.M., Nie, S.: Quantum dots in biology and medicine. Phys. E **25**(1), 1–12 (2004)
15. Bonilla, J.C., et al.: Applications of quantum dots in food science and biology. Trends Food Sci. Technol. **53**, 75–89 (2016)
16. Das, P., et al.: Carbon dot biopolymer-based flexible functional films for antioxidant and food monitoring applications. ACS Appl. Polym. Mater. **4**(12), 9323–9340 (2022)
17. Das, P., et al.: Tailor made magnetic nanolights: fabrication to cancer theranostics applications. Nanosc. Adv. **3**(24), 6762–6796 (2021)
18. Das, P., et al.: Carbon-dots-initiated photopolymerization: an in situ synthetic approach for MXene/poly (norepinephrine)/copper hybrid and its application for mitigating water pollution. ACS Appl. Mater. Interfaces **13**(26), 31038–31050 (2021)
19. Rajabzadeh, A.R., et al.: Magnetic Quantum Dots for Bioimaging. CRC Press (2023)
20. Das, P., et al.: Waste-derived sustainable fluorescent nanocarbon-coated breathable functional fabric for antioxidant and antimicrobial applications. ACS Appl. Mater. Interfaces (2023)
21. Das, P., et al.: MXene/0D nanocomposite architectures: design, properties and emerging applications. Mater. Today Nano **24**, 100428 (2023)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

22. Das, P., et al.: Naturally derived carbon dots in situ confined self-healing and breathable hydrogel monolith for anomalous diffusion-driven phytomedicine release. ACS Appl. Bio Mater. **5**(12), 5617–5633 (2022)
23. Das, P., et al.: One-step synthesis of fluorescent carbon dots for bio-labeling assay. In: Macromolecular Symposia. Wiley Online Library (2018)
24. Jamieson, T., et al.: Biological applications of quantum dots. Biomaterials **28**(31), 4717–4732 (2007)
25. Jelinek, R.: Carbon Quantum Dots, pp. 29–46. Carbon quantum dots. Springer International Publishing, Cham (2017)
26. Lent, C.S., Tougaw, P.D.: A device architecture for computing with quantum dots. Proc. IEEE **85**(4), 541–557 (1997)
27. Van Dam, J.A., et al.: Supercurrent reversal in quantum dots. Nature **442**(7103), 667–670 (2006)
28. Parak, W.J., Pellegrino, T., Plank, C.: Labelling of cells with quantum dots. Nanotechnology **16**(2), R9 (2005)
29. Shiohara, A., et al.: On the cyto-toxicity caused by quantum dots. Microbiol. Immunol. **48**(9), 669–675 (2004)
30. Güçlü, A.D., et al.: Graphene Quantum Dots. Springer (2014)
31. Das, P., et al.: Carbon dots for heavy-metal sensing, pH-sensitive cargo delivery, and antibacterial applications. ACS Appl. Nano Mater. **3**(12), 11777–11790 (2020)
32. Tian, P., et al.: Graphene quantum dots from chemistry to applications. Mater. Today Chem. **10**, 221–258 (2018)
33. Smith, A.M., Nie, S.: Next-generation quantum dots. Nat. Biotechnol. **27**(8), 732–733 (2009)
34. Bimberg, D., Pohl, U.W.: Quantum dots: promises and accomplishments. Mater. Today **14**(9), 388–397 (2011)
35. Das, P., et al.: Dual doped biocompatible multicolor luminescent carbon dots for bio labeling, UV-active marker and fluorescent polymer composite. Luminescence **33**(6), 1136–1145 (2018)
36. Bawendi, M.G., Steigerwald, M.L., Brus, L.E.: The quantum mechanics of larger semiconductor clusters ("quantum dots"). Annu. Rev. Phys. Chem. **41**(1), 477–496 (1990)
37. Ganguly, S., et al.: Microwave-synthesized polysaccharide-derived carbon dots as therapeutic cargoes and toughening agents for elastomeric gels. ACS Appl. Mater. Interfaces **12**(46), 51940–51951 (2020)
38. Ganguly, S., et al.: Microwave assisted green synthesis of Zwitterionic photolumenescent N-doped carbon dots: an efficient 'on-off' chemosensor for tracer Cr (+ 6) considering the inner filter effect and nano drug-delivery vector. Colloids Surf. A **579**, 123604 (2019)
39. Saravanan, A., et al.: Green synthesis of multifunctional carbon dots with antibacterial activities. Nanomaterials **11**(2), 369 (2021)
40. Dai, X., et al.: Solution-processed, high-performance light-emitting diodes based on quantum dots. Nature **515**(7525), 96–99 (2014)
41. Ganguly, S., et al.: Strongly blue-luminescent N-doped carbogenic dots as a tracer metal sensing probe in aqueous medium and its potential activity towards in situ Ag-nanoparticle synthesis. Sens. Actuators, B Chem. **252**, 735–746 (2017)
42. Liu, Z., et al.: Micro-light-emitting diodes with quantum dots in display technology. Light Sci. Appl. **9**(1), 83 (2020)
43. Sun, Q., et al.: Bright, multicoloured light-emitting diodes based on quantum dots. Nat. Photon. **1**(12), 717–722 (2007)
44. Das, P., et al.: Graphene based emergent nanolights: a short review on the synthesis, properties and application. Res. Chem. Intermed. **45**, 3823–3853 (2019)
45. Ahmed, S.R., et al.: Graphdiyne quantum dots for H2O2 and dopamine detection. ACS Appl. Nano Mater. **6**(10), 8434–8443 (2023)
46. Maity, P.P., et al.: Capra cartilage-derived peptide delivery via carbon nano-dots for cartilage regeneration. Front. Bioeng. Biotechnol. **11** (2023)
47. Zhao, G., et al.: Orbital mixing between colloidal quantum dots and surface-bound molecules. J. Phys. Chem. Lett. **13**(51), 11892–11898 (2022)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

48. Xu, Q., et al.: Recent progress of quantum dots for energy storage applications. Carbon Neutrality **1**(1), 13 (2022)
49. Abdellatif, A.A., et al.: Biomedical applications of quantum dots: overview, challenges, and clinical potential. Int. J. Nanomed. 1951–1970 (2022)
50. Rainò, G., et al.: Ultra-narrow room-temperature emission from single CsPbBr 3 perovskite quantum dots. Nat. Commun. **13**(1), 2587 (2022)
51. Efros, A.L., Brus, L.E.: Nanocrystal quantum dots: from discovery to modern development. ACS Nano **15**(4), 6192–6210 (2021)
52. Raja, A., et al.: Energy transfer from quantum dots to graphene and MoS2: the role of absorption and screening in two-dimensional materials. Nano Lett. **16**(4), 2328–2333 (2016)
53. Shirasaki, Y., et al.: Emergence of colloidal quantum-dot light-emitting technologies. Nat. Photon. **7**(1), 13–23 (2013)
54. Somers, R.C., Bawendi, M.G., Nocera, D.G.: CdSe nanocrystal based chem-/bio-sensors. Chem. Soc. Rev. **36**(4), 579–591 (2007)
55. Ramalingam, G., et al.: Quantum Confinement. IntechOpen (2020)
56. Hines, D.A., Kamat, P.V.: Recent advances in quantum dot surface chemistry. ACS Appl. Mater. Interfaces **6**(5), 3041–3057 (2014)
57. Kilina, S.V., Tamukong, P.K., Kilin, D.S.: Surface chemistry of semiconducting quantum dots: theoretical perspectives. Acc. Chem. Res. **49**(10), 2127–2135 (2016)
58. Bilan, R., et al.: Quantum dot surface chemistry and functionalization for cell targeting and imaging. Bioconjug. Chem. **26**(4), 609–624 (2015)
59. Ganguly, S., et al.: Sonochemical green reduction to prepare Ag nanoparticles decorated graphene sheets for catalytic performance and antibacterial application. Ultrason. Sonochem. **39**, 577–588 (2017)
60. Das, P., et al.: Surface quaternized nanosensor as a one-arrow-two-hawks approach for fluorescence turn “on–off–on” bifunctional sensing and antibacterial activity. New J. Chem. **43**(16), 6205–6219 (2019)
61. Ganguly, S., Margel, S.: Bioimaging probes based on magneto-fluorescent nanoparticles. Pharmaceutics **15**(2), 686 (2023)
62. Devi, S., et al.: Quantum dots: an emerging approach for cancer therapy. Front. Mater. **8**, 798440 (2022)
63. Bukowski, T.J., Simmons, J.H.: Quantum dot research: current state and future prospects. Crit. Rev. Solid State Mater. Sci. **27**(3–4), 119–142 (2002)
64. Coe-Sullivan, S.: Quantum dot developments. Nat. Photonics **3**(6), 315–316 (2009)
65. Winnik, F.M., Maysinger, D.: Quantum dot cytotoxicity and ways to reduce it. Acc. Chem. Res. **46**(3), 672–680 (2013)
66. Lim, S.Y., Shen, W., Gao, Z.: Carbon quantum dots and their applications. Chem. Soc. Rev. **44**(1), 362–381 (2015)
67. Ganguly, S., Margel, S.: Fluorescent quantum dots-based hydrogels: Synthesis, Fabrication and multimodal biosensing. Talanta Open 100243 (2023)
68. Ganguly, S.: Reinforcement mechanisms of quantum dot-polymer composites. In: Quantum Dots and Polymer Nanocomposites, pp. 151–169. CRC Press (2022)
69. Ganguly, S.: 13 Challenges prospects of and magnetic future quantum dots. Magnetic Quantum Dots for Bioimaging 269 (2023)
70. Das, P., et al.: Converting waste Allium sativum peel to nitrogen and sulphur co-doped photoluminescence carbon dots for solar conversion, cell labeling, and photobleaching diligences: a path from discarded waste to value-added products. J. Photochem. Photobiol. B. **197**, 111545 (2019)
71. Jang, E., Jang, H.: Quantum dot light-emitting diodes. Chem. Rev. **123**(8), 4663–4692 (2023)
72. Liu, S.-F., et al.: 3D nanoprinting of semiconductor quantum dots by photoexcitation-induced chemical bonding. Science **377**(6610), 1112–1116 (2022)
73. Wu, X.-G., et al.: Industry outlook of perovskite quantum dots for display applications. Nat. Nanotechnol. **17**(8), 813–816 (2022)

74. Karagianni, A., et al.: Application of carbon-based quantum dots in photodynamic therapy. Carbon **203**, 273–310 (2023)
75. Manikandan, V., Lee, N.Y.: Green synthesis of carbon quantum dots and their environmental applications. Environ. Res. **212**, 113283 (2022)
76. Kaur, A., et al.: Nanocomposites of carbon quantum dots and graphene quantum dots: environmental applications as sensors. Chemosensors **10**(9), 367 (2022)
77. Deng, S., et al.: Rational design of $ZnMn_2O_4$ quantum dots in a carbon framework for durable aqueous zinc-ion batteries. Angew. Chem. **134**(12), e202115877 (2022)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Author Queries

Chapter 2

Query Refs.	Details Required	Author's response
AQ1	Please check and confirm if the author names and initials are correct.	
AQ2	Please confirm if the section headings identified are correct.	

Metadata of the chapter that will be visualized in SpringerLink

Book Title	Quantum Dots Based Nanocomposites	
Series Title		
Chapter Title	Life Cycle Assessment of Quantum Dots and Its Composites	
Copyright Year	2024	
Copyright HolderName	The Author(s), under exclusive license to Springer Nature Switzerland AG	
Author	Family Name	**Jeevitha**
	Particle	
	Given Name	**M.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutics
	Organization	Shri Venkateswara College of Pharmacy
	Address	13A, Pondy, Main Road, Ariyur, Puducherry, 605102, India
	Email	
Author	Family Name	**Gupta**
	Particle	
	Given Name	**Jeetendra Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Institute of Pharmaceutical Research
	Organization	GLA University, Uttar Pradesh
	Address	17 Km Stone, NH-2, Mathura-Delhi Road Mathura, Chaumuhan, 281406, India
	Email	
Author	Family Name	**Sahithi**
	Particle	
	Given Name	**Alapati**
	Prefix	
	Suffix	
	Role	
	Division	
	Organization	Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Educational Society's Group of Institutions
	Address	Hyderabad, 500088, Telangana, India
	Email	
Author	Family Name	**Tallam**
	Particle	
	Given Name	**Anil Kumar**
	Prefix	

	Suffix	
	Role	
	Division	Department of Pharmacy
	Organization	Shri Venkateshwara University, Uttar Pradesh
	Address	Rajabpur, NH-24, Venkateshwara Nagar, Gajraula, 244236, India
	Email	
Author	Family Name	**Dantinapalli**
	Particle	
	Given Name	**Venkata Lakshamana Sagar**
	Prefix	
	Suffix	
	Role	
	Division	
	Organization	Analytical Scientist
	Address	435 Devon Park Dr Suite 400, Wayne, PA, 19087, USA
	Email	
Author	Family Name	**Elumalai**
	Particle	
	Given Name	**Selvaraja**
	Prefix	
	Suffix	
	Role	
	Division	Senior Director Quality Control
	Organization	Ambiopharm Inc.
	Address	Dittman ct, Beech Island, SC, 29842, USA
	Email	
Author	Family Name	**Devadhas**
	Particle	
	Given Name	**Jeslin**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutics, Faculty of Pharmacy
	Organization	Sree Balaji Medical College & Hospital Campus, Bharath Institute of Higher Education & Research
	Address	Chromepet, Chennai, 600044, Tamil Nadu, India
	Email	
Corresponding Author	Family Name	**Muzib**
	Particle	
	Given Name	**Yallamalli Indira**
	Prefix	
	Suffix	
	Role	
	Division	Institute of Pharmaceutical Technology
	Organization	Sri Padmavati Mahila Visvavidyalayam

Address	Tirupati, 517502, Andhra Pradesh, India
Email	yindira1415@gmail.com

Abstract	In this chapter, we take a close look at the environmental friendliness of quantum dots (QDs) and their composites via the lens of a life cycle assessment (LCA). The importance of QDs and their widespread practicality are first elucidated. The environmental effects of extracting raw materials, producing, transporting, using, and disposing of QDs are all considered in the LCA analysis. This chapter focuses on the trade-offs between performance and sustainability, and it explores the environmental effects of various QD composite materials. QDs' use in low-power uses like lighting and screens is also highlighted. Carbon emissions, resource use, and trash output are only some of the environmental measures used to calculate the extent of these effects. This chapter provides a thorough analysis of the environmental impacts of quantum dots (QDs) in an effort to educate researchers, industry professionals, and policymakers so that they can make educated decisions about the research, application, and management of QDs and their composites.

Life Cycle Assessment of Quantum Dots and Its Composites

M. Jeevitha, Jeetendra Kumar Gupta, Alapati Sahithi, Anil Kumar Tallam, Venkata Lakshamana Sagar Dantinapalli, Selvaraja Elumalai, Jeslin Devadhas, and Yallamalli Indira Muzib

Abstract In this chapter, we take a close look at the environmental friendliness of quantum dots (QDs) and their composites via the lens of a life cycle assessment (LCA). The importance of QDs and their widespread practicality are first elucidated. The environmental effects of extracting raw materials, producing, transporting, using, and disposing of QDs are all considered in the LCA analysis. This chapter focuses on the trade-offs between performance and sustainability, and it explores the environmental effects of various QD composite materials. QDs' use in low-power uses like lighting and screens is also highlighted. Carbon emissions, resource use, and trash output are only some of the environmental measures used to calculate the

M. Jeevitha
Department of Pharmaceutics, Shri Venkateswara College of Pharmacy, 13A, Pondy, Main Road, Ariyur, Puducherry 605102, India

J. K. Gupta
Institute of Pharmaceutical Research, GLA University, Uttar Pradesh, 17 Km Stone, NH-2, Mathura-Delhi Road Mathura, Chaumuhan 281406, India

A. Sahithi
Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Educational Society's Group of Institutions, Hyderabad 500088, Telangana, India

A. K. Tallam
Department of Pharmacy, Shri Venkateshwara University, Uttar Pradesh, Rajabpur, NH-24, Venkateshwara Nagar, Gajraula 244236, India

V. L. S. Dantinapalli
Analytical Scientist, 435 Devon Park Dr Suite 400, Wayne, PA 19087, USA

S. Elumalai
Senior Director Quality Control, Ambiopharm Inc., Dittman ct, Beech Island, SC 29842, USA

J. Devadhas
Department of Pharmaceutics, Faculty of Pharmacy, Sree Balaji Medical College & Hospital Campus, Bharath Institute of Higher Education & Research, Chromepet, Chennai 600044, Tamil Nadu, India

Y. I. Muzib (✉)
Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati 517502, Andhra Pradesh, India
e-mail: yindira1415@gmail.com

T. Sabu et al. (eds.), *Quantum Dots Based Nanocomposites*, Engineering Materials,
https://doi.org/10.1007/978-3-031-54779-9_23

602599_1_En_23_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:24/2/2024 Pages: 10 Layout: T1-Standard

extent of these effects. This chapter provides a thorough analysis of the environmental impacts of quantum dots (QDs) in an effort to educate researchers, industry professionals, and policymakers so that they can make educated decisions about the research, application, and management of QDs and their composites.

1 Introduction

The environmental impact of composites is measured across their full life cycle using a method called life cycle assessment (LCA). It's an all-encompassing method that considers the composite material's lifecycle from raw material extraction to final disposal [1]. The fundamental objective of a life cycle assessment (LCA) is to provide an all-encompassing view of the environmental effects connected with composites by quantifying and assessing the energy consumption, emissions, resource utilisation, and waste generation at each stage. Composite materials' life cycle kicks off with raw material extraction and processing. Carbon fibres, glass fibres, and different resins are common components of composites [2]. The mining, refining, and processing of these basic materials all have environmental implications that may be assessed using an LCA at this point. It takes into account things like energy use, water use, and pollution caused by these procedures. Composite material fabrication and manufacturing is the next step. Manufacturing processes in this sector range from pultrusion and filament winding to resin transfer moulding. The LCA analyses the resources used, pollution released, and trash produced by these activities [3]. Energy is expended to shape and bond materials and emissions are released into the atmosphere [4]. If you want to know how alternative manufacturing methods could affect sustainability, you need to know the environmental impact of the production phase [5]. Distribution and transport are also crucial components of a life cycle assessment. At this point, we factor in the emissions and energy used to move raw materials to production facilities and completed composite products to consumers [6–8]. The environmental impact of composites can be greatly affected by factors like as the mode of transportation utilised and the geographic distance between suppliers, manufacturers, and consumers. After composites have been put into practise, their effect on the natural world is still being studied. Composite parts are commonly used in the aerospace sector, for instance [9]. The environmental benefits of employing composites instead of traditional materials can be determined by evaluating aspects such as fuel economy, energy savings, and emissions reduction during the use phase. The life cycle of composites also includes the crucial step of maintenance and repairs [10]. Consequences to the environment, such as the energy and materials needed for repairs or replacements, should be taken into account when dealing with composites. The long-term durability of composites can be seriously compromised by these actions [11, 12]. Composites' end-of-life management is the last phase of their LCA. In this stage, we examine the processes used to dispose of or recycle composite materials once they have served their purpose. It considers the ecological effects of various

602599_1_En_23_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:24/2/2024 Pages: 10 Layout: T1-Standard

waste management options such landfilling, incineration, and recycling. To lessen the impact that composites have on the environment, proper end-of-life management is crucial.

2 Background of LCA of Materials

Rising global consumption of plastics over the past few years has resulted in a rise in plastic trash. About half of all plastics are put to use in packaging and agricultural films are two examples of single-use usage [13]. Pipes, cable coatings, and structural materials only account for 20–25% of all plastic usage. The rest goes into applications with a shorter to medium-term lifespan in the consumer market, such as electronics, furniture, and auto parts [14]. The short useful lives of plastic products contribute significantly to the difficulties inherent in plastics disposal. Plastic packaging is just one example of an area where this period can be significantly less than a month.

Because of their low density and widespread use in hollow objects (making their apparent density even lower), plastics are a glaring problem in our landfills and oceans [15]. However, while plastics may account for 20–30% of the volume weight fraction of MSW, they account for just 7–9% of the overall MSW mass [16]. However, plastic trash can be found in much larger concentrations in certain streams, such as those from the manufacturing and service sectors. The fact that plastics are typically not biodegradable means they will stay in the environment for a very long time and contribute to the problem [17]. The public's awareness of the plastics problem has grown as a result of their pervasiveness. In response, numerous LCAs have been conducted to analyse the effects of plastic items over their entire lifespan because of public interest in the topic. Recently, economic evaluations have been added to the mix to round out the research.

3 LCA of Polymer Composites

Cradle-to-factory gate and cradle-to-grave are the two most popular systems utilised in LCA research. All processes from raw material and fuel extraction to final product delivery at the factory gate are factored into a cradle-to-factory-gate LCA analysis [18]. Material manufacturers frequently provide Cradle to Factory Gate studies. Every stage, from initial creation to final disposal, is accounted for in the cradle-to-grave system. The full life cycle can be accounted for in cradle-to-grave studies. Since waste management varies from nation to country and not all waste treatment alternatives may be considered, the results of cradle-to-grave evaluations for the same product can vary greatly [19]. Cradle-to-factory-gate assessments can provide initial insight into environmental implications if comparisons across different waste disposal strategies are unavailable. Multiple formats exist for reporting LCA findings. Results from the "middle" of the range are typically given in studies. At this

stage, information from the life cycle inventory is transformed into environmental effect categories, such as the contribution to global warming or acidification. The final environmental score for a product is determined by adding up the results from several impact categories using appropriate weighting factors. Single-score analyses are another name for analyses with a focus on the final score. The weighting factors for the different effect categories are determined based on subjective assessment. When one product is demonstrably superior to another in all impact categories (or is comparable to the other option in all categories), it may be possible to draw conclusions from a comparative LCA research based on results from the middle of the range. If, on the other hand, some types of environmental consequences are more severe than others, then prioritisation decisions must be made among the many types of impacts.

A natural target of the movement to get rid of everything that isn't "green" appears to be plastics [20]. The huge amount of energy they contain and their pervasiveness as litter are typically highlighted when discussing their impact on the environment. Recent quantitative investigations, however, rarely back up this prejudice [21]. In fact, plastics typically show very favourable life cycle (LC) profiles when compared to other materials in studies evaluating the environmental and economic effect of alternative materials. In terms of Global Warming Potential (GWP) and Total Energy Use (TEU) [22]. The current significance of greenhouse gases enhancement led to the selection of these classes of environmental impact. Additional areas of environmental impact are reported by some research. These include the possibility for ozone depletion, photochemical oxidation, acidification, and eutrophication. The findings reveal that, contrary to popular belief, ordinary polymers typically cause fewer adverse effects on the environment in terms of GWP and TEU than do other materials. Reuse, which prevents the use of nonrenewable resources, has also shown to have a positive effect on both measures of environmental sustainability.

Many engineering projects hinge on the material choice made, since it affects the longevity, cost, and manufacturability of the end result. In addition, manufacturers are under increased regulatory pressure from government agencies to reduce the environmental impact of their operations and the goods they produce. Since recycling potential and/or end-of-life disposal options differ from material to material, material selection can be particularly important for green design. Identifying multiple mechanical, electrical, chemical, thermal qualities, environmental impact variables, and life cycle costs of candidate materials is the first step in modern integrated design processes (IDP) for systematically selecting the optimal material for a specific application (Fig. 1). For an IDP to be successful, multidisciplinary design teams must collaborate from the start of a project to provide solutions with many uses [23]. However, when several criteria from several fields must be met in a material selection problem, complications arise due to potential conflicts between the criteria and/or the relative relevance of the various criteria. Additionally, correct indices within each area require specialist expertise to define [24]. For a wing spar's leaf spring/beam, for instance, it may be preferable that it not only be light but also strong enough to withstand a specified bending force without buckling.

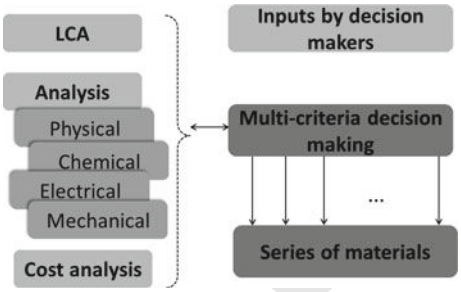


Fig. 1 A diagram showing how to choose materials in an integrated design process

4 LCA of Quantum Dots and Its Composites

Specifically designed and manufactured materials having dimensions between 1 and 100 nm are known as engineered nanomaterials (ENMs) [25]. In addition, ENMs show unique characteristics in comparison to bulk materials of the same composition [26]. The environmental implications of ENM production and use are unknown, despite the fact that their commercial production volumes have increased [27]. Therefore, in order to guarantee their sustainable production and utilisation, it is crucial to have a thorough awareness of the impacts made by ENMs throughout their life cycle. Since LCA attempts to quantify the environmental consequences of a system over the course of its life cycle [28], it is the most suited instrument for tackling this challenge [29]. However, the environmental evaluation of a significant and unique ENM, carbon dots (CDs), has not been the subject of any prior research. Carbon nanospheres are a new type of nanoparticle with a round shape and a size between 1 and 10 nm [30]. Nonetheless, making them in a way that doesn't harm the environment hasn't received much attention. Consequently, it is important and essential to provide information on the potential environmental implications of representative synthesis processes for the creation of CDs [31]. Here, we apply a cradle-to-gate life cycle assessment (LCA) to compare and comprehend the environmental effects of carbon dots (CDs) produced using six distinct bottom-up synthetic techniques. The most common methods now used to synthesise CDs are hydrothermal synthesis and microwave-assisted synthesis, both of which use citric acid as a starting material (and sometimes urea as well). According to the findings, power consumption is the most significant environmental factor in hydrothermal synthesis, while citric acid is the main source of pollution in microwave-assisted synthesis. Rescaling results using the CDs' fluorescence quantum yield allowed for a performance-based comparison as well. This method substantially altered the previous preferred order across all classes. The most environmentally friendly method, according to a recent study, was the microwave-assisted synthesis of citric acid-derived CDs; however, today both urea- and citric acid-derived CDs can be synthesised (by hydrothermal or microwave-assisted treatment) [32]. Different acid catalysts based on transition metal phosphates, such as vanadium and niobium, have been evaluated for their performance in the hydrothermal synthesis of carbon dots (CDs). Commercial xylose and

liquor of xylose extracted from olive pits were used as the carbohydrate sources. The NH3-TPD, DTA/TG, XRD, and XPS methods were used to determine the identity of the catalysts. At a temperature of 180 degrees Celsius, the reaction was run for 4 h. Analysis of the properties and characteristics of CDs nanoparticles revealed their existence, regardless of the carbohydrate source. Simultaneously, highly fluorescent N-doped CDs were synthesised via the same hydrothermal method, and their photocatalytic activity was studied. To compare the environmental consequences of the synthesis using commercial xylose to those of the synthesis using biomass, a Life Cycle Assessment (LCA) was performed on both synthesis methods [33]. Organic light-emitting diodes (OLEDs) and inorganic nanoparticle-based quantum LEDs (QLEDs) are two rival forms of light-emitting technology used in displays. For these purposes, innovative nanomaterials and organics can be found in the next substance classes of perovskites and Q-OLED displays. However, due to their complexity, intrinsically diverse structures, and rapid growth in the literature, assessing the safety and viability of these emissive compounds in a timely and comprehensive manner is challenging. To compare these potential alternatives to incombent cadmium-containing quantum dots, we propose adopting an alternatives assessment centred on danger, cost, and performance. Chemical substitution is a growing trend, and this type of assessment is employed by both industry and government. It makes advantage of existing data while highlighting crucial information gaps that must be considered. The low quantities required in their application for display make OLEDs cost-effective, although performance evaluations do not single out a superior option. According to the risk assessment, there is no better option because each unique nanomaterial or organic compound has its own set of drawbacks [34]. The study provides a framework for future researchers to analyse their own unique drugs, and the results highlight the need for a low-hazard high-performance replacement substance. New domains of application can be explored with the advent of emerging photovoltaic systems (EPVs) such organic solar cells, dye-sensitized solar cells, perovskite solar cells, and quantum dots solar cells. Life cycle analysis is essential for determining the environmental impact of EPV technology developments and sophisticated materials. Materials and production methods responsible for the bulk of a product's environmental effect can be isolated with the help of life cycle evaluations (LCAs). Recent life cycle assessments (LCAs) have shown that EPV production may result in reduced energy consumption and faster energy payback time compared to conventional PV technologies, although these results are sometimes hard to compare due to differences in methodology and system boundaries. However, the examined LCAs also identify some "environmental hotspots" regarding the materials, energy, and chemicals used. The existing use of vital raw materials, precious metals, and hazardous as well as energy-intensive products means there is still opportunity for optimisation in terms of environmental sustainability and the circular economy [35]. Carbohydrates, lipids, phenolic compounds, and proteins are only few of the many organic substances found in spent coffee grounds (SCGs). As a result, we looked at them as a feasible option for obtaining carbon dots (CDs) via a nanotechnology method. In this study, CDs made by SCGs were compared to those made from more conventional precursors like citric acid and urea. The SCG-based CDs were made

by carbonising solid samples in a single pot without using any solvents, yielding particles on the nanoscale (2.1–3.9 nm). These nanoparticles displayed the signature blue fluorescence of carbon dots as well as modest quantum yields (2.9–5.8%) and excitation-dependent emission. The SCG-based CDs showed promise as fluorescent probes for Fe3+ in water that are also environmentally relevant. Furthermore, life cycle assessment studies confirmed that making CDs out of SCG samples is a more environmentally friendly way than making CDs out of classic reported precursors, when looking at it from both a weight-based and a function-based perspective [36]. Among the many potential uses for quantum dot nanoparticles (NPs) is in photon upconversion devices, which boost the solar panels' ability to convert light into power. In this study, we present ready-to-use LCA unit process data for four NPs (cadmium selenide, cadmium sulphide, lead selenide, and lead sulphide) that are well-suited for photon upconversion applications. The information is presented for two potential futures: an optimistic and a pessimistic one. The effectiveness of the NPs in mitigating climate change is evaluated using an impact assessment, which reveals that solvent-related operations, like steam production for recycling and hazardous waste treatment, are major contributors to this issue. To demonstrate the relevance of the findings, an upconversion-layer solar module is evaluated prospectively to determine whether adding more solar modules or retrofitting existing ones with upconversion devices is preferable from a climate perspective [37]. The evaluation reveals that, depending on the circumstance, solar modules would need to increase their efficiency by 0.05 to 2 percentage points per gramme of applied NPs for the upconversion layer to be desirable.

5 Conclusions

The environmental implications of well-established processes and products can be effectively evaluated with the help of life cycle assessment (LCA). However, incorporating it into decision-making for the long-term success of cutting-edge technology presents a formidable obstacle. It is challenging to do LCA assessments at the outset of product design for new nano-enabled products (NEPs) due to the high levels of uncertainty and lack of data along the whole value chain. Data scarcity and quality difficulties are common for LCA practitioners working on developing technologies due to the proprietary nature of industrial data, necessitating some assumptions based on prior scientific literature and industry reports. These assumptions are standard practise in LCA, and while they are not false, they are likely to add some degree of uncertainty to the findings. To facilitate the growth of collaborative research across the life cycle and the generation of fresh datasets, the dLCA framework has been established. By feeding the experimental data back into the LCA model, uncertainty in various LCA stages can be reduced with each iteration, while also pointing experimentalists in the direction of questions they should be asking in the future. Although this research focuses on quantum dot (QD) applications,

the suggested dLCA framework and the interdisciplinary cooperation it encourages can be applied to the estimation of environmental impacts across a wide range of developing technologies.

Future developments in assessment methodologies for Life Cycle Assessment (LCA) of quantum dots (QDs) and their composites will take into account shifting synthesis methods, expanding applications, shifting regulations on nanomaterials, and a heightened emphasis on circular economy principles and recycling practises. In addition to promoting better data gathering, transparency, and accessibility, future LCA studies will cover a wider range of uses across a variety of sectors. The results of life cycle assessments (LCAs) will also be used in real-time decision making to promote ethically sound product and policy creation. Researchers hope that by effectively disseminating their findings, LCA studies will help raise public awareness of the environmental impact of QDs and ultimately lead to policy changes that promote sustainability and environmental responsibility in the QD industry.

References

1. Bachmann, J., Hidalgo, C., Bricout, S.: Environmental analysis of innovative sustainable composites with potential use in aviation sector—A life cycle assessment review. Sci. China Technol. Sci. **60**, 1301–1317 (2017)
2. Karuppannan Gopalraj, S., Kärki, T.: A review on the recycling of waste carbon fibre/glass fibre-reinforced composites: Fibre recovery, properties and life-cycle analysis. SN Appl. Sci. **2**(3), 433 (2020)
3. Tapper, R.J., et al.: An evaluation of life cycle assessment and its application to the closed-loop recycling of carbon fibre reinforced polymers. Compos. B Eng. **184**, 107665 (2020)
4. Das, P., et al.: Dual doped biocompatible multicolor luminescent carbon dots for bio labeling, UV-active marker and fluorescent polymer composite. Luminescence **33**(6), 1136–1145 (2018)
5. Ead, A.S., et al.: Life cycle analysis for green composites: a review of literature including considerations for local and global agricultural use. J. Eng. Fibers Fabr.Fibers Fabr. **16**, 15589250211026940 (2021)
6. Ardente, F., et al.: Energy performances and life cycle assessment of an Italian wind farm. Renew. Sustain. Energy Rev. **12**(1), 200–217 (2008)
7. Das, P., et al.: One-step synthesis of fluorescent carbon dots for bio-labeling assay. In: Macromolecular Symposia. Wiley Online Library (2018)
8. Das, P., et al.: Green approach to photoluminescent carbon dots for imaging of gram-negative bacteria Escherichia coli. Nanotechnology **28**(19), 195501 (2017)
9. Das, S.: Life cycle assessment of carbon fiber-reinforced polymer composites. Int. J. Life Cycle Assess. **16**, 268–282 (2011)
10. Blanco, I., Ingrao, C., Siracusa, V.: Life-cycle assessment in the polymeric sector: a comprehensive review of application experiences on the Italian scale. Polymers **12**(6), 1212 (2020)
11. Maruthapandi, M., et al.: Biocompatible N-doped carbon dots for the eradication of methicillin-resistant S. aureus (MRSA) and sensitive analysis for europium (III). Nano-Struct. Nano-Objects **26**, 100724 (2021)
12. Saravanan, A., et al.: Green synthesis of multifunctional carbon dots with antibacterial activities. Nanomaterials **11**(2), 369 (2021)
13. Dissanayake, N.P., Summerscales, J.: Life cycle assessment for natural fibre composites. Green Compos. Nat. Resour. **8**, 157–186 (2013)

602599_1_En_23_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:24/2/2024 Pages: 10 Layout: T1-Standard

14. Bosner, A., Poršinsky, T., Stankić, I.: Forestry and Life Cycle Assessment. InTech Rijeka (2012)
15. Achilias, D., et al.: Chemical recycling of plastic wastes made from polyethylene (LDPE and HDPE) and polypropylene (PP). J. Hazard. Mater. **149**(3), 536–542 (2007)
16. Scott, D., et al.: Fast pyrolysis of plastic wastes. Energy Fuels **4**(4), 407–411 (1990)
17. Das, S.C., La Rosa, A.D., Grammatikos, S.A.: Life cycle assessment of plant fibers and their composites. In: Plant Fibers, their Composites, and Applications, pp. 457–484. Elsevier (2022)
18. Cao, C.: Sustainability and life assessment of high strength natural fibre composites in construction. In: Advanced High Strength Natural Fibre Composites in Construction, pp. 529–544. Elsevier (2017)
19. Karjalainen, T., et al.: Energy, carbon and other material flows in the life cycle assessment of forestry and forest products. Joensuu: European Forest Institute Discussion Paper, vol. 10, pp. 1–67 (2001).
20. Papanek, V.: The Green Imperative: Ecology and Ethics in Design and Architecture. Thames & Hudson (2022)
21. Liboiron, M., Lepawsky, J.: Discard Studies: Wasting, Systems, and Power. MIT Press (2022)
22. Bernardo, C., Simões, C.L., Pinto, L.M.C.: Environmental and economic life cycle assessment of polymers and polymer matrix composites: a review. Ciência & Tecnologia dos Materiais **28**(1), 55–59 (2016)
23. Milani, A., et al.: Multiple criteria decision making with life cycle assessment for material selection of composites. Express Polym. Lett. **5**(12) (2011)
24. Akin, Ö.: Necessity of Cognitive Modeling in BIM's Future. Building Information Modeling: BIM in Current and Future Practice, pp. 17–27 (2015)
25. Auffan, M., et al.: Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective. Nat. Nanotechnol.Nanotechnol. **4**(10), 634–641 (2009)
26. Feijoo, S., et al.: Comparative life cycle assessment of different synthesis routes of magnetic nanoparticles. J. Clean. Prod. **143**, 528–538 (2017)
27. Salieri, B., et al.: Life cycle assessment of manufactured nanomaterials: where are we? NanoImpact **10**, 108–120 (2018)
28. Upadhyayula, V.K., et al.: Life cycle assessment as a tool to enhance the environmental performance of carbon nanotube products: a review. J. Clean. Prod. **26**, 37–47 (2012)
29. Ramos, A., Afonso Teixeira, C., Rouboa, A.: Environmental analysis of waste-to-energy—A Portuguese case study. Energies **11**(3), 548 (2018)
30. Das, P., et al.: Tailor made magnetic nanolights: fabrication to cancer theranostics applications. Nanoscale Adv. **3**(24), 6762–6796 (2021)
31. Das, P., et al.: Graphene based emergent nanolights: a short review on the synthesis, properties and application. Res. Chem. Intermed.Intermed. **45**, 3823–3853 (2019)
32. Sendao, R., et al.: Comparative life cycle assessment of bottom-up synthesis routes for carbon dots derived from citric acid and urea. J. Clean. Prod. **254**, 120080 (2020)
33. Rodríguez-Carballo, G., et al.: Nitrogen doped carbon dots as a photocatalyst based on biomass. A life cycle assessment. J. Clean. Prod. **423**, 138728 (2023)
34. Bechu, A., et al.: Are substitutes to Cd-based quantum dots in displays more sustainable, effective, and cost competitive? An alternatives assessment approach. ACS Sustain. Chem. Eng. **10**(7), 2294–2307 (2022)
35. Gressler, S., et al.: Advanced materials for emerging photovoltaic systems – Environmental hotspots in the production and end-of-life phase of organic, dye-sensitized, perovskite, and quantum dots solar cells. Sustain. Mater. Technol. **34**, e00501 (2022)
36. Crista, D.M., et al.: Turning spent coffee grounds into sustainable precursors for the fabrication of carbon dots. Nanomaterials **10**(6), 1209 (2020)
37. Wickerts, S., et al.: Prospective life-cycle modeling of quantum dot nanoparticles for use in photon upconversion devices. ACS Sustain. Chem. Eng. **9**(14), 5187–5195 (2021)

Author Queries

Chapter 23

Query Refs.	Details Required	Author's response
AQ1	Please check and confirm if the author names and initials are correct.	
AQ2	Please be aware that your name and affiliation and if applicable those of your co-author(s) will be published as presented in this proof. If you want to make any changes, please correct the details now. Please note that after publication corrections won't be possible. Due to data protection we standardly publish professional email addresses, but not private ones, even if they have been provided in the manuscript and are visible in this proof. If you or your co-author(s) have a different preference regarding the publication of your mail address(s) please indicate this clearly. If no changes are required for your name(s) and affiliation(s) and if you agree with the handling of email addresses, please respond with "Ok".	

Engineering Materials

Sabu Thomas
Poushali Das
Sayan Ganguly *Editors*

Quantum Dots Based Nanocomposites

Design, Fabrication and Emerging Applications

Springer

Metadata of the chapter that will be visualized in SpringerLink

Book Title	Quantum Dots Based Nanocomposites	
Series Title		
Chapter Title	Discovery and History of Quantum Dots	
Copyright Year	2024	
Copyright HolderName	The Author(s), under exclusive license to Springer Nature Switzerland AG	
Author	Family Name	**Reddy**
	Particle	
	Given Name	**Konatham Teja Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmacy
	Organization	University College of Technology, Osmania University
	Address	Amberpet, Hyderabad, Telangana, 500007, India
	Email	
Author	Family Name	**Madhavi Latha**
	Particle	
	Given Name	**B.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Chemistry, School of Pharmacy
	Organization	Nalla Narasimha Reddy Education Society's Group of Institution
	Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
	Email	
Author	Family Name	**Gupta**
	Particle	
	Given Name	**Jeetendra Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Institute of Pharmaceutical Research
	Organization	GLA University Mathura
	Address	Bharthia, Uttar Pradesh, India
	Email	
Author	Family Name	**Chaitanya**
	Particle	
	Given Name	**A.**
	Prefix	
	Suffix	

	Role	
	Division	
	Organization	Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution
	Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
	Email	
Author	Family Name	**Srinivasa Babu**
	Particle	
	Given Name	**P.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutics
	Organization	Vignan Pharmacy College
	Address	Vadlamudi, Guntur, Andhra Pradesh, 522213, India
	Email	
Author	Family Name	**G.**
	Particle	
	Given Name	**Vamseekrishna.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Analysis
	Organization	NRI College of Pharmacy
	Address	Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh, 521212, India
	Email	
Author	Family Name	**Manikanta**
	Particle	
	Given Name	**Yeluguri**
	Prefix	
	Suffix	
	Role	
	Division	School of Pharmaceutical Sciences
	Organization	Velsinstitute of Science Technology and Advanced Studies (VISTAS)
	Address	Pallavaram, Tamilnadu, 600117, India
	Email	
Corresponding Author	Family Name	**Sahithi**
	Particle	
	Given Name	**Alapati**
	Prefix	
	Suffix	
	Role	
	Division	
	Organization	Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution

Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India
Email	sahithi.a@pharma.nnrg.edu.in

Abstract

Quantum dots are a type of semiconducting material that possesses distinctive electronic and optical characteristics at the nanoscale level. As a result, they have found extensive utility in a diverse array of scientific and technological domains. The present chapter provides a historical account of quantum dots, beginning with their initial discovery in the 1980s and extending to contemporary times. The chapter provides an overview of the different techniques employed in the synthesis and fabrication of quantum dots, which include colloidal synthesis, vapor-phase synthesis, and epitaxial growth. The text delineates the various categories of quantum dots, including core-shell and alloyed quantum dots, and elucidates how their characteristics can be adjusted to cater to particular use cases. Moreover, the chapter explores the diverse implementations of quantum dots in domains such as photovoltaic technology, illumination, medical visualisation, and quantum information processing. The text also addresses the potential hazards linked to quantum dots, such as apprehensions regarding toxicity and ecological consequences.

Discovery and History of Quantum Dots

Konatham Teja Kumar Reddy, B. Madhavi Latha, Jeetendra Kumar Gupta, A. Chaitanya, P. Srinivasa Babu, Vamseekrishna. G., Yeluguri Manikanta, and Alapati Sahithi

Abstract Quantum dots are a type of semiconducting material that possesses distinctive electronic and optical characteristics at the nanoscale level. As a result, they have found extensive utility in a diverse array of scientific and technological domains. The present chapter provides a historical account of quantum dots, beginning with their initial discovery in the 1980s and extending to contemporary times. The chapter provides an overview of the different techniques employed in the synthesis and fabrication of quantum dots, which include colloidal synthesis, vapor-phase synthesis, and epitaxial growth. The text delineates the various categories of quantum dots, including core-shell and alloyed quantum dots, and elucidates how their characteristics can be adjusted to cater to particular use cases. Moreover, the chapter explores the diverse implementations of quantum dots in domains such as

K. T. K. Reddy
Department of Pharmacy, University College of Technology, Osmania University, Amberpet, Hyderabad, Telangana 500007, India

B. Madhavi Latha
Department of Pharmaceutical Chemistry, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution, Chowdariguda, Ghatkesar, Ranga Reddy 500088, India

J. K. Gupta
Institute of Pharmaceutical Research, GLA University Mathura, Bharthia, Uttar Pradesh, India

A. Chaitanya · A. Sahithi (✉)
Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution, Chowdariguda, Ghatkesar, Ranga Reddy 500088, India
e-mail: sahithi.a@pharma.nnrg.edu.in

P. Srinivasa Babu
Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, Andhra Pradesh 522213, India

Vamseekrishna. G.
Department of Pharmaceutical Analysis, NRI College of Pharmacy, Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh 521212, India

Y. Manikanta
School of Pharmaceutical Sciences, Velsinstitute of Science Technology and Advanced Studies (VISTAS), Pallavaram, Tamilnadu 600117, India

T. Sabu et al. (eds.), *Quantum Dots Based Nanocomposites*, Engineering Materials,
https://doi.org/10.1007/978-3-031-54779-9_2

photovoltaic technology, illumination, medical visualisation, and quantum information processing. The text also addresses the potential hazards linked to quantum dots, such as apprehensions regarding toxicity and ecological consequences.

1 Introduction

1.1 What Are Quantum Dots?

Quantum dots are incredibly small nanocrystals with sizes in the region of a few nanometers that are formed of semiconducting materials. They can be compared to synthetic atoms because of the distinct electrical and optical characteristics they display that are not present in their bulk counterparts [1]. Due to their tiny size, which causes the material's electrical characteristics to become quantized, quantum dots have peculiar properties [2]. Particularly, the quantization of the electronic energy levels occurs when a quantum dot is created and its electrons are constrained within a constrained area of space [3]. Due to this, discrete energy levels are created, and these levels are governed by the quantum dot's size, composition, and shape [4]. These energy levels are known as the "quantum confinement effect," and they give birth to a variety of intriguing features that may be tweaked and controlled by altering the quantum dot's size and make-up [5]. Optoelectronics is one of the most promising fields in which quantum dots can be used. In example, photovoltaic cells and highly efficient light-emitting diodes (LEDs) can be produced using quantum dots [6–8]. The colour of the light emitted by the LED may be precisely modified due to the controllable quantum dot size [9, 10]. Quantum dots can also be employed as down-converters to boost solar cells' efficiency by expanding the quantity of light that can be absorbed. Biomedicine is a promising area for using quantum dots. Quantum dots are fluorescent probes that can be utilised for imaging and disease diagnostics [11–13]. Due to their tiny size, quantum dots can enter cells and tissues and produce high-resolution photographs of biological structures. Quantum dots can also be functionalized with particular targeting molecules to bind to certain cells or tissues with a specific preference, enabling tailored drug administration [14]. Quantum dots are an exciting area of study that could revolutionise a variety of industries, including optoelectronics, healthcare, and energy [15–22]. Due to their special qualities, such as the quantum confinement effect, quantum dots are highly adaptable materials that can be tweaked and controlled to fit various needs [23]. They will therefore probably continue to play a significant role in many fields of science and technology going forward.

The distinctive characteristics and potential uses of quantum dots render them significant in both technological and research domains [24]. Nanoparticles of semiconductors can be accurately designed to exhibit distinct electronic and optical characteristics, rendering them advantageous in various domains such as optoelectronics,

biomedicine, and energy [14]. Quantum dots possess the potential to yield light-emitting diodes (LEDs) and photovoltaic cells with exceptional efficiency in the field of optoelectronics. Quantum dots possess the potential to enhance colour accuracy and diminish power consumption in displays and lighting applications due to their capability to emit light at highly specific wavelengths [25]. Furthermore, quantum dots possess the potential to serve as down-converters, thereby enhancing the efficacy of photovoltaic cells through the amplification of light absorption [26]. Quantum dots have been identified as potential fluorescent probes for imaging and diagnosis of diverse diseases in the field of biomedicine [27]. The diminutive dimensions of quantum dots facilitate their infiltration into tissues and cells, thereby affording high-fidelity visual representations of biological structures [28–30]. Furthermore, quantum dots possess the ability to be functionalized with particular targeting molecules, which can facilitate the selective binding to specific cells or tissues. This feature allows for the possibility of targeted drug delivery [16, 20, 31]. Quantum dots possess the potential to enhance the efficacy of solar cells by augmenting the extent of light absorption in the field of energy. Researchers have the ability to produce materials that can absorb light across a wide range of wavelengths by adjusting the size and composition of quantum dots [32]. Quantum dots hold significant importance in the realm of fundamental research in physics and materials science, in addition to their specific applications [33]. Quantum dots can be employed by researchers to investigate the conduct of electrons within a restricted area, thereby facilitating an enhanced comprehension of quantum mechanics and the emergence of novel materials and technologies [34]. Quantum dots possess distinctive characteristics and hold significant potential for utilisation in diverse domains, rendering them crucial in both technological and research contexts [35]. Nanoparticles possess the capability to bring about a significant transformation in domains such as optoelectronics, biomedicine, and energy. It is highly probable that they will persist in playing a crucial role in various fields of science and technology in the forthcoming years.

1.2 Early History of Quantum Dots

The inception of quantum dots can be traced back to the early 1980s, when the Russian physicist Alexei Ekimov and the American physicist Louis E. Brus conducted groundbreaking research in this field. In the year 1982, Ekimov made a discovery regarding small semiconductor crystals that were referred to as “zero-dimensional” entities. These crystals displayed quantum confinement effects that were not observable in bulk semiconductors [36]. In 1983, Brus made independent discoveries that yielded similar effects and subsequently introduced the term “quantum dots” to refer to these minute nanocrystals. The research conducted by Brus was centred on the optical characteristics of said materials, demonstrating that they discharged light at distinct wavelengths which were contingent on their dimensions. During the decades of 1980s and 1990s, scholars conducted further investigations on the characteristics of quantum dots and devised novel approaches for their synthesis and

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

manipulation. In 1994, a group of researchers from Bell Labs conducted a demonstration that showcased the potential of quantum dots in the development of light-emitting diodes (LEDs) with superior efficiency. This breakthrough discovery paved the way for novel applications in the field of optoelectronics. Subsequent to that time, scholars have achieved noteworthy progress in the production and analysis of quantum dots, resulting in novel implementations in the domains of biomedicine, energy, and other related areas [2]. Quantum dots represent a burgeoning field of study that is currently experiencing rapid growth, owing to their numerous potential applications and substantial commercial appeal [37–39].

Quantum mechanics underpins quantum confinement effects in quantum dots. Knowing electron behaviour in quantum dots requires knowing the wave-particle duality of matter and energy quantization in restricted systems. Electrons travel freely in a three-dimensional lattice structure in bulk semiconductor materials. Electrons can occupy any energy level in these continuous materials. However, nanoscale semiconductor materials restrict electron movement in all three dimensions. Electron energy levels are quantized by confinement, depending on the quantum dot's size and shape [40]. Quantized energy levels in quantum dots provide them unique features not found in bulk semiconductors. Quantum dots produce light at specified wavelengths depending on their size and shape, hence their emission spectra are crisp and narrow. Quantum dots are potential for LEDs and solar cells due to their emission spectrum tenability [41, 42]. The effective mass approximation and k-p approach are used to calculate quantum dot electron energy levels and wave functions. These models take into account quantum confinement, semiconductor crystal structure, and composition. Quantum physics predicts that electron energy levels become quantized in restricted systems, which underlies quantum confinement effects in quantum dots [17, 43, 44]. Quantization of energy levels in quantum dots produces unique electrical and optical features that have many uses in science and technology [45, 46].

The investigation of size-dependent properties of nanocrystals was initiated in the 1980s through early experimental studies. The phenomenon of the shift in absorption and emission spectra towards higher energies was observed by researchers in certain semiconductor nanocrystals, as the size of the nanocrystals decreased. The observed blue-shift in the spectra has been ascribed to the quantum confinement effect, which emerges from the confinement of electrons and holes within a limited volume of the nanocrystal [47]. The phenomenon in question leads to the quantization of energy levels of both electrons and holes, thereby causing alterations in the optical and electronic characteristics of the nanocrystals that are dependent on their size [48]. The initial investigations initiated a novel area of inquiry regarding the characteristics and prospective uses of nanocrystals. Apart from the blue-shifted absorption and emission spectra, the scholars also noted alterations in various characteristics of nanocrystals, including their magnetic behaviour and conductivity, which were dependent on their size. As particle size decreases in certain materials, such as gold and silver, the melting point exhibits a corresponding decrease [49]. The observed phenomenon, commonly referred to as "melting point depression", can be attributed to the heightened surface area-to-volume ratio of the particles. This characteristic renders the particles more vulnerable to surface melting and thermal

fluctuations [50]. Size-dependent properties of nanocrystals have been investigated, including their mechanical characteristics, such as hardness and ductility, as well as their catalytic activity in chemical reactions. The impact of the morphology and constitution of nanocrystals on their characteristics, as well as their interplay with other substances and biological systems, has been examined by scholars. In general, the initial experimental investigations concerning the size-dependent characteristics of nanocrystals have initiated a novel area of inquiry into the attributes and prospective uses of materials at the nanoscale. Currently, the investigation of nanocrystals and other nanomaterials is a swiftly expanding field of study with numerous potential applications in domains such as electronics, energy, biomedicine, and other related fields.

1.3 First Synthesis of Quantum Dots

Louis E. Brus and his team accomplished the initial prosperous amalgamation of quantum dots in 1984. The researchers employed solution-phase methodologies to produce colloidal quantum dots composed of semiconductors, specifically CdSe, CdTe, and CdS [51]. The process of synthesis entailed the introduction of precursors, namely cadmium and selenium, into a heated solution of a coordinating solvent, such as tri-n-octylphosphine oxide (TOPO) and trioctylphosphine (TOP). Subsequent to the reaction, a coordinating ligand, namely hexadecylamine (HDA), was introduced to serve as a capping agent with the purpose of regulating the dimensions and morphology of the quantum dots [52]. The quantum dots obtained exhibited a high degree of uniformity in size, superior quantum efficiency, and a robust luminescent property, rendering them a desirable candidate for a diverse array of applications. The triumph of this particular method of synthesis has paved the way for further exploration into the synthesis and characteristics of colloidal quantum dots. Currently, solution-phase synthesis is a frequently employed technique for the production of quantum dots, with numerous modifications and advancements implemented over time to enhance regulation of the quantum dots' size, shape, and characteristics. Brief explanation of the synthesis technique.

2 Key Contributions from Early Researchers

The initial investigators of quantum dots made significant advancements that facilitated their current utilisation in various domains. The identification of the quantum confinement effect stands out as a significant contribution. During the initial years of the 1980s, Alexei Ekimov and Louis E. Brus conducted research and made observations that revealed the absorption and emission spectra of specific semiconductor nanocrystals underwent a shift towards higher energies with a decrease in the size of the nanocrystals. The observed blue-shifted spectra can be explained by the quantum

confinement effect, which is a result of the confinement of electrons and holes within a limited volume of the nanocrystal. The phenomenon under consideration leads to the quantization of energy levels of both electrons and holes thereby causing alterations in the optical and electronic characteristics of the nanocrystals that are dependent on their size. The development of synthetic methods for quantum dots was deemed a significant contribution. The synthesis of colloidal quantum dots through solution-phase techniques was pioneered by Louis E. Brus and R. Murray. The techniques employed in this study entailed the introduction of precursor substances into a coordinating solvent, succeeded by the incorporation of a capping agent to regulate the dimensions and morphology of the quantum dots. The quantum dots that were produced exhibited a limited range of sizes, a high quantum yield, and robust luminescence, rendering them appealing for utilisation in a diverse array of applications. In the initial stages of research, quantum dots were subjected to diverse methodologies to determine their properties [53]. The optical properties of quantum dots were investigated using absorption and emission spectroscopy, while their structural properties were examined through X-ray diffraction and transmission electron microscopy. The researchers additionally examined the impacts of dimensions, morphology, and constitution on the characteristics of quantum dots. Early researchers have demonstrated the potential applications of quantum dots in various fields. The distinct optical and electronic characteristics of quantum dots were demonstrated by Paul Alivisatos and Moungi Bawendi, which could be utilised for various purposes including optoelectronics, sensing, and biolabeling [54]. The research conducted by the authors established the fundamental principles for the emergence of quantum dots as a distinct area of study, and facilitated their integration into a diverse array of contemporary applications. In brief the finds can be uttered like these:

- The quantum confinement effect was initially observed by early researchers. This phenomenon causes the energy levels of electrons and holes in a nanocrystal to become quantized. Consequently, the optical and electronic properties of the nanocrystal undergo size-dependent changes [55].
- The researchers additionally devised synthetic procedures for quantum dots through solution-phase methodologies, yielding nanocrystals characterised by a limited size range, elevated quantum efficiency, and robust luminescence.
- Quantum dots were characterised by early researchers through a range of techniques such as absorption and emission spectroscopy, X-ray diffraction, and transmission electron microscopy.
- The researchers conducted an investigation into the impact of quantum dot size, shape, and composition on their respective properties.
- The initial researchers exhibited the potential uses of quantum dots in domains such as optoelectronics, sensing, and biolabeling, thereby establishing the groundwork for their current utilisation in a diverse array of applications.

3 Advancements in Quantum Dot Synthesis

Various techniques have been devised for the production of quantum dots, each possessing unique merits and drawbacks. Several frequently employed techniques include:

1. The colloidal synthesis method is a commonly employed technique for the production of quantum dots in a liquid medium. The present technique involves the dissolution of precursors in a suitable solvent, subsequent to which a reducing agent and stabilising agent are introduced. Quantum dots are generated via a process of nucleation and growth.
2. The sol-gel synthesis technique entails the chemical reactions of hydrolysis and condensation of metal alkoxides in a solution, resulting in the formation of a substance with a gel-like consistency. Subsequently, the gel is subjected to a drying process and subsequently exposed to heat in order to generate the quantum dots.
3. The process of chemical vapour deposition entails the application of a slender layer of a precursor substance onto a substrate, succeeded by the reaction of the precursor with a reactant in the gas phase, resulting in the formation of quantum dots.
4. The electrochemical synthesis technique entails the deposition of metal ions onto a substrate while a reducing agent is present, resulting in the formation of quantum dots.
5. The process of plasma synthesis entails the utilisation of a plasma discharge to produce exceedingly reactive species that can interact with precursor gases, resulting in the formation of quantum dots.
6. The process of laser ablation entails utilising a laser beam to ablate a solid target, thereby producing plasma that can interact with a gas-phase reactant to create quantum dots.

Each of the aforementioned techniques possesses unique benefits and drawbacks with respect to regulating the dimensions, morphology, and chemical makeup of the quantum dots, as well as their potential for expansion and consistency in results. The selection of the appropriate technique is contingent upon the particular usage scenario and the intended characteristics of the quantum dots.

4 Discussion of the Role of Surface Chemistry in Quantum Dot Synthesis

Quantum dots are semiconductor materials at the nanoscale level that possess distinctive electronic and optical characteristics, rendering them exceedingly appealing for utilisation in various domains, including but not limited to biological imaging, optoelectronics, and energy. The process of synthesising quantum dots is intricate and

demands meticulous regulation of the nanocrystals' size, shape, and composition. The significance of surface chemistry in quantum dot synthesis cannot be overstated, as it has a profound impact on the growth kinetics, stability, and properties of the nanocrystals [56]. The manipulation of the surface chemistry of quantum dots can be achieved through the incorporation of ligands or surface coatings during the process of synthesis. The ligands exhibit an interaction with the surface of the quantum dots, thereby influencing their size, shape, and properties. Ligands serve multiple pivotal functions in the process of quantum dot fabrication [57]. Primarily, they function as capping agents that impede the agglomeration of quantum dots, which is a pivotal element in regulating the dimensions of the nanocrystals. The presence of ligands induces steric hindrance among the quantum dots, thereby constraining their capacity to approach one another and coalesce into aggregates. The growth kinetics of nanocrystals can be influenced by ligands, which have the ability to modulate the surface energy of quantum dots. The quantum dot's surface energy plays a crucial role in determining its propensity to accept atoms or molecules during the growth process, thereby influencing its size and morphology [58]. The modulation of surface energy through the use of ligands can effectively decelerate the rate of nanocrystal growth, ultimately resulting in the production of smaller and more homogenous particles. In addition, it should be noted that ligands have the potential to modify the surface charge of quantum dots, thereby affecting their stability and interactions with chemical or biological surroundings [4, 59–61]. The determination of nanoparticle stability in a solution is reliant on the crucial factor of surface charge. The manipulation of surface charge by ligands can establish a protective enclosure around quantum dots, thereby impeding their aggregation or interaction with other molecules present in the solution. The selection of ligands employed in the process of synthesis plays a crucial role in determining the surface chemistry of quantum dots [62]. This, in turn, has a significant impact on their properties and potential applications. Hydrophilic ligands, such as carboxylic acids or amines, can generate a water-soluble surface, which facilitates the utilisation of quantum dots in biological imaging and sensing applications. In contrast, ligands that exhibit hydrophobic properties have the ability to augment the stability of quantum dots in solvents that lack polarity, thereby conferring utility in optoelectronic domains.

Over the years, there have been notable developments in the production of quantum dots. Presented below is a concise summary of some of the principal progressions.

The initial methods of synthesising quantum dots involved colloidal synthesis and were accomplished in the early 1990s. Subsequently, additional methodologies, including sol-gel synthesis and chemical vapour deposition, were also established. The technique of size-tunable synthesis was developed by researchers in the late 1990s, which enabled accurate manipulation of the size of quantum dots. The aforementioned outcome was attained via alterations in the reaction parameters, including but not limited to adjustments in temperature, duration, and concentration of the precursor substances [63]. The development of high-quality synthesis methods in the early 2000s resulted in significant progress in the production of quantum dots with superior optical and electronic properties, as reported by researchers. The

aforementioned outcome was attained through the utilisation of materials with high levels of purity and the optimisation of synthesis conditions to reduce the occurrence of defects [64]. The development of quantum dots has garnered increasing attention in recent times, with a focus on utilising novel materials like perovskites and metal-organic frameworks. The aforementioned materials possess distinctive benefits, including elevated quantum yields and adjustable bandgaps [65]. The escalating demand for quantum dots across diverse applications has prompted a concentration on the advancement of large-scale synthesis techniques. Recent developments in this field encompass the implementation of continuous flow synthesis and microwave-assisted synthesis techniques.

5 Properties of Quantum Dots

The optical properties of quantum dots are dependent on their size, shape, and composition, which give rise to their distinctive characteristics. The quantization of energy levels arises due to the confinement of electrons and holes within a small volume in quantum dots, resulting in size-dependent properties. As the dimensions of the quantum dot decrease, the energy levels exhibit greater discreteness, leading to an increase in the bandgap and a corresponding shift in the absorption and emission spectra towards higher energies [66]. The phenomenon being referred to is commonly recognised as the quantum confinement effect. The surface area-to-volume ratio of a quantum dot is influenced by its size, which in turn affects its reactivity and stability, as well as its bandgap.

The properties of quantum dots can be significantly influenced by their shape [67–70]. Quantum dots that are anisotropic in nature, such as nanorods or nanowires, demonstrate absorption and emission spectra that are dependent on polarisation. This is attributed to the alignment of the dipoles along the longitudinal axis of the particle [71]. The electronic structure and optical properties of a quantum dot can be altered by its shape, resulting in modifications to its energy levels. Quantum dots possessing faceted geometries may manifest distinct surface terminations, thereby influencing their surface chemistry and stability.

The properties of a quantum dot can be significantly influenced by its composition, particularly its chemical makeup. The determination of the bandgap of a quantum dot is contingent upon the disparity in energy levels between the conduction and valence bands, a factor that is subject to the quantum dot's size and composition [72]. Cadmium-based quantum dots are known to demonstrate a greater bandgap in comparison to lead-based quantum dots of equivalent size. The chemical composition of a quantum dot can have a significant impact on its surface chemistry, thereby influencing its stability and reactivity.

The optical characteristics of quantum dots have garnered significant attention owing to their potential utility in diverse domains [73]. Quantum dots possess a narrow emission spectra and high quantum yields, rendering them suitable for deployment as fluorescent probes. Furthermore, the tunability of quantum dots' emission

spectra can be achieved through alterations in their size, shape, and composition, rendering them remarkably versatile [74]. Quantum dots possess the capability to be deliberately designed to emit at particular wavelengths within the visible or near-infrared spectrum, thereby rendering them advantageous for employment in imaging and sensing applications.

To summarise, the characteristics of quantum dots are significantly influenced by their dimensions, morphology, and chemical makeup. Comprehending the aforementioned characteristics holds paramount significance in customising quantum dots for particular uses in domains such as optoelectronics, biomedicine, and energy transformation. Furthermore, current investigations within the discipline are concentrated on enhancing the stability and quantum yield of quantum dots, while also delving into novel applications for these distinctive nanomaterials.

6 Overview of the Application of Quantum Dots in Various Fields

Semiconductor nanoparticles known as quantum dots possess distinctive electronic and optical characteristics that render them highly advantageous instruments across a range of disciplines. Nanocrystals are commonly composed of materials like cadmium selenide, cadmium telluride, and indium arsenide, and exhibit a size distribution ranging from a few to several hundred nanometers. The field of optoelectronics has witnessed a significant utilisation of quantum dots. Quantum dots possess distinctive optical characteristics owing to their high surface-to-volume ratio, which is attributed to their diminutive size. Particularly, they possess the ability to produce light at exact wavelengths, rendering them suitable for implementation in superior quality screens, light-emitting diodes, and photovoltaic cells. The capacity of emitting light in various hues, coupled with their elevated luminosity, renders them advantageous in the context of illuminative purposes. Quantum dots have the potential to serve as a labelling tool for biological molecules and cells in the field of biological imaging, thereby facilitating their visualisation and monitoring. Compared to conventional organic dyes, they present various benefits, including enhanced luminosity, improved resistance to photodegradation, and narrower emission spectra. Moreover, the diminutive dimensions of quantum dots render them capable of infiltrating tissues to a significant extent, thereby rendering them well-suited for deployment in the realm of in vivo imaging. The utilisation of quantum dots in the domain of energy production is currently under investigation. Quantum dots have the ability to absorb a wider spectrum of light wavelengths in comparison to conventional solar cells, thereby enhancing their capacity to transform solar energy into electrical energy. Furthermore, quantum dots exhibit promising prospects for utilisation in energy storage systems, including batteries and supercapacitors. Quantum dots are currently under investigation in the realm of information technology due to their potential to serve as qubits, which are fundamental units in the construction of quantum computers.

The utilisation of quantum dots is applicable in the advancement of memory and data storage devices that possess high-speed and high-capacity capabilities. Quantum dots exhibit potential for utilisation in sensing and detection applications. These devices have the capability to function as sensors for detecting alterations in environmental factors such as temperature, pressure, and others. Furthermore, they have the capability to detect and distinguish diverse categories of molecules such as biomolecules, contaminants, and explosives. Quantum dots exhibit distinctive electronic and optical characteristics that render them highly favourable for diverse applications spanning multiple domains. Anticipated progress in research endeavours is poised to yield noteworthy breakthroughs in the utilisation and creation of these nanoparticles across domains encompassing energy, healthcare, and information technology.

7 Quantum Dot Technology

The distinct characteristics exhibited by quantum dots have resulted in their utilisation across a diverse array of technological domains (Fig. 1). The principal implementations of quantum dots are as follows.

Quantum dots have found extensive application in the realm of display technology, particularly in LED backlit displays. The utilisation of these elements results in the

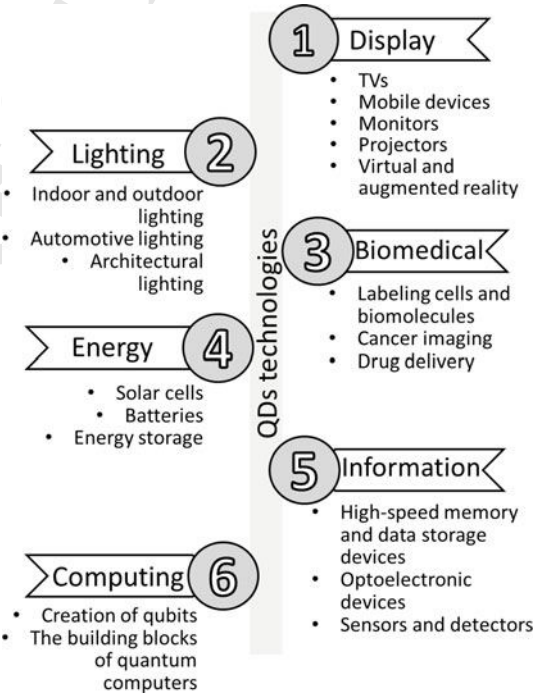


Fig. 1 Various types of applications of QDs nanoparticles

generation of hues that are more pronounced, accompanied by an elevated degree of luminosity and differentiation [75]. Conventional LED displays typically employ white LEDs in conjunction with colour filters to generate diverse hues; however, this approach may lead to energy dissipation and a reduced range of colours. In contrast, displays utilising quantum dots employ blue light emitting diodes (LEDs) in conjunction with quantum dots that generate red and green light upon being stimulated by the blue light source. The outcome of this is an expanded range of colours and a display that consumes less energy.

Quantum dots exhibit distinctive optical characteristics that render them valuable for medical imaging purposes. Fluorescent tags can be utilised for the purpose of identifying and tracking particular cells or molecules within the human body. Quantum dots possess the ability to be tailored to emit light at precise wavelengths, rendering them highly suitable for imaging purposes that necessitate superior resolution and sensitivity [76]. Furthermore, they are currently under development as contrast agents to facilitate more accurate imaging of neoplasms and other anomalous tissues.

The utilisation of quantum dots is being explored as a means of enhancing the efficacy of solar cells through the capture of a wider range of light wavelengths, which can subsequently be converted into electrical energy [77]. Solar cells conventionally comprise crystalline silicon and possess a limited capacity to absorb light wavelengths. The incorporation of quantum dots into the solar cell enables the capture of a wider range of light wavelengths, thereby facilitating the conversion of light energy into electrical energy [49]. The utilisation of quantum dots in conjunction with other materials has the potential to yield multi-junction solar cells that exhibit superior levels of efficiency.

Quantum dots have the potential to serve as qubits within quantum computing frameworks. Qubits serve as the fundamental units of quantum computers and possess the ability to exist in numerous states concurrently, thereby facilitating expedited processing as compared to conventional computers. Quantum dots exhibit extended coherence times and are amenable to facile manipulation, rendering them a propitious substrate for constructing quantum computers on a macroscopic scale.

Quantum dots are currently being utilised in the development of energy-efficient lighting solutions that offer superior quality [16, 49, 69]. Light-emitting diodes (LEDs) have the potential to serve as a substitute for conventional fluorescent or incandescent bulbs, as they are capable of emitting light with a broader spectrum of colours and a greater luminosity. Quantum dot lighting possesses the added benefit of enhanced energy efficiency, thereby resulting in considerable cost reductions in the long run.

Quantum dots are currently under development for various biotechnology purposes such as drug delivery, biomolecule detection, and disease diagnosis. Nanoparticles possess the capability to selectively target particular cells or molecules, thereby rendering them a potent instrument in the realm of nanomedicine. Quantum dots possess the capability of being tailored to selectively bind with particular proteins or nucleic acids, thereby enabling their application in the detection of biomolecules or diagnosis of diseases.

In general, quantum dots exhibit a broad spectrum of potential applications across diverse domains, and continued scientific inquiry and innovation is anticipated to yield further compelling utilities in the times ahead. Quantum dots possess distinctive characteristics that render them highly adaptable and multifaceted, thereby positioning them as a technology with considerable potential for diverse applications.

The field of optoelectronics has shown interest in utilising quantum dots due to their distinctive optical characteristics. Quantum dots exhibit a quantized energy spectrum owing to their diminutive size, resulting in the emission of light at distinct wavelengths. The aforementioned characteristic renders them highly suitable for utilisation in light-emitting diodes and laser devices, wherein meticulous regulation of the emanated wavelengths holds paramount significance. Quantum dots exhibit a broad absorption spectrum, enabling them to capture light across a diverse range of wavelengths. The aforementioned characteristic holds practical significance in down-conversion scenarios, wherein photons with high energy levels are transformed into photons with lower energy levels that can be assimilated by conventional semiconductor materials, such as silicon.

Furthermore, quantum dot light-emitting diodes (QLEDs) possess the capability to offer superior visual displays featuring an extensive range of colours. Quantum dots have the capability to emit light across a diverse range of colours, encompassing those within the visible spectrum. Quantum dot light-emitting diodes (LEDs) exhibit high efficiency and are capable of generating vivid and intense hues, rendering them a compelling substitute for conventional LEDs in lighting and display contexts.

Quantum dots have been identified as a potential material for advanced solar cells owing to their distinctive characteristics. Quantum dots possess a significant benefit in their ability to effectively absorb light across a wide spectrum of wavelengths. This implies that the light-capturing capacity of conventional semiconductor materials, such as silicon, is restricted to a limited range of wavelengths, whereas the aforementioned materials can capture a broader spectrum of light. Furthermore, quantum dots possess the capability to function as down-converting layers. This feature facilitates the enhancement of the light-capturing capacity of conventional silicon solar cells by transforming high-energy photons into lower-energy photons that can be assimilated by silicon.

Quantum dots possess the capability to enhance the efficacy of solar cells by enabling them to apprehend light in the infrared segment of the spectrum, which is beyond the reach of silicon-based solar cells. The reason for this is that quantum dots can be customised to possess a band gap that can be adjusted to the targeted wavelength spectrum. The integration of quantum dots into photovoltaic cells is being investigated by scholars as a means of enhancing their efficacy and diminishing the expense of solar power.

The utilisation of quantum dots as qubits, which are the fundamental units of quantum computers, is a viable option in the field of quantum computing. The utilisation of the spin of an electron in a quantum dot as a qubit and the exploitation of the quantum properties of these systems for the purpose of executing quantum computations can be achieved. The scalability of quantum dots and their compatibility with current semiconductor manufacturing processes make them a promising

technology. This implies that they possess the capability of being manufactured in significant quantities and incorporated into pre-existing electronic apparatus.

Nevertheless, there are still obstacles to be overcome with regards to preserving the consistency of the qubits for extended durations. The reason for the susceptibility of qubits to decoherence is attributed to the high sensitivity of quantum dots to their surrounding environment, whereby any form of noise or fluctuations can result in the loss of coherence. Scholars are currently engaged in the development of methodologies aimed at regulating the ambient conditions surrounding quantum dots, with the objective of mitigating the deleterious effects of noise on their operational efficacy.

The distinctive optical characteristics of quantum dots render them a desirable option for application in the fields of biotechnology and medical imaging. Fluorescent probes have the potential to serve as tracking agents for cellular or molecular movements within biological systems. Quantum dots exhibit exceptional stability and emit bright and persistent light, rendering them a highly suitable option for various imaging applications. Moreover, quantum dots have the potential to serve as contrast agents in medical imaging, offering superior resolution and heightened sensitivity in comparison to conventional imaging techniques.

Quantum dots possess potential for utilisation in drug delivery and therapeutic applications. Due to their diminutive dimensions, nanoparticles possess the ability to infiltrate cells and tissues. Additionally, their surface can be modified with targeting molecules, thereby enabling the transportation of therapeutic agents or drugs to precise cells or tissues.

Quantum dots exhibit potential applications in diverse fields including catalysis, sensing, and data storage performance in various chemical reactions. The electronic and optical properties of nanoparticles, which are dependent on their size, have been found to have a significant impact on their catalytic activity. As a result, they have been employed as catalysts in a variety of chemical reactions.

8 Commercialization of Quantum Dots

The inception of quantum dots' commercialization dates back to the latter part of the 1990s. Subsequently, there has been a notable surge in their manufacturing and utilisation. Quantum dots are extensively utilised in display technology as a primary application, facilitating the creation of energy-efficient and high-quality displays. Quantum dots have been employed in medical imaging due to their ability to selectively bind to particular tissues and produce more precise images compared to conventional imaging methods. Quantum dots have recently gained traction in the realm of quantum computing as a potential application, serving as fundamental units or qubits for quantum computers. The potential application of quantum dots in solar cells is currently under investigation, with the aim of enhancing the efficiency of the cells and decreasing the expenses associated with solar energy production. The commercialization of quantum dots has encountered various obstacles, such as the exorbitant

expenses associated with their manufacturing and apprehensions regarding their plausible toxicity. Notwithstanding the challenges, scholars and enterprises are endeavouring to surmount them by devising novel production techniques and investigating measures to enhance the safety of quantum dots for human utilisation.

The process of commercialising quantum dots has been in progress for a number of years, and it is anticipated that the quantum dots market will experience substantial growth in the near future. Several prominent corporations are engaged in the process of commercialising quantum dots.

1. Nanosys is a prominent enterprise that specialises in the advancement and monetization of quantum dots. The corporation provides a variety of display technology products, such as quantum dot films, LED backlights, and colour conversion layers.
2. QD Vision is a prominent enterprise that specialises in the advancement and dissemination of quantum dots. The corporation provides quantum dot merchandise that caters to display technology, lighting, and biomedical applications.
3. Samsung is a significant participant in the market for quantum dot displays. The QLED (Quantum Dot LED) technology employed by the company is utilised in its premium-grade televisions and monitors.
4. LG is a significant participant in the quantum dot display industry. The NanoCell TVs manufactured by the company utilise quantum dot technology to augment colour precision and luminosity.
5. Quantum Materials Corp is a corporation that specialises in the research, development, and manufacturing of quantum dots for a wide range of applications, including but not limited to display, lighting, solar cells, and biomedical imaging.
6. Crystalplex Corporation is a specialised enterprise that focuses on the advancement of quantum dots for the purpose of biomedical imaging and diagnostics.
7. NN-Labs is a corporation that specialises in the production of top-notch quantum dots for various purposes such as LED illumination, display technology, and biomedical imaging.
8. Ocean NanoTech is a commercial enterprise that specialises in the manufacture and distribution of quantum dots, which are utilised in various fields such as imaging, diagnostics, and sensing.
9. Quantum Solutions is a corporation that specialises in the production of top-tier quantum dots utilised in various applications, including but not limited to solar cells, LED lighting, and display technology.

Other leading companies are also in market which is depicted in Table 1.

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Table 1 Different companies those are working in quantum dots and their focus on the market

Company	Industry	Focus
IBM	Computing	Quantum computing
Google	Computing	Quantum computing
Microsoft	Computing	Quantum computing
Rigetti Computing	Computing	Quantum computing
IonQ	Computing	Quantum computing
Honeywell	Computing	Quantum computing
PsiQuantum	Computing	Quantum computing
Cambridge Quantum Computing	Computing	Quantum computing
Zapata Computing	Computing	Quantum software
Xanadu	Computing	Quantum computing and photonics
Q-CTRL	Computing	Quantum control
Atom Computing	Computing	Neutral atom quantum computing
D-Wave Systems	Computing	Quantum computing (quantum annealing)
Airbus	Aerospace	Quantum computing, communication and sensing
Lockheed Martin	Aerospace	Quantum computing, communication and sensing
Honeywell Quantum Solutions	Aerospace	Quantum computing, communication and sensing
Qrypt	Cybersecurity	Quantum key distribution
ID Quantique	Cybersecurity	Quantum key distribution
Crypta Labs	Cybersecurity	Quantum random number generators
Toshiba	Electronics	Quantum communication and encryption
Alibaba Group	Cloud services	Quantum computing
Amazon Web Services	Cloud services	Quantum computing
IBM Q Network	Network	Collaborative quantum computing
QuTech	Academic/research	Quantum computing
Max Planck Institute	Academic/research	Quantum computing, communication and sensing
University of Oxford	Academic/research	Quantum computing
University of Waterloo	Academic/research	Quantum computing
Harvard Quantum Initiative	Academic/research	Quantum computing
Nanosys	Materials science	Quantum dot films for display technology
QD Vision	Materials science	Quantum dots for display technology and lighting

(continued)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Table 1 (continued)

Company	Industry	Focus
Quantum Materials Corp	Materials science	Quantum dots for display technology, solar cells, and biomedical imaging
NN-Labs	Materials science	Quantum dots for led lighting, display technology, and biomedical imaging
Ocean NanoTech	Materials science	Quantum dots for biomedical imaging, diagnostics, and sensing
Crystalplex Corporation	Biotechnology	Quantum dots for biomedical imaging and diagnostics

9 Challenges and Opportunities in the Commercialization of Quantum Dots

Quantum dots exhibit several characteristics that render them a highly favourable material for a diverse array of applications, such as optoelectronics, biotechnology, and energy harvesting. Notwithstanding, there exist a number of obstacles and prospects that necessitate resolution in order to effectively bring quantum dots to market.

Challenges:

The commercialization potential of quantum dots is limited due to the relatively high production cost of producing high-quality ones. The elevated expense can be attributed to the intricate process of synthesis, utilisation of costly initial components, and the requirement for specialised equipment. The presence of heavy metals, such as cadmium, in certain quantum dots has raised concerns regarding their potential toxicity during production and use. The development of non-toxic and biocompatible quantum dots is imperative for their effective utilisation in biomedical applications. The long-term stability of quantum dots is limited due to their susceptibility to degradation, which ultimately impacts their performance. The cause of this instability can be attributed to various factors, including exposure to light, oxygen, and temperature fluctuations. This presents a notable obstacle that must be overcome in order to facilitate the commercialization of these products.

Opportunities:

Quantum dots exhibit distinctive optical characteristics that render them advantageous for various optoelectronic applications, including but not limited to display technology, lighting, and solar cells. Quantum dot displays exhibit superior colour gamut, colour accuracy, and energy efficiency in comparison to conventional LCD displays. The field of biotechnology has shown great potential in utilising quantum dots as effective instruments for biomedical imaging and drug delivery. Quantum dots possess high luminosity and stability, and their emission characteristics can be adjusted to precise wavelengths, rendering them valuable for visualising particular

biological structures and functions. Quantum dots possess the capability to absorb light across a broad spectrum of wavelengths, rendering them a viable option for solar energy harvesting. These can be utilised to augment the efficacy of photovoltaic cells, and to fabricate novel substances for energy retention.

To summarise, the commercialization of quantum dots encounters various obstacles such as high production expenses, apprehensions regarding toxicity, and durability. Quantum dots have emerged as a promising material for a diverse array of applications, including optoelectronics, biotechnology, and energy harvesting, presenting significant opportunities in these fields. The realisation of the complete potential of quantum dots in the future will necessitate the resolution of challenges and the development of novel applications.

10 Future of Quantum Dots

The particular optical, electrical, and physical characteristics of quantum dots render them a propitious domain of investigation. Quantum dots are utilised in optoelectronics for various purposes, including but not limited to display technology, lighting, and solar cells. Ongoing research endeavours are focused on enhancing the performance and efficiency of quantum dot displays, exploring novel lighting technologies, and optimising the efficacy of solar cells. Quantum dots exhibit promising potential in the realm of biomedical applications, specifically in the areas of drug delivery and imaging. Scholars are currently exploring methods to enhance the biocompatibility of quantum dots and mitigate their toxicity. Additionally, they are devising novel imaging techniques and targeting strategies for drug administration. Quantum dots exhibit promise in the realm of quantum computing owing to their capacity to confine and manoeuvre individual electrons. Scholars are currently investigating potential applications of quantum dots in the development of qubits, which serve as the fundamental building blocks of quantum information, with the aim of enhancing the efficacy of quantum computing platforms. Quantum dots have potential applications in energy storage, including but not limited to batteries and capacitors. Ongoing research endeavours are focused on the development of novel materials and devices for the purpose of energy storage, utilising quantum dots. Quantum dots exhibit potential applications in the realm of environmental monitoring and remediation, including the detection of pollutants and the augmentation of water purification processes. Ongoing research endeavours are focused on the development of novel sensing and treatment technologies utilising quantum dots. In recent decades, scholars have achieved notable advancements in comprehending the conduct of quantum dots and devising novel techniques for their amalgamation and integration into apparatus. The following discourse outlines potential advancements and future trajectories in the realm of quantum dot research and its practical applications. Quantum dot sensors have been employed for the detection of minute variations in temperature, pressure, and magnetic fields. Currently, scholars are investigating the potential of quantum dots as biosensors for the identification of biomolecules, including proteins and DNA.

The potential applications of these biosensors encompass medical diagnostics and drug discovery. The utilisation of quantum dots in solar cells has been shown to increase their efficacy by augmenting light absorption and subsequent conversion into electrical energy. Scientists are currently engaged in enhancing the reliability and expandability of solar cells that are based on quantum dots, with the aim of rendering them feasible for commercial purposes. The utilisation of quantum dots as qubits in quantum computing is a promising avenue for exploration. Quantum dots are being investigated by researchers as a potential foundation for constructing quantum computers that exhibit greater stability and scalability in comparison to alternative qubit configurations. Quantum dot-based light-emitting diodes (LEDs) have been developed as a promising solution for efficient and adjustable lighting and display applications. Scholars are currently engaged in enhancing the effectiveness and chromatic accuracy of light-emitting diodes that utilise quantum dots, with the aim of rendering them comparable to conventional LEDs. Quantum dots have the potential to serve as memory devices in electronic systems. Quantum dots are being investigated by scholars as a potential non-volatile memory storage alternative that can be downsized to dimensions smaller than those of existing memory technologies. To attain these advancements and fully exploit the capabilities of quantum dots, it is imperative for researchers to enhance their comprehension of the fundamental physics of quantum dots and devise novel techniques for their synthesis and integration into devices. Furthermore, the progression of fabrication and manufacturing methodologies will play a crucial role in the expansion of quantum dot-centered devices for commercial purposes.

11 Conclusion

The potential application of quantum dots in solid-state lighting, specifically in LED lights, is a noteworthy impact. The utilisation of quantum dots as colour conversion agents enables the generation of white light that exhibits superior energy efficiency and colour rendering characteristics in comparison to conventional lighting sources.

Quantum dots are currently being investigated in the realm of biology and medicine due to their potential applications in targeted drug delivery and gene therapy. Biological molecules can be applied as a coating to enable targeted delivery of drugs or genes to affected cells or tissues, thereby minimising the risk of unintended impacts. Quantum dots possess the capability to transform the domain of quantum cryptography by facilitating the creation and transmission of secure quantum keys for data encryption. Similar to other nascent technologies, quantum dots present certain potential hazards, including apprehensions regarding toxicity and ecological consequences. Scholars are currently investigating methods to tackle these issues and guarantee the secure and ethical advancement of quantum dot technology. To conclude, quantum dots represent an intriguing and auspicious realm of investigation that harbours the possibility of transforming diverse domains of science and technology. Due to their distinctive characteristics and adaptability, they are deemed

indispensable instruments for scientists and professionals who are engaged in the advancement of novel applications and technologies.

References

1. Bacon, M., Bradley, S.J., Nann, T.: Graphene quantum dots. Part. Part. Syst. Charact. **31**(4), 415–428 (2014)
2. Ganguly, S., et al.: Advancement in science and technology of carbon dot-polymer hybrid composites: a review. Funct. Compos. Struct. **1**(2), 022001 (2019)
3. Mansur, H.S.: Quantum dots and nanocomposites. Wiley Interdisc. Rev. Nanomed. Nanobiotechnol. **2**(2), 113–129 (2010)
4. Das, P., et al.: Heteroatom doped photoluminescent carbon dots for sensitive detection of acetone in human fluids. Sens. Actuators, B Chem. **266**, 583–593 (2018)
5. Semonin, O.E., Luther, J.M., Beard, M.C.: Quantum dots for next-generation photovoltaics. Mater. Today **15**(11), 508–515 (2012)
6. Bozyigit, D., Yarema, O., Wood, V.: Origins of low quantum efficiencies in quantum dot LEDs. Adv. Func. Mater. **23**(24), 3024–3029 (2013)
7. Latief, U., et al.: Luminescent Manganese/Europium doped ZnS quantum dots: tunable emission and their application as fluorescent sensor. J. Alloy. Compd. **910**, 164889 (2022)
8. Mukherjee, C., et al.: Layered T full adder using quantum-dot cellular automata. In: 2015 IEEE International Conference on Electronics, Computing and Communication Technologies (CONECCT). IEEE (2015)
9. Piloto, A.M.L., et al.: Cellulose-based hydrogel on quantum dots with molecularly imprinted polymers for the detection of CA19-9 protein cancer biomarker. Microchim. Acta **189**(4), 134 (2022)
10. Ahmed, S.R., et al.: Target specific aptamer-induced self-assembly of fluorescent graphene quantum dots on palladium nanoparticles for sensitive detection of tetracycline in raw milk. Food Chem. **346**, 128893 (2021)
11. Sol-Fernández, D., et al.: Digging on the application of novel rod-like particles of polydopamine-CdTe quantum dots for photohermal cancer therapy (2021)
12. Reimann, S.M., Manninen, M.: Electronic structure of quantum dots. Rev. Mod. Phys. **74**(4), 1283 (2002)
13. Kouwenhoven, L.P., Austing, D., Tarucha, S.: Few-electron quantum dots. Rep. Prog. Phys. **64**(6), 701 (2001)
14. Bailey, R.E., Smith, A.M., Nie, S.: Quantum dots in biology and medicine. Phys. E **25**(1), 1–12 (2004)
15. Bonilla, J.C., et al.: Applications of quantum dots in food science and biology. Trends Food Sci. Technol. **53**, 75–89 (2016)
16. Das, P., et al.: Carbon dot biopolymer-based flexible functional films for antioxidant and food monitoring applications. ACS Appl. Polym. Mater. **4**(12), 9323–9340 (2022)
17. Das, P., et al.: Tailor made magnetic nanolights: fabrication to cancer theranostics applications. Nanosc. Adv. **3**(24), 6762–6796 (2021)
18. Das, P., et al.: Carbon-dots-initiated photopolymerization: an in situ synthetic approach for MXene/poly (norepinephrine)/copper hybrid and its application for mitigating water pollution. ACS Appl. Mater. Interfaces **13**(26), 31038–31050 (2021)
19. Rajabzadeh, A.R., et al.: Magnetic Quantum Dots for Bioimaging. CRC Press (2023)
20. Das, P., et al.: Waste-derived sustainable fluorescent nanocarbon-coated breathable functional fabric for antioxidant and antimicrobial applications. ACS Appl. Mater. Interfaces (2023)
21. Das, P., et al.: MXene/0D nanocomposite architectures: design, properties and emerging applications. Mater. Today Nano **24**, 100428 (2023)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

22. Das, P., et al.: Naturally derived carbon dots in situ confined self-healing and breathable hydrogel monolith for anomalous diffusion-driven phytomedicine release. ACS Appl. Bio Mater. **5**(12), 5617–5633 (2022)
23. Das, P., et al.: One-step synthesis of fluorescent carbon dots for bio-labeling assay. In: Macromolecular Symposia. Wiley Online Library (2018)
24. Jamieson, T., et al.: Biological applications of quantum dots. Biomaterials **28**(31), 4717–4732 (2007)
25. Jelinek, R.: Carbon Quantum Dots, pp. 29–46. Carbon quantum dots. Springer International Publishing, Cham (2017)
26. Lent, C.S., Tougaw, P.D.: A device architecture for computing with quantum dots. Proc. IEEE **85**(4), 541–557 (1997)
27. Van Dam, J.A., et al.: Supercurrent reversal in quantum dots. Nature **442**(7103), 667–670 (2006)
28. Parak, W.J., Pellegrino, T., Plank, C.: Labelling of cells with quantum dots. Nanotechnology **16**(2), R9 (2005)
29. Shiohara, A., et al.: On the cyto-toxicity caused by quantum dots. Microbiol. Immunol. **48**(9), 669–675 (2004)
30. Güçlü, A.D., et al.: Graphene Quantum Dots. Springer (2014)
31. Das, P., et al.: Carbon dots for heavy-metal sensing, pH-sensitive cargo delivery, and antibacterial applications. ACS Appl. Nano Mater. **3**(12), 11777–11790 (2020)
32. Tian, P., et al.: Graphene quantum dots from chemistry to applications. Mater. Today Chem. **10**, 221–258 (2018)
33. Smith, A.M., Nie, S.: Next-generation quantum dots. Nat. Biotechnol. **27**(8), 732–733 (2009)
34. Bimberg, D., Pohl, U.W.: Quantum dots: promises and accomplishments. Mater. Today **14**(9), 388–397 (2011)
35. Das, P., et al.: Dual doped biocompatible multicolor luminescent carbon dots for bio labeling, UV-active marker and fluorescent polymer composite. Luminescence **33**(6), 1136–1145 (2018)
36. Bawendi, M.G., Steigerwald, M.L., Brus, L.E.: The quantum mechanics of larger semiconductor clusters ("quantum dots"). Annu. Rev. Phys. Chem. **41**(1), 477–496 (1990)
37. Ganguly, S., et al.: Microwave-synthesized polysaccharide-derived carbon dots as therapeutic cargoes and toughening agents for elastomeric gels. ACS Appl. Mater. Interfaces **12**(46), 51940–51951 (2020)
38. Ganguly, S., et al.: Microwave assisted green synthesis of Zwitterionic photolumenescent N-doped carbon dots: an efficient 'on-off' chemosensor for tracer Cr (+ 6) considering the inner filter effect and nano drug-delivery vector. Colloids Surf. A **579**, 123604 (2019)
39. Saravanan, A., et al.: Green synthesis of multifunctional carbon dots with antibacterial activities. Nanomaterials **11**(2), 369 (2021)
40. Dai, X., et al.: Solution-processed, high-performance light-emitting diodes based on quantum dots. Nature **515**(7525), 96–99 (2014)
41. Ganguly, S., et al.: Strongly blue-luminescent N-doped carbogenic dots as a tracer metal sensing probe in aqueous medium and its potential activity towards in situ Ag-nanoparticle synthesis. Sens. Actuators, B Chem. **252**, 735–746 (2017)
42. Liu, Z., et al.: Micro-light-emitting diodes with quantum dots in display technology. Light Sci. Appl. **9**(1), 83 (2020)
43. Sun, Q., et al.: Bright, multicoloured light-emitting diodes based on quantum dots. Nat. Photon. **1**(12), 717–722 (2007)
44. Das, P., et al.: Graphene based emergent nanolights: a short review on the synthesis, properties and application. Res. Chem. Intermed. **45**, 3823–3853 (2019)
45. Ahmed, S.R., et al.: Graphdiyne quantum dots for H2O2 and dopamine detection. ACS Appl. Nano Mater. **6**(10), 8434–8443 (2023)
46. Maity, P.P., et al.: Capra cartilage-derived peptide delivery via carbon nano-dots for cartilage regeneration. Front. Bioeng. Biotechnol. **11** (2023)
47. Zhao, G., et al.: Orbital mixing between colloidal quantum dots and surface-bound molecules. J. Phys. Chem. Lett. **13**(51), 11892–11898 (2022)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

48. Xu, Q., et al.: Recent progress of quantum dots for energy storage applications. Carbon Neutrality **1**(1), 13 (2022)
49. Abdellatif, A.A., et al.: Biomedical applications of quantum dots: overview, challenges, and clinical potential. Int. J. Nanomed. 1951–1970 (2022)
50. Rainò, G., et al.: Ultra-narrow room-temperature emission from single CsPbBr 3 perovskite quantum dots. Nat. Commun. **13**(1), 2587 (2022)
51. Efros, A.L., Brus, L.E.: Nanocrystal quantum dots: from discovery to modern development. ACS Nano **15**(4), 6192–6210 (2021)
52. Raja, A., et al.: Energy transfer from quantum dots to graphene and MoS2: the role of absorption and screening in two-dimensional materials. Nano Lett. **16**(4), 2328–2333 (2016)
53. Shirasaki, Y., et al.: Emergence of colloidal quantum-dot light-emitting technologies. Nat. Photon. **7**(1), 13–23 (2013)
54. Somers, R.C., Bawendi, M.G., Nocera, D.G.: CdSe nanocrystal based chem-/bio-sensors. Chem. Soc. Rev. **36**(4), 579–591 (2007)
55. Ramalingam, G., et al.: Quantum Confinement. IntechOpen (2020)
56. Hines, D.A., Kamat, P.V.: Recent advances in quantum dot surface chemistry. ACS Appl. Mater. Interfaces **6**(5), 3041–3057 (2014)
57. Kilina, S.V., Tamukong, P.K., Kilin, D.S.: Surface chemistry of semiconducting quantum dots: theoretical perspectives. Acc. Chem. Res. **49**(10), 2127–2135 (2016)
58. Bilan, R., et al.: Quantum dot surface chemistry and functionalization for cell targeting and imaging. Bioconjug. Chem. **26**(4), 609–624 (2015)
59. Ganguly, S., et al.: Sonochemical green reduction to prepare Ag nanoparticles decorated graphene sheets for catalytic performance and antibacterial application. Ultrason. Sonochem. **39**, 577–588 (2017)
60. Das, P., et al.: Surface quaternized nanosensor as a one-arrow-two-hawks approach for fluorescence turn “on–off–on” bifunctional sensing and antibacterial activity. New J. Chem. **43**(16), 6205–6219 (2019)
61. Ganguly, S., Margel, S.: Bioimaging probes based on magneto-fluorescent nanoparticles. Pharmaceutics **15**(2), 686 (2023)
62. Devi, S., et al.: Quantum dots: an emerging approach for cancer therapy. Front. Mater. **8**, 798440 (2022)
63. Bukowski, T.J., Simmons, J.H.: Quantum dot research: current state and future prospects. Crit. Rev. Solid State Mater. Sci. **27**(3–4), 119–142 (2002)
64. Coe-Sullivan, S.: Quantum dot developments. Nat. Photonics **3**(6), 315–316 (2009)
65. Winnik, F.M., Maysinger, D.: Quantum dot cytotoxicity and ways to reduce it. Acc. Chem. Res. **46**(3), 672–680 (2013)
66. Lim, S.Y., Shen, W., Gao, Z.: Carbon quantum dots and their applications. Chem. Soc. Rev. **44**(1), 362–381 (2015)
67. Ganguly, S., Margel, S.: Fluorescent quantum dots-based hydrogels: Synthesis, Fabrication and multimodal biosensing. Talanta Open 100243 (2023)
68. Ganguly, S.: Reinforcement mechanisms of quantum dot-polymer composites. In: Quantum Dots and Polymer Nanocomposites, pp. 151–169. CRC Press (2022)
69. Ganguly, S.: 13 Challenges prospects of and magnetic future quantum dots. Magnetic Quantum Dots for Bioimaging 269 (2023)
70. Das, P., et al.: Converting waste Allium sativum peel to nitrogen and sulphur co-doped photoluminescence carbon dots for solar conversion, cell labeling, and photobleaching diligences: a path from discarded waste to value-added products. J. Photochem. Photobiol. B. **197**, 111545 (2019)
71. Jang, E., Jang, H.: Quantum dot light-emitting diodes. Chem. Rev. **123**(8), 4663–4692 (2023)
72. Liu, S.-F., et al.: 3D nanoprinting of semiconductor quantum dots by photoexcitation-induced chemical bonding. Science **377**(6610), 1112–1116 (2022)
73. Wu, X.-G., et al.: Industry outlook of perovskite quantum dots for display applications. Nat. Nanotechnol. **17**(8), 813–816 (2022)

74. Karagianni, A., et al.: Application of carbon-based quantum dots in photodynamic therapy. Carbon **203**, 273–310 (2023)
75. Manikandan, V., Lee, N.Y.: Green synthesis of carbon quantum dots and their environmental applications. Environ. Res. **212**, 113283 (2022)
76. Kaur, A., et al.: Nanocomposites of carbon quantum dots and graphene quantum dots: environmental applications as sensors. Chemosensors **10**(9), 367 (2022)
77. Deng, S., et al.: Rational design of $ZnMn_2O_4$ quantum dots in a carbon framework for durable aqueous zinc-ion batteries. Angew. Chem. **134**(12), e202115877 (2022)

602599_1_En_2_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 24 Layout: T1-Standard

Author Queries

Chapter 2

Query Refs.	Details Required	Author's response
AQ1	Please check and confirm if the author names and initials are correct.	
AQ2	Please confirm if the section headings identified are correct.	

Metadata of the chapter that will be visualized in SpringerLink

Book Title	Quantum Dots Based Nanocomposites	
Series Title		
Chapter Title	Synthesis Strategies of Doped QDs	
Copyright Year	2024	
Copyright HolderName	The Author(s), under exclusive license to Springer Nature Switzerland AG	
Author	Family Name	**Reddy**
	Particle	
	Given Name	**Konatham Teja Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmacy
	Organization	University College of Technology, Osmania University
	Address	Amberpet, Hyderabad, Telangana, 500007, India
	Email	
Author	Family Name	**Venkata Badarinath**
	Particle	
	Given Name	**A.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutics
	Organization	Santhiram College of Pharmacy
	Address	Kurnool, Nandyala, Andhra Pradesh, NH-18, India
	Email	
Author	Family Name	**Gupta**
	Particle	
	Given Name	**Jeetendra Kumar**
	Prefix	
	Suffix	
	Role	
	Division	Institute of Pharmaceutical Research
	Organization	GLA University Mathura
	Address	Bharthia, Uttar Pradesh, India
	Email	
Author	Family Name	**Manikanta**
	Particle	
	Given Name	**Yeluguri**
	Prefix	
	Suffix	

	Role	
	Division	School of Pharmaceutical Sciences
	Organization	Vels Institute of Science Technology and Advanced Studies (VISTAS)
	Address	Pallavaram, Tamilnadu, 600117, India
	Email	
Author	Family Name	**Priya**
	Particle	
	Given Name	**Nagam Santhi**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutics
	Organization	Vignan Pharmacy College
	Address	Vadlamudi, Guntur, Andhra Pradesh, 522213, India
	Email	
Author	Family Name	**Vamseekrishna**
	Particle	
	Given Name	**G.**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Analysis
	Organization	NRI College of Pharmacy
	Address	Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh, 521212, India
	Email	
Author	Family Name	**Alex**
	Particle	
	Given Name	**Jimmy**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharma Chemistry
	Organization	Sri Shanmugha College of Pharmacy
	Address	Sankari, Salem, Tamilnadu, 637304, India
	Email	
Corresponding Author	Family Name	**Sahithi**
	Particle	
	Given Name	**Alapati**
	Prefix	
	Suffix	
	Role	
	Division	Department of Pharmaceutical Analysis, School of Pharmacy
	Organization	Nalla Narasimha Reddy Education Society’s Group of Institution
	Address	Chowdariguda, Ghatkesar, Ranga Reddy, 500088, India

Email sahithi.a@pharma.nnrg.edu.in

Abstract

The implementation of synthesis strategies for doped QDs (QDs) is of paramount importance in the customization of their electronic and optical characteristics, thereby facilitating their utilisation in a diverse array of fields such as optoelectronics, biomedicine, energy, sensing, and others. This abstract presents a succinct summary of the synthesis methodologies utilised in the fabrication of doped QDs (QDs). The aforementioned tactics encompass codoping, post-synthetic doping, ion exchange, alloying, and core-shell architectures. The process of codoping entails the concurrent introduction of multiple dopants during the synthesis of QDs, thereby enabling accurate regulation of their concentration and amalgamation. The process of post-synthetic doping involves the introduction of dopants onto pre-synthesized QDs (QDs) through surface modification or ligand exchange procedures. The process of ion exchange involves the substitution of dopant ions for the original cations or anions present in the lattice of QDs. The process of alloying involves the combination of distinct semiconductor materials, with the inclusion of dopants during the alloying procedure. Core-shell architectures facilitate the encapsulation of doped QDs (QDs) within a safeguarding shell, thereby providing the ability to regulate dopant diffusion and associated characteristics. The utilisation of synthesis strategies offers a degree of adaptability in customising the characteristics of doped QDs to suit particular applications. The objective of future investigations in this domain is to devise novel doping methodologies and refine current techniques with the aim of augmenting the efficacy and broadening the scope of applications of doped QDs.

Keywords (separated by '-')

Doped QDs - Codoping - Encapsulation - Biomedicine - Optoelectronics

Synthesis Strategies of Doped QDs

Konatham Teja Kumar Reddy, A. Venkata Badarinath, Jeetendra Kumar Gupta, Yeluguri Manikanta, Nagam Santhi Priya, G. Vamseekrishna, Jimmy Alex, and Alapati Sahithi

Abstract The implementation of synthesis strategies for doped QDs (QDs) is of paramount importance in the customization of their electronic and optical characteristics, thereby facilitating their utilisation in a diverse array of fields such as optoelectronics, biomedicine, energy, sensing, and others. This abstract presents a succinct summary of the synthesis methodologies utilised in the fabrication of doped QDs (QDs). The aforementioned tactics encompass codoping, post-synthetic doping, ion exchange, alloying, and core-shell architectures. The process of codoping entails the concurrent introduction of multiple dopants during the synthesis of QDs, thereby enabling accurate regulation of their concentration and amalgamation. The process

K. T. K. Reddy
Department of Pharmacy, University College of Technology, Osmania University, Amberpet, Hyderabad, Telangana 500007, India

A. Venkata Badarinath
Department of Pharmaceutics, Santhiram College of Pharmacy, Kurnool, Nandyala, Andhra Pradesh NH-18, India

J. K. Gupta
Institute of Pharmaceutical Research, GLA University Mathura, Bharthia, Uttar Pradesh, India

Y. Manikanta
School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies (VISTAS), Pallavaram, Tamilnadu 600117, India

N. S. Priya
Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, Andhra Pradesh 522213, India

G. Vamseekrishna
Department of Pharmaceutical Analysis, NRI College of Pharmacy, Pothavarappadu (V), Agiripalli (M), Krishna (D.T), Andhra Pradesh 521212, India

J. Alex
Department of Pharma Chemistry, Sri Shanmugha College of Pharmacy, Sankari, Salem, Tamilnadu 637304, India

A. Sahithi (✉)
Department of Pharmaceutical Analysis, School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institution, Chowdariguda, Ghatkesar, Ranga Reddy 500088, India
e-mail: sahithi.a@pharma.nnrg.edu.in

T. Sabu et al. (eds.), *Quantum Dots Based Nanocomposites*, Engineering Materials,
https://doi.org/10.1007/978-3-031-54779-9_3

602599_1_En_3_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 29 Layout: T1-Standard

of post-synthetic doping involves the introduction of dopants onto pre-synthesized QDs (QDs) through surface modification or ligand exchange procedures. The process of ion exchange involves the substitution of dopant ions for the original cations or anions present in the lattice of QDs. The process of alloying involves the combination of distinct semiconductor materials, with the inclusion of dopants during the alloying procedure. Core-shell architectures facilitate the encapsulation of doped QDs (QDs) within a safeguarding shell, thereby providing the ability to regulate dopant diffusion and associated characteristics. The utilisation of synthesis strategies offers a degree of adaptability in customising the characteristics of doped QDs to suit particular applications. The objective of future investigations in this domain is to devise novel doping methodologies and refine current techniques with the aim of augmenting the efficacy and broadening the scope of applications of doped QDs.

Keywords Doped QDs · Codoping · Encapsulation · Biomedicine · Optoelectronics

1 Introduction

QDs are semiconductor particles at the nanoscale that display distinctive optical and electronic characteristics as a result of quantum confinement phenomena [1, 2]. In recent times, there has been a notable surge in interest towards them owing to their prospective utilisation in diverse domains, including optoelectronics, biomedicine, and renewable energy [3–6]. The extent to which their properties can be adjusted is restricted by their dimensions and constituents. The utilisation of impurities to dope QDs has emerged as a promising strategy to overcome their limitations and improve their performance. The process of doping QDs entails the incorporation of dopants or impurities into the crystal lattice of the semiconductor material [1]. The alteration of the electronic structure and bandgap of QDs through this process can result in modifications of their optical and electronic characteristics. Doping has the potential to enhance the stability, biocompatibility, and solubility of QDs, thereby expanding their applicability across various domains [7]. Numerous methodologies have been devised to fabricate doped QDs with regulated composition and characteristics. The aforementioned strategies can be categorised into two distinct groups: (1) doping after synthesis and (2) co-doping during the synthesis process. The process of post-synthesis doping pertains to the incorporation of dopants into QDs that have already undergone synthesis. The aforementioned methodology facilitates the alteration of characteristics of extant QDs while preserving their dimensions and morphology. Ion implantation is a frequently utilised technique for post-synthesis doping [8]. The process of introducing dopants into QDs involves ion bombardment. The ion implantation methodology is characterised by a high degree of precision and enables the incorporation of a diverse array of dopants. Nevertheless, it has the potential to impair the crystal structure of the QDs and diminish their efficacy in emitting light.

Molecular doping represents an alternative strategy for post-synthesis doping [9]. The present technique involves the introduction of dopants into the QDs through either surface adsorption or lattice diffusion. The utilisation of this particular methodology is comparatively less deleterious to the crystal structure of QDs in contrast to ion implantation, while also having the capability to incorporate a more extensive spectrum of dopants. Nevertheless, the process of molecular doping may result in the formation of quantum dot aggregates, thereby diminishing their stability. The process of co-doping in the synthesis of QDs refers to the concurrent integration of dopants into the synthesis procedure. The aforementioned methodology facilitates meticulous regulation of the QDs' composition and characteristics, while concurrently mitigating the incidence of flaws and impairment to the crystal lattice. The hot-injection method is a frequently employed technique for co-doping. The present methodology involves the injection of a blend of precursor substances and dopants into a heated solution to produce QDs with regulated composition and characteristics. The hot-injection technique is a remarkably effective approach that enables the production of doped QDs of exceptional quality while providing accurate regulation over their characteristics [10]. The one-pot synthesis method represents an alternative approach to co-doping. The present methodology involves the introduction of a blend of precursor substances, dopants, and ligands into a solitary reaction container to effectuate the production of doped QDs in a unified step [11]. The aforementioned methodology is characterised by its straightforwardness and effectiveness, as well as its capacity to generate substantial volumes of doped QDs. The intricate reaction environment may pose challenges in regulating the characteristics of the QDs produced. Various dopants have been employed to alter the characteristics of QDs, encompassing metals, metal oxides, rare-earth elements, and organic molecules. The incorporation of dopants has the potential to modify the optical and electronic characteristics of QDs, including their quantum yield, emission wavelength, and bandgap [12–14]. The selection of a dopant is contingent upon the intended characteristics of the QDs and their particular usage. To sum up, the introduction of impurities into QDs through doping has surfaced as a propitious method for altering their characteristics and amplifying their efficacy. Various techniques have been devised to fabricate doped QDs with regulated composition and characteristics, such as doping after synthesis and co-doping during synthesis [15–20].

2 Different Doping Strategies of QDs

Doping is an effective tool for modifying the characteristics of QDs. Doping of impurities into QDs can be broadly categorised as either extrinsic or intrinsic doping.

AQ2

2.1 Extrinsic Doping Strategies

The traditional technique of doping, which involves the introduction of impurity atoms, proved to be ineffective in several initial instances due to the tendency of the impurities to be expelled from the small crystalline cores. Additionally, the thermal ionization of impurities, which generates free carriers, was impeded by strong confinement. A potential avenue for addressing these limitations involves the extrinsic introduction of dopant ions. The study conducted by Guyot-Sionnest et al. [21, 22] explored into the examination of colloidal QDs composed of different materials, namely CdSe, CdS, and ZnO. The results of the study demonstrated that these materials can undergo n-type reduction through the use of Na, K, biphenyl radical anions, or electrochemical doping, wherein electrons occupy the quantum confined states of the conduction band. The present study showcases the impact of sodium biphenyl on the infrared and visible absorption spectra of CdSe nanocrystals. The results revealed a noticeable reduction in the intensity and broadening of the first and second excitonic peaks, indicating bleaching. The manifestation of the 1Se–1Pe infrared absorption peak at 0.3 eV provides evidence for the n-type nature of the nanocrystals. Additional prospects encompass the investigation of the electrical conductivity of n-type QDs films, attributed to their increased inter-QD electron transfer, which may yield photovoltaic or electronic implementations [21, 23]. Another technique for extrinsic doping involves the utilization of a Bronsted base, such as hydrazine, to modify the surface of the quantum dot (QD). This process replaces the bulky oleic acid groups, resulting in a reduction of intermolecular spacing. Additionally, the dangling bonds on the surface are passivated by the lone pair of electrons on the base, which is comparable to primary amines. The improvement of conductivity in QD solids is facilitated by this process, thereby enhancing the efficacy of QDs in diverse applications such as field effect transistors. The conductance of PbSe nanocrystal solids was observed to escalate by ten orders of magnitude subsequent to hydrazine treatment. The technique has been demonstrated to have a broad range of applications on various materials; however, its widespread applicability is constrained by the instability of the ligands involved [24]. In recent times, hydrazine molecules have been substituted with more stable and environmentally friendly molecules, thereby showcasing the extended practicality of this approach [25].

2.2 Intrinsic Doping

Extrinsic doping is not a very feasible choice for imparting functionalities such as magnetic, optical, or optoelectronic functions, despite the modest results that have been achieved with this technique. As a result, it is essential to find procedures that are capable of producing effective intrinsic doping of dopant ions [26]. While doping has been widely conducted and has yielded high-quality QDs (QDs) in certain instances,

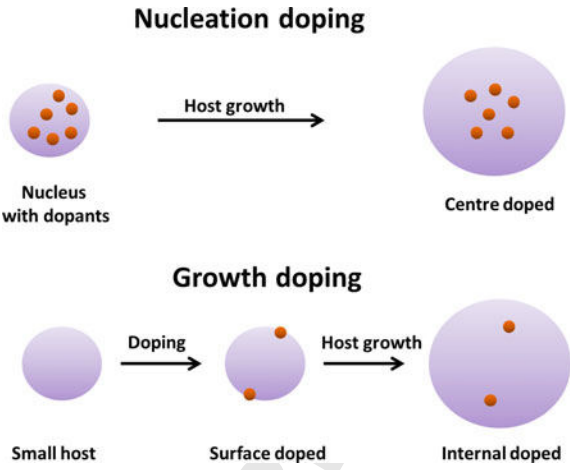


Fig. 1 Graphical representation of the proposed radial positions of the dopant in nucleation and growth doping

Pradhan et al. were the first to propose mechanistically significant techniques for doping Mn and Cu in ZnSe-based systems [26]. The authors proposed techniques to dissociate the dopant and host precursors to account for their distinct reactivities. These techniques involve nucleation or growth doping to achieve efficient doping of the QDs, as illustrated in Fig. 1.

In the context of nucleation doping, the initial step involves the formation of a small dopant compound. In the context of nucleation doping, a small dopant compound was initially generated. Subsequently, the aforementioned core nuclei were coated with a host shell, leading to the formation of either graded alloys or sharp interfaces, dependent upon the prevailing conditions. In the context of growth doping, the authors presented evidence of the emergence of small host QDs, succeeded by the adsorption of the dopant ion on the surface at a reduced temperature, and the introduction of the dopant metal precursor. In order to encapsulate the dopant ions, isocrystalline or heterocrystalline shells were formed, which demonstrates the extensive applicability of this method [3, 27]. As shown in Fig. 2, effective doping and decoupling from nucleation and growth are demonstrated by the rise in the photoluminescence (PL) intensity of the dopant emission and the reduction in the PL intensity of the host (top, left). This prototype demonstration of the proposed mechanism was carried out for Cu or Mn-doped ZnSe QDs. The PL undergoes a redshift as a consequence of the regrowth of ZnSe on the surface of the doped QDs (top, right). Because it took 100 min to finish, the procedure described above would have been tough to control if it hadn't been for the decoupling technique. On the other hand, nucleation doping was accomplished for Mn-doped ZnSe by utilizing a variety of dopant precursors. Due to the fact that Mn^{2+} is a harder Lewis acid than Zn^{2+}, it is anticipated that the Mn^{2+} precursor will exhibit lower levels of reactivity when combined with the same ligand. When manganese stearate was utilised as the nucleation precursor, zinc acetate was preferred over zinc stearate for the production

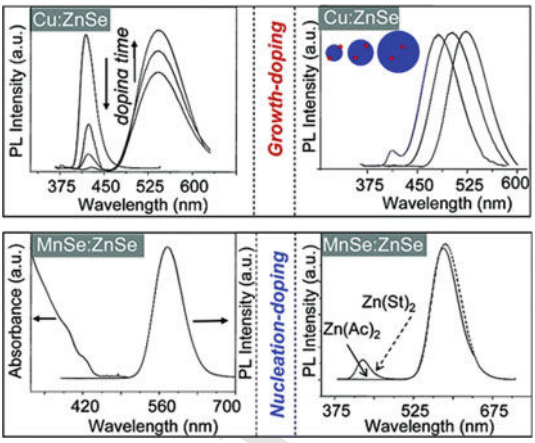


Fig. 2 Spectroscopic data for nucleation- and growth-doped QDs. Reproduced with permission from Ref. [26]

of MnSe: ZnSe nanocrystals. Zinc stearate necessitated a higher reaction temperature, leading in homogenous nucleation of ZnSe and a band gap PL. The main disadvantage of this approach is high-temperature annealing during shell formation, which causes dopants to escape and eventually leach out of the surface, leading to self-purification. This was specifically demonstrated in the instance of Cu-doped ZnSe QDs. The overcoating process carried out at a temperature of 210 °C effectively confined the dopants within the host lattice, thereby preventing any diffusion of dopants from the nucleus to the surface. Nevertheless, it was observed that upon annealing at 220 °C or above, the expulsion of dopants from the lattice occurred for all sizes. Furthermore, a notable reduction of the dopant photoluminescence was observed during annealing in the temperature range of 20–80 °C, as the overcoating temperature was raised. The process of overcoating ZnSe at elevated temperatures leads to a significant diffusion of Cu dopants toward the surface. Therefore, despite the prolonged endeavours of diverse groups on different systems to acquire internally doped QDs, the attainment of internally doped QDs has remained elusive.

The process of cation exchange reactions is extensively utilised in the doping of QDs, wherein the cation of the QDs is replaced with a dopant cation [28–30]. The extent of cation exchange can be tuned by varying the solution concentration of the incoming dopant cations and the type of ligands bound to them. These processes, however, are not trivial in semiconductor QDs, as evidenced by the large energies involved in doping. Furthermore, clustering or directional doping based on reactivity is inherent in this doping strategy. While the directed nature has been employed constructively to generate various hetero-structure topologies, clustering of dopant ions does not allow for homogenous impurity doping [31–33]. Another technique called diffusion doping, originally developed by Saha and colleagues, employs the self-purification mechanism instead of attempting to address it as an obstacle, a commonly perceived notion [34]. Using the SILAR (successive ionic layer adsorption and reaction) approach, a tiny magnetic core was over-coated with a thick shell

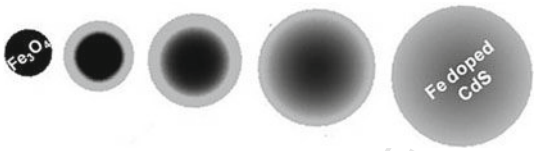


Fig. 3 Dopant diffusion into the CdS matrix to produce Fe-doped CdS QDs. Reproduced with permission from Ref. [34]

of the host semiconductor. High-temperature annealing of this core-shell arrangement causes the core to diffuse at the interface and into the semiconductor shell, eventually allowing it to diffuse out of the system. As illustrated in Fig. 3, the model system examined by Saha et al. comprised a Fe3O4 core overcoated with a CdS shell. The strained interface with a lattice mismatch of around 4% and high-temperature annealing causes core diffusion into the shell with a decrease in core size, eventually leading to uniformly doped QDs. Furthermore, the technique's generality and universality were shown for various dopant ions, such as M^{2+} (Fe^{2+}, Ni^{2+}, Co^{2+}, Mn^{2+}). The efficiency of inside-out diffusion doping is determined by the core's capacity to enter the CdS lattice, followed by the metal ion's ability to diffuse within the lattice and the ease of cation exchange [35].

3 Factors Influencing Doping Efficiency

The distinctive electronic and optical characteristics of QDs (QDs) have generated considerable interest in contemporary times. Nanoscale semiconductor crystals exhibit significant potential across a diverse array of applications, encompassing electronics, optoelectronics, and biomedicine. The deliberate incorporation of impurities into QDs, commonly known as doping, is a pivotal technique in customising their characteristics and augmenting their efficacy. This discourse aims to investigate the variables that impact the efficacy of doping in QDs.

4 Role of Doping Precursor Concentration

The degree of dopant incorporation into the quantum dot lattice during synthesis is directly influenced by the concentration of the doping precursor. Elevated concentrations of doping precursors may augment the likelihood of the integration of dopant atoms into the quantum dot (QD) framework. On the other hand, reduced concentrations of precursors may yield a restricted quantity of dopants, thereby causing inadequate levels of doping. Attaining the targeted dopant concentration requires precise management of the precursor concentration throughout the synthesis procedure. The distribution and homogeneity of dopants within a quantum dot ensemble are influenced by the concentration of the doping precursor. An increased concentration of precursors frequently leads to a homogeneous dispersion of dopants within

the QDs. The homogeneity of the doped quantum dot (QD) population is a favourable attribute that facilitates the attainment of consistent and foreseeable characteristics. In contrast, reduced levels of precursor concentrations may give rise to dopants that are either spatially separated or clustered, thereby causing non-uniform doping and fluctuations in the performance of QDs. The control of size and composition in doped QDs can be influenced by the concentration of doping precursors. The growth kinetics and nucleation process of QDs in various synthesis methods, including colloidal synthesis, are influenced by the concentration of the precursor. Elevated concentrations of precursors typically facilitate accelerated rates of growth and increased sizes of QDs. Furthermore, it should be noted that the dopant material has the potential to impact the nucleation and growth patterns of the QDs. As a result, it becomes imperative to fine-tune the precursor concentration in order to attain the desired size and composition of the QDs. The optical and electronic characteristics of doped QDs are influenced by the concentration of the doping precursor. The concentration of dopant atoms within the QD lattice can exert an influence on optical properties, including emission wavelength and quantum yield. Elevated levels of precursor concentrations have the potential to augment the transfer of energy and the dynamics of charge carriers, ultimately resulting in alterations to the optical characteristics. The electronic characteristics of doped QDs (QDs), including energy levels and charge transport, are significantly influenced by the concentration of dopants, which ultimately affects the overall functionality of these QDs. The concentration of the doping precursor has an impact on the stability of QDs that have been doped, as well as their impurity effects. Elevated levels of dopant concentrations have the potential to introduce impurities and defects, thereby impacting the structural integrity and stability of QDs (QDs). Elevated precursor concentrations have the potential to cause non-uniform or inadequate doping, thereby leading to heightened impurity scattering or carrier recombination. These consequences can negatively impact the efficiency and stability of QDs.

Nair et al. have exhibited that the synthesis of metal- and nonmetal-codoped graphene QDs (GQDs) with improved optical properties can be achieved through the co-reaction of lignosulfonate (Fig. 4), which contains heteroatoms such as sulphur (S) and nitrogen (N) in its structure, and a metal precursor [36]. The GQDs derived from lignosulfonate synthesis exhibited notable blue fluorescence, displaying a substantial quantum yield of 23%. This phenomenon is ascribed to the presence of S and N doping, which was verified through the utilisation of X-ray photoelectron spectroscopy and Fourier transform infrared spectroscopy analyses. The lignosulfonate-derived GQDs were subjected to in situ doping to facilitate their modification. Additionally, a metal atom dopant was introduced to further engineer the GQDs, resulting in an improved quantum yield of 31%. This is noteworthy as it represents the highest quantum yield achieved for any GQDs derived from lignin.

A technique has been reported for the production of diluted magnetic semiconductor QDs (DMS-QDs) consisting of colloidal ZnO. This method involves the alkaline-activated hydrolysis and condensation of zinc acetate solutions in dimethyl sulfoxide (DMSO) [37]. The critical nuclei exhibit quantitative exclusion of dopants, while the nanocrystals' subsequent growth incorporates them in an almost isotropic

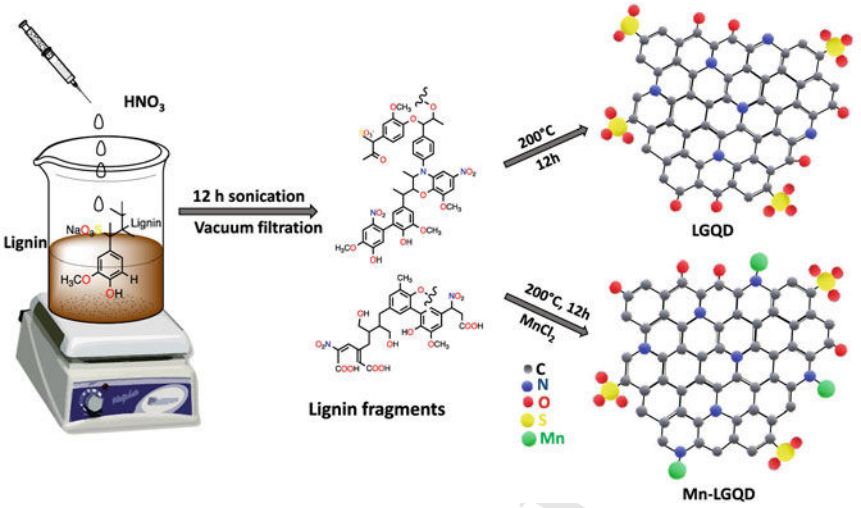


Fig. 4 A diagrammatic representation of the hydrothermal process for the synthesis of LGQDs and Mn-LGQDs. Reproduced with the permission from Ref. [36] © 2020 American chemical society

manner. The reduction in nanocrystal diameters that occurs as a result of doping can be elucidated by the Gibbs-Thompson relationship, which describes the correlation between lattice strain and crystal solubility. The process of synthesising graphene QDs (GQDs) involved the utilisation of femtosecond laser ablation in liquid, with laser induced graphene serving as the carbon source. The synthesis of Nitrogen-doped graphene QDs (N-GQDs) was achieved through the introduction of ammonia water into the graphene suspension [38]. The structure of GQDs/N-GQDs is composed of a graphitic core that exhibits oxygen and nitrogen functionalities, with a particle size that is smaller than 10 nm. This has been demonstrated through the use of various analytical techniques such as x-ray photoelectron spectroscopy, Fourier infrared spectrometer spectroscopy, and transmission electron microscopy. Lead halide perovskite QDs (PQDs) doped with transition metal cations are a promising group of materials for advanced photonic devices in the future. This is because of their fascinating properties induced by dopants and enhanced stabilities against photo-, moisture-, and thermal factors. The multifaceted nature of metal cation-doped PQDs in colloidal synthesis presents a challenging task when utilising conventional batch reactors. Bateni et al., employed a modular microfluidic platform that was equipped with a mobile spectral monitoring probe to investigate the kinetics and elucidate the chemical transformation mechanism of the rapid cation doping of cesium lead chloride QDs [39]. The authors additionally presented a design framework that enables accurate adjustment of the optical characteristics of QDs (QDs) through a post-synthetic doping mechanism in a flow-based system. The present study has developed a modular microfluidic platform that, in conjunction with facile doping chemistry, can facilitate the uninterrupted production of metal cation-doped PQDs possessing optoelectronic properties tailored to specific applications.

4.1 Role of Reaction Temperature and Time

The production of doped QDs (QDs) necessitates a meticulous equilibrium of multiple parameters to attain the intended characteristics. The reaction temperature and reaction time are significant parameters that impact the properties and efficacy of doped QDs. The present discourse aims to examine the importance of reaction temperature and duration and their influence on the production of doped QDs.

The incorporation of dopants into the quantum dot lattice during synthesis is directly influenced by the reaction temperature and time. Elevated temperatures typically facilitate the diffusion of dopant precursors into the quantum dot (QD) architecture, resulting in heightened levels of doping. Excessive temperatures can lead to agglomeration or thermal decomposition, which can have adverse effects on the quality and consistency of the doped QDs. Similarly, the duration of the reaction permits ample time for the inclusion of dopant atoms, and extended reaction times can result in increased levels of doping given suitable temperature conditions. The manipulation of reaction temperature and duration exerts a notable impact on the regulation of size and composition of doped QDs. Elevated temperatures frequently facilitate accelerated nucleation and growth kinetics, leading to the formation of comparatively larger QDs. In contrast, reduced temperatures could hinder the developmental mechanism and result in the formation of diminutive QDs. The overall size distribution and size homogeneity of the doped QDs are influenced by the reaction time in a similar manner. The manipulation of temperature and reaction time allows for precise regulation of the dimensions and constitution of QDs, which is imperative in customising their optical and electronic characteristics. The crystal structure and stability of doped QDs are also influenced by the reaction temperature and duration. The kinetics of nucleation and growth processes, as well as the crystal structure of QDs, is impacted by temperature. Elevated temperatures have the potential to facilitate the process of crystal growth and enhance the degree of crystallinity, thereby resulting in heightened stability. Nevertheless, elevated temperatures have the potential to cause imperfections or separation of phases. The growth dynamics are influenced by the reaction time, which provides adequate time for the development of a clearly defined crystal structure. Achieving stable and structurally well-defined doped QDs (QDs) requires the optimisation of temperature and reaction time.

The manipulation of reaction temperature and time is a crucial aspect in customising the optical and electronic characteristics of doped QDs. The manipulation of reaction conditions enables regulation of the quantum yield, energy levels, and emission wavelength of the QDs. Elevated temperatures have the potential to facilitate energy transfer mechanisms and the dynamics of charge carriers, leading to alterations in optical characteristics. Furthermore, the duration of the reaction time has an impact on the creation of imperfections and obstructions within the QDs, potentially altering their electronic characteristics, including the movement of charge carriers and the rate of recombination.

The kinetics of the synthesis process and the controllability of doped QDs are influenced by the reaction temperature and time. Incomplete doping or undesired

side reactions may occur due to rapid temperature changes or shorter reaction times. Conversely, extended reaction times or reduced temperatures may facilitate the occurrence of secondary reactions or undesired contaminants. Attaining the ideal reaction parameters in terms of temperature and duration facilitates superior regulation of the synthesis procedure, culminating in the production of doped QDs of exceptional quality.

4.2 Role of QD Size and Shape

The optical, electronic, and chemical properties of QDs (QDs) are significantly influenced by their size and shape. The size and shape parameters are critical factors in determining the doping efficiency and resulting characteristics of synthesised doped QDs. The present discourse aims to investigate the significance of quantum dot dimensions and configurations in the production of doped QDs.

The doping efficiency during synthesis is influenced by the size of QDs. In general, QDs that is smaller in size exhibit a greater surface-to-volume ratio, thereby augmenting the interaction between the dopant precursor and the surface of the quantum dot. The enhanced surface interaction promotes the integration of dopant atoms into the lattice of the quantum dot, leading to an enhancement in the efficiency of doping. In contrast, QDs of greater size exhibit a diminished surface-to-volume ratio, thereby limiting the surface area accessible for dopant integration and potentially resulting in decreased doping efficacy.

The doping process is also influenced by the shape anisotropy of QDs, which may take on various forms such as spherical, rod-shaped, or plate-like. The surface energies and reactivity of crystallographic facets on various quantum dot shapes can differ. The surface characteristics have the potential to impact the adsorption and diffusion of dopant precursors in the course of synthesis. The phenomenon of preferential doping on specific facets due to shape anisotropy can result in a non-uniform distribution of doping within the ensemble of QDs. Comprehending the doping behaviour that is contingent on the shape is of utmost importance in regulating the characteristics of doped QDs.

The electronic and optical properties of QDs are directly impacted by their size, thereby exerting an influence on the doping behaviour. As the size of the quantum dot diminishes, the quantum confinement effect becomes increasingly conspicuous, resulting in distinct energy levels and adjustable optical characteristics. The size-dependency of QDs significantly impacts their energy levels and bandgap, thereby influencing the arrangement of dopant energy levels in the QD band structure. The properties of QDs that are dependent on their size are of utmost importance in the optimisation of doping techniques and the attainment of desired functionalities. The carrier dynamics, which encompass charge carrier generation, recombination, and transport, are notably impacted by the dimensions of QDs. The discrete energy levels and reduced non-radiative recombination pathways of smaller QDs typically result in faster carrier relaxation and radiative recombination rates. The utilisation of doping

has the potential to modify the dynamics of carriers through the alteration of charge transfer processes and the modification of energy states. Comprehending the carrier dynamics that are dependent on the size is of utmost importance in order to enhance doping techniques and achieve the highest possible efficiency of doped QDs. The stability and surface passivation requirements of QDs are also influenced by their size. QDs with larger dimensions exhibit a greater density of surface defects and trap states, owing to their increased surface area (Table 1). The introduction of impurities or dopant-induced defects due to doping can have an impact on the surface passivation requirements. QDs exhibit a greater surface-to-volume ratio, which necessitates the implementation of more efficient surface passivation techniques to counteract surface-related recombination and improve their stability. The management of size-dependent stability and surface passivation is a crucial factor in attaining sustained efficacy and robustness of doped QDs.

5 Strategies to Optimize Doping Efficiency

Various approaches can be utilised to enhance doping efficacy in QDs (QDs) for optimal performance. The present strategies are centred on augmenting the integration of dopants into the quantum dot lattice and attaining the targeted levels of doping. The following are several fundamental methods for enhancing doping efficiency:

- The selection of a suitable dopant material is a critical factor in achieving optimal doping efficiency. Efficient energy level alignment and charge transfer can be achieved by selecting a dopant material that possesses electronic properties that are compatible with those of the QD matrix. Furthermore, it is imperative that the dopant material demonstrates favourable solubility within the quantum dot (QD) matrix and maintains stability throughout the doping procedure. Thorough evaluation of the dopant material characteristics is crucial for the effective integration of said material into the quantum dot lattice.
- In the field of engineering, it is imperative to optimise the doping precursor in order to enhance the efficiency of doping. The process entails the careful selection of dopant precursors with high reactivity and favourable thermodynamics for the doping reaction. Advanced engineering methodologies, such as the manipulation or creation of ligands, can be utilised to amplify the responsiveness and durability of the precursor, thereby facilitating its interaction with the quantum dot surface and promoting effective doping.
- The optimisation of different process parameters can enhance the efficiency of doping. The aforementioned parameters encompass temperature, duration of reaction, concentration of precursor, and atmosphere of reaction. Optimising these parameters according to the particular doping scheme and target doping concentrations can improve the integration of dopants into the quantum dot crystal structure. Modulating the temperature and reaction duration can exert an impact on the

Table 1 Sum up the major strategies and their examples

Strategies	Description	Examples/considerations	References
Selection of suitable dopant material	Choose dopant materials with compatible electronic properties to achieve desired energy level alignment and charge transfer	ZnSe QDs doped with Mn^{2+}, CdSe QDs doped with Cu^{+} ions	[40]
Precursor engineering	Modify dopant precursors to enhance reactivity, stability, and solubility in the QD matrix, improving dopant incorporation efficiency	Ligand design, precursor synthesis optimization, chelating agents for stabilization	[41, 42]
Control over doping process parameters	Optimize temperature, reaction time, precursor concentration, and atmosphere to enhance diffusion kinetics and achieve desired doping levels	Higher temperatures for increased diffusion, longer reaction times for improved incorporation	[1, 43, 44]
Surface engineering and passivation	Employ surface ligands, shell layers, or surface treatments to passivate QD surface, reducing surface defects and improving doping efficiency	Ligand exchange, shell growth, surface passivation techniques	[45, 46]
Core-shell doping	Utilize core-shell QDs to selectively dope the core or shell regions, enabling precise control over doping levels and charge transfer processes	CdSe/CdS core-shell QDs doped with transition metal ions	[47]
Hybrid doping approaches	Combine multiple doping techniques, such as ion implantation, chemical doping, or cation exchange, to enhance doping efficiency synergistically	Sequential doping processes, simultaneous doping with different dopants	[48]
Characterization and feedback	Employ various characterization techniques (e.g., spectroscopy, microscopy, electrical measurements) to assess doping efficiency and optimize	Photoluminescence spectroscopy, TEM/SEM imaging, current-voltage characteristics	[49, 50]

diffusion and kinetics of dopant incorporation, whereas fine-tuning the precursor concentration guarantees the attainment of the intended doping levels.

- The efficiency of doping can be hindered by non-radiative recombination or impurity scattering caused by surface defects and trap states. Therefore, surface engineering and passivation are crucial in addressing this issue. The implementation of proficient surface engineering and passivation methodologies can alleviate these concerns and amplify the efficacy of doping. The implementation of surface ligands, shell layers, or surface treatments can serve as a means of passivating the surface of QDs (QDs), thereby reducing surface defects and enhancing carrier

confinement. The implementation of surface engineering techniques enhances the general stability, optical characteristics, and doping efficacy of QDs.

- Core-shell doping is a technique that can be utilised to improve doping efficiency in QDs (QDs). Specifically, the efficiency can be enhanced by selectively doping either the core or shell regions of the QDs. The utilisation of a core-shell structure enables a regulated milieu for the inclusion of dopants, thereby facilitating meticulous modulation of the doping levels. Through the strategic introduction of dopants into either the core or shell, it is feasible to enhance charge transfer mechanisms, mitigate the emergence of dopant-induced flaws, and enhance the efficacy of doping.
- Hybrid doping approaches refer to the combination of various doping techniques with the aim of optimising their effectiveness. Multiple dopants can be introduced or the doping process can be enhanced through the use of sequential or simultaneous doping techniques. The simultaneous utilisation of ion implantation, chemical doping, or cation exchange methods can result in a synergistic enhancement of doping efficiency, as each technique can leverage its unique advantages.
- The utilisation of characterization techniques, such as spectroscopy, microscopy, and electrical measurements, can offer significant insights into the effectiveness of doping. The assessment of various doping strategies and optimisation of the doping process can be achieved by monitoring the optical and electronic properties of doped QDs (QDs). The iterative enhancement of doping efficiency is facilitated by the approach that is driven by feedback.

6 Applications of Doped QDs

6.1 Bioimaging

QDs that have been doped have been utilised in diverse areas such as bioimaging and biosensing. The following are several significant implementations:

The utilisation of doped QDs as imaging agents in biological systems is highly advantageous due to their distinctive optical properties in the field of bioimaging. Due to their diminutive size, exceptional photostability, and customizable emission spectra, they are well-suited for a diverse array of imaging methodologies, including fluorescence microscopy and in vivo imaging. Through the conjugation of doped QDs with targeting molecules, scientists are able to selectively label and monitor different cellular components, biomolecules, or particular disease markers within living organisms. The utilisation of doped QDs in biosensing applications based on Fluorescence Resonance Energy Transfer (FRET) is feasible. Förster resonance energy transfer (FRET) is a phenomenon of energy transfer that transpires non-radiatively between a donor fluorophore and an acceptor fluorophore when they are in close proximity. Through the utilisation of Förster resonance energy transfer (FRET), scientists can effectively track and analyse targeted biochemical reactions or interactions by combining a doped quantum dot with an acceptor fluorophore.

This technique allows for the detection of biomolecular events with exceptional sensitivity and spatial resolution. Proximity-based assays employ doped QDs to measure the spatial proximity of target molecules. The detection and quantification of target molecules can be achieved by conjugating target-specific molecules, such as antibodies or aptamers, to doped QDs. This approach relies on the proximity-induced changes in the optical properties of the QDs. This approach is useful for various applications, including protein-protein interaction studies and the detection of biomarkers in clinical samples. The application of doped QDs in single-molecule tracking provides exceptional photostability, facilitating the extended and precise visualisation of singular molecules. This property is particularly useful in single-molecule tracking experiments, where the movement and behavior of individual biomolecules (such as proteins or nucleic acids) can be monitored in real-time. Through the utilisation of doped QDs, scientists can acquire significant knowledge regarding the dynamics, interactions, and cellular processes of these molecules. The integration of doped QDs with other imaging modalities, such as magnetic resonance imaging (MRI) or computed tomography (CT), can result in the development of multimodal imaging agents. These hybrid agents can provide complementary information and enable enhanced imaging capabilities, such as combining the high-resolution imaging of doped QDs with the anatomical information from MRI or CT, leading to improved diagnosis and monitoring of diseases. In general, doped QDs have demonstrated their versatility and significance in the fields of bioimaging and biosensing, providing improved sensitivity, photostability, and multiplexing abilities for various biological investigations. A facile hydrothermal technique was employed to synthesise nitrogen-sulfur doped graphene QDs (NS-GQDs). The stability of fluorescence signals exhibited by NS-GQDs remains high even in the presence of diverse metal ions [51]. Aspartic acid and cysteine were employed as carbon precursors and heteroatomic sources of nitrogen and sulphur, respectively. The NS-GQDs that were generated exhibited a quantum yield of up to $19.3 \pm 1.7\%$ and a peak emission of 480 nm when excited by 400 nm. The results depicted in Fig. 5a demonstrate a noteworthy decrease in the fluorescence of Pdots within cells upon the introduction of 200 μM Cu^{2+}. This finding suggests that Cu^{2+} has a quenching effect on Pdots in the context of bioimaging. On the other hand, it was observed that the fluorescence imaging ability of cells stained with NS-GQDs remained unaffected upon treatment with 200 μM Cu^{2+}, as depicted in Fig. 5b. The findings indicate that the NS-GQDs that were created exhibit exceptional resistance to metal ions in the context of bioimaging.

6.2 Optoelectronics

The unique properties and potential applications of doped QDs (QDs) have garnered a lot of attention in optoelectronics. The wide applicability of QDs and their ongoing works have been tabulated in Table 2. Researchers have found that by doping or

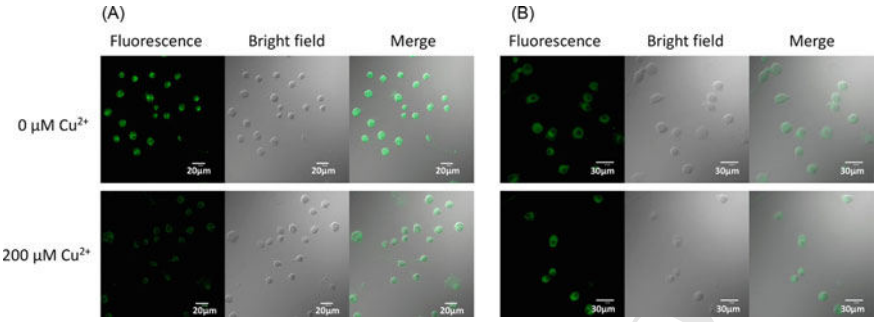


Fig. 5 LSCM images of RAW 264.7 cells incubated with **a** 10.0 μg/mL Pdots, **b** 1.0 mg/mL NS-GQDs with 200 μM Cu^{2+}. Reproduced with the permission from Ref. [51] © 2019 American chemical society

introducing impurities into the QDs, they can alter their electronic and optical properties, expanding their potential for use in optoelectronic devices. Some examples of where doped QDs have found use in optoelectronics are as follows:

Doped QDs can function as emitters in light-emitting diodes (LEDs). Researchers have found that they can tune the QDs' emission wavelength across the visible and near-infrared spectrum by adjusting their size and composition. QDs are promising candidates for next-generation display technologies because their efficiency, stability, and colour purity can be further improved by doping them with specific impurities.

Doped QDs may improve the efficiency of solar cells, which is important in the field of photovoltaics. It is possible to increase the solar cell's absorption range by incorporating doped QDs into the active layer. Dopants can also help with charge separation and transport, which boosts the solar cell's overall efficiency.

Doped QDs are an active material that can be used in photodetectors. Scientists can design QDs to be exceptionally sensitive to certain colours of light by adjusting the bandgap and the amount of doping. This paves the way for the creation of photodetectors with enhanced responsivity, rapid response, and minimal noise.

When it comes to lasers, doped QDs can be used as gain media. In order to achieve population inversion and stimulated emission, the dopants introduce energy levels within the QD bandgap. Doped QD lasers are useful for telecommunications, spectroscopy, and medical diagnostics because they can operate at a wide range of wavelengths, from the near-infrared to the visible and even the mid-infrared.

When it comes to quantum computing and information processing, doped QDs can serve as qubits. Implementing quantum logic operations requires manipulating electron spins and charge states in the QDs, which is made possible through the controlled introduction of dopants. Doped QDs have the potential to contribute to the growth of quantum technologies by enabling scalable and coherent qubit systems.

Table 2 Various applications of QDs device making and fabrications

Application	Description	Benefits	References
Light-emitting diodes	Doped QDs serve as emitters in LEDs, enabling tunable and efficient displays with enhanced color purity	Wide color gamut, high efficiency, long operational lifetime, solution processability	[52]
Photovoltaics	Doped QDs enhance the absorption range and charge transport in solar cells, improving overall efficiency	Broadband light absorption, enhanced charge collection, compatibility with flexible substrates	[53–55]
Photodetectors	Doped QDs enable the development of highly sensitive and fast photodetectors with low noise characteristics	High responsivity, wide spectral range, low dark current, ultrafast response time	[56]
Lasers	Doped QDs act as gain media, facilitating population inversion and stimulated emission for lasers in various wavelengths	Wavelength tunability, low threshold current, high quantum efficiency, compact size	[57]
Quantum computing	Doped QDs can be used as qubits for quantum computing and information processing, leveraging controlled electron spins and charge states	Scalability, long coherence times, high-fidelity operations, interfacing with solid-state platforms	[58]
Biological imaging	Doped QDs offer excellent optical properties for bioimaging, including high brightness, photostability, and tunable emission wavelengths	Bright and stable fluorescence, multiplexed imaging capabilities, targeted molecular imaging, high signal-to-noise ratio	[13]
Sensing applications	Doped QDs are utilized for sensing applications, such as chemical and biological sensing, due to their high sensitivity and selectivity	High sensitivity and selectivity, label-free detection, real-time monitoring, miniaturization potential	[59]
Display technologies	Doped QDs enable the development of vibrant and energy-efficient displays with wide color gamut and high contrast ratios	Vivid and accurate colors, energy efficiency, high contrast ratio, flexible and transparent displays	[60, 61]

(continued)

Table 2 (continued)

Application	Description	Benefits	References
Optical data storage	Doped QDs have potential applications in optical data storage due to their stable and controllable optical properties	High storage density, long-term data retention, fast data writing and reading, compatibility with existing technology	[62]
Energy-efficient lighting	Doped QDs can be used in solid-state lighting to achieve energy efficiency and long lifetimes, such as in quantum dot-based down-converters for LEDs	High color quality, energy efficiency, long operational lifetime, warm white lighting	[63, 64]

6.3 Photovoltaics

The utilisation of doped QDs is currently being extensively investigated for their potential application in photovoltaics [65–68], with a particular focus on enhancing light absorption and overall conversion efficiency. The bandgap of QDs can be precisely adjusted to enhance the absorption of a wider range of wavelengths in the solar spectrum by introducing various materials or impurities. Furthermore, it has been observed that QDs that have been doped possess the capability to produce numerous excitons from a solitary high-energy photon. This occurrence is commonly referred to as multiple exciton generation (MEG) and has the potential to augment the effectiveness of solar cells. Moreover, the introduction of precise impurities can result in the formation of intermediate bands within the bandgap of QDs, which facilitates the absorption of photons possessing energies lower than the material's bandgap. The utilisation of intermediate band solar cells presents a potentially auspicious pathway towards achieving enhanced efficiency in the conversion of solar energy. In addition, doped QDs have the potential to serve as sensitizers in the context of QDs sensitised solar cells [69–71], wherein they are capable of absorbing photons and subsequently transferring the resulting electrons to a photoactive material. This methodology enables the utilisation of economical and solution-deposited substances while upholding elevated conversion efficacy. Ongoing investigation and innovation in the application of doped QDs exhibit significant promise in propelling the domain of photovoltaics forward.

The synthesis of N, S-doped carbon QDs (N, S-CQDs) was reported through a straightforward hydrothermal treatment approach utilising ascorbic acid and ammonium persulfate as reagents [72]. The enhancements in performance and the removal of the light-soaking phenomenon in ZnO:N, S-CQDs cells are ascribed to the passivation of surface defects in ZnO by N, S-CQDs (Fig. 6). This conclusion is supported by fluorescence spectroscopy and scanning Kelvin probe microscopy. The power conversion efficiency of cells with N, S-CQDs-modified ZnO ETL was observed to be 9.31%, indicating a significant improvement compared to the reference ZnO cells.

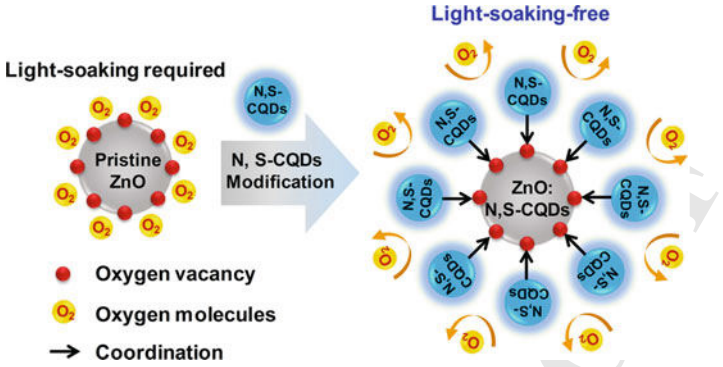


Fig. 6 The mechanism for the passivation of surface defects on ZnO nanoparticles through the utilisation of N, S-functionalized carbon QDs (CQDs). Reproduced with the permission from Ref. [72] © 2019 American chemical society

Si QDs (QDs) were synthesised in SiO2 using a co-sputtering technique, resulting in multiple layers with a narrow size distribution. The present study investigates the structural, electrical, and optical characteristics of multilayer films composed of Si QDs (QDs) and SiO2. The films were prepared by introducing varying concentrations of boron (B) during the sputtering process [73]. It was observed that the intensity of photoluminescence (PL) decreased as the concentration of boron increased. Yang et al. conducted a study in which they produced a range of nitrogen-doped carbon QDs (N-CQDs) through hydrothermal synthesis at varying temperatures, utilising Eichhornia crassipes (ECs) as the source material [74]. The researchers conducted an experimental fabrication of N-CQDs sensitised solar cells, resulting in lower power conversion efficiency when compared to state-of-the-art devices that are based on silicon, polymer, dye, CdS, CdSe, or perovskite.

6.4 Catalysis

Doped QDs have exhibited considerable potential in the domain of catalysis, wherein they can augment the efficacy and specificity of diverse chemical reactions. Several potential uses of doped QDs in catalysis have been identified. The utilisation of doped QDs as photocatalysts is a promising approach for facilitating chemical reactions through the conversion of light energy. The process of doping allows for accurate manipulation of the electronic configuration, thereby facilitating the production and transmission of charge carriers. The aforementioned ability amplifies the effectiveness of photocatalytic processes, such as the division of water for the purpose of producing hydrogen or the breakdown of pollutants. QDs, upon doping with particular atoms or functional groups, exhibit remarkable catalytic activity and selectivity for diverse reactions in the realm of heterogeneous catalysis. The process of doping

induces modifications in the surface characteristics and electronic configuration, thereby facilitating improved adsorption, activation, and reaction kinetics. The utilisation of doped QDs has been investigated for catalysing various reactions, including carbon dioxide reduction, nitrogen fixation, and organic transformations. The utilisation of doped QDs as electrocatalysts has been observed in facilitating electrochemical reactions, specifically oxygen reduction and hydrogen evolution [75–77]. This process is known as electrocatalysis. The process of doping has the potential to enhance the electronic structure, thereby facilitating charge transfer kinetics and augmenting catalytic performance. QDs that have been doped exhibit enhanced electrocatalytic performance in comparison to conventional catalysts, thereby presenting promising prospects for utilisation in fuel cells, batteries, and electrolyzers. Doped QDs have the ability to imitate the catalytic activity of enzymes, which is commonly referred to as artificial enzyme mimetics or nanozymes. The catalytic properties of enzymes, such as oxidase, peroxidase, or catalase-like activities, can be emulated by doping QDs with particular ions or functional groups [78, 79]. Nanozymes present several benefits, including enhanced stability, customizable properties, and economical feasibility in contrast to their natural enzyme counterparts. These attributes create opportunities for their implementation in various domains, such as biosensing, environmental restoration, and medical research.

Prekodravac et al. presented a rapid and efficient method for synthesising nitrogen-doped carbon QDs in an aqueous medium without the use of metal catalysts. This was achieved through the utilisation of a microwave reactor [80]. A synthesis was conducted on a glucose water solution utilising a microwave reactor under low temperature and applied microwave power for a duration of only 1 min. The N-doped carbon QDs that were synthesised exhibit noteworthy photocatalytic efficacy in eliminating hazardous organic dye (Rose Bengal) when subjected to visible light radiation. A significant degradation of approximately 93% of the dye is attained within a brief period of 30 min of radiation. The synthesis of fluorescent nitrogen doped carbon dots (N-CDs) was discussed in a report, using a straightforward hydrothermal method [81]. The N-CDs exhibit remarkable catalytic efficacy in the sodium borohydride-mediated reduction of methylene blue. Elsewhere, a report was made on the green synthesis of fluorescent nitrogen-doped carbon dots (N-CDs) utilising *Actinidia deliciosa* (A. deliciosa) fruit extract as a carbon precursor and aqueous ammonia as a nitrogen dopant [82]. Chandrasekaran et al. have documented a straightforward and environmentally-friendly hydrothermal method for synthesising nitrogen-doped carbon dots (N-CDs) utilising *C.grandis* and aq.NH3 as carbon and nitrogen sources, respectively [83]. The catalytic activity of NaBH4 in the reduction of methyl orange was affected by the synthesised N-CDs. The rate constant of the reduction process of organic dye, specifically methyl orange, by NaBH4 in the presence of the synthesised green catalyst was also ascertained.

7 Prospects for Future Developments and Applications

The potential for advancements and utilisation of doped QDs (QDs) in the future is exceedingly auspicious. The following are prospective domains of progress.

Doped QDs (QDs) can be customised to demonstrate distinct optical and electronic characteristics, rendering them highly suitable for advanced optoelectronic devices. Enhancements in synthesis methodologies have the potential to facilitate the creation of lasers, LEDs, and photodetectors based on QDs, which exhibit superior efficiency, colour purity, and stability.

Doped QDs (QDs) exhibit significant promise in sensing applications owing to their exceptional sensitivity and selectivity. The optical properties of materials can be adjusted to enable the detection of particular molecules or ions by introducing precise dopants. Prospective advancements could result in the production of exceedingly responsive and easily transportable sensors based on QDs (QDs) for the purposes of monitoring the environment, diagnosing medical conditions, and ensuring food safety.

Doped QDs (QDs) have the potential to significantly contribute to the advancement of renewable energy technologies through energy harvesting and storage. By enhancing their electronic characteristics, they can be employed in high-performance photovoltaic cells for the conversion of solar energy into electrical energy. Moreover, the utilisation of doped QDs (QDs) can be investigated for the purpose of energy storage in various applications, including supercapacitors and electrochemical reactions as catalysts.

Doped QDs (QDs) have garnered significant interest as contrast agents in bioimaging and as targeted drug delivery systems for biomedical applications. The distinctive optical characteristics of nanoparticles, in conjunction with surface alterations, facilitate the accurate visualisation of biological structures and the regulated dispensation of therapeutic agents. Subsequent progressions may potentially result in the creation of diagnostic and therapeutic instruments that are safer and more effective in the field of medicine.

Doped QDs (QDs) exhibit potential for utilisation in quantum computing and quantum information processing, as they possess the capability to confine and manipulate individual charges and spins. Advancements in dopant engineering and control have the potential to facilitate the achievement of quantum computing architectures that are both scalable and resilient.

Doped QDs (QDs) have potential for utilisation in environmental applications, specifically in photocatalysis for the purpose of water purification or pollutant degradation. Moreover, these can be incorporated into lighting systems that are designed to be energy-efficient, thereby mitigating energy usage and environmental repercussions. Prospective progressions may facilitate the creation of more environmentally friendly technologies that entail diminished resource consumption and enhanced efficacy.

In general, the potential applications and advancements of doped QDs are extensive and offer significant promise in diverse scientific and technological domains.

Further investigation, refinement of manufacturing techniques, and examination of innovative additives and structures will facilitate the realisation of their complete potential and broaden their pragmatic implementations.

8 Present Market of Doped QDs

The market for doped QDs (QDs) is still in its early stages but is projected to experience substantial growth in the coming years. The unique characteristics and potential applications of doped QDs (QDs) are the primary drivers behind the increasing demand for them across diverse industrial sectors. The market for QDs (Fig. 7), including doped QDs, is expected to grow significantly in the coming years. Several market research reports indicate that the QDs market is anticipated to attain a significant valuation in the billions by the year 2026, exhibiting a compound annual growth rate (CAGR) exceeding 20%. The growth in question is being propelled by several factors, including but not limited to the escalating demand for displays that are energy-efficient, the progress made in healthcare imaging technologies, and the increasing acceptance of sensors that are based on QDs. While it's challenging to provide specific market figures, here are some key insights into the current market of doped QDs:

Doped QDs (QDs) are increasingly being utilised in the optoelectronics sector, specifically in display technologies like quantum dot LED (QLED) displays. QLED displays provide several benefits, including superior colour precision, a broad range of colours, and low power consumption. Doped QDs are progressively gaining popularity in the realm of consumer electronics, encompassing devices such as televisions, smartphones, and monitors.

Doped QDs (QDs) are employed as fluorescent markers in biomedical imaging owing to their exceptional optical characteristics, including high luminosity and

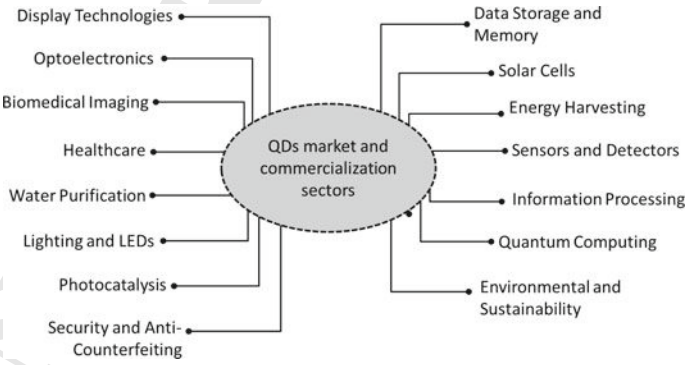


Fig. 7 Different types of application areas for QDs based products

resistance to photobleaching. They offer enhanced imaging capabilities for applications in biological research, diagnostics, and drug delivery. Ongoing research and commercialization efforts have identified the biomedical imaging sector as a significant market for doped QDs.

Energy and Solar Cells: Doped QDs hold promise in the field of energy conversion and storage. The tunable bandgap and high absorption efficiency of these materials have rendered them a subject of exploration for their potential application as constituents of next-generation solar cells. Doped QDs offer the potential for increased solar cell efficiency and reduced production costs, driving their adoption in the renewable energy sector.

Sensors and Detectors: Doped QDs are being developed for various sensing applications. They exhibit high sensitivity, selectivity, and stability, making them suitable for environmental monitoring, biosensing, and chemical detection. Doped QD-based sensors and detectors have the potential to provide rapid, accurate, and cost-effective solutions for diverse industries.

Research and Development: The market for doped QDs is also supported by ongoing research and development activities. Researchers are exploring new doping strategies, optimizing synthesis techniques, and investigating novel applications. This continuous innovation fuels the growth of the doped QD market and opens up possibilities for emerging applications.

It's important to note that the market for doped QDs is dynamic and evolving, with ongoing technological advancements and increasing commercialization efforts. The integration of doped QDs into various industrial applications is anticipated to result in an increase in market size and revenue.

9 Conclusion

To summarise, the synthesis strategies utilised for doped QDs comprise a variety of methods with the objective of integrating dopants into the QD lattice to attain specific electronic and optical characteristics. The aforementioned tactics encompass codoping, post-synthetic doping, ion exchange, alloying, and core-shell architectures. The process of codoping entails the concurrent introduction of multiple dopants during the synthesis of QDs, thereby enabling accurate regulation of both dopant concentration and combination. The process of post-synthetic doping pertains to the introduction of dopants onto pre-synthesized QDs through surface modification or ligand exchange procedures. The process of ion exchange entails the substitution of the initial cations or anions present in the quantum dot lattice with dopant ions. The process of alloying involves the integration of distinct semiconductor materials, along with the inclusion of dopants during the alloying procedure. The utilisation of core-shell structures allows for the confinement of doped QDs within a safeguarding shell, thereby facilitating the regulation of dopant diffusion and associated characteristics.

The implementation of synthesis strategies provides a malleable and adaptable approach to customise the characteristics of doped QDs to meet particular utilisation

requirements. The optimisation of doped QDs for various applications such as optoelectronics, photovoltaics, sensing, and bioimaging can be achieved by manipulating dopant concentration, distribution, and combination, as per the research findings. In summary, the implementation of synthesis strategies involving doped QDs has resulted in notable progressions within the realm of nanotechnology and nanomaterials. The deliberate incorporation of impurities into QDs has presented novel opportunities for the manipulation of their optical and electronic characteristics, resulting in improved functionalities and innovative applications. Further investigation in this domain exhibits potential for enhancing these amalgamation approaches, broadening the scope of dopants and substrates, and unleashing the complete potential of doped QDs in various domains.

References

1. Makkar, M., Viswanatha, R.: Frontier challenges in doping quantum dots: synthesis and characterization. RSC Adv. **8**(39), 22103–22112 (2018)
2. Mocatta, D., Cohen, G., Schattner, J., Millo, O., Rabani, E., Banin, U.: Heavily doped semiconductor nanocrystal quantum dots. Science **332**(6025), 77–81 (2011)
3. Grandhi, G.K., Tomar, R., Viswanatha, R.: Study of surface and bulk electronic structure of II–VI semiconductor nanocrystals using Cu as a nanosensor. ACS Nano **6**(11), 9751–9763 (2012)
4. Hanif, K.M., Meulenberg, R.W., Strouse, G.F.: Magnetic ordering in doped Cd1-x Co x Se diluted magnetic quantum dots. J. Am. Chem. Soc. **124**(38), 11495–11502 (2002)
5. Grandhi, G.K., Swathi, K., Narayan, K., Viswanatha, R.: Cu doping in ligand free CdS nanocrystals: conductivity and electronic structure study. The J. Phys. Chem. Lett. **5**(13), 2382–2389 (2014)
6. Shanker, G.S., Tandon, B., Shibata, T., Chattopadhyay, S., Nag, A.: Doping controls plasmonics, electrical conductivity, and carrier-mediated magnetic coupling in Fe and Sn codoped In_2O_3 nanocrystals: local structure is the key. Chem. Mater. **27**(3), 892–900 (2015)
7. Baker, S.N., Baker, G.A.: Luminescent carbon nanodots: emergent nanolights. Angew. Chem. Int. Ed. **49**(38), 6726–6744 (2010)
8. Larson, L.A., Williams, J.M., Current, M.I.: Ion implantation for semiconductor doping and materials modification. Rev. Accel. Sci. Technol. **4**(01), 11–40 (2011)
9. Salzmann, I., Heimel, G., Oehzelt, M., Winkler, S., Koch, N.: Molecular electrical doping of organic semiconductors: fundamental mechanisms and emerging dopant design rules. Acc. Chem. Res. **49**(3), 370–378 (2016)
10. Sinatra, L., Pan, J., Bakr, O.M.: Methods of synthesizing monodisperse colloidal quantum dots. Mater. Matters **12**, 3–7 (2017)
11. Salaheldin, A.M., Walter, J., Herre, P., Levchuk, I., Jabbari, Y., Kolle, J.M., Brabec, C.J., Peukert, W., Segets, D.: Automated synthesis of quantum dot nanocrystals by hot injection: mixing induced self-focusing. Chem. Eng. J. **320**, 232–243 (2017)
12. Xu, Q., Kuang, T., Liu, Y., Cai, L., Peng, X., Sreeprasad, T.S., Zhao, P., Yu, Z., Li, N.: Heteroatom-doped carbon dots: synthesis, characterization, properties, photoluminescence mechanism and biological applications. J. Mater. Chem. B **4**(45), 7204–7219 (2016)
13. Das, P., Ganguly, S., Margel, S., Gedanken, A.: Tailor made magnetic nanolights: fabrication to cancer theranostics applications. Nanoscale Adv. **3**(24), 6762–6796 (2021)
14. Das, P., Ganguly, S., Margel, S., Gedanken, A.: Immobilization of heteroatom-doped carbon dots onto nonpolar plastics for antifogging, antioxidant, and food monitoring applications. Langmuir **37**(11), 3508–3520 (2021)

602599_1_En_3_Chapter ☑ TYPESET ☐ DISK ☐ LE ☑ CP Disp.:23/2/2024 Pages: 29 Layout: T1-Standard

15. Das, P., Ganguly, S., Saravanan, A., Margel, S., Gedanken, A., Srinivasan, S., Rajabzadeh, A.R.: Naturally derived carbon dots in situ confined self-healing and breathable hydrogel monolith for anomalous diffusion-driven phytomedicine release. ACS Appl. Bio Mater. (2022)
16. Das, P., Ganguly, S., Ahmed, S.R., Sherazee, M., Margel, S., Gedanken, A., Srinivasan, S., Rajabzadeh, A.R.: Carbon dot biopolymer-based flexible functional films for antioxidant and food monitoring applications. ACS Appl. Polym. Mater. **4**(12), 9323–9340 (2022)
17. Das, P., Ganguly, S., Saha, A., Noked, M., Margel, S., Gedanken, A.: Carbon-dots-initiated photopolymerization: an in situ synthetic approach for MXene/poly (norepinephrine)/copper hybrid and its application for mitigating water pollution. ACS Appl. Mater. Interfaces **13**(26), 31038–31050 (2021)
18. Das, P., Maruthapandi, M., Saravanan, A., Natan, M., Jacobi, G., Banin, E., Gedanken, A.: Carbon dots for heavy-metal sensing, pH-sensitive cargo delivery, and antibacterial applications. ACS Appl. Nano Mater. **3**(12), 11777–11790 (2020)
19. Ganguly, S., Das, P., Itzhaki, E., Hadad, E., Gedanken, A., Margel, S.: Microwave-synthesized polysaccharide-derived carbon dots as therapeutic cargoes and toughening agents for elastomeric gels. ACS Appl. Mater. Interfaces **12**(46), 51940–51951 (2020)
20. Saravanan, A., Maruthapandi, M., Das, P., Ganguly, S., Margel, S., Luong, J.H., Gedanken, A.: Applications of N-doped carbon dots as antimicrobial agents, antibiotic carriers, and selective fluorescent probes for nitro explosives. ACS Appl. Bio Mater. **3**(11), 8023–8031 (2020)
21. Shim, M., Guyot-Sionnest, P.: N-type colloidal semiconductor nanocrystals. Nature **407**(6807), 981–983 (2000)
22. Shim, M., Wang, C., Guyot-Sionnest, P.: Charge-tunable optical properties in colloidal semiconductor nanocrystals. J. Phys. Chem. B **105**(12), 2369–2373 (2001)
23. Yu, D., Wang, C., Guyot-Sionnest, P.: N-Type conducting CdSe nanocrystal solids. Science **300**(5623), 1277–1280 (2003)
24. Talapin, D.V., Murray, C.B.: PbSe nanocrystal solids for n-and p-channel thin film field-effect transistors. Science **310**(5745), 86–89 (2005)
25. Kovalenko, M.V., Bodnarchuk, M.I., Zaumseil, J., Lee, J.-S., Talapin, D.V.: Expanding the chemical versatility of colloidal nanocrystals capped with molecular metal chalcogenide ligands. J. Am. Chem. Soc. **132**(29), 10085–10092 (2010)
26. Pradhan, N., Goorskey, D., Thessing, J., Peng, X.: An alternative of CdSe nanocrystal emitters: pure and tunable impurity emissions in ZnSe nanocrystals. J. Am. Chem. Soc. **127**(50), 17586–17587 (2005)
27. Grandhi, G.K., Viswanatha, R.: Demystifying complex quantum dot heterostructures using photogenerated charge carriers. J. Phys. Chem. Lett. **8**(9), 2043–2048 (2017)
28. Barrows, C.J., Chakraborty, P., Kornowske, L.M., Gamelin, D.R.: Tuning equilibrium compositions in colloidal Cd1–x Mn x Se nanocrystals using diffusion doping and cation exchange. ACS Nano **10**(1), 910–918 (2016)
29. Son, D.H., Hughes, S.M., Yin, Y., Paul Alivisatos, A.: Cation exchange reactions in ionic nanocrystals. Science **306**(5698), 1009–1012 (2004)
30. Beberwyck, B.J., Surendranath, Y., Alivisatos, A.P.: Cation exchange: a versatile tool for nanomaterials synthesis. J. Phys. Chem. C **117**(39), 19759–19770 (2013)
31. Robinson, R.D., Sadtler, B., Demchenko, D.O., Erdonmez, C.K., Wang, L.-W., Alivisatos, A.P.: Spontaneous superlattice formation in nanorods through partial cation exchange. Science **317**(5836), 355–358 (2007)
32. Sadtler, B., Demchenko, D.O., Zheng, H., Hughes, S.M., Merkle, M.G., Dahmen, U., Wang, L.-W., Alivisatos, A.P.: Selective facet reactivity during cation exchange in cadmium sulfide nanorods. J. Am. Chem. Soc. **131**(14), 5285–5293 (2009)
33. Demchenko, D.O., Robinson, R.D., Sadtler, B., Erdonmez, C.K., Alivisatos, A.P., Wang, L.-W.: Formation mechanism and properties of CdS-Ag2S nanorod superlattices. ACS Nano **2**(4), 627–636 (2008)
34. Saha, A., Shetty, A., Pavan, A., Chattopadhyay, S., Shibata, T., Viswanatha, R.: Uniform doping in quantum-dots-based dilute magnetic semiconductor. J. Phys. Chem. Lett. **7**(13), 2420–2428 (2016)

35. Saha, A., Makkar, M., Shetty, A., Gahlot, K., Pavan, A., Viswanatha, R.: Diffusion doping in quantum dots: bond strength and diffusivity. Nanoscale **9**(8), 2806–2813 (2017)
36. Nair, A.N., Chava, V.S.N., Bose, S., Zheng, T., Pilla, S., Sreenivasan, S.T.: In situ doping-enabled metal and nonmetal codoping in graphene quantum dots: synthesis and application for contaminant sensing. ACS Sustain. Chem. Eng. **8**(44), 16565–16576 (2020). https://doi.org/10.1021/acssuschemeng.0c05789
37. Schwartz, D.A., Norberg, N.S., Nguyen, Q.P., Parker, J.M., Gamelin, D.R.: Magnetic quantum dots: synthesis, spectroscopy, and magnetism of Co^{2+}- and Ni^{2+}-doped ZnO nanocrystals. J. Am. Chem. Soc. **125**(43), 13205–13218 (2003). https://doi.org/10.1021/ja036811v
38. Shen, L., Zhou, S., Huang, F., Zhou, H., Zhang, H., Wang, S., Zhou, S.: Nitrogen-doped graphene quantum dots synthesized by femtosecond laser ablation in liquid from laser induced graphene. Nanotechnology **33**(11), 115602 (2021)
39. Bateni, F., Epps, R.W., Abdel-latif, K., Dargis, R., Han, S., Volk, A.A., Ramezani, M., Cai, T., Chen, O., Abolhasani, M.: Ultrafast cation doping of perovskite quantum dots in flow. Matter **4**(7), 2429–2447 (2021)
40. Wang, H., Gao, J., Zhang, M., Liu, P., Guo, Y., Li, H., Zhao, G., Hu, S., Cheng, Z., Zang, J.: ZnSe/ZnS core-shell quantum dots doped with Mn^{2+} ions for magnetic state-manipulated light sources. ACS Appl. Nano Mater. **5**(6), 8448–8456 (2022)
41. Shaik, S.A., Sengupta, S., Varma, R.S., Gawande, M.B., Goswami, A.: Syntheses of N-doped carbon quantum dots (NCQDs) from bioderived precursors: a timely update. ACS Sustain. Chem. Eng. **9**(1), 3–49 (2020)
42. Soheyli, E., Behrouzi, S., Sharifirad, Z., Sahraei, R.: Multi-colored type-I Ag-doped ZnCdS/ZnS core/shell quantum dots with intense emission. Ceram. Int. **45**(9), 11501–11507 (2019)
43. Schwartz, D.A., Norberg, N.S., Nguyen, Q.P., Parker, J.M., Gamelin, D.R.: Magnetic quantum dots: synthesis, spectroscopy, and magnetism of Co^{2+}-and Ni^{2+}-doped ZnO nanocrystals. J. Am. Chem. Soc. **125**(43), 13205–13218 (2003)
44. Das, P., Ganguly, S., Agarwal, T., Maity, P., Ghosh, S., Choudhary, S., Gangopadhyay, S., Maiti, T.K., Dhara, S., Banerjee, S.: Heteroatom doped blue luminescent carbon dots as a nano-probe for targeted cell labeling and anticancer drug delivery vehicle. Mater. Chem. Phys. **237**, 121860 (2019)
45. Das, P., Ganguly, S., Bose, M., Mondal, S., Choudhary, S., Gangopadhyay, S., Das, A.K., Banerjee, S., Das, N.C.: Zinc and nitrogen ornamented bluish white luminescent carbon dots for engrossing bacteriostatic activity and Fenton based bio-sensor. Mater. Sci. Eng. C **88**, 115–129 (2018)
46. Tavakoli, M.M.: Surface engineering of Pbs colloidal quantum dots using atomic passivation for photovoltaic applications. Proc. Eng. **139**, 117–122 (2016)
47. Radovanovic, P.V., Gamelin, D.R.: Electronic absorption spectroscopy of cobalt ions in diluted magnetic semiconductor quantum dots: demonstration of an isocrystalline core/shell synthetic method. J. Am. Chem. Soc. **123**(49), 12207–12214 (2001)
48. Tejwan, N., Saini, A.K., Sharma, A., Singh, T.A., Kumar, N., Das, J.: Metal-doped and hybrid carbon dots: a comprehensive review on their synthesis and biomedical applications. J. Control. Release **330**, 132–150 (2021)
49. Jing, H.H., Bardakci, F., Akgöl, S., Kusat, K., Adnan, M., Alam, M.J., Gupta, R., Sahreen, S., Chen, Y., Gopinath, S.C.: Green carbon dots: synthesis, characterization, properties and biomedical applications. J. Funct. Biomater. **14**(1), 27 (2023)
50. Stroyuk, O., Raievska, O., Langner, S., Kupfer, C., Barabash, A., Solonenko, D., Azhniuk, Y., Hauch, J., Osvet, A., Batentschuk, M.: High-throughput robotic synthesis and photoluminescence characterization of aqueous multinary copper–silver indium chalcogenide quantum dots. Part. Part. Syst. Charact. **38**(10), 2100169 (2021)
51. Schroer, Z.S., Wu, Y., Xing, Y., Wu, X., Liu, X., Wang, X., Pino, O.G., Zhou, C., Combs, C., Pu, Q., Wu, M., Zhao, J.X., Chen, J.: Nitrogen–sulfur-doped graphene quantum dots with metal ion-resistance for bioimaging. ACS Appl. Nano Mater. **2**(11), 6858–6865 (2019). https://doi.org/10.1021/acsanm.9b01309

52. Bozyigit, D., Wood, V.: Challenges and solutions for high-efficiency quantum dot-based LEDs. MRS Bull. **38**, 731–736 (2013)
53. Blokhin, S., Sakharov, A., Nadtochy, A., Pauysov, A., Maximov, M., Ledentsov, N., Kovsh, A., Mikhrin, S., Lantratov, V., Mintairov, S.: AlGaAs/GaAs photovoltaic cells with an array of InGaAs QDs. Semiconductors **43**, 514–518 (2009)
54. Nozik, A.J., Beard, M.C., Luther, J.M., Law, M., Ellingson, R.J., Johnson, J.C.: Semiconductor quantum dots and quantum dot arrays and applications of multiple exciton generation to third-generation photovoltaic solar cells. Chem. Rev. **110**(11), 6873–6890 (2010)
55. Sanehira, E.M., Marshall, A.R., Christians, J.A., Harvey, S.P., Ciesielski, P.N., Wheeler, L.M., Schulz, P., Lin, L.Y., Beard, M.C., Luther, J.M.: Enhanced mobility CsPbI3 quantum dot arrays for record-efficiency, high-voltage photovoltaic cells. Sci. Adv. **3**(10), eaao4204 (2017)
56. Oertel, D.C., Bawendi, M.G., Arango, A.C., Bulović, V.: Photodetectors based on treated CdSe quantum-dot films. Appl. Phys. Lett. **87**(21), 213505 (2005)
57. Ledentsov, N.N., Grundmann, M., Heinrichsdorff, F., Bimberg, D., Ustinov, V., Zhukov, A., Maximov, M., Alferov, Z.I., Lott, J.: Quantum-dot heterostructure lasers. IEEE J. Sel. Top. Quantum Electron. **6**(3), 439–451 (2000)
58. De Rinaldis, S., D'Amico, I., Biolatti, E., Rinaldi, R., Cingolani, R., Rossi, F.: Intrinsic exciton-exciton coupling in GaN-based quantum dots: application to solid-state quantum computing. Phys. Rev. B **65**(8), 081309 (2002)
59. Molaei, M.J.: Principles, mechanisms, and application of carbon quantum dots in sensors: a review. Anal. Meth. **12**(10), 1266–1287 (2020)
60. Frecker, T., Bailey, D., Arzeta-Ferrer, X., McBride, J., Rosenthal, S.J.: Quantum dots and their application in lighting, displays, and biology. ECS J. Solid State Sci. Technol. **5**(1), R3019 (2015)
61. Bourzac, K.: Quantum dots go on display. Nature **493**(7432), 283 (2013)
62. Bimberg, D., Pohl, U.W.: Quantum dots: promises and accomplishments. Mater. Today **14**(9), 388–397 (2011)
63. Pode, R.: Organic light emitting diode devices: an energy efficient solid state lighting for applications. Renew. Sustain. Energy Rev. **133**, 110043 (2020)
64. Shirasaki, Y., Supran, G.J., Bawendi, M.G., Bulović, V.: Emergence of colloidal quantum-dot light-emitting technologies. Nat. Photon. **7**(1), 13–23 (2013)
65. Liu, F., Ding, C., Zhang, Y., Kamisaka, T., Zhao, Q., Luther, J.M., Toyoda, T., Hayase, S., Minemoto, T., Yoshino, K.: GeI2 additive for high optoelectronic quality CsPbI3 quantum dots and their application in photovoltaic devices. Chem. Mater. **31**(3), 798–807 (2019)
66. Liu, B., Wang, D., Zhang, Y., Fan, H., Lin, Y., Jiang, T., Xie, T.: Photoelectrical properties of Ag_2S quantum dot-modified TiO_2 nanorod arrays and their application for photovoltaic devices. Dalton Trans. **42**(6), 2232–2237 (2013)
67. Jabeen, U., Adhikari, T., Shah, S.M., Pathak, D., Kumar, V., Nunzi, J.-M., Aamir, M., Mushtaq, A.: Synthesis, characterization and photovoltaic applications of noble metal—doped ZnS quantum dots. Chin. J. Phys. **58**, 348–362 (2019)
68. Veerathangam, K., Pandian, M.S., Ramasamy, P.: Photovoltaic performance of Ag-doped CdS quantum dots for solar cell application. Mater. Res. Bull. **94**, 371–377 (2017)
69. Rühle, S., Shalom, M., Zaban, A.: Quantum-dot-sensitized solar cells. ChemPhysChem **11**(11), 2290–2304 (2010)
70. Mora-Sero, I., Giménez, S., Fabregat-Santiago, F., Gómez, R., Shen, Q., Toyoda, T., Bisquert, J.: Recombination in quantum dot sensitized solar cells. Acc. Chem. Res. **42**(11), 1848–1857 (2009)
71. Tian, J., Cao, G.: Semiconductor quantum dot-sensitized solar cells. Nano Rev. **4**(1), 22578 (2013)
72. Wang, Y., Yan, L., Ji, G., Wang, C., Gu, H., Luo, Q., Chen, Q., Chen, L., Yang, Y., Ma, C.-Q., Liu, X.: Synthesis of N, S-doped carbon quantum dots for use in organic solar cells as the ZnO modifier to eliminate the light-soaking effect. ACS Appl. Mater. Interfaces **11**(2), 2243–2253 (2019). https://doi.org/10.1021/acsami.8b17128

73. Hao, X., Cho, E.-C., Flynn, C., Shen, Y., Park, S.-C., Conibeer, G., Green, M.A.: Synthesis and characterization of boron-doped Si quantum dots for all-Si quantum dot tandem solar cells. Sol. Energy Mater. Sol. Cells **93**(2), 273–279 (2009)
74. Yang, Q., Duan, J., Yang, W., Li, X., Mo, J., Yang, P., Tang, Q.: Nitrogen-doped carbon quantum dots from biomass via simple one-pot method and exploration of their application. Appl. Surf. Sci. **434**, 1079–1085 (2018)
75. Tian, L., Li, Z., Wang, P., Zhai, X., Wang, X., Li, T.: Carbon quantum dots for advanced electrocatalysis. J. Energy Chem. **55**, 279–294 (2021)
76. Liu, Z.Q., Cheng, H., Li, N., Ma, T.Y., Su, Y.Z.: $ZnCo_2O_4$ quantum dots anchored on nitrogen-doped carbon nanotubes as reversible oxygen reduction/evolution electrocatalysts. Adv. Mater. **28**(19), 3777–3784 (2016)
77. Fei, H., Ye, R., Ye, G., Gong, Y., Peng, Z., Fan, X., Samuel, E.L., Ajayan, P.M., Tour, J.M.: Boron-and nitrogen-doped graphene quantum dots/graphene hybrid nanoplatelets as efficient electrocatalysts for oxygen reduction. ACS Nano **8**(10), 10837–10843 (2014)
78. Lopez-Cantu, D.O., González-González, R.B., Melchor-Martínez, E.M., Martínez, S.A.H., Araújo, R.G., Parra-Arroyo, L., Sosa-Hernández, J.E., Parra-Saldívar, R., Iqbal, H.M.: Enzyme-mimicking capacities of carbon-dots nanozymes: properties, catalytic mechanism, and applications—a review. Int. J. Biol. Macromol. **194**, 676–687 (2022)
79. Nirala, N.R., Abraham, S., Kumar, V., Bansal, A., Srivastava, A., Saxena, P.S.: Colorimetric detection of cholesterol based on highly efficient peroxidase mimetic activity of graphene quantum dots. Sens. Actuators B Chem. **218**, 42–50 (2015)
80. Prekodravac, J., Vasiljević, B., Marković, Z., Jovanović, D., Kleut, D., Špitalský, Z., Mičušik, M., Danko, M., Bajuk-Bogdanović, D., Todorović–Marković B,: Green and facile microwave assisted synthesis of (metal-free) N-doped carbon quantum dots for catalytic applications. Ceram. Int. **45**(14), 17006–17013 (2019)
81. Arul, V., Edison, T.N.J.I., Lee, Y.R., Sethuraman, M.G.: Biological and catalytic applications of green synthesized fluorescent N-doped carbon dots using Hylocereus undatus. J. Photochem. Photobiol. B. **168**, 142–148 (2017)
82. Arul, V., Sethuraman, M.G.: Facile green synthesis of fluorescent N-doped carbon dots from Actinidia deliciosa and their catalytic activity and cytotoxicity applications. Opt. Mater. **78**, 181–190 (2018). https://doi.org/10.1016/j.optmat.2018.02.029
83. Chandrasekaran, P., Arul, V., Sethuraman, M.G.: Ecofriendly synthesis of fluorescent nitrogen-doped carbon dots from coccinia grandis and its efficient catalytic application in the reduction of methyl orange. J. Fluoresc. **30**, 103–112 (2020)

Author Queries

Chapter 3

Query Refs.	Details Required	Author's response
AQ1	Please check and confirm if the author names and initials are correct.	
AQ2	Please confirm if the section headings identified are correct.	

Advanced Research in Medical Science & Technology

Volume - 3

Chief Editor

Dr. Anil Meena
Associate Professor, Department of Pathology, Government Medical College, Ratlam, Madhya Pradesh, India

Integrated Publications ™
New Delhi

Published By: *Integrated Publications*

Integrated Publications
H. No. - 3 Pocket - H34, Sector - 3,
Rohini, Delhi-110085, India

Chief Editor: Dr. Anil Meena

Publication Year: 2024

Pages: 92

ISBN: 978-93-5834-559-9

Price: ₹ 702/-

Contents

Chapter - 1

Amyloids and Alzheimer's disease: An Examination of Screening Methods

Authors

Mahavir M. Sharma
Assistant Professor, Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Harsh Kumar Brahmbhatt
Assistant Professor, Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Chapter - 1

Amyloids and Alzheimer's disease: An Examination of Screening Methods

Mahavir M. Sharma and Harsh Kumar Brahmbhatt

Abstract

Amyloid fibrils are lengthy protein aggregates that may form on their own. They are associated with a number of diseases, including Alzheimer's and Parkinson's, which are now incurable and affect a large number of people throughout the world. In this page, you will find an overview of the unique β-structure, various morphological patterns, development dynamics, and detrimental consequences of amyloid fibrils and oligomers. Several approaches to diseases caused by amyloid are shown using Alzheimer's disease as an example. In addition, the article delves into the biological and nanotechnology uses of amyloid fibrils and gives a rundown of the typical biological mechanisms that remove them and their precursors.

Keywords: Amyloidfibrils, alzheimer's disease, fibrilstructure, *In vitro & In vivo* model

1. Introduction

Cognitive loss and neuronal death are hallmarks of Alzheimer's disease (AD), a neuropsychiatric disorder that worsens with time and cannot be reversed [1]. More than 80% of dementia cases in the elderly are caused by it [2]. The German psychiatrist and neuropathologist Dr. Alois Alzheimer was the first to notice and record the symptoms of this illness, which was subsequently named after him. Memory loss, aphasia, disorientation, behavioural abnormalities, and psychological impairment were among of the symptoms seen in Auguste D, a 51-year-old lady who was the first case study of Dr. Alzheimer. Over a century ago, Alzheimer presented a range of clinical observations and pathological findings that continue to form the foundation of our current understanding of AD [3].

The cortex and hippocampus are two regions of the brain that are particularly vulnerable to the devastating effects of Alzheimer's disease (AD), a complicated neurodegenerative disorder [2]. Deterioration of cortical

neurons, especially pyramidal cells that are in charge of higher-level cognitive functions, occurs over time. The development of β-amyloid plaques outside the neurons and the buildup of hyper phosphorylated tau (tangles) within the neurons are important pathogenic characteristics of Alzheimer's disease. These alterations ultimately lead to the degeneration and demise of neurons in the brain [4].

2. Epidemiology

Alzheimer's disease stands as a prevalent neurodegenerative condition [2]. Worldwide, 46.8 million people were impacted by dementia in 2015, with predictions that number would increase to 74.7 million in 2030 and 131.5 million in 2050, based on the World Alzheimer Report 2015. Of the overall number of persons living with dementia in 2015, 9.8 million were in East Asia, 7.4 million in Western Europe, 5.1 million in South Asia, and 4.8 million in North America [4, 5].

3. Etiology [6]

- **Genetic factors**
  - Alterations to chromosomes1.
  - Alterations tochromosomes14.
  - Alterations tochromosomes21.
  - Inheritance of the apo E4 iso form.
- **Environmental and other factors**
  - Stroke
  - Alcohol abuse
  - Small head circumference
  - Repeated or severe head trauma
  - Down syndrome
  - Lower levels of education
  - Diabetes

4. Pathophysiology

Some of the neuropathological hallmarks of Alzheimer's disease (AD) include amyloid angiopathy, dystrophic neuritis, intracellular neurofibrillary tangles (NFTs), and extracellular amyloid plaques [7]. The pathophysiology of Alzheimer's disease has been the subject of several hypothesised theories, including as the amyloid cascade, tau, vascular, oxidative stress,

inflammatory and cholesterol hypotheses. Proteolytic cleavages of the amyloid precursor protein lead to the buildup of amyloid plaques, namely Aβ42, according to the amyloid cascade theory, which is the fundamental pathology of Alzheimer's disease (APP). In the process that does not lead to amyloid development, α-secretase breaks down APP, which stops the production of Aβ peptides. In the amyloidogenic pathway, β-secretase and γ-secretases cleave APP, leading to the generation of Aβ40 and Aβ42, with Aβ42 being more prone to accumulation and neurotoxic effects [2, 7].

The tau hypothesis centers on the abnormal phosphorylation of tau, a microtubule-associated protein, leading to the formation of neurofibrillary tangles (NFTs). Hyperphosphorylated tau destabilizes microtubules and aggregates into paired helical filaments (PHFs), causing damage to neuronal functions and cell death [7].

The inflammatory hypothesis highlights the active role of the immune system in AD pathophysiology. Microglia, astrocytes, and neurons are inflammatory mediators that contribute to neurodegeneration via their roles in plaque formation and the production of pro-inflammatory cytokines [6-7].

The oxidative stress hypothesis posits that reactive oxygen species (ROS) generated as a by product of mitochondrial electron transport chain cause oxidative cell injury and cell death in AD. Dysfunctional electron transport chain in mitochondria leads to the accumulation of free radicals, resulting in neuronal damage [7].

The vascular hypothesis suggests that vascular risk factors and age-related changes in cerebral capillaries contribute to cerebral hypoperfusion, which leads to capillary degeneration and subsequent AD pathology [7].

The cholesterol hypothesis indicates that elevated cholesterol levels contribute to AD progression. Amyloid plaques are more likely to develop when cellular membrane cholesterol levels are high; the apoE4 gene is linked to elevated cholesterol levels in neurons and altered membrane function [6-7].

Insulin signaling plays a crucial role in AD pathogenesis. Impaired insulin signaling leads to brain insulin resistance, reduced autophosphorylation of insulin receptors and activation of detrimental signaling pathways, resulting in neurotoxicity and AD-related changes [8].

Multiple neurotransmitter pathways are affected in AD, particularly the cholinergic, serotonergic, noradrenergic and glutamatergic systems, leading

to memory and cognitive impairments [6-7]. The dysregulation of these neurotransmitters contributes to excitotoxicity and neurotoxic effects in AD.

5. Signs & Symptoms

The onset of Alzheimer's disease (AD) is typically gradual, with no sudden changes in cognition or function. AD leads to progressive deficits over time, affecting various aspects of cognition. Cognitive symptoms and non-cognitive (behavioural) symptoms are the two primary kinds of Alzheimer's symptoms that are used for diagnostic and therapy purposes. While non-cognitive symptoms might come and go, cognitive problems tend to stick around for the duration of the disease [6].

Cognitive symptoms

Memory loss, including difficulties with recall and misplacing items. Aphasia, characterized by difficulties in language, such as circumlocution (talking around a word) and anomia (difficulty finding words). Apraxia, which is the inability to perform purposeful movements or actions. Agnosia, leading to the failure to recognize familiar objects or people. Disorientation, causing problems in perceiving time and recognizing familiar individuals. Impaired executive function, leading to difficulties in planning, problem-solving, and decision-making.

No cognitive symptoms Depression's symptoms Inability to perform self-care tasks, such as dressing, bathing, toileting, and eating.

Functional symptoms

Inability to perform self-care tasks, such as dressing, bathing, toileting and eating.

6. Diagnosis

To diagnose Alzheimer's disease, doctors may:

Interview the patient and a friend or family member to gather information about the patient's overall health, changes in personality and behavior over time, ability to perform regular activities, and past medical issues. Conduct cognitive tests to assess abstract thinking, memory, problem-solving, counting, attention, and language skills.

Perform various medical tests, including urine and blood tests, to rule out other potential causes for the disease.

For a preliminary assessment, use brain scans like computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI).

Repeated administration of these tests can provide insight into changes in the patient's behavior, memory, and cognitive function over time. Additionally, these tests can help differentiate Alzheimer's disease from other conditions like vascular dementia and mild cognitive impairment. However, autopsies and biopsies of brain matter are the only ways to confirm a diagnosis of Alzheimer's disease [9, 10].

7. Pharmacological treatment [2-3, 11-13]

Timely and accurate diagnosis is essential for Alzheimer's disease, as it allows for targeted treatments based on its underlying causes. While current therapeutic options can alleviate AD-related symptoms and slow down the disease's progression in the brain, they do not offer a complete reversal of the condition. Prevention is a preferable approach since no treatment exists to fully reverse the disease progression.

At present, available treatments for AD include glutamate antagonists and cholinesterase inhibitors, which provide limited symptomatic relief. However, drugs aimed at addressing the disease's root causes are still undergoing clinical trials, offering hope for more effective and etiology-based treatment options in the future.

Acetylcholinesterase inhibitors

Cholinesterase inhibitors are the primary drugs used for treating Alzheimer's disease, as they target acetylcholine (ACh), a neurotransmitter crucial for memory and learning. Several compounds, including tacrine, donepezil, rivastigmine, xanthostigmine, galantamine, pyrroloisoxazole analogs, para-aminobenzoic acid, flavonoid, and coumarin, have been studied for AD treatment. Approved drugs such as rivastigmine, galantamine, and donepezil inhibit the acetylcholinesterase enzyme responsible for degrading acetylcholine, thus improving cholinergic brain function. Apart from tacrine, cholinesterase inhibitors are generally well-tolerated, but some dose-related adverse effects may occur. Ladostigil (TV3326), another acetylcholinesterase inhibitor, is currently in phase II clinical trial. The N-Methyl-D-aspartate receptor (NMDA) antagonist, memantine, is used to block overstimulation of cells by glutamate, which leads to excitotoxicity, harmful to neurons. Memantine protects neurons by reducing glycogen synthase kinase 3β activity, thereby attenuating tau hyper phosphorylation. It is marginally effective in treating mild-to-moderate AD and can be used alone or in combination with a cholinesterase inhibitor.

Other neurotransmitter systems are also considered in Alzheimer's disease, particularly those in the hippocampus involved in memory and

learning. Serotonin receptors have been investigated, and 5-HT6 receptor inhibition has shown potential for promoting acetylcholine release. Histamine receptors, especially H3 receptors found in cognition-related brain areas, suggest a role for histamine in AD. Clinical studies for histamine antagonists are currently in the phase I and II stages.

For etiology-based treatment

Secretase inhibitors or modulators have been studied to affect amyloid precursor protein (APP) cleavage by α-secretase or β-secretase enzymes. Certain metalloproteinases and gemfibrozil (PPAR-α agonist) have been explored as modulators of α-secretase to inhibit amyloid beta generation. Melatonin stimulates non-amyloidogenic pathway processing. Inhibitors of γ-secretase, which is involved in APP proteolysis, have been considered, but they may induce side effects like skin cancer and gastrointestinal disorders.

Anti-A Aggregation Compounds like tramiprosate and ELND005 (Scyllo-Inositol) aim to prevent Aβ oligomerization and aggregation. Colostrinin (CLN) inhibits Aβ peptide aggregation and dissolves pre-formed fibrils.

Amyloid-based vaccination therapy involves immunizing individuals with Aβ oligomers, leading to an immune response that inhibits Aβ aggregation and facilitates its clearance from the body. This therapy generates anti-Aβ antibodies and reduces cerebrospinal levels of tau.

Tau therapies target tau proteins, which stabilize microtubules for proper neuron functioning. Drugs like lithium and valproate inhibit GSK3, a key enzyme involved in tau phosphorylation. Astemizole and lansoprazole indirectly reduce tau-tau interaction, and methylene blue prevents tau interactions, inhibits Aβ aggregation, and decreases oxidative stress. Curcumin inhibits heat shock protein 90 (Hsp 90), reducing tau degradation. Tau-based vaccination therapy aims to enhance the immunological clearance of tau tangles.

1. Herbal drugs used in Alzheimer's disease

Table 1.1: Herbal drugs used in Alzheimer's disease [13]

Sr. No.	Herbal drugs	Biological source/Family
1.	Ginkgo	*Ginkgo biloba*/Ginkgoaceae
2.	Sage	*Salvia officinalis*/Lamiaceae
3.	Rosemary	*Rosmarinus officinalis*/Lamiaceae
4.	Turmeric	*Curcuma longa*/Zingiberaceae
5.	German chamomile	*Chamomilla recutita*/Asteraceae

6.	Ginseng	*Panax ginseng*/Araliaceae
7.	Liquorice	*Glycyrrhiza glabra*/Leguminoceae
8.	White willow bark	*Salix alba*/Salicaceae
9.	Ginger	*Zingiber officinale*/Zingiberaceae
10.	Chinese knotweed	*Polygonum multiflorum*/polygonaceae
11.	Stinging nettle	*Urtica dioica*/Urticaceae
12.	Maca	*Lepidium meyenii*/Brassicaceae
13.	Maritime pine bark	*Pinus pinaster*/Pinaceae
14.	Lemon balm	*Melissa officinalis*/Lamiaceae
15.	Huperzine A	*Huperzia serrata*/Huperziaceae

2. Screening models of alzheimers disease

- Transgenic animal models of AD
- Non-transgenic animal models of AD
- *In vitro* models of AD

✓ Non-transgenic animal models of AD

✓ Models of high-fat diet (HFD)-induced AD [14]

The high-fat diet-induced model of Alzheimer's disease (AD) demonstrates hypercholesterolemia, which leads to dementia over a period of three months, accompanied by increased Aβ deposits. However, this model lacks other metabolic abnormalities that are typically present in AD, making it less realistic as an AD model. Raising cholesterol levels in the brain causes the production and extracellular deposition of Aβ peptides, which is triggered by a high-fat diet. Cognitive impairments may be caused by Aβ accumulation via the activation of several inflammatory responses, nitrosative stress, and oxidative stress. Furthermore, animals who are given a high-fat diet also show less insulin sensitivity and glucose intolerance, which are precursors of Alzheimer's disease. Scientists may use this model to look at how various food components contribute to AD. However, it should be noted that this model is time-consuming due to its long experimental procedure.

- **Intervention models of AD [14]**

Using this model, researchers can examine how different neurotransmitters contribute to the development of Alzheimer's disease. This model is established by administering various chemical compounds intracranially to animals or by inducing lesions in particular areas of the brain. As a result, this model exhibits certain features of Alzheimer's disease, including impaired learning and deficits in cholinergic function in the brain.

The lesion model is built upon prior research that shown that damage to certain areas of the brain, including the medial temporal lobe, may lead to memory loss. The learning and memory abilities of rats are impaired when certain brain areas, such as the hippocampus fimbria-fornix, are cut in two. Additionally, radiofrequency lesions in brain regions like the lateral internal medullary lamina lead to significant cognitive deficits in rats. Neurodegeneration, observed in areas distant from the site of injury, mirrors aspects of Alzheimer's disease seen in humans. These models are particularly useful for developing symptomatic treatments for dementia.

Scopolamine affects cholinergic neurons, L-methionine activates NMDA receptors, okadaic acid phosphorylates tau, sodium azide causes mitochondrial dysfunction, and heavy metals produce reactive oxygen species; these are some of the chemicals used to generate the pathology of Alzheimer's disease. Blocking various neurotransmitter pathways in the brain through these chemicals is the mechanism responsible for inducing dementia. Therefore, these models can be employed to evaluate the effects of damaging specific neurotransmitter pathways on normal brain function, such as learning and memory, and also for developing drugs that target these pathways.

- **Non-transgenic metabolic model of sporadic AD**

In the non-transgenic metabolic model of Alzheimer's dementia (AD), streptozotocin is administered intracerebroventricularly (ICV) [15]. By influencing brain glucose levels and energy metabolism, this model causes learning and memory impairments in rats [16]. Reduced glucose utilisation, cholinergic insufficiency, increased oxidative stress, and glial activation are the outcomes of STZ icv injection in the brain. In addition to these negative effects, it causes tau hyperphosphorylation, neurofibrillary tangles (NFTs) to form, increases GSK-3 activation, decreases major brain glucose transporters, downregulates O-GlcNAcylation protein, and decreases tau binding capacity to microtubules. Similar to the STZ rat model of AD, sporadic AD individuals have these impairments.

There are two mechanisms in which insulin resistance in the brain causes neurofibrillary degeneration. This is true in both AD-affected brains and STZ-injected rats' brains. First, reduced PI3K-AKT signalling activity in the brain causes overactivation of GSK-3, which in turn triggers the production of Aβ via γ-secretase and tau hyperphosphorylation. This is the first effect of brain insulin resistance. Additionally, a drop in tau O-GlcNAcylation and a reduction in glucose uptake/metabolism are both caused by insulin resistance in the brain. This is because insulin resistance

affects GLUT1/3 expression and glucose uptake/metabolism. The phosphorylation of tau is inversely regulated by O-GlcNAcylation. Thus, loss of O-GlcNAcylation causes hyperphosphorylation of tau, which in turn causes protein tau to form hazardous oligomers. These oligomers cause neurodegeneration in Alzheimer's disease and learning and memory impairments in rats injected with icv STZ [17].

- **Dosing and Characteristics**

This model depicts the intracerebroventricular administration of a 3 mg/kg dosage of STZ. A lower dose of STZ, 1.5 mg/kg [sub diabetogenic dose], only leads to deficits in cognition in 40% of the animals. Nevertheless, peripheral blood glucose levels are unaffected by the increased dosage of 3mg/kg STZ when contrasted with the sham control group. This being said, no animal shows any improvement in cognition at the higher dosage. Animals given intracerebroventricular STZ show cognitive impairments two weeks after treatment and continue to be impaired for a minimum of three weeks after therapy [16].

- ***In vitro* models of AD [14]**

These models for AD offer efficient and direct methods to investigate the pathophysiological changes that occur in AD. *In vitro* models of AD include tissue models, cell models, and molecular simulation models.

Tissue model: One powerful feature for researching the impact of chemicals linked to Alzheimer's disease is cultured brain tissue. Brain slices with metabolic competence can also serve as models for studying the regulation of AD pathology.

Cell model: Induced pluripotent stem cell (iPSC) lines derived from patients with familial or sporadic AD offer a practical approach for drug discovery and disease modeling. Neuroblast cell lines from humans can also be utilized as AD models.

Molecular simulation model: In an effort to speed up the process of medication development, researchers have tried to create model systems that mimic the molecular mechanisms involved in the pathophysiology of AD *in vitro*.

Conclusion

Amyloid fibrils are aggregations of misfolded proteins rich in β-sheet structures. The fact that amyloid fibrils may be generated by different, unrelated proteins suggests that this trait is present in all proteins. These fibrils are linked to several incurable disorders. Lag, elongation, and plateau

phases characterise the usual self-assembly of these fibrils. The rate and shape of fibril production are sensitive to variables such as temperature, pH, metal ions, and stirring speed.

The control of functional amyloid fibrils requires chaperones and ubiquitination; they naturally exist in different biological processes, including melanin formation. Once fibrils have grown, they are difficult to eliminate, however phagocytosis may assist. But amyloid fibrils may cause a number of amyloid disorders by damaging cells and organs. Although the exact relationship between Alzheimer's disease and Ab amyloid fibrils is still unclear, the illness is well-known to be an amyloid disease". Treatment for Alzheimer's disease mostly aims at symptom management at the moment, since there is no known cure for the condition. Efforts are underway to develop therapeutic approaches to combat amyloid diseases, including amyloid fibril inhibitors and regulation of Ab production. However, satisfactory therapeutics for these diseases have not been fully realized despite ongoing clinical trials. In order to develop new therapeutic chemicals that may cure these incurable illnesses, our knowledge of amyloid fibrils and their precursors must advance in many important areas: structure, kinetics, biology, and toxicity.

Authors contribution

Mahavir M. Sharma: Drafting of Manuscript, Concept of Manuscript, Final Correction of Manuscript.

Rajesh Rathod: Critical Analysis of the Article Harsh Kumar Brahmbgatt: Critical Analysis of the Article.

References

1. Tiwari V, Kuhad A, Bishnoi M, Chopra K. Chronic treatment with tocotrienol, an isoform of vitamin E, prevents intracerebroventricular streptozotocin-induced cognitive impairment and oxidative-nitrosative stress in rats Pharmacology, Biochemistry and Behavior. 2009;93:183-189.
2. Kumar A, Singh A, Ekavali. A review on Alzheimer’s disease pathophysiology and its management: An update Pharmacological reports. 2015;67:195-203.
3. Korolev I. Alzheimer’s Disease: A Clinical and Basic Science Review. Medical Student Research Journal. 2014;4:24-33.
4. Alzheimer’s Association, Alzheimer’s Disease Facts and Figures. Alzheimer’s & Dementia. 2016;12(4):459-509.

5. World Alzhrimer's day. 4.1 million People in India living with dementia says report, 2015 Sep. www.dnaindia.com›HealthNews, 2015.
6. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A Pathophysiologic Approach; 6th Edn; MCGRAW-HILL Medical Publishing Division, New York, 2005, 11-57.
7. Mohandas E, Rajmohan V, Raghunath B. Neurobiology of Alzheimer's disease Indian Journal of Psychiatry. 2009;51(1):55-61.
8. Suzanne M. Insulin resistance and Alzheimer's disease. BMB Rep. 2009;42(8):475-481.
9. Najem D, Bamji-Mirza M, Chang N, Liu Q, Zhang W. Insulin resistance, neuro inflammation and Alzheimer's disease. Rev. Neuro Sci. 2014;25(4):509-525.
10. Diagnosing Alzheimer's: How Alzheimer's is diagnosed, 2016. www.mayoclinic.org/diseases.../alzheimers-disease/in-depth/alzheimers/art- 20048075
11. Precoma J, Berumen L, Padilla K, Alcocer G. The rapies for Prevention and Treatment of Alzheimer's disease. Bio Med Research International, 2016, 1-17.
12. Folch J, Petrov D, Ettcheto M, Abad S, Sánchez-López E, García M, *et al*. Current Research Therapeutic Strategies for Alzheimer's Disease Treatment. Neural Plasticity, 2016, 1-15.
13. Agarwal P, Alok S, Fatima A, Singh P. Herbal Remedies for Neurodegenerative Disorder (Alzheimer's disease): A review. International Journal of Pharmaceutical Science and research. 2013;4(9):3328-3340.
14. Li X, Bao X, Wang R. Experimental models of Alzheimer's disease for deciphering the pathogenesis and therapeutic screening (Review). International Journal of Molecular Medicine. 2016;37:271-283.
15. Grieb P. Intracerebroventricular Streptozotocin Injection sasa Model of Alzheimer's disease: in Search of a Relevant Mechanism. Mol. Neurobiol. 2016;53:1741-1752.
16. Sharma M, Gupta Y. Intracerebroventricular Injection of Streptozotocin in rats produces both oxidative stress in the brain and cognitive impairment. Life Sciences. 2001;68:1021-1029.
17. Deng Y, Li B, Liu B, Iqbal K, Iqbal I, Gong C. Dysregulation of Insulin

Signaling, Glucose Transporters, O-GlcN Acylation, and Phosphorylation of Tau and Neuro-filaments in the Brain. The American Journal of Pathology. 2009;175:2089-2098.

Chapter - 2

Pharmacy Practice in the Era of Personalized Medicine: Challenges and Opportunities

Authors

Rajesh Hadia
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Rahul Trivedi
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Cyril Sajan
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Varunsingh Saggu
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Sunil Baile
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Sunil Kardani
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Hemraj Singh Rajput
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Chapter - 2

Pharmacy Practice in the Era of Personalized Medicine: Challenges and Opportunities

Rajesh Hadia, Rahul Trivedi, Cyril Sajan, Varunsingh Saggu, Sunil Baile, Sunil Kardani and Hemraj Singh Rajput

Abstract

Pharmacy Practice in the Era of Personalized Medicine: Challenges and Opportunities delves into the transformative landscape of personalized medicine and its profound impact on pharmacy practice. The chapter is structured to provide a comprehensive understanding of this dynamic field. It begins by introducing personalized medicine, emphasizing the significance of tailoring medical decisions to individual characteristics and the evolving role of pharmacists. The purpose is to explore the challenges and opportunities pharmacists face in this context. The chapter delves into the concept of personalized medicine, discussing its principles, historical development, and the shift from a one-size-fits-all approach to individualized treatment. Pharmacogenomics takes center stage, explaining how genetics influence drug responses and how pharmacogenomic testing is being integrated into pharmacy practice. Challenges in pharmacy practice are addressed, encompassing ethical and legal considerations, integration of pharmacogenomic data, and ensuring patient privacy and informed consent. Opportunities and advancements highlight how technology and collaboration with healthcare teams are reshaping pharmacy practice. Pharmacists are central in medication therapy management, ensuring optimal patient outcomes. Education and training are pivotal, with a focus on the requirements for pharmacists in personalized medicine and continuous professional development. This section ensures that pharmacists remain well-equipped to navigate the complexities of pharmacogenomics. Case studies and practical applications offer real-world examples of personalized medicine's impact on patient care, illustrating its transformative power and offering valuable lessons. The future trends and prospects section highlights emerging trends, the potential of AI and machine learning, and the expanding scope of personalized medicine services. Pharmacists are positioned to excel in this

evolving field. The chapter concludes by recapitulating key challenges and opportunities, emphasizing the importance of adapting to personalized medicine, and calling pharmacists to embrace and excel in this transformative field. In a rapidly evolving healthcare landscape, pharmacists have the opportunity to lead the way in providing patient-centered, genetics-informed care, ultimately improving healthcare outcomes and patient satisfaction.

Keywords: Personalized medicine, pharmacy practice, pharmacists, pharmacogenomics, healthcare, genetics, individualized treatment.

Introduction

Definition and significance of personalized medicine

Personalized medicine, also known as precision medicine, is an innovative approach to medical treatment and healthcare that tailors medical decisions, practices, interventions, and products to the individual patient. It recognizes that each patient is unique, and their genetic makeup, lifestyle, and environment influence their response to treatments and medications. Personalized medicine aims to optimize the effectiveness of medical interventions while minimizing side effects and adverse reactions. The significance of personalized medicine lies in its potential to revolutionize healthcare. Traditionally, medicine followed a one-size-fits-all approach, where the same treatment was applied to all patients with a particular condition. However, this approach often led to suboptimal outcomes, as patients' responses to treatments could vary significantly. Personalized medicine allows for more precise and targeted interventions, resulting in better patient outcomes, reduced healthcare costs, and improved quality of life.

Overview of the evolving role of pharmacists

In the evolving landscape of healthcare, pharmacists have traditionally been integral in ensuring the safe and effective use of medications. However, in the era of personalized medicine, their role is undergoing a profound transformation, making them even more vital to patient care. No longer limited to merely dispensing medications, pharmacists are assuming multifaceted roles. Firstly, in the field of pharmacogenomics, they are actively engaged in deciphering pharmacogenomic data, interpreting how an individual's genetic makeup influences their drug responses, and advising healthcare providers on the most appropriate medications and dosages tailored to a patient's unique genetic profile. Secondly, medication therapy management (MTM) services have become a primary focus, where pharmacists assess and optimize a patient's medication regimen, taking into account their individual medical history, genetic information, and potential drug interactions. This personalized

approach to medication management significantly enhances patient outcomes. Moreover, pharmacists are now educators, imparting crucial knowledge to patients about their medications, possible side effects, and the significance of adherence to prescribed treatment plans. Lastly, the evolving collaborative care model has pharmacists working in interdisciplinary healthcare teams alongside physicians, nurses, and other healthcare professionals, ensuring comprehensive patient care. The purpose of this chapter is to delve into the challenges and opportunities pharmacists encounter within the context of personalized medicine, providing a comprehensive understanding of how this paradigm is reshaping pharmacy practice. The chapter's structure adheres to a logical progression. It commences with an introduction to the concept of personalized medicine, emphasizing its significance and its profound impact on the role of pharmacists. Subsequent sections delve into the multifaceted challenges and opportunities faced by pharmacists, encompassing ethical and legal considerations, the integration of cutting-edge technological advancements into their practice, and the ever-evolving educational prerequisites for pharmacists. In addition, the chapter elucidates these concepts with the aid of case studies and real-world examples, showcasing the practical applications of personalized medicine in pharmacy practice. The chapter's concluding segment forecasts the future trends and prospects, highlighting the potential influence of artificial intelligence and machine learning, and it underscores the need for pharmacists to embrace and excel in the era of personalized medicine. This introduction establishes the foundation for the chapter, providing readers with a comprehensive overview of personalized medicine, the evolving role of pharmacists, and the intended structure and purpose of the chapter. It serves as a guide, preparing readers for an in-depth exploration of the multifaceted challenges and opportunities presented in the context of pharmacy practice within the era of personalized medicine.

The concept of personalized medicine

Personalized medicine, often referred to as precision medicine, represents a ground-breaking approach to healthcare that centers on the customization of medical decisions, treatments, and interventions to the unique characteristics of each patient. It is rooted in the fundamental principle that every patient is inherently distinct, encompassing not only their medical conditions but also their genetic makeup, lifestyle, and environmental influences. The core principles of personalized medicine encompass several critical facets. Genomic profiling, at its core, delves into deciphering an individual's genetic code, enabling healthcare providers to pinpoint specific genetic variations that

can significantly influence drug responses, disease susceptibility, and the efficacy of treatment regimens. The notion of targeted therapies underpins personalized medicine, involving the development and prescription of drugs and treatments tailored to the specific genetic or molecular mechanisms driving a patient's disease. This tailored approach minimizes adverse effects while maximizing therapeutic efficacy. Furthermore, personalized medicine fosters a shift from a disease-centered to a patient-centered model of care. It goes beyond a patient's clinical symptoms, considering their genetic, environmental, and lifestyle factors to forge a treatment plan bespoke to their unique needs. Predictive and preventive medicine is another key aspect, identifying genetic predispositions and risk factors that allow for the anticipation of disease susceptibility, thus initiating preventative measures even before disease onset, potentially offering early intervention and improved health outcomes.

The historical background and development of personalized medicine can be traced back to the ambitious Human Genome Project, initiated in the 1990s, with the primary objective of unravelling the entire human genome. This monumental undertaking furnished an extensive reservoir of genetic information and laid the groundwork for comprehending how genetic variations affect individual responses to drugs and vulnerability to diseases. Subsequent technological advancements, particularly in DNA sequencing and molecular biology, accelerated the evolution of personalized medicine across various domains. In the realm of pharmacogenomics, the discipline scrutinizes the influence of an individual's genetic constitution on their response to drugs, leading to the identification of specific genetic markers associated with drug metabolism, effectiveness, and adverse reactions. In the context of cancer genomics, personalized medicine has made remarkable strides. Genomic profiling of tumors enables the identification of specific mutations and alterations, ushering in the development of targeted therapies and ground-breaking immunotherapies. In addressing rare genetic disorders, personalized medicine has offered a glimmer of hope by facilitating the development of tailored treatments that directly target the underlying genetic causes. Moreover, on a population scale, large-scale genetic studies have unveiled insights into the genetic underpinnings of common diseases, opening doors to population-level interventions and preventive strategies. Perhaps one of the most transformative facets of personalized medicine is the shift away from the traditional "one-size-fits-all" approach to healthcare. Historically, medical treatments and interventions were constructed based on population averages, resulting in a universal treatment plan applied to all individuals with a specific

condition. However, this conventional approach failed to account for the substantial variability in individual patient responses. Personalized medicine embodies a paradigm shift towards individualized treatment, where healthcare decisions are crafted in accordance with the unique attributes of each patient. These attributes encompass genetic, environmental, and lifestyle factors. This shift is underpinned by the growing recognition that patients with the same disease can exhibit varied responses to identical treatments owing to their unique genetic variations. Personalized medicine leverages this understanding to optimize the efficacy of medical interventions while mitigating the risks of adverse reactions and side effects. It is intrinsically aligned with broader healthcare goals, including improving patient outcomes, enhancing healthcare quality, and mitigating healthcare costs, all of which are achieved through the tailoring of treatments to individuals, thus ensuring the most significant benefit to each patient. This section provides an extensive exploration of the concept of personalized medicine, expounding upon its core principles, tracing its historical development, and elucidating the profound shift from the traditional one-size-fits-all approach to healthcare, showcasing the critical importance of recognizing and addressing the uniqueness of each patient. The tenets of personalized medicine usher in a patient-centered model of care, ultimately translating into superior healthcare outcomes.

Pharmacogenomics and drug interactions

Pharmacogenomics, the focus of this section, represents a transformative field of medicine that examines the influence of an individual's genetic makeup on their response to drugs. This critical component of personalized medicine recognizes that genetic variations play a pivotal role in drug metabolism, efficacy, and safety, revolutionizing our understanding of how drugs interact with the human body. At its core, pharmacogenomics involves the identification of specific genetic variations, such as single nucleotide polymorphisms (SNPs), that affect the activity of enzymes responsible for drug metabolism, drug transporters, and drug targets. For instance, certain individuals may carry genetic variants that alter the rate at which they metabolize a particular medication, leading to variations in drug effectiveness and the potential for adverse reactions. Furthermore, genetic factors can predispose patients to drug-induced toxicities. By delving into the genetic underpinnings of drug response, pharmacogenomics not only elucidates why patients exhibit diverse reactions to the same medication but also empowers healthcare providers to make informed decisions about drug selection and dosing, thus tailoring treatment plans to individual patients based on their genetic profiles. The integration of pharmacogenomic testing into pharmacy

practice is a monumental advancement that equips pharmacists with the ability to leverage genetic information for enhanced medication management. Pharmacogenomic testing involves a thorough analysis of a patient's genetic makeup to identify specific genetic variants that have the potential to influence their response to medications. In the realm of pharmacy practice, this genetic data is harnessed to make informed decisions regarding drug selection, dosing, and the ongoing monitoring of patients' responses to medications. Pharmacists play an instrumental role in facilitating this process, collaborating closely with other healthcare providers to identify patients who stand to benefit from pharmacogenomic testing, especially those with a history of medication-related complications or those prescribed medications with known genetic interactions. They also engage in genetic counselling, effectively educating patients about the advantages and limitations of pharmacogenomic testing and the potential ramifications for their medication regimens. Pharmacists, having received specialized training, possess the expertise needed to interpret the results of pharmacogenomic tests and offer well-informed recommendations to other healthcare providers about medication choices and dosages that are tailored to each patient's unique genetic profile. Moreover, they assume responsibility for the ongoing monitoring of patients, ensuring that their prescribed medications align with their genetic information, thus optimizing treatment outcomes. The incorporation of pharmacogenomic testing into pharmacy practice represents a significant stride towards personalized medicine, endowing healthcare providers with the means to fine-tune medication regimens for each individual patient, ultimately culminating in superior treatment outcomes. Real-world case studies stand as potent illustrations of the tangible impact of pharmacogenomics on patient care and medication management. These cases present vivid, practical examples of how genetic information has influenced clinical decision-making and patient outcomes. They effectively spotlight scenarios where pharmacogenomic testing has played a pivotal role in the realm of personalized medicine. For instance, a case study might recount the experience of a patient who, due to a specific genetic variant, suffered severe side effects when administered a standard dose of medication, necessitating hospitalization. However, following pharmacogenomic testing that unveiled this genetic variant, the patient's medication regimen was adjusted based on the genetic data, leading to improved tolerance and therapeutic effectiveness. Additionally, these case studies can underscore the economic advantages of pharmacogenomics by demonstrating how it mitigates hospitalizations and emergency department visits linked to adverse drug events, thereby resulting in cost savings within healthcare systems. In sum, this section offers a comprehensive exploration of

pharmacogenomics and its far-reaching implications in pharmacy practice. It underscores the importance of understanding the role of genetics in drug response, the seamless implementation of pharmacogenomic testing, and the practical impact of this approach through the use of case studies. Pharmacogenomics is not merely advancing the field of personalized medicine; it is a game-changer in enhancing patient safety and boosting treatment outcomes through the precise customization of drug therapies based on individual genetic profiles.

Challenges in pharmacy practice

Challenges in pharmacy practice within the context of personalized medicine are multifaceted and encompass ethical, legal, and operational dimensions. The advent of personalized medicine raises complex ethical and legal considerations, such as informed consent, patient autonomy, data privacy, and genetic discrimination. Pharmacists, as integral healthcare providers, must navigate these ethical dilemmas when offering pharmacogenomic testing and incorporating genetic data into treatment decisions. Legal frameworks, like the Genetic Information Non-discrimination Act (GINA) in the United States, have been established to safeguard individuals from genetic discrimination in employment and health insurance. In parallel, the integration of pharmacogenomic data into patient care presents a formidable challenge, requiring the establishment of efficient systems for the storage, retrieval, and utilization of genetic information. This includes the creation of electronic health records (EHRs) that can seamlessly incorporate pharmacogenomic data and make it readily accessible to healthcare providers at the point of care. Pharmacists need to work collaboratively with other healthcare professionals, navigating the complexities of a fragmented healthcare system, to ensure the effective application of genetic data in clinical decision-making. Additionally, equipping pharmacists with the necessary training to interpret and apply pharmacogenomic data is pivotal for the seamless integration of this information into patient care. Ensuring patient privacy and obtaining informed consent are critical ethical considerations as well. Pharmacists must meticulously adhere to stringent data privacy regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States, to protect the confidentiality of patients' genetic information. Moreover, the acquisition of informed consent, a fundamental ethical requirement before conducting genetic testing, can be intricate. Pharmacists play a pivotal role in educating patients about the implications and potential consequences of pharmacogenomic testing while respecting their autonomy. This section

underscores the need for robust ethical guidelines, evolving legal frameworks, and sophisticated data security measures to support the successful integration of pharmacogenomics into pharmacy practice while prioritizing patient well-being and rights. It illuminates the intricate landscape that pharmacists must navigate in this era of personalized medicine, where patient-centric, data-driven care is on the rise.

Opportunities and advancements

In the era of personalized medicine, there is a confluence of remarkable opportunities and advancements that are reshaping pharmacy practice. Innovations in technology and data analysis stand at the forefront of this transformation. High-throughput genomic sequencing, sophisticated bioinformatics tools, and the integration of electronic health records (EHRs) empower pharmacists to harness pharmacogenomic data for truly personalized medication management. These advancements enable pharmacists to identify specific genetic variants affecting drug responses, guiding informed decisions about medication selection and dosing. The use of artificial intelligence and machine learning further augments the predictive capacity, enhancing treatment precision. Moreover, collaborative care models within healthcare teams ensure that pharmacists play a central role, working in tandem with other healthcare professionals to deliver patient-centered care. They provide expertise in areas like pharmacogenomics and medication therapy management (MTM), enabling tailored treatment plans based on individual patients' genetic profiles. This collaborative approach fosters open communication, ensuring that genetic data is accessible and well-understood by all healthcare team members, leading to optimized treatment outcomes. Additionally, pharmacists' role in MTM has expanded significantly, with their expertise in pharmacology, drug interactions, and patient counselling making them pivotal in the era of personalized medicine. They can leverage pharmacogenomic data to optimize medication regimens, reducing the risk of adverse drug events and enhancing patient outcomes. Moreover, pharmacists are instrumental in patient education, ensuring that patients comprehend the significance of their genetic information and the reasoning behind personalized treatment plans. These advancements reflect the evolving nature of pharmacy practice and its essential role in providing safer and more effective medications, tailored to the unique genetic profiles of patients, ultimately promoting adherence and patient satisfaction.

Education and training

Education and training are pivotal in preparing pharmacists for the evolving landscape of personalized medicine. In this era, pharmacists are

required to possess a profound understanding of pharmacogenomics, which underpins the entire field, allowing them to interpret genetic data, make informed medication-related decisions, and effectively communicate with healthcare teams and patients about personalized treatment plans. Accredited pharmacy programs and institutions are actively incorporating pharmacogenomics into their curricula to ensure that future pharmacists are well-equipped with the necessary knowledge. Furthermore, continuous professional development and certification enable practicing pharmacists to stay current in this dynamic field, with certifications like BCPS showcasing their expertise. Professional organizations offer resources, training, and certifications in personalized medicine and pharmacogenomics to maintain the highest standards of care and enhance patient outcomes. The integration of genetics, pharmacogenomics, and personalized medicine into pharmacy education programs ensures that future pharmacists are adequately prepared for their roles, with clinical rotations and research opportunities providing practical experience. This commitment to education and training empowers pharmacists to excel in personalized medicine practice, ultimately optimizing patient care and safety in this ever-advancing healthcare landscape.

Case studies and practical applications

The "Case Studies and Practical Applications" section of the chapter on personalized medicine in pharmacy practice plays a crucial role in illustrating the real-world impact of genetic information on patient care. These case studies provide tangible examples of how pharmacogenomics is revolutionizing medication management, leading to improved patient outcomes and satisfaction. They showcase how specific genetic variations can influence drug responses and how tailoring medication regimens based on this information can reduce adverse reactions and enhance the efficacy of treatments. Furthermore, patient success stories emphasize the human dimension of personalized medicine, demonstrating the life-changing improvements it can bring to individuals who have previously struggled with medication-related issues. These narratives highlight the importance of considering genetic information in treatment decisions and the profound positive effects it can have on patients' lives. Additionally, lessons learned from case studies offer valuable insights into the challenges and solutions encountered in the implementation of pharmacogenomics, helping healthcare professionals refine best practices and enhance the quality of care. Overall, this section underscores the practical significance of personalized medicine in pharmacy practice, emphasizing its role in optimizing medication management and improving patient well-being.

Future trends and prospects

The field of personalized medicine is rapidly evolving, with emerging trends and technological advancements reshaping its landscape. Liquid biopsy tests for detecting genetic alterations in cancer patients, the adoption of multi-omics approaches, and advancements in single-cell sequencing technology are at the forefront of this transformation. These trends offer pharmacists new opportunities to play a central role in patient care by interpreting complex multi-omics data and providing individualized treatment recommendations. Additionally, artificial intelligence (AI) and machine learning are set to revolutionize personalized medicine, efficiently analyzing vast genetic datasets to predict patient responses to specific medications and streamline pharmacogenomic data interpretation. Furthermore, personalized medicine services are expanding beyond genetics to encompass environmental and lifestyle factors, allowing pharmacists to contribute to holistic medication management and population health initiatives. This ever-evolving landscape positions pharmacists as essential contributors to enhancing patient outcomes and healthcare quality in the personalized medicine era.

Conclusion

In conclusion, the era of personalized medicine presents pharmacists with both challenges and opportunities. The integration of pharmacogenomics and the shift towards individualized treatment plans offer the potential for improved patient outcomes and safety. However, ethical and legal considerations, as well as the need for effective data integration and patient consent, pose significant challenges. Pharmacists must adapt to this evolving landscape, embracing technology, collaborating with healthcare teams, and continuously updating their knowledge. By doing so, they can excel in providing personalized medication management, making a positive impact on patient care and the broader healthcare system. It is a call to action for pharmacists to lead the way in this transformative era of healthcare.

References

1. Lee JK, Brett AS. Patient expectations and personalized medicine. JAMA. 2016;315(21):2221-2222.
2. Pinto SL, Menezes CE, Kurokawa CS. Role of pharmacists in personalized medicine. Pharmacy Practice (Granada). 2016;14(3):752.
3. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372(9):793-795.
4. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010;363(4):301-304.

5. Jameson JL, Longo DL, Loscalzo J, Kasper DL. Precision medicine-Personalized, problematic, and promising. N Engl J Med. 2019;380(10):947-954.

6. Dunnenberger HM, Crews KR, Hoffman JM *et al*. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. Annu Rev Pharmacol Toxicol. 2015;55:89-106.

7. Van Driest SL, Shi Y, Bowton EA *et al*. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. Clin Pharmacol Ther. 2014;95(4):423-431.

8. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526(7573):343-350.

9. Fink AK, Lederle FA, Roth CS. Ensuring privacy and data protection in a pharmacogenetics study. Personalized Medicine. 2014;11(4):331-341.

10. Dressler LG, Terry SF. How will GINA influence participation in pharmacogenomics research and clinical testing? Clin Pharmacol Ther. 2015;97(5):468-471.

11. Padiyara RS, Schell G. Medication therapy management in pharmacy practice: Core elements of an MTM service model (version 2.0). J Am Pharm Assoc. 2017;57(1):24-32.

12. Hines LE, Murphy JE. Potentially harmful drug–gene interactions: A systematic review. Ann Pharmacother. 2011;45(12):1579-1589.

13. Phillips KA, Deverka PA, Hooker GW, Douglas MP. Genetic test availability and spending: Where are we now? Where are we going? Health Aff. 2014;33(5):935-942.

14. Anderson S, Marrs JC. Clinical implementation of pharmacogenetic testing in a hospital setting. Am J Health-Syst Pharm. 2017;74(13):957-968.

15. Hicks JK, Swen JJ, Gaedigk A. Challenges in CYP2D6 phenotype assignment from genotype data: A critical assessment and call for standardization. Curr Drug Metab. 2018;19(3):256-266.

16. Formea CM, Hays DP. Implementation of a pharmacogenomics education program for pharmacists. Am J Pharm Educ. 2014;78(8):154.

17. Lee JW, Amamoo MA. Evaluation of pharmacogenomic information for patients in the electronic health record. J Manag Care Spec Pharm. 2017;23(10):1093-1099.

18. Stanek EJ, Sanders CL, Frueh FW. Adoption of pharmacogenomic testing

by US physicians: Results of a nationwide survey. Clin Pharmacol Ther. 2012;91(3):450-458.

19. Gottesman O, Scott SA, Ellis SB. The CLIPMERGE PGx Program: Clinical implementation of personalized medicine through electronic health records and genomics-pharmacogenomics. Clin Pharmacol Ther. 2013;94(2):214-217.
20. Lek M, Karczewski KJ, Samocha KE. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536(7616):285-291.
21. Mamoshina P, Vieira A, Putin E. Applications of deep learning in biomedicine. Mol Pharm. 2016;13(5):1445-1454.
22. Meldrum C, Doyle MA, Tothill RW. Next-generation sequencing for cancer diagnostics: A practical perspective. Clin Biochem Rev. 2011;32(4):177-195.

Chapter - 3

Role of Essential Oils in Therapy: Much More than a Pleasant Scent

Authors

Parijatha Bandigari
Associate Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy, Chowdariguda, Ghatkesar, Medchal, Telangana, India

Sunitha Chintala
Associate Professor, Princeton College of Pharmacy, Chowdariguda, Narapally, Ghatkesar, Medchal, Telangana, India

Dr. Baba Shankar Rao Garige
Associate Professor, School of Pharmacy, Anurag University, Venkatapur, Ghatkesar, Medchal, Hyderabad, Telangana, India

Dr. Kadasi Sundeep
Associate Professor, Princeton College of Pharmacy, Chowdariguda, Narapally, Ghatkesar, Medchal, Telangana, India

Jyothirmaye J
Assistant Professor, Gurram Bala Narsaiah Institute of Pharmacy, Edulabad, Ghatkesar, Medchal, Telangana, India

Chapter - 3

Role of Essential Oils in Therapy: Much More than a Pleasant Scent

Parijatha Bandigari, Sunitha Chintala, Dr. Baba Shankar Rao Garige, Dr. Kadasi Sundeep and Jyothirmaye J

Abstract

Herbal medicine is receiving increasing attention and has been applied more extensively in disease treatments or promoting health during the last decades. A growing amount of data demonstrates the efficacy of herbal products, but in many cases the available evidences are still scarce. Nowadays, use of alternative and complementary therapies with mainstream medicine has gained the momentum. Aromatherapy is one of the complementary therapies which use essential oils as the major therapeutic agents to treat several diseases. Aromatherapy - the therapeutic use of essential oils from plants (flowers, herbs or trees) to treat ill health and promote physical, emotional and spiritual well-being is one of the most widely used natural therapies reported by consumers in Western countries. The aim of this review is to evaluate the research behind the application of essential oils (EOs) in treatment of different diseases. The essential or volatile oils are extracted from the flowers, barks, stem, leaves, roots, fruits and other parts of the plant by various methods. It came into existence after the scientists deciphered the antiseptic and skin permeability properties of essential oils (EOs). Once the oils are in the system, they remodulate themselves and work in a friendly manner at the site of malfunction or at the affected area. This type of therapy utilizes various permutation and combinations to get relief from numerous ailments like depression, indigestion, headache, insomnia, muscular pain, respiratory problems, skin ailments, swollen joints, urine associated complications etc. The essential oils are found to be more beneficial when other aspects of life and diet are given due consideration. This review explores the information available in the literature regarding therapeutic, medical, cosmetic, psychological, olfactory, massage aromatherapy, safety issues and different plants used in aromatherapy.

Keywords: Essential oils, anti-cancer, aromatherapy, anti-stress effect.

Introduction

The discovery of natural plant-based products is rightly recognized as a milestone in the history of health care, and their introduction into the market in combination with synthetic medicines has resolved many health concerns. As a result, the extraction of plant secondary metabolites' such as essential oils (EOs) through steam or hydro-distillation processes, has witnessed a significant progress over the years. Stored in oil/resin ducts, glands or trichomes (glandular hairs) of plants, these EOs play important roles in defence against external agents and participate in signal transduction pathways. Besides, myriads of biological and medicinal properties are attributed to EOs, and their aromatic nature finds use in cosmetics, perfumery, and as flavouring agents in food industry. EOs are a complex mixture of various chemical compounds; primarily characterized by volatility, aroma, low molecular weight, and density < 1. The diverse biological properties of EOs arise from the differences in their chemical constitution and structure. At present, three main classes of EOs are identified, namely terpenes and terpenoids (major contributors), phenolics, and aliphatic compounds [1-3].

Aromatherapy derived its name from the word aroma, which means fragrance or smell and therapy which means treatment. This therapy is a natural way of healing a person's mind, body and soul. Many ancient civilizations like Egypt, China and India have used this as a popular complementary and alternative therapy from at least 6,000 years. Aromatherapy has established itself for the treatment of various arrays of complications and conditions. Literature survey reveals that this therapy has gained a lot of attention in the late 20th century and is very popular in the 21st century too, and due to its importance, popularity and widespread use, it is recognized as aroma science therapy. The essential oils have gained their importance in therapeutic, cosmetic, aromatic, fragrant and spiritual uses. Aromatherapy uses essential oils, as the main therapeutic agents, which are said to be highly concentrated substances extracted from flowers, leaves, stalks, fruits and roots, and also distilled from resins. Essential oils are a mixture of saturated and unsaturated hydrocarbons, alcohol, aldehydes, esters, ethers, ketones, oxides phenols and terpenes, which may produce characteristic odours. They are colourless pleasant-smelling liquids with high refractive index. These oils are so potent and concentrated that they work on pressure points and rejuvenate [4-6].

The essential oils in plants are present in different areas like, pockets and reservoirs, glandular hairs, specialized cells, or even in the intercellular spaces. Essences evaporation from the plants, shields them from bacterial

attack and a warming aura due to essences protects the plant from temperature fluctuations. There are various methods by which they are administered in small quantity like inhalation, massage or simple applications on the skin surface and rarely, they are taken internally. Inhalation and the external application of these oils for the treatment of mental and physical balance are the very basics of aromatherapy. The therapy of these oils is known to relieve the stress, rejuvenate and regenerate the individual for a next day's work. Olfactory nerves from nose to the brain are the site of action for these essential oils. These oils have well proven anti-bacterial, anti-biotic, and anti-viral properties and many published reports elsewhere as well as folkloric practitioners have suggested them to be useful in many other diseases like alzheimer, cardiovascular, cancer and labor pain in pregnancy etc. There is an increased trend nowadays to use this therapy in the treatment of cancer and sleep disorder. Their organic character and to act in a supportive manner with the body, provide a feeling of well beingness. It was found that the locomotor activity of mice increased significantly by inhalation of rosemary essential oils, which are used in phytotherapy as activating and refreshing remedy for exhaustion [7-10].

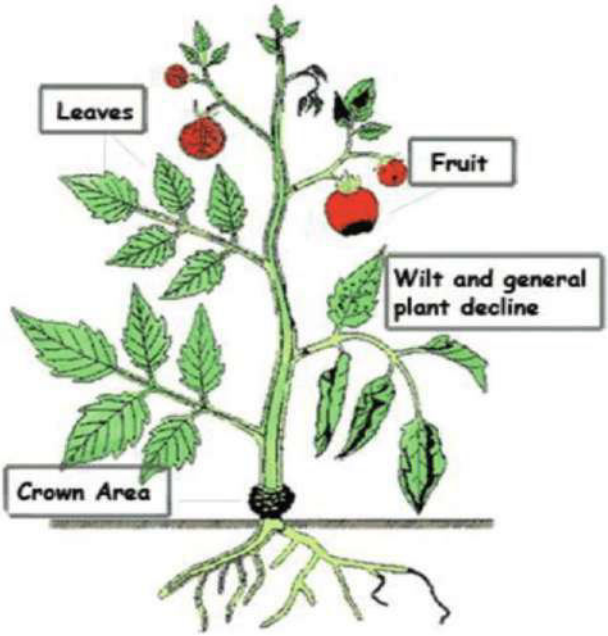


Fig 1: Plants and their parts used for the isolation of essential oils

The use of aromatherapy in holistic medicine has taken a long leap within a couple of years. On reviewing the literature on this therapy, it is found that

numerous studies have been carried out to study the effects of this therapy on human brain and its emotions. Its role in mood, alertness, and mental stress in healthy subjects was a topic of hot discussion among scientific community recently. Some researchers tried to investigate the effects on work ability, reaction time, and some spontaneous actions on the brain through electroencephalograph patterns and functional imaging studies. This therapy was found to be superior when compared to synthetic odours. Synthetic fragrances generally contain irritants, like solvents and propellants causing irritation in some people. According to aroma therapists, synthetic odour does not match the importance of essential oils as they are deficient in natural or vital energy; however, this has been remained a matter of debate between odour psychologists and biochemists [11-13].

How aromatherapy works?

For centuries, the essential oils have found their importance as a fragrance with a curative potential on the body, mind and spirit. These aroma molecules are very potent organic plant chemicals that make the surroundings free from disease, bacteria, virus and fungus. Their versatile character of anti-bacterial, anti-viral, anti-inflammatory nature along with immune booster body with hormonal, glandular, emotional, circulatory, calming effect, memory and alertness enhancer, is well documented by many scientists. Many pilot projects and studies have been conducted on humans to decipher their nature and role with disease and disorder. These oils are known for their energy specific character, as their potency is not lost with time and age. The stimulation properties of these oils lay in their structure which are closely in resemblance with actual hormones.

The penetration potential of these oils to reach the subcutaneous tissues is one of the important characters of this therapy. Their effects are also complex and subtle due to their complex structure and chemical properties. The mechanism of their action involves integration of essential oils into a biological signal of the receptor cells in the nose when inhaled. The signal is transmitted to limbic and hypothalamus parts of the brain via olfactory bulb. These signals cause brain to release neuro messengers like serotonin, endorphin etc., to link our nervous and other body systems assuring a desired change and to provide a feeling of relief. Serotonin, endorphin and noradrenalin are released from calming oil, euphoric, and stimulating oil respectively to give expected effect on mind and body [14-16].

Table 1: Some plant species essential oils and their usage

S. No.	Plant species	Essential oil	Uses
1	*Apium graveolens*	Celery seed oil	Treat of gout, anti-fungal, diuretic, blood pressure, anti-septic, reduces sedative, urinary anti-rheumatic.
2	*Artemisia pallens*	Davana oil	Coughs, including menstruation, anxiety, healing of wounds, anti-septic.
3	*Alpinia galanga*	Galanga oil	Aphrodisiac, easing heart pain and angina, dizziness and fatigue. Stomach, spleen, relief of pain, treatment of flu and colds, travel sickness.
4	*Ammi visnaga*	Khella oil	Anti-asthmatic, diuretic, anti-spasmodic, relaxant.
5	*Angelica glauca*	Root oil	Anti-oxidant, anti-fungal, anti-bacterial, and phytotoxicity.
6	*Backhousia citriodora*	Lemon myrtle oil	Insect repellent, stress, athletes' foot, colds, flu, skin blemishes.
7	*Cinnamon species*	Cinnamon oil	Anti-fungal, uterine stimulant, anti-bacterial.
8	*Canarium luzonicum*	Elemi oil	Coughs, healing wounds, stress.
9	*Citrus reticulata*	Mandarin oil	Blemishes, stress and wrinkles, acne, insomnia, scars, skin.
10	*Citrus sinensis*	Sweet orange oil	Constipation, cough relief, flu, gum treatment, calms nerves, digestive stimulant, aids energy.
11	*Cananga odorata*	Ylang oil	Hypertension, palpitations, stress, anxiety, anti-depression, frigidity, hypertension.
12	*Daucus carota*	Carrot seed oil	Detoxification, eczema.
13	*Eucalyptus globulus*	*Eucalyptus* oil	Anti-septic, anti-spasmodic, treatment of scarlet fever, influenza, measles and typhoid, infusion reduces blood sugar levels.
14	*Mentha species*	Mint oil	Analgesic, calming, cooling for migraines, anti-bacterial, clear nasal congestion, prevents vomiting, relaxes peripheral blood vessels, promotes bile flow.
15	*Pimenta racemosa*	Bay oil	Aches, muscle circulation, improve dandruff.

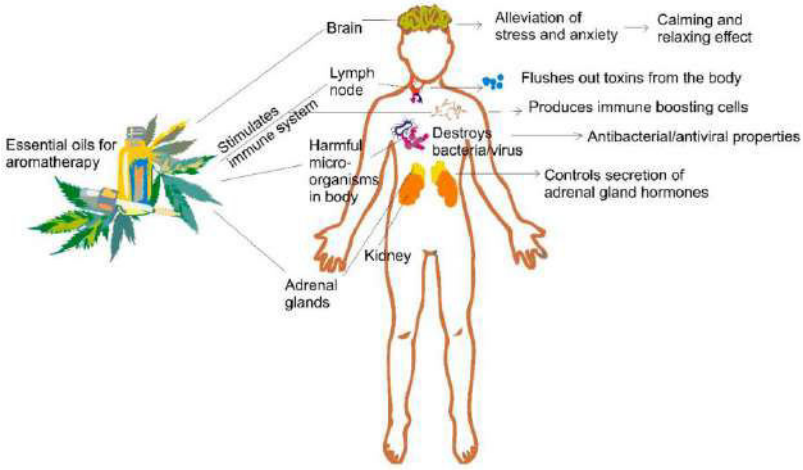


Fig 2: The role of essential oil-based aromatherapy in strengthening immunity and producing anti-stress effects

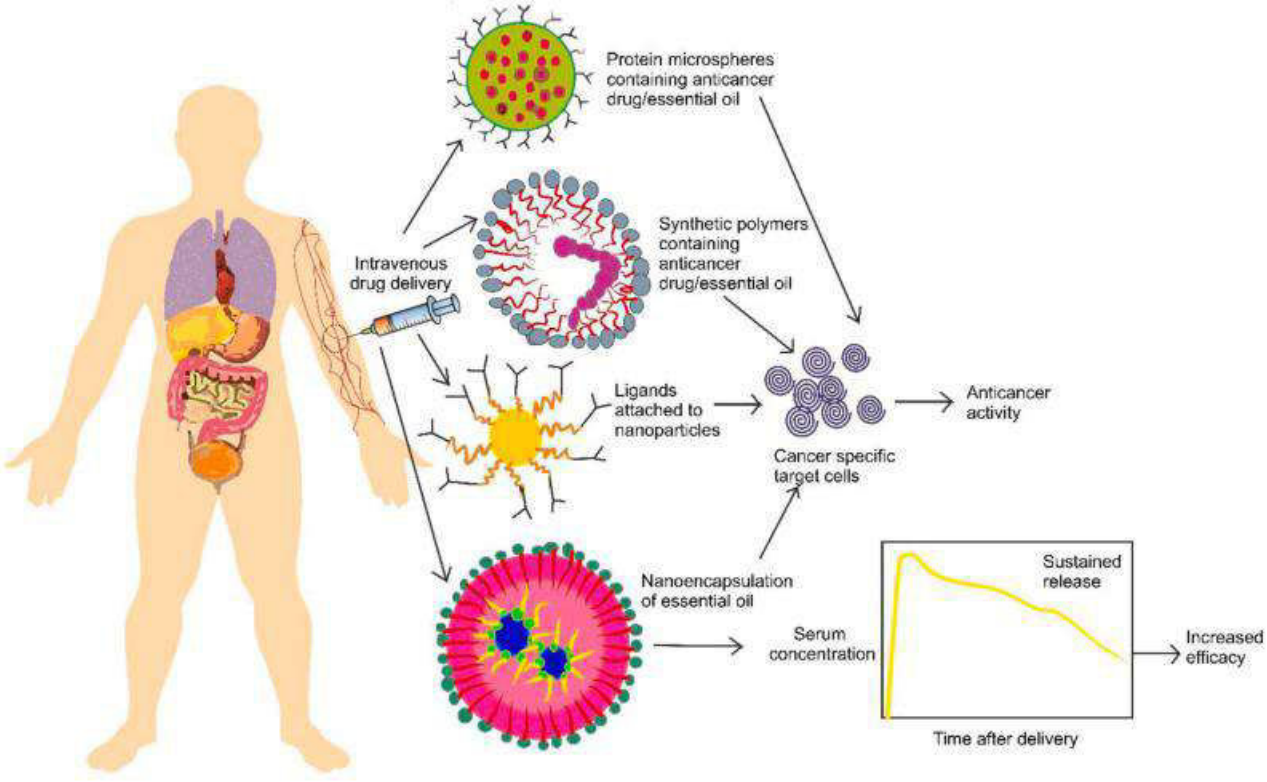


Fig 3: Various intravenous essential oil-loaded drug delivery systems for targeting cancer cell cytotoxicity

Essential oils are cytotoxic in nature

Essential oils (EOs) induce programmed cell death of cancer cells via apoptosis, necrosis, arrest of cell cycle, and dysfunctioning of main cell organelles. This is coordinated by an increase in membrane fluidity of the affected cell, reduced adenosine triphosphate (ATP) generation, alteration in pH gradient, and loss of mitochondrial potential, which are the major precursors of cell death. All the three major types of chemical constituents in EOs i.e., phenols, aldehydes, and alcohols, have been proposed to carry out this function. For instance, plant isoprenoids could possibly reduce the size of tumour cell in cancer patients.

Likewise, the EO of *Eucalyptus camaldulensis* penetrated the membrane of Caco-2 colorectal cancer cells and induced programmed cell death via reduction in cell size, membrane damage, and fragmentation of nuclei. Moreover, a link between type of organism (eukaryotes versus prokaryotes) and lipophilic nature of EO components is indicative of the toxic potential of EOs. In eukaryotes, toxicity decreases with increase in lipophilicity of components, while in prokaryotes, it increases with increasing lipophilicity. In general, the anti-cancer potential of EOs is largely ascribed to their anti-oxidant, anti-mutagenic, and anti-proliferative properties [17-19].

Some plants used in aromatherapy [20-28]

Many plants have been reported to use in the aromatherapy due to presence of essential or volatile oils in different plants' materials like flowers, barks, stem, leaves, roots, fruits etc.

Lavender

Lavender (*Lavandula officinalis* Chaix.) belonging to the family of Lamiaceae, is a beautiful herb of the garden (Figure 4). It contains camphor, terpinen-4-ol, linalool, linalyl acetate, beta-ocimene and 1,8-cineole. Its constituent varies in concentration and therapeutic effects with the different species. Linalool and linalyl acetate have maximum and great absorbing properties from skin during massage with a depression of central nervous system. Linalool shows sedative effects and linalyl acetate shows marked narcotic actions. These two actions may be responsible for its use in lavender pillow anxiety patients with sleep disturbance pattern, improving the feeling of well-being, supporting mental alertness and suppressing aggression and anxiety. Lavender oil shows its anti-bacterial and anti-fungal properties against many species of bacteria, especially when anti-biotics fail to work, but the exact mechanisms are yet to be established. When talking about its use in aromatherapy, it is well documented for the treatment of abrasions, burns,

stress, headaches, in promotion of new cell growth, skin problems, painful muscles and boosting an immune system. This oil is used in the treatment of primary dysmenorrheal and has shown some promising results in one of the randomized, double-blind clinical trials.

Fig 4: *Lavandula officinalis*

Lemon

Lemon (*Citrus limon* Linn.) belongs to the family of Rutaceae (Figure 5). *C. limon* long trees grow up to the 15 feet height and bear rich scented lemon fruits all year round. Its oil constituents are abundant in the terpenes, D-limonene and L-limonene, together forming about 90 percent of the bulk of the oil. Traces of phellandrene, pinene and sesquiterpene are also present. The valuable portion of the oil is the remaining 10 percent which consists of oxygenated bodies, chiefly the aldehyde citral, to which the odour of the oil is largely due and of which there is 3.5–5% odour present in the oil. When compared to other essential oils, its constituents have anti-septic, astringent and detoxifying properties, for blemishes associated with oily skin. Its oil brightens and rejuvenates dull skin. Lemon essential oil is mainly used to boost the immune system and to accelerate the white corpuscles production along with counteracting acidity and ulcers through citric acid, which helps digestion, by forming carbonates and bicarbonates of potassium and calcium. A recently conducted double-blinded, randomized, controlled clinical trial study on aromatherapy has suggested that citrus oil is good in relieving the

first stage labor pain. It is effective in controlling the nausea and vomiting along with its mood elevating properties.

Fig 5: *Citrus limon*

Peppermint

Peppermint (*Mentha piperita* Linn.) belongs to the family of Lamiaceae (Figure 6). Till date, all the 600 kinds of mints are raised from 25 well-defined species. The two most important are peppermint (*M. piperita*) and spearmint (*Mentha spicata*). Spearmint bears the strong aroma of sweet character with a sharp menthol undertone. Its oil constituents include carvacrol, menthol, carvone, methyl acetate, limonene and menthone. The pharmacological action is due to menthol, a primary constituent of peppermint oil. At least 44% free menthol is present in peppermint oil. Components are sensitive to climate, latitude and maturity of the plant. Inhalation and application of menthol on skin causes a skin reaction. It is used in many liniments dosage form to relieve pain spasms and arthritic problems. Peppermint oil is studied and documented for its anti-inflammatory, analgesic, anti-infectious, anti-microbial, anti-septic, anti-spasmodic, astringent, digestive, carminative, fungicidal effects, nervine stimulant, vasoconstrictor, decongestant and stomachic properties [29].

Fig 6: *Mentha piperita*

Rosemary

Rosemary (*Rosmarinus officinalis* Linn.) belonging to the family of Lamiaceae bears small pale blue flowers in late spring/ early summer and grows up to the height of 90 cm (Figure 7). It has three varieties (silver, gold and green stripe); it's the green variety that is used for its medicinal properties. This plant is rich in bitter principle, resin, tannic acid and volatile oil. The active constituents are bornyl acetate, borneol along with other esters and, special camphor similar to that possessed by the myrtle, cineol, pinene and camphene. Its oil has a marked action on the digestive system, with relieving the symptoms of indigestion, constipation and colitis. It works as liver and gallbladder tonic. The oil also possesses some good action on the cardiovascular system. It regularizes the blood pressure and retards the hardening of arteries. In winter, it used to relieve the rheumatic pain which aggravates due to cold. Its stimulating properties on the nervous system have found to be beneficial in hysteria and paralysis. In latest human trials, aromatherapy is an efficacious non-pharmacological therapy for dementia and may have some potential for improving cognitive function, especially in alzheimer's disease patients, due to its free radical scavenging activity. Excellent skin tonic properties, a soothing, positive effect on menstrual cramps, for hair growth are some of the other important properties of this oil. The other benefits of rosemary include a stimulant for the scalp encouraging hair growth and providing treatment for dandruff and greasy hair [30].

Fig 7: *Rosmarinus officinalis*

Eucalyptus

Eucalyptus (*Eucalyptus globulus* Labill) belonging to the family of Myrtaceae, is a long evergreen plant with a height up to 250 feet (Figure 8). It is known for its constituents like cineole (70%–85%), aromadendrene limonene terpinene, cymene, phellandrene, and pinene. Its oils have been used to regulate and activate the various systems like nervous system for neuralgia, headache and debility. The immune system boosts the immunity against measles, flu, cold and chickenpox. Leucorrhea and cystitis of genitourinary system can also be well treated with it. Throat infections, catarrh, coughs, bronchitis, asthma and sinusitis associated with respiratory system have been taken care of by oils of this plant. Moreover, skin problems like wounds, cuts, burns, herpes, lice, insect repellent and insect bites can be treated with it. Treatment of rheumatoid arthritis, muscle and joint pains and aches is well reported from the essential oils of this plant. Eucalyptus oil has demonstrated its anti-oxidant, anti-inflammatory, anti-proliferative and anti-bacterial activities and researchers have proved its efficacy beyond doubt in treatment of various metabolic and infectious diseases. The results are promising and can be utilized for treatment of multifactorial diseases of various origins in humans.

Fig 8: *Eucalyptus globulus*

Ylang ylang

Ylang–ylang (*Cananga odorata* Hook. F. & Thoms) belonging to the family of Annonaceae, native to Madagascar, Indonesia and Philippines is a small tree (Figure 9). Its chemical constituent includes geranyl acetate, linalol, geraniol, farnesol, benzyl acetate, geranial, methyl chavicol, beta-caryophyllene, eugenol, pinene and farnesene. The best property of this tree is to retard the heart beat and rapid breathing with perfect use in shock and trauma situations. It is anti-depressive in nature with euphoric properties, thus giving the feeling of well-being. Low self-esteem and women suffering from the post-menopausal syndrome have better results on them. Further, its aphrodisiac properties are due to its exotic fragrance advantageous for both dry and oily skins. It is also indicated in depression, anxiety, hypertension, frigidity, stress and palpitations.

Fig 9: *Cananga odorata*

Roman chamomile

Roman chamomile (*Anthemis nobilis* Linn.) belongs to the family of Asteraceae (Figure 10). A prized plant for centuries with a potential to calm, moderate and strong emotions bear a daisy like flowers. Major constituents of Roman chamomile oil are esters of angelic acid, tiglic acid and 2-methyl butanoic acid. The freshly distilled oil has a bluish tint due to the sesquiterpenoid chamazulene. It is rich in pinocarvone, farnesol, pinene, bisabolol, cineole, pinocarveol, beta-caryophyllene, azulene, camphene and myrcene. Chamomile preparations have made inroads in the treatment of human ailments such as hay fever, inflammation, muscle spasms, menstrual disorders, insomnia, ulcers, wounds, gastrointestinal disorders, rheumatic pain, and hemorrhoids. In cosmetics and aromatherapy, it is employed for its anxiolytic properties [31, 32].

Fig 10: *Anthemis nobilis*

Anti-oxidant proprieties of EOs

Mitochondrial DNA damage can result from oxidative stress, and defects on the electron transport chain (ETC) result in the further release of reactive oxygen species (ROS) and further DNA, lipid, and protein damage. Anti-oxidant properties of EOs can, therefore, contribute to cancer preventative mechanisms. Specific EO components such as eugenol, the main constituent extracted from clove oil, can react with ROS to form reactive phenoxy radicals, which can then combine with further ROS and prevent further damage. Other cancer protective mechanisms induced by EOs include the induction of the expression of anti-oxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and glutathione, as shown by Manjamalai and Berlin Grace. Treatment with EO extracts of *Wedelia chinensis* (96% of the components being carvacrol and trans-caryophyllene) lead to an increase in intracellular anti-oxidant activity, subsequently leading to a significant reduction in tumor mass volume as well and regeneration of surrounding healthy tissue [33-36].

Essential oil safety issue

The essential oils are generally safe with minimum adverse effects. Several of these have been approved as food additives and fall in the category of generally recognized as safe by the U.S. Food and Drug Administration. The most common adverse events are eye, mucous membrane and skin

irritation and sensitization particularly to oils containing aldehydes and phenols. Photo toxicity of essential oil that contains furocoumarins, for example *Citrus bergamia*, is also reported. Contact sensitization is more likely to occur due to oxidation of monoterpenes, often due to inappropriate storage conditions. Cross-sensitization to other essential oils and foods is also possible. Allergy from inhaled essential oils can occur; however, data about exposure levels are limited and many of the reports concern perfumes rather than aromatherapy essential oils. An exceptional case of airborne contact dermatitis was reported only once in context to aromatherapy without massage [37-40].

The aromatherapy utilizes non-defined mixtures of these essential oils without disclosing their plant sources. Allergic reactions have been reported in few instances, especially with topical administration. These oils are not free from oxidization reaction with age and are reported for the change in their chemical composition on storage for long time. Reversible prepubertal gynecomastia was reported in one study on repeated exposure to lavender and tea tree oils by topical administration. There is always a big controversy which arises when the safety of these essential is discussed. No well-defined studies have proved that these essential oils are harmful. In case of some isolated studies, we have observed that these are not safe, but the majority of studies have not proved these oils if used in aromatherapy are harmful [41-44].

Table 2: Plants producing essential oils [45, 46]

Parts of the plant	Essential oils
Leaves	Citronella, lemon grass, petitgrain, palmarosa, patchouli
Flowers	Jasmine, neroli (orange blossom), rose, ylang ylang
Fruit peel	Bergamot, lemon, lime, sweet orange, tangerine, mandarin
Entire plant	Geranium, lavender, rosemary, spike lavender
Root	Ginger, vetiver
Bark	Cinnamon

Table 3: List of plant essential oils (EO) and their major constituent(s) with potential implications [46-50]

Plant name	Major constituent(s)	Bioactivity
Abies alba	Cone oil: α-pinene, β-pinene, limonene; Seed oil: α-pinene, limonene, β-myrcene	Cytotoxicity
Abies koreana	Cone oil: α-pinene, β-pinene, limonene; Seed oil: camphene, α-pinene, limonene, bornyl acetate	Cytotoxicity

Allium sativum	Diallyl disulfide (DADS), Diallyl trisulfide (DATriS)	Apoptosis
Lavandula angustifolia	Linalool, borneol, linalyl acetate	Cytotoxicity
Boswellia sacra	α-Pinene, α-thujene, β-pinene, myrcene, boswellic acid	Apoptosis
Curcuma longa	α-Turmerone, β-turmerone, ar-turmerone, α-phellandrene, 1,8-cineole	Cytotoxicity
Cyperus articulatus	Sesquiterpenes, monoterpenes, nootkatone, 6-methyl-3,5-heptadien-2-one, retinene, nopinone, cycloeucalenol, anozol, toosendanin, furanone, ethanone, vitamin A	Cytotoxicity
Mentha pulegium	Pulegone, piperitone, trans-isocitral, limonene	Cytotoxicity
Neolitsea variabillima	trans-β-Ocimene, sabinene, α-cadinol, terpinen-4-ol, β-caryophyllene, α-pinene, β-pinene, 1,8-cineole	Anti-proliferative
Pinus pinea	Limonene, β-caryophyllene, α-terpineol	Cytotoxicity
Piper cernuum	Carvacrol, thymol, α-terpineol, linalol, α-pinene, camphene, limonene, myrcene, p-cymene	Anti-tumour
Thymus carmanicus	Carvacrol, cymene, thymol, borneol, γ-terpinene, β-myrcene	Anti-oxidant
Xylopia laevigata	γ-Muurolene, δ-cadinene, germacrene B, α-copaene, germacrene D, bicyclogermacrene, (E)-caryophyllene	Cytotoxicity; Anti-tumour
Zingiber officinale	β-Phellandrene, β-funebrene, selina-4(14), 7(11)-diene, camphene, α-pinene	Cytotoxicity; Anti-tumour
Zornia brasiliensis	trans-Nerolidol, germacrene D, trans-caryophyllene, α-humulene, (Z,E)- α-farnesene	Cytotoxicity; Anti-tumour

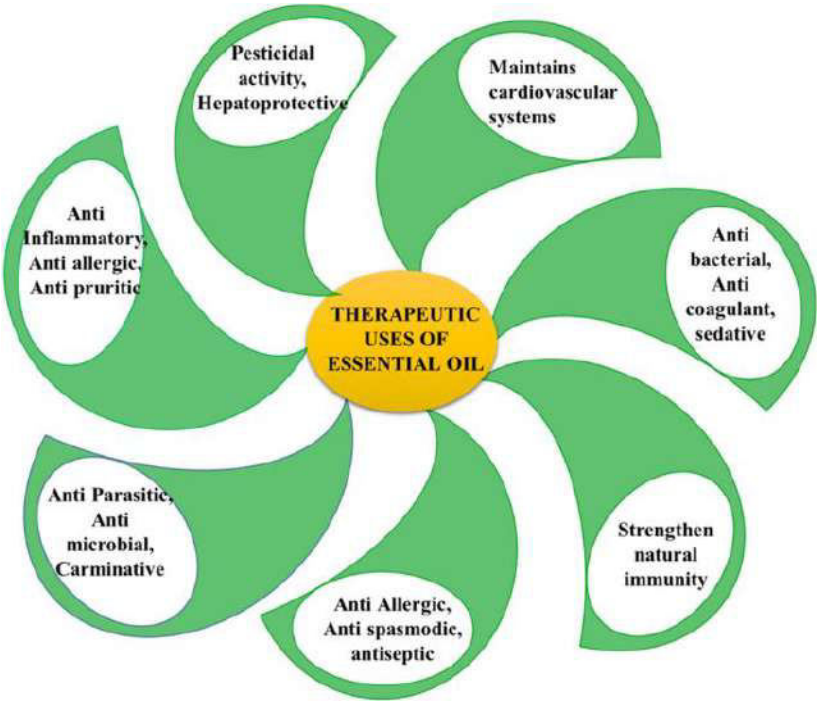


Fig 11: Therapeutic applications of essential oils

Pharmaceutical applications of essential oils

Essential oils have gained attention in the pharmaceutical industry for their potential therapeutic properties. While more research is needed to fully understand their mechanisms of action and to establish their efficacy and safety, some pharmaceutical applications of essential oils are being explored. It's important to note that essential oils are not a substitute for traditional pharmaceutical drugs, and their use in pharmaceutical settings is often in the early stages of research. Here are some potential pharmaceutical applications of essential oils:

Anti-microbial agents

- **Antibacterial:** Essential oils like tea tree, oregano, and thyme have shown antimicrobial properties and may be explored as potential agents against bacterial infections.
- **Antifungal:** Oils such as tea tree, cinnamon, and clove have demonstrated antifungal properties, which may be useful in the development of antifungal medications.

Anti-viral applications

- **Influenza and respiratory viruses:** Some essential oils, including eucalyptus and tea tree, have shown antiviral activity in laboratory studies. Research is ongoing to explore their potential use in combating respiratory viruses.

Anti-inflammatory medications

- **Inflammation control:** Essential oils like frankincense, myrrh, and turmeric contain compounds with anti-inflammatory properties. These oils may be investigated for their potential use in developing anti-inflammatory drugs.

Analgesic and pain management

- **Pain relief:** Certain essential oils, such as lavender, peppermint, and chamomile, have analgesic properties and may be explored for their potential use in pain management.

Anti-cancer properties

- **Cancer research:** Some essential oils, including frankincense and myrrh, have been studied for their potential anticancer properties. Research is ongoing to understand their effects on cancer cells and their potential role in cancer treatment.

Neurological disorders

- **Alzheimer's and Parkinson's disease:** Essential oils such as rosemary and lavender have been investigated for their potential neuroprotective effects. Research is exploring their role in neurodegenerative diseases.

Wound healing

- **Topical applications:** Essential oils like lavender, tea tree, and helichrysum are studied for their potential wound-healing properties. They may be explored as components of topical formulations for wound care.

Cardiovascular health

- **Blood pressure regulation:** Some essential oils, including lavender and ylang-ylang, are being studied for their potential to help regulate blood pressure.

Sleep aid

- **Sedative effects:** Lavender, chamomile, and sandalwood oils are often used to promote relaxation and improve sleep. These oils may be diffused or applied topically before bedtime.

Headache relief

- **Peppermint oil:** Inhalation of peppermint oil or topical application to the temples may provide relief from headaches and migraines.

Digestive health

- **Peppermint and ginger:** These oils are thought to have digestive benefits and may be used to alleviate symptoms such as indigestion and nausea.

Insect repellent

- **Citronella, tea tree, and eucalyptus:** These oils are often used as natural insect repellents.

It's important to emphasize that while these applications show promise, more rigorous research and clinical trials are needed to establish the safety and efficacy of essential oils in pharmaceutical contexts. Additionally, the development of pharmaceutical products based on essential oils requires careful formulation and standardization processes to ensure consistent and controlled dosages. Always consult with healthcare professionals or researchers for the most up-to-date information on the pharmaceutical applications of essential oils. It's crucial to dilute essential oils properly before applying them to the skin, as they can be irritating or cause allergic reactions in concentrated form. Pregnant women, individuals with certain medical conditions, and young children should exercise caution or avoid certain essential oils altogether. Always consult with a qualified healthcare professional or aromatherapist before using essential oils for therapeutic purposes.

Conclusion

This review attempts to shed light on essential oils and their pharmacotherapeutic applications. Various EOs have been known to possess myriads of biological activities. Further, the therapeutic effects (analgesic, anti-inflammatory, calming and relaxing) of EOs during aromatherapy render them potential adjuvants for clinical cancer treatments and help in alleviating cancer related physical and emotional disorders. Thus, the use of EOs/their components in combination with conventional chemotherapy drugs may

provide a new impetus for cancer treatment and toxicity reduction. However, with fewer preclinical studies on the anti-cancer properties of EOs and a dearth of studies in humans, their potential in cancer treatment is largely limited. Accordingly, studies investigating the pharmacokinetic profile, safety, and toxicity of EOs are required before they can be incorporated into anti-cancer drug regimes.

From above reports and study, we can conclude that aromatherapy is natural and non-invasive gift of nature for humans. It's not only the disease symptoms which are eradicated but the whole body is rejuvenated by the use of aroma. Aromatherapy regulates the physiological, spiritual and psychological upliftment for the new phase of life. This therapy is not only preventive but also can be used in the acute and chronic stages of disease. Pharmaceutical industries are trying for environmental friendly, alternative and natural medicine for disease associated with pathogens and metabolism. There may be a possibility of enhancing the rate of reaction and bioavailability of drugs from the use of these essential oils.

If properly studied, these volatile oils may have the synergistic effect with the drugs used in the treatment of central nervous system disorder. Moreover, the time at which the plant contains the maximum amount of volatile oil with various chemical constituents also is a matter of discussion. Essential oils can be a useful non-medicinal option or can also be combined with conventional care for some health conditions, provided safety and quality issues are considered. The tilt of the scientific community towards complementary and alternative medicine has given the new hope to reduce the unwanted effects of modern medicine by these essential oils and if properly explored to their full potential, this therapy can be a boon not only to the patients but also to a common man.

EOs are very interesting natural products and they possess various biological properties. An essential oil may contain hundreds of individual chemical components, mainly mono and sesquiterpenoids, and phenylpropanoids. For therapeutic purposes, they are administered via inhalation (e.g., eucalyptus oil), orally (e.g., peppermint oil) and trans-dermally (e.g., rosemary oil). Oils with a high phenol content, for instance thyme and clove, have anti-septic properties. Because of their wide-ranging and complex effects, e.g., anti-bacterial, anti-viral, anti-inflammatory, mucolytic, bronchodilator, etc., they can be used as valuable materials in the treatment of different respiratory tract diseases. Some EOs are applied exclusively based upon long-standing use, but some EOs can be used based upon well-established use.

References

1. Craig WJ. Health-promoting properties of common herbs. Am. J. Clin. Nutr. 1999;70:491s-499s.
2. Worwood VA. Aromatherapy for the healthy child: more than 300 natural, non-toxic, and fragrant essential oil blends. Novato: New World Library, 2000.
3. Esposito ER, Bystrek MV, Klein JS. An elective course in aromatherapy science. Am J Pharm Educ. 2014;78(4):79.
4. Evans WC. Trease and Evans pharmacognosy. 4th ed. London: WB Saunders Co, 2000.
5. Voboda KP, Deans SG. Biological activities of essential oils from selected aromatic plants. Acta Hort. 1995;390:203-209.
6. Dunning T. Aromatherapy: overview, safety and quality issues. OA Altern Med. 2013;1(1):6.
7. Oyedeji AO, Afolayan AJ, Hutchings A. Compositional variation of the essential oils of *Artemisia afra* Jacq. from three provinces in South Africa–a case study of its safety. Nat Prod Commun. 2009;4(6):849-852.
8. Marchand L. Integrative and complementary therapies for patients with advanced cancer. Ann Palliat Med. 2014;3(3):160-171.
9. Lee KB, Cho E, Kang YS. Changes in 5-hydroxytryptamine and cortisol plasma levels in menopausal women after inhalation of clary sage oil. Phytother Res. 2014;28(11):1599-1605.
10. Aazza S, Lyoussi B, Megias C, Cortes-Giraldo I, Vioque J, Figueiredo AC *et al*. Anti-oxidant, anti-inflammatory and antiproliferative activities of Moroccan commercial essential oils. Nat Prod Commun. 2014;9(4):587-594.
11. Ghannadi A, Bagherinejad M, Abedi D, Jalali M, Absalan B, Sadeghi N. Antibacterial activity and composition of essential oils from Pelargonium graveolens L'Her and *Vitex agnus-castus* L. Iran J Microbiol 2012;4(4):171-176.
12. Krishna A, Tiwari R, Kumar S. Aromatherapy-an alternative health care through essential oils. J Med Aromat Plant Sci. 2000;22:798-804.
13. Edris AE. Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: a review. Phytotherapy Research. 2007;21(4):308-323.

14. Yang Y, Yue Y, Runwei Y, Guolin Z. Cytotoxic, apoptotic and antioxidant activity of the essential oil of Amomum tsao-ko. Bioresource Technology. 2010;101(11):4205-4211.

15. Furstenberg-Hagg J, Zagrobelny M, Bak S. Plant defense against insect herbivores. International Journal of Molecular Sciences. 2013;14(5):10242-10297.

16. Raut JS, Karuppayil SM. A status review on the medicinal properties of essential oils. Industrial Crops and Products. 2014;62:250-264.

17. Bhalla Y, Gupta VK, Jaitak V. Anticancer activity of essential oils: a review. Journal of the Science of Food and Agriculture. 2013;93(15):3643-3653.

18. Da Silva SL, Chaar JDS, Figueiredo PDMS, Yano TC. Cytotoxic evaluation of essential oil from *Casearia sylvestris* Sw on human cancer cells and erythrocytes. Acta Amazonica. 2008;38(1):107-112.

19. Da Silva SL, Figueiredo PM, Yano TC. Cytotoxic evaluation of essential oil from *Zanthoxylum rhoifolium* Lam. leaves. Acta Amazonica. 2007;37(2):281-286.

20. Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y *et al*. Engineered nanoparticles for drug delivery in cancer therapy. Angewandte Chemie International Edition. 2014;53(46):12320-12364.

21. Hwang E, Shin S. The effects of aromatherapy on sleep improvement: a systematic literature review and meta-analysis. J Altern Complement Med. 2015;21(2):61-68.

22. Farooqi AHA, Sharma S. Aromatherapy-a promising holistic system. J Med Aromat Plant Sci. 2000;22:704-706.

23. Kovar KA, Gropper B, Friess D, Ammon HP. Blood levels of 1,8-cineole and locomotor activity of mice after inhalation and oral administration of rosemary oil. Planta Med. 1987;53:315-318.

24. Ou MC, Hsu TF, Lai AC, Lin YT, Lin CC. Pain relief assessment by aromatic essential oil massage on outpatients with primary dysmenorrhea: a randomized, double-blind clinical trial. J Obstet Gynaecol Res. 2012;38(5):817-822.

25. Han SH, Hur MH, Buckle J, Choi J, Lee MS. Effect of aromatherapy on symptoms of dysmenorrhea in college students: a randomized placebo-controlled clinical trial. J Altern Complement Med. 2006;12(6):535-541.

26. Tisserand R, Young R. Essential oil safety: a guide for health care professional. 2nd ed. London: Churchill Livingstone, 2013.

27. Yavari Kia P, Safajou F, Shahnazi M, Nazemiyeh H. The effect of lemon inhalation aromatherapy on nausea and vomiting of pregnancy: a double-blinded, randomized, controlled clinical trial. Iran Red Crescent Med J. 2014;16(3):e14360.

28. Rajivgandhi G, Saravanan K, Ramachandran G, Li JL, Yin L, Quero F *et al*. Enhanced anti-cancer activity of chitosan loaded *Morinda citrifolia* essential oil against A549 human lung cancer cells. Int J Biol Macromol. 2020;164:4010-4021.

29. Pavithra PS, Mehta A, Verma RS. Essential oils: from prevention to treatment of skin cancer. Drug Discovery Today. 2019;24(2):644-655.

30. Kompelly A, Kompelly S, Vasudha B, Narender B. *Rosmarinus officinalis* L.: an update review of its phytochemistry and biological activity. Journal of Drug Delivery and Therapeutics. 2019;9(1):323-330.

31. Kim BJ, Jeong H, Park S, Lee S. Forest adjuvant anti-cancer therapy to enhance natural cytotoxicity in urban women with breast cancer: A preliminary prospective interventional study. Eur J Integr Med. 2015;7:474-478.

32. Standen MD, Myers SP. The roles of essential oils in the modulation of immune function and inflammation: Survey of aromatherapy educators. Int J Aromather. 2004;14:150-161.

33. Erdogan A, Ozkan A. A comparative study of cytotoxic, membrane and DNA damaging effects of *Origanum majorana's* essential oil and its oxygenated monoterpene component linalool on parental and epirubicin-resistant H1299 cells. Biologia. 2013;68:754-761.

34. Arafa ESA, Zhu Q, Shah ZI, Wani G, Barakat BM, Racoma I *et al*. Thymoquinone up-regulates PTEN expression and induces apoptosis in doxorubicin-resistant human breast cancer cells. Mutat Res. 2011;706:28-35.

35. Horvath G, Acs K. Essential oils in the treatment of respiratory tract diseases highlighting their role in bacterial infections and their anti-inflammatory action: a review. Flavour Fragr J. 2015;30(5):331-341.

36. Peterfalvi A, Miko E, Nagy T, Reger B, Simon D, Miseta A *et al*. Much more than a pleasant scent: a review on essential oils supporting the immune system. Molecules. 2019;24(24):4530.

37. Candy B, Armstrong M, Flemming K, Kupeli N, Stone P, Vickerstaff V *et al*. The effectiveness of aromatherapy, massage and reflexology in people with palliative care needs: a systematic review. Palliat Med. 2020;34(2):179-194.

38. Armstrong M, Flemming K, Kupeli N, Stone P, Wilkinson S, Candy B *et al*. Aromatherapy, massage and reflexology: a systematic review and thematic synthesis of the perspectives from people with palliative care needs. Palliat Med. 2019;33(7):757-769.

39. Anderson C, Lis-Balchin M, Kirk-Smith M. Evaluation of massage with essential oils on childhood atopic eczema. Phytother Res. 2000;14(6):452-456.

40. Stevenson C. Measuring the effects of aromatherapy. Nurs Times. 1992;88(41):62-63.

41. Hartman D, Coetzee JC. Two US practitioners' experience of using essential oils for wound care. J Wound Care. 2002;11(8):317-320.

42. Asquith S. The use of aromatherapy in wound care. J Wound Care. 1999;8(6):318-320.

43. Buckle J. Aromatherapy. Nurs Times. 1993;89(20):32-35.

44. Hadfield N. The role of aromatherapy massage in reducing anxiety in patients with malignant brain tumours. Int J Palliat Nurs. 2001;7(6):279-285.

45. Wilkinson S. Aromatherapy and massage in palliative care. Int J Palliat Nurs. 1995;1(1):21-30.

46. Rajput MS, Agrawal P. Microspheres in cancer therapy. Indian Journal of Cancer. 2010;47(4):458-468.

47. Ferruggiari L, Ragione B, Rich ER, Lock K. The effect of aromatherapy on postoperative nausea in women undergoing surgical procedures. Journal of PeriAnesthesia Nursing. 2012;27(4):246-251.

48. Ozkaraman A, Dugum O, Ozen Yilmaz H, Usta Yesilbalkan O. Aromatherapy: the effect of lavender on anxiety and sleep quality in patients treated with chemotherapy. Clin J Oncol Nurs. 2018;22:203-210.

49. Jerbi A, Derbali A, Elfeki A, Kammoun M. Essential oil composition and biological activities of Eucalyptus globulus leaves extracts from Tunisia. J Essent Oil Bear Plants. 2017;20:438-448.

50. Bakkali F, Averbeck S, Averbeck D, Idaomar M. Biological effects of essential oils-a review. Food Chem Toxicol. 2008;46(2):446-475.

Chapter - 4

Maternal-Fetal Medicine: Optimizing Outcomes in High-Risk Pregnancies

Authors

Shital Patel
Assistant Professor, Department of Obstetrics & Gynaecological Nursing, Sumandeep Nursing College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Dr. Anita Prakasam
Principal & HOD, Department of Obstetrics & Gynaecological Nursing, Sumandeep Nursing College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Vruti Patel
Associate Professor, Department of Obstetrics & Gynaecological Nursing, Sumandeep Nursing College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Mittal Panchal
Assistant Professor, Department of Obstetrics & Gynaecological Nursing, Sumandeep Nursing College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Nilam Patel
Nursing Tutor, Department of Obstetrics & Gynaecological Nursing, Sumandeep Nursing College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Chapter - 4

Maternal-Fetal Medicine: Optimizing Outcomes in High-Risk Pregnancies

Shital Patel, Dr. Anita Prakasam, Dr. Vruti Patel, Mittal Panchal and Nilam Patel

Abstract

Although the influence of advanced maternal age (AMA) and delayed childbearing on adverse maternal and perinatal outcomes has been studied extensively, no universal consensus on the definition of AMA exists. This terminology currently refers to the later years of a woman's reproductive life span and generally applies to women age ≥35 years. AMA increases the risk of pregnancy complications, including ectopic pregnancy, spontaneous abortion, fetal chromosomal abnormalities, congenital anomalies, placenta previa and abruption, gestational diabetes, preeclampsia, and cesarean delivery. Such complications could be the cause of preterm birth and increase the risk of perinatal mortality. For women who have a chronic illness, pregnancy may lead to additional risk that demands increased monitoring or surveillance. The management of pregnant women of AMA requires understanding the relationship between age and pre-existing comorbidities. The outcomes from pregnancy in AMA may have a negative impact on women's health as they age because of both the changes from the pregnancy itself and the increased risk of pregnancy-related complications. Postpartum depression affects women of AMA at higher rates. Links between preeclampsia and the risk of future development of cardiovascular disease require follow-up surveillance. The association between hypertensive pregnancy disorders and cognitive and brain functions needs further investigation of sex-specific risk factors across the life span. Educating providers and women of AMA is crucial to facilitate clinical decision making and such education should consider cultural influences, risk perception, and women's health literacy, as well as providers' biases and system issues.

Keywords: Advanced maternal age, pregnancy outcomes, adverse maternal outcomes, maternal mortality and morbidity, beliefs and behaviours, health equity.

Introduction

Definition: Small for gestational age, fetal growth restriction and intrauterine growth restriction are terms used interchangeably in scientific literature. Fetal growth restriction (FGR) refers to the fetus with estimated fetal weight (EFW) of less than the 10th percentile while small for gestational age (SGA) refers to a new born with a birthweight (BW) of less than the 10th percentile for gestational age. The Society for Maternal-Fetal Medicine (SMFM) recommends abandoning the term intrauterine growth restriction. Other national guidelines defined SGA and FGR differently. The Royal College of Obstetricians and Gynaecologists (RCOG) defines SGA as an infant born with a BW < 10th centile, SGA birth is a fetus with an EFW or abdominal circumference (AC) <10th centile while FGR is a fetus with a pathological restriction of genetic growth potential and thus need an additional sign such as an abnormal Doppler studies or oligohydramnios. The Society of Obstetricians and Gynaecologists of Canada (SOGC) likewise defines SGA as an EFW <10th centile and intrauterine growth restriction (IUGR) is a fetus with EFW <10th centile who has not attained its growth potential because of a pathological process. All of these societies recommend screening all pregnancies for the risk of FGR and do serial weight measurements for those at risk.

The field of maternal-fetal medicine is a highly specialized branch of obstetrics that focuses on the comprehensive care and management of high-risk pregnancies, addressing the complex medical needs of both the expectant mother and the developing fetus. This subspecialty plays a vital role in ensuring optimal outcomes for pregnancies characterized by medical, genetic, or obstetric complications. Maternal-fetal medicine specialists, often referred to as primatologists, work in close collaboration with obstetricians, neonatologists, genetic counsellors, and other healthcare professionals to provide a multidisciplinary approach to prenatal care.

High-risk pregnancies can arise from a variety of factors, including pre-existing maternal medical conditions, such as diabetes or hypertension, as well as conditions that develop during pregnancy, like gestational diabetes or pre-eclampsia. Multiple pregnancies, pregnancies in women of advanced maternal age, and pregnancies with fetal anomalies or genetic disorders also fall within the scope of maternal-fetal medicine. As a result, the care provided by maternal-fetal medicine specialists is highly individualized, tailoring diagnostic and management strategies to the specific needs of each pregnancy.

One of the key areas of focus in maternal-fetal medicine is the early

detection of fetal abnormalities and genetic conditions. Advanced prenatal screening and diagnostic techniques, such as non-invasive prenatal testing (NIPT), amniocentesis, and detailed ultrasound examinations, are used to assess fetal health and to provide expectant parents with crucial information about their child's well-being. This allows for informed decision-making and the development of appropriate care plans.

In cases where intervention is necessary, maternal-fetal medicine specialists may perform in utero procedures or surgeries to address specific fetal conditions. These interventions are often complex and require a high degree of expertise, as well as careful consideration of the potential risks and benefits to both the mother and the fetus.

The field of maternal-fetal medicine is not only focused on the physical health of the mother and fetus but also on the psychological and emotional well-being of expectant parents. Perinatologists provide comprehensive counselling and support, particularly in cases where a pregnancy is complicated by a fetal anomaly or genetic disorder.

As medical technology continues to advance, the field of maternal-fetal medicine evolves to embrace innovative diagnostic tools, telehealth solutions, and personalized medicine approaches. Research within this discipline aims to improve the accuracy of prenatal assessments and interventions, reduce maternal and fetal complications, and enhance the overall quality of care delivered to pregnant individuals and their developing babies.

Ultimately, maternal-fetal medicine is dedicated to ensuring that every pregnancy has the best possible chance for a healthy outcome. The expertise and care provided by perinatologists are essential in managing and mitigating the risks associated with high-risk pregnancies, thereby promoting the well-being of both the mother and the unborn child. This introduction provides an overview of the essential role that maternal-fetal medicine plays in modern obstetrics and highlights its significance in the realm of women's and fetal health.

A TREND HAS developed worldwide for women to delay childbearing into their 30s and, in some cases, their 40s. According to the Centers for Disease Control and Prevention, the number of pregnancies in women of advanced maternal age (AMA) continues to escalate in the United States, especially among women ≥40 years. In 2014, 9% of first births were to women age ≥35 years, an increase of 23% from 2000. Numerous reasons underlie the increased rates of AMA pregnancies or births. Demographic data show an increased population of women age 35–45 influenced by evolving social and cultural

changes, including higher rates of divorce, having multiple partners before settling down, living together before marriage, and having a later or second marriage. Women with higher socioeconomic status (SES) and higher level of education tend to delay motherhood into their mid-to-late 30s. Advances in medical sciences have provided women with better contraceptive options and more available fertility treatment, but SES affects access to and utilization of assisted reproductive technology (ART). Limited job-related policies (*e.g.*, unavailability or limitations with childcare, low benefit levels, policies un favourable to motherhood and work/career) are among other reasons for delaying motherhood. Education and job opportunities thus contribute to delaying motherhood to later in life. Maternal education is shown to be among the strongest predictors of contraceptive use, with college-educated women generally having low first-birth rates in their 20s and higher birth rates in their 30s.

Despite having become more common, older expectant mothers remain a stigmatized social identity, with some still referring to the outdated term "geriatric pregnancy." Although the impact of AMA and delayed childbearing on maternal and perinatal outcomes has been studied extensively, no universal consensus on its definition exists. This terminology currently refers to the later years of a woman's reproductive life span and generally applies to women age ≥35 years. The effects of increasing age, however, occur as a continuum, with a decline in fertility, particularly observed after their mid-30s. Regardless of the age used to define AMA, pregnancies in women age ≥35 years are considered at risk of both obstetric complications and interventions.

Timing of delivery: The timing of delivery depends on the age of gestation and the result of the fetal surveillance tests. Once FGR is suspected, the best fetal surveillance method used to help time the delivery is the Doppler ultrasound. SMFM recommends delivery of FGR with normal umbilical artery (UA) Doppler and EFW between the 3rd and the 10th centile at 38–39 weeks. If there is an elevated UA Doppler or the EFW < 3rd centile, SMFM (2020) recommends delivery at 37 weeks. For FGR with absent end diastolic velocity (AEDV) in the umbilical artery Doppler, their recommendation is delivery at 34 weeks and for those with reversed end diastolic velocity (REDV), delivery at 30–32 weeks [3]. The RCOG [5] recommends delivery when FGR is detected before 32 weeks when there is AEDV or REDV and abnormal ductus venosus (DV) Doppler or when there are umbilical vein pulsations. Even if the DV Doppler is normal, delivery is still recommended at 32 weeks for the FGR with AEDV or REDV. After 32 weeks but before 37 weeks, delivery is recommended when the middle cerebral artery (MCA) Doppler or the UA

Doppler is abnormal, with the involvement of a senior obstetrician in the decision of the timing and mode of delivery [5]. SOGC [7] recommends delivery at 38–40 weeks in FGR with no other issues. For FGR <34 weeks with abnormal UA Doppler, add MCA and DV Doppler and biophysical profile (BPP) or BPP with nonstress test (NST). If there is AEDV or REDV of the UA, and normal BPP/NST, more intensive monitoring is done and delivery is recommended if BPP worsen or MCA or DV is abnormal. In a fetus >34 weeks, if normal amniotic fluid volume, BPP and Doppler studies, continue monitoring and discuss delivery at 37 weeks or continue monitoring after 37 weeks. If amniotic fluid or BPP or Doppler study is abnormal, delivery should be considered.

Mode of delivery: The guidelines also differ with their recommendation on the mode of delivery. SMFM (2020) suggests cesarean section (CS) for FGR with AEDV or REDV (weak recommendation, low quality evidence). RCOG [5] likewise recommends cesarean delivery for FGR with AEDV or REDV (good practice point, GPP, based on the clinical experience of the guideline development group) and induction of labor with continuous cardiotocography (CTG) if there is UA end diastolic flow (B, from high quality systematic reviews, cohort or case control studies with low confounding bias). SOGC [7] did not specify their recommended mode of delivery. The Philippine Obstetrical and Gynecological Society Clinical Practice Guidelines on Cesarean Section recommends abdominal delivery when fetal growth restriction is complicated by at least AEDV or REDV of the umbilical artery on Doppler. Local consensus guidelines of the United States (SMFM) and the United Kingdom (RCOG) both suggest cesarean delivery in FGR with AEDV OR REDV of the UA on Doppler. Our review of evidence, as shown below, supported this recommendation since there is an associated increased risk of adverse perinatal outcomes in FGR with AEDV OR REDV of the UA. The studies however are all observational studies with serious methodological flaws and risk of bias. Where induction of labor is chosen however as the mode of delivery, consider mechanical methods over dinoprostone since the latter is associated more with CS for no reassuring fetal status. There were significantly higher risks of CS OR 19.43 (95% CI 9.10–41.47), admission to NICU OR 15.83 (7.40–33.85), intrauterine death OR 6.97 (2.90–16.77), respiratory distress OR 5.58 (3–10.38) and cerebral haemorrhage OR 7.42 (3.05–18.01) among pregnancies with absent or reversed end diastolic flow in the umbilical arteries compared to those with positive diastolic flow.

Culture and risk perception of providers and women

Comparing studies assessing pregnancy risk perception of providers, midwives, and women is challenging because of the differences in their methodological approaches [11]. Risk perception is multifaceted and influenced by various personal, psychological, and societal factors. Differences in perception among providers, midwives, and women have been attributed to women's more subjective views and limited knowledge related to risk. Most pregnant women express fears with the birth process and the wellbeing of babies, but the risk usually is accepted as part of the psychological strategies of pregnancy that women use to cope with their apprehensions. These strategies likely help them endure the higher degrees of risk, because they believe that better outcomes for themselves and for their babies will be reached. Women generally go beyond the medical and social models of care to include feelings of experienced risk and resilience factors (*e.g.*, prior use of ART). Providers express a more objective and science-based perception because they focus on the biomedical risk and physiological outcomes. Midwives adopt a more holistic attitude that encompasses the psychological and social wellbeing of the patient.

Culture contributes to increased maternal mortality because of harms to the mother during the perinatal period (*e.g.*, direct harmful acts, inaction, use of care, and social status). Direct harmful practices and factors that contribute to maternal mortality include burning, cutting, food and water shortages, forced or delayed placental expulsion, and exposure to infectious agents. A woman may not respond adequately to prevent adverse outcomes; obstetric emergencies may not be recognized, or cultural beliefs about their causes, treatment, and implications may preclude her from seeking help. Culture may affect maternal mortality because of a lack of or limited access to health services during pregnancy and childbirth. Several factors may contribute to a woman's perception of pregnancy risk, including medical risk, psychological factors, risk characteristics, stage of pregnancy, and the judgment of health care providers.

Pregnancy outcomes in AMA

Maternal mortality rate (MMR) has increased considerably in the United States during the past 25 years and is currently the highest among developed countries. In 2016, 658 women died of maternal causes, with a MMR of 17.4 deaths per 100,000 live births; racial and ethnic groups were affected disproportionately, with the MMR for non-Hispanic Black women (37.1 deaths/100,000 live births) being 2.5 times the rate for non-Hispanic White

women (14.7) and 3.1 times the rate for Hispanic women (11.8). Age, disabilities, geographic areas, and social and structural determinants of health are significant contributing factors. One-third of pregnancy-related deaths occur during pregnancy, one-third during or in the week after delivery, and one-third between 1 week and 1 year postpartum. The leading mortality causes in the United States include hemorrhage, infection, and cardiovascular disease.

Although all women can suffer complications early or later in pregnancy, the risk for some of these complications is higher with AMA. From 1991 to 1997, the risk of pregnancy-related mortality in the United States was five-fold higher for women age >40 years and more than double for women age 35–39 years compared with that of women age 25–29 (9 vs. 21 vs. 46/100,000 live births, respectively).In 2016, the MMR in the United States increased with successively older age groups, with the rate for women age ≥40 years (81.9) equal to 7.7 times that for women age <25 years (10.6). In developing countries, maternal mortality remains a significant problem; limitations in access to and quality of care contribute significantly to maternal losses, but maternal characteristics (*e.g.*, increasing age, parity) also are important factors.

Early pregnancy outcomes

Ectopic pregnancy

Maternal age of ≥35 years is associated with a four- to eight-fold increased risk of ectopic pregnancy, a major cause of maternal mortality and morbidity in early pregnancy. This finding likely reflects accumulated risk factors over time (*e.g.*, multiple sexual partners, pelvic infection, tubal conditions).

Gene and chromosomal abnormalities, congenital malformations

Except for ART, the data on AMA's effect on gene abnormalities (*e.g.*, single gene disorders, epigenetic events) are limited. Epidemiological studies show an association between advanced maternal and paternal ages and the risk of autism spectrum disorders in the offspring. As women age, a stable increase in the risk of chromosomal abnormalities (*e.g.*, aneuploidy [autosomal trisomy]) is reported in karyotype analysis from spontaneous abortions, pregnancy terminations, genetic amniocenteses, and both live-born and stillborn infants. These age-related errors seem to augment the risk of nondisjunction resulting in unequal chromosome products at completion of cell division. Furthermore, the risk of AMA-associated non chromosomal anomalies includes the highest rates of cardiac anomalies. AMA also is a risk

factor for Down's syndrome; mothers who give birth to a child with this syndrome often have characteristics consistent with accelerated aging.

Spontaneous abortion

With AMA, the rates of spontaneous abortion increase, with most losses occurring between 6 and 14 weeks of pregnancy. Trisomic and euploid losses are linked to a decline in the quality of the oocyte and possible functional changes (*i.e.*, uterine, hormonal). An overall rate of 11% in spontaneous abortion has been reported in a large Scandinavian study of hospitalized women. The risk of loss in different age groups was based on the hypothesis that only 80% of women with abortions were hospitalized. Higher rates of loss were associated with AMA versus younger age groups (<30 years, 12%; 30-34 years, 15%; 35-39 years, 25%; 40-44 years, 51%; ≥45 years, 93%). Spontaneous abortion was affected by maternal age independently of parity and previous abortion history. However, Magnus *et al*. found that the risk of miscarriage varied significantly with maternal age, showed a strong pattern of recurrence, and was increased after adverse pregnancy outcomes. This risk increased if there was a history of prior preterm delivery, stillbirth, cesarean section, or gestational diabetes. Women who were small for their baby's gestational age were at slightly greater risk for miscarriage. These findings suggest that biological conditions or unmeasured common risk factors may be among the shared underlying causes for miscarriages and other complications. The highest rates of spontaneous abortion with AMA have been confirmed in a study of pregnancies resulting from ART use.

Multiple gestation

An increased prevalence of multiple gestation is seen with AMA. Multiple gestation is related to a higher risk of naturally conceived twins and higher ART use. In contrast to singletons, the outcome of multiple pregnancies in AMA is as good or better than the outcome reported for younger women.

Late pregnancy outcomes

Preeclampsia

Preeclampsia affects 4%-8% of all pregnancies. The rates of preeclampsia have increased by 25% over the past two decades. In the general obstetric population, the incidence of preeclampsia is 3%-4%, increasing to 5%-10% in women >40 years of age, becoming as high as 35% in those >50 years. In a large study in Ontario (2012-2015) mothers at very AMA were at greater risk of developing multiple adverse outcomes consisting of preeclampsia, intrauterine growth retardation, stillbirth, or placental abruption.

Interpregnancy interval

Maternal and perinatal outcomes at different birth intervals in a cohort of 148,000 pregnancies revealed an increased risk of severe maternal morbidity or mortality for women ≥35 years of age at the time of index birth. Women at 6-month Interpregnancy intervals presented with adverse fetal and neonatal outcomes, particularly spontaneous preterm delivery. Women age 20-34 years giving birth at a similar time interval showed no such risks.

Placenta previa and placental abruption

AMA is linked to a higher prevalence of placenta previa and placental abruption, both of which cause bleeding in late pregnancy (after about 20 weeks). Placental abruption is a rare but serious complication in the second half of pregnancy and life-threatening for both the mother and the fetus. Death is inevitable if a complete or near-placental separation occurs, unless an immediate cesarean section is performed. Fetal mortality rates of 1%-40% have been reported, but these rates depend on the age of the fetus and extent of separation. Around 1%–5% of maternal deaths each year are linked to placental abruption. Mothers at very AMA also are at a higher risk for placental abruption. Multiparty is associated with a considerable proportion of the excess risk for both placental abruption and placenta previa; however, no significant correlation was observed between maternal age and abruption when parity and hypertension were considered.

Age and parity seem to be independent risk factors for placenta previa. Despite a small absolute risk (0.25% vs. 0.03%), nulliparous women age ≥40 years have a 10-fold increased risk of placenta previa compared with nulliparous women age 20-29 years.

Amniotic fluid embolism and obstetric shock

Although the Etiology of amniotic fluid embolism remains unknown, the embolism may occur in healthy women during, including cesarean section; after abnormal vaginal delivery; during the second trimester of pregnancy; up to 48 hours post-delivery or during abortion; after abdominal trauma; and during amnio infusion. In a population-based study (830,000 singleton births), women ≥40 years of age showed an eight-fold increased risk of amniotic fluid embolism and a three-fold increased risk of obstetric shock compared with women age 25-29 years.

Peripartum cardiomyopathy

Peripartum cardiomyopathy is a rare, generally dilated form of cardiomyopathy with systolic dysfunction that presents in late pregnancy or,

more commonly, in the early postpartum period. Black-descendent women are at highest risk, with high rates seen in Nigeria and Haiti. Preeclampsia, AMA, and multiple gestation pregnancy are among the risk factors for cardiomyopathy. Although its pathophysiology is still unclear, vascular/ hormonal pathways likely play a role in women with underlying susceptibility (*e.g.*, sarcomere gene mutation). In general, more than half of affected women recover from systolic function, but some develop chronic cardiomyopathy, and few require mechanical support or cardiac transplantation (or both). Thromboembolism and arrhythmias are potential negative outcomes, as well.

Cesarean delivery

The optimal gestational age for labor or cesarean delivery at AMA is unclear. Some support delivery in the 39th week of gestation. Studies consistently report that women ≥35 years of age are more likely to experience labor dystocia and undergo a cesarean procedure. A cohort of >78,000 singleton births in the United States (2003–2012) showed that the proportion of a primary cesarean delivery (PCD) increased with age for both primi parous and multiparous women. The PCD rate was 20% for women age 25–34 years, 26% for those 35–39 years, 31% for those 40–44 years, 36% for those 45–49 years, and 61% for those ≥50 years. The overall PCD rate for singleton births in the United States was ~22% during a similar time period. The reasons for such high rates in older women are controversial, but they involve an increased frequency of medical complications, labor induction, fetal malposition, and a lower threshold among patients and physicians for performing a cesarean delivery. Maternal request for cesarean delivery is becoming more common, particularly among women of AMA. These women appear to have an increased risk of failure of labor to progress normally.

Throughout the childbearing years, the association between uterine dysfunction increases with maternal age. Findings have not been consistent in recent studies that examine the effect of age on the length of the first stage of labor; however, the length of the second stage seems to increase as age increases. Despite the impact of age on uterine function, a meta-analysis of five trials (>2,600 women) reported that labor induction at term in women age ≥35 years did not increase the cesarean delivery rate compared with women undergoing expectant management. Women of AMA subjected to a trial of labor after a previous cesarean delivery appear to be at increased risk for both failed trial and uterine rupture. Regardless of the known risks, older pregnant women frequently are treated as "higher risk," resulting in elevated rates of cesarean section for nonmedical reasons and more frequent induced labor. Because worse outcomes are more prevalent in this group, poorer outcomes are likely to increase with increasing age.

Preterm delivery, low birth weight, and stillbirth

Few studies have examined the associations between maternal age and pregnancy perinatal outcomes in low- and middle-income countries. Data from Consortium for Health Orientated Research in Transitioning Societies (COHORTS), a collaboration of five birth cohorts from low- and middle-income countries (Brazil, Guatemala, India, the Philippines, and South Africa) evaluated mothers who were recruited before or during pregnancy, and their children were followed up to adulthood. Unadjusted and adjusted analyses for maternal SES, height, parity, and breastfeeding duration were conducted using data from 22,188 mothers (1969-1989). After adjustment, AMA remained associated with increased risk of preterm birth, but children of older mothers had less 2-year stunting and failure to complete secondary schooling compared with those whose mothers were age 20-24 years. Extreme maternal ages showed higher adult fasting glucose concentrations (roughly 0.05 mmol/L), likely reflecting compromised offspring glucose metabolism.

Several population-based studies have documented the link between AMA and increased rates of low birth weight (LBW) and preterm delivery. A cohort of 173,715 healthy nulliparous women delivering singletons showed that being of age 35–40 related to a significantly higher risk of very and moderate LBW and preterm birth and to a small-for-gestational-age infant compared birth outcome. A subsequent study (32,000 women ≥40 years) confirmed the increased risk of preterm delivery after adjusting for confounders (*e.g.*, multiple gestation, smoking, parity, maternal disease). The rates of preterm delivery in <32 weeks for women age 20–29 years, 40–44 years, and ≥45 years were 1.01%, 1.80%, and 2.24%, respectively. In the United States, the adjusted odds ratios (OR) for delivering an LBW White infant increased progressively, with each 5-year increase in maternal age, reaching 2.3 in women ≥40 years of age. The maternal age effect on both very LBW and preterm delivery was similar. Although women of AMA have more preterm deliveries, their neonates are not at an increased risk for morbidity compared with those of younger women.

Large studies worldwide consistently report a significant increased risk for stillbirth in women age ≥35 years. A systematic review and meta-analysis showed that the maternal age of >35 years was associated with a 65% increased risk of a stillbirth, with a higher relative risk at age 40 years. This risk is most notable after ~37 weeks of gestation. In addition, the extra perinatal mortality involving women of AMA is mainly caused by no anomalous fetal deaths (often unexplained), even after adjusting risk factors (*e.g.*, hypertension, diabetes, antepartum bleeding, smoking, multiple

gestation). In developed countries, the absolute risk of stillbirth is small, even at very AMA. In a Swedish study, the absolute risk of an intrauterine fetal death at ≥28 weeks of gestation or death of the live-born child within the first 28 days of life was 1.1% in women age ≥40 years (343 deaths/31,662 deliveries) and 1.7% in women age ≥45 years (20 deaths/1,205 deliveries) after adjusting for confounders (*e.g.*, parity, congenital malformations, smoking, maternal disease) versus women age 20–29 years (5,246 deaths/876,361 deliveries).In the United States, the risk of stillbirth at 37–41 weeks for prim parous women increased considerably with maternal age in an analysis of more than 5 million no anomalous singleton gestations 3.73 (women <35 years), 6.41 (35–39 years), and 8.65 (>40 years) per 1,000 ongoing pregnancies. This persisted after controlling for disease and race/ethnicity and increased abruptly at 40 weeks of gestation, suggesting that women of AMA are "post term" sooner than younger women.

Antepartum and postpartum haemorrhage

An adjusted analysis of a cohort (37 million deliveries, 2006–2015) demonstrated that women age 45–54 years had 3.5 times the risk of severe maternal morbidity and showed the highest rates of caesarean delivery, preeclampsia, postpartum haemorrhage, gestational diabetes, thrombosis, and hysterectomy. Another cohort study (64,886 pregnant women) also analysed multiple risk factors and found that women age ≥35 years ($n = 12,686$) had increased frequency for antepartum haemorrhage, placenta Previa, hypertension, gestational diabetes, and overweight or obesity. In the multiple logistic regression analysis, advanced age had a negative effect. Authors concluded that AMA served as a surrogate factor for postpartum haemorrhage due to the associated increased risk factors, obstetric complications, and interventions.

Maternal-fetal medicine is a specialized branch of obstetrics that focuses on managing and monitoring high-risk pregnancies and complex medical conditions that may affect both the mother and the developing fetus. This field of medicine plays a crucial role in ensuring the health and well-being of both the pregnant woman and her unborn child. Here are some related topics and content areas within maternal-fetal medicine

Prenatal screening and diagnosis

a) **Non-Invasive Prenatal Testing (NIPT):** This is a blood test that screens for common chromosomal abnormalities, such as Down syndrome, during early pregnancy.
b) **Amniocentesis and Chorionic Villus Sampling (CVS):** These are

invasive diagnostic tests that provide more detailed genetic information about the fetus.

c) **Ultrasound and imaging:** Advanced ultrasound technology allows for detailed visualization of the fetus, the placenta, and amniotic fluid, helping identify structural anomalies and monitor fetal growth.

Certainly, here is additional related content for the topic of "Prenatal Screening and Diagnosis" in maternal-fetal medicine:

1. **First trimester combined screening**: This screening combines a maternal blood test (measuring serum markers like PAPP-A and hCG) and nuchal translucency ultrasound to assess the risk of chromosomal abnormalities, particularly in the first trimester.
2. **Quad marker screening:** A second-trimester blood test that measures alpha-fetoprotein (AFP), hCG, estriol, and inhibin-A to screen for neural tube defects and certain chromosomal abnormalities.
3. **Cell-free DNA testing:** An extension of NIPT that examines cell-free fetal DNA in the maternal bloodstream for more comprehensive genetic screening.
4. **Fetal echocardiography:** Specialized ultrasound to assess the structure and function of the fetal heart, crucial for early detection of congenital heart defects.
5. **Integrated screening:** A combination of multiple screenings and tests, such as first and second-trimester screenings, to provide a more comprehensive assessment of the fetus's health.
6. **Prenatal genetic counselling:** Counselling services for expectant parents who have received abnormal screening results, providing information, support, and guidance for making informed decisions**.**
7. **Preconception carrier screening:** Genetic testing for prospective parents to identify whether they are carriers of specific genetic disorders that could be passed on to their offspring.
8. **Maternal serum screening:** Blood tests during pregnancy that assess the risk of certain conditions in the fetus, such as neural tube defects and chromosomal abnormalities.
9. **Fetal Magnetic Resonance Imaging (MRI):** A diagnostic tool used to obtain detailed images of the developing fetus when additional information is needed beyond traditional ultrasound.
10. **Preimplantation genetic testing:** Genetic testing performed on

embryos before they are implanted during *in vitro* fertilization (IVF) to select embryos without specific genetic disorders.

11. **Emerging technologies:** Ongoing research into new and innovative screening methods and technologies that aim to further improve the accuracy and accessibility of prenatal screening and diagnosis.

These additional topics expand on various aspects of prenatal screening and diagnosis, providing a comprehensive overview of the different methods, technologies, and counselling services used to assess fetal health and genetic risks during pregnancy. Researchers and healthcare providers continue to explore these areas to enhance the quality of care for expectant parents and their unborn children.

High-risk pregnancy conditions

a) **Gestational diabetes:** Management and treatment strategies for pregnant women with diabetes.
b) **Hypertensive disorders:** Pre-eclampsia and gestational hypertension management.
c) **Multiple pregnancies:** Care for women carrying twins, triplets, or more.
d) **Preterm labor:** Strategies for identifying and managing preterm labor to optimize fetal outcomes.
e) **Fetal growth restriction:** Evaluation and management of fetuses with growth issues.
f) **Maternal infections:** How certain infections during pregnancy may affect the fetus.

Fetal intervention

a) **In utero procedures:** Some fetal conditions may require interventions before birth, such as fetal surgery for conditions like spina bifida.
b) **Fetal therapy:** Treatments and procedures aimed at improving outcomes for fetuses with specific medical conditions.

Fetal intervention refers to medical procedures and treatments that are performed on a developing fetus in utero (inside the womb) to address various congenital or developmental conditions. These procedures aim to improve the health and well-being of the unborn child. Here are some key points NLU and topics related to fetal intervention:

Indications for fetal intervention: Fetal interventions are typically considered when a prenatal diagnosis reveals a condition that could lead to significant health problems or disabilities for the child after birth. Common indications include congenital heart defects, neural tube defects, twin-to-twin transfusion syndrome (TTTS), and diaphragmatic hernias.

Types of fetal interventions

a) **Fetoscopic surgery:** This minimally invasive approach involves using a fetoscope to access the fetus and perform surgery. It is often used for conditions like TTTS or spina bifida.

b) **Open fetal surgery:** In some cases, open surgery may be required to access and treat the fetus. This is more invasive and typically used for severe conditions like congenital diaphragmatic hernias.

c) **Fetal blood transfusions:** In cases of severe anemia or blood disorders, fetal blood transfusions can be performed.

d) **Fetal shunting:** Shunts can be placed in the fetus to address conditions like hydrocephalus (excess cerebrospinal fluid in the brain).

Risks and benefits: Fetal interventions come with risks, including premature labor, infection, and injury to the fetus. The potential benefits, however, include improving the child's health and reducing long-term complications.

Multidisciplinary teams: Fetal intervention often involves a team of specialists, including maternal-fetal medicine specialists, pediatric surgeons, neonatologists, and radiologists, to ensure the best possible outcome.

Ethical and legal considerations: Fetal intervention raises ethical questions, including the decision-making process, informed consent, and the balance between maternal autonomy and fetal well-being.

Advancements in fetal surgery: Research and technological advancements have improved the safety and effectiveness of fetal interventions. This includes innovations in imaging techniques, surgical instruments, and anaesthesia for the fetus.

Outcomes and long-term follow-up: Many children who undergo fetal interventions require ongoing medical care and follow-up after birth. Long-term outcomes and quality of life are important considerations.

Support and counselling: Parents facing the prospect of fetal intervention may benefit from counselling and support to make informed

decisions and cope with the emotional and psychological aspects of the process.

Research and future directions: Ongoing research aims to improve the success rates and expand the range of conditions that can be treated through fetal intervention.

It's important to note that fetal intervention is a complex and specialized field of medicine, and the decision to pursue it is made on a case-by-case basis after thorough evaluation by a medical team. Patients should consult with healthcare professionals to discuss their specific situation and treatment options.

Genetic counselling

a) **Genetic counselling and testing:** Counselling services for couples at risk of passing on genetic conditions to their offspring.

b) **Carrier screening:** Identifying carriers of specific genetic disorders to inform family planning.

Genetic counselling is a specialized healthcare service that provides information, support, and guidance to individuals and families who are dealing with or at risk for genetic conditions or hereditary diseases. Genetic counsellors are trained professionals who help people understand their genetic risks, make informed decisions, and cope with the emotional and psychological aspects of genetic testing and diagnosis. Here are some key points and topics related to genetic counselling:

Role of genetic counsellors

Genetic counsellors are trained to assess a patient's risk for genetic conditions based on their personal and family medical history.

They provide education and information about the potential genetic risks, including the likelihood of inheriting or passing on a genetic disorder.

Common reasons for genetic counselling

Family history of genetic conditions (e.g., cystic fibrosis, Huntington's disease).

Advanced maternal age (increased risk of chromosomal abnormalities).

Carrier testing for recessive genetic disorders (e.g., sickle cell anemia, Tay-Sachs disease).

Prenatal genetic counselling for expectant parents.

Cancer risk assessment (e.g., BRCA gene mutations).

Preconception counselling: Genetic counsellors can help couples assess their genetic risks before pregnancy, offering guidance on potential issues that may affect their future children.

Prenatal counselling: Genetic counselling during pregnancy can help parents understand the risks of genetic conditions in the developing fetus, facilitating informed decisions about prenatal testing and potential interventions.

Informed decision-making: Genetic counsellors provide information on the available genetic tests, their accuracy, benefits, and limitations. They help individuals and couples make informed decisions about testing and reproductive options.

Interpretation of genetic test results: Genetic counsellors explain the results of genetic tests, helping patients understand the implications and offering guidance on future steps, including medical management and family planning.

Psychosocial support: Genetic counsellors provide emotional support, helping patients and families cope with the psychological and emotional aspects of genetic conditions and related decisions.

Genetic privacy and confidentiality: Genetic counsellors adhere to strict ethical standards regarding patient privacy and the confidentiality of genetic information.

Genomic medicine: Advances in genomics have expanded the role of genetic counsellors to include counselling on the interpretation of genomic data and the implications for precision medicine and targeted therapies.

Paediatric genetic counselling: Genetic counsellors also work with children and their families, addressing genetic conditions that are diagnosed in childhood.

Cultural and ethical considerations: Genetic counselling must take into account cultural and ethical beliefs and values, respecting the diversity of patients' backgrounds.

Professional certification: Genetic counsellors typically hold certification from the American Board of Genetic Counselling (ABGC) or the American Board of Medical Genetics and Genomics (ABMGG).

Genetic counselling plays a crucial role in helping individuals and families make informed decisions about their genetic health. It empowers people to understand their genetic risks and make choices that can impact their future health and family planning

Maternal health and well-being

a) **Perinatal mental health:** The impact of maternal mental health on pregnancy and fetal development.
b) **Maternal nutrition:** The role of diet and nutrition in supporting fetal development.
c) **Medication management:** Safe medication use during pregnancy for women with pre-existing medical conditions.

Fetal monitoring and surveillance

a) **Antepartum testing:** Methods to monitor fetal well-being, including non-stress tests and biophysical profiles.
b) **Continuous fetal monitoring:** Monitoring the fetal heart rate during labor and delivery.
c) **Doppler ultrasound:** Assessing blood flow in the umbilical cord and fetal vessels.
d) **Home monitoring:** Remote monitoring for high-risk pregnancies, especially relevant during the COVID-19 pandemic.

Fetal monitoring and surveillance are essential aspects of prenatal care, labor, and delivery to assess the well-being of the developing fetus. These processes aim to identify and address any potential issues, ensuring a safe and healthy outcome for both the baby and the mother. Here are some key points and topics related to fetal monitoring and surveillance:

Antenatal (Prenatal) fetal monitoring

Ultrasound: Ultrasound scans are used during pregnancy to monitor the fetus's growth and development. It can also help detect structural abnormalities and estimate the due date.

Doppler flow studies: These studies measure blood flow in the umbilical cord and fetal vessels, providing information about fetal well-being.

Non-Stress Test (NST)

NST is a common method for antenatal fetal monitoring. It measures the fetal heart rate in response to the baby's movements.

It is often used in the third trimester to assess fetal well-being, particularly in high-risk pregnancies.

Biophysical Profile (BPP)

BPP combines ultrasound and NST to evaluate fetal well-being by

assessing fetal movements, muscle tone, breathing, amniotic fluid levels, and heart rate.

BPP is often used in high-risk pregnancies or when there are concerns about fetal health.

Amniotic fluid assessment

Measuring the amniotic fluid volume is important as too little (oligohydramnios) or too much (polyhydramnios) can impact fetal well-being.

This can be done using ultrasound techniques like the amniotic fluid index (AFI).

Intrapartum fetal monitoring

During labor, continuous fetal monitoring is often performed to assess the baby's well-being.

Electronic fetal monitoring (EFM) involves the use of sensors placed on the mother's abdomen to record the fetal heart rate and uterine contractions.

Cardiotocography (CTG)

CTG is a common method for intrapartum fetal monitoring. It records the fetal heart rate and uterine contractions to detect changes that may indicate fetal distress.

Fetal Scalp Electrode (FSE)

In some cases, a scalp electrode may be placed on the baby's head to obtain a more direct and accurate recording of the fetal heart rate during labor.

Amniocentesis

In rare cases, amniocentesis can be used to directly sample amniotic fluid for analysis, particularly when there are concerns about infection or bilirubin levels.

Interventions based on monitoring

The results of fetal monitoring can lead to interventions such as changes in the mother's position, intravenous fluids, oxygen administration, or emergency caesarean section if fetal distress is detected.

Limitations and false alarms: Fetal monitoring is not without limitations and can lead to false alarms or over diagnosis. Interpretation by skilled healthcare professionals is crucial.

Informed decision-making: It's important for expectant parents to be

informed about the purpose, benefits, and limitations of fetal monitoring and to be involved in the decision-making process.

Home fetal monitoring: In some cases, expectant mothers may be provided with home fetal monitoring devices for periodic monitoring, especially in high-risk pregnancies.

Fetal monitoring and surveillance are critical tools in modern obstetric care, allowing healthcare providers to assess and respond to potential issues during pregnancy and labor, ultimately improving the chances of a healthy outcome for both the mother and the baby.

Patient education and support

a) **Pregnancy complications:** Information and guidance for pregnant individuals with high-risk conditions.

b) **Patient resources:** Educational materials and support groups for expectant mothers and their families.

Research and advancements

a) **Clinical trials:** Research studies focused on improving maternal-fetal care.

b) **Technological advances:** Innovations in medical technology that improve diagnostic accuracy and patient outcomes.

Maternal-fetal medicine is an evolving field, and ongoing research and advances continue to shape the care provided to expectant mothers and their unborn children. For the most current and detailed information in this field, consult with healthcare professionals specializing in maternal-fetal medicine and refer to the latest medical literature

Conclusion

Maternal-fetal medicine plays a pivotal role in optimizing outcomes for high-risk pregnancies. The field of maternal-fetal medicine encompasses a range of specialized medical services, including prenatal diagnosis, fetal interventions, genetic counselling, and fetal monitoring, among others. High-risk pregnancies can result from various factors, such as medical conditions, multiple pregnancies, or fetal abnormalities, and often require a multidisciplinary approach to ensure the best possible outcomes.

Maternal-fetal medicine specialists work in tandem with obstetricians, neonatologists, genetic counselors, and other healthcare professionals to provide comprehensive care tailored to the specific needs of each patient.

Their expertise and interventions can significantly impact both maternal and fetal well-being, from the early stages of pregnancy to childbirth and beyond.

By utilizing advanced diagnostic techniques, providing emotional support, guiding informed decision-making, and implementing timely interventions, maternal-fetal medicine contributes to the reduction of adverse pregnancy outcomes and the improvement of the health and quality of life for mothers and new borns facing high-risk situations.

As ongoing research and technological advancements continue to enhance our understanding of high-risk pregnancies, maternal-fetal medicine remains at the forefront of medical innovation, dedicated to improving the chances of successful pregnancies and healthy outcomes for all. The field's commitment to individualized care and a patient-centered approach ensures that each high-risk pregnancy receives the attention and resources necessary to optimize the chances of a positive result, reflecting the remarkable progress made in maternal-fetal medicine in recent years

References

1. Tough SC, Newburn-Cook C, Johnston DW *et al*. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. Pediatrics. 2002;109:399-403. [PubMed] [Google Scholar]
2. Chan BCP, Lao TT. Effect of parity and advanced maternal age on obstetric outcome. Obstet Gynecol Surv. 2008;63:761-763 [Google Scholar]
3. Martin JA, Hamilton BE, Osterman MJK *et al*. Births: Final data for 2016. National vital statistics reports. Hyattsville, MD: National Center for Health Statistics, 2018, 67(1). [PubMed] [Google Scholar]
4. Cook A, Mills TA, Lavender T. Informed and uninformed decision making - women's reasoning, experiences, and perceptions with regard to advanced maternal age and delayed childbearing: A meta-synthesis. Int J Nurs Stud. 2010;47:1317-1329 [PubMed] [Google Scholar]
5. Mills M, Rindfuss RR, McDonald P *et al*. ESHRE reproduction and society task force. Why do people postpone parenthood? Reasons and social policy incentives. Hum Reprod Update. 2011;17:848-860 [PMC free article] [PubMed] [Google Scholar]
6. Chambers GM, Hoang VP, Illingworth PJ. Socioeconomic disparities in access to ART treatment and the differential impact of a policy that

increased consumer costs. Hum Reprod. 2013;28:3111-3117. [PubMed] [Google Scholar]

7. Van Roode T, Sharples K, Dickson N *et al*. Life-course relationship between socioeconomic circumstances and timing of first birth in a birth cohort. PLoS One. 2017;12:e0170170. [PMC free article] [PubMed] [Google Scholar]
8. Abdou CM. Age-based reproductive healthcare stereotype threat (HCST) as a stressor affecting prenatal mental health in pregnant women of advanced maternal age: Measurement, process, outcomes, and interactions with ethnicity/race, SES, and other social identities. Curr Epidemiol Rep. 2017;4:133-144. [PMC free article] [PubMed] [Google Scholar]
9. Fretts RC, Usher RH. Causes of fetal death in women of advanced maternal age. Obstet Gynecol. 1997;89:40-45. [PubMed] [Google Scholar]
10. van Katwijk C, Peeters LL. Clinical aspects of pregnancy after the age of 35 years: A review of the literature. Hum Reprod Update. 1998;4:185-194. [PubMed] [Google Scholar]
11. Lee S, Holden D, Webb R *et al*. Pregnancy related risk perception in pregnant women, midwives and doctors: A cross-sectional survey. BMC Pregnancy Childbirth. 2019;19:335. [PMC free article] [PubMed] [Google Scholar]
12. Evans EC. A review of cultural influence on maternal mortality in the developing world. Midwifery. 2013;29:490-496. [PubMed] [Google Scholar]
13. Ndiaye K, Portillo E, Ouedraogo D *et al*. High-risk advanced maternal age and high parity pregnancy: Tackling a neglected need through formative research and action. Glob Health Sci Pract. 2018;6:372-383. [PMC free article] [PubMed] [Google Scholar]
14. Bayrampour H, Heaman M, Duncan KA *et al*. Advanced maternal age, and risk perception: A qualitative study. BMC Pregnancy Childbirth. 2012;12:100. [PMC free article] [PubMed] [Google Scholar]
15. Tyer-Viola LA, Lopez RP. Pregnancy with chronic illness. JOGNN. 2014;43:25-37. [PubMed] [Google Scholar]
16. Dulitzki M, Soriano D, Schiff E *et al*. Effect of very advanced maternal age on pregnancy outcome and rate of cesarean delivery. Obstet Gynecol. 1998;92:935-939. [PubMed] [Google Scholar]

17. Bianco A, Stone J, Lynch L *et al*. Pregnancy outcome at age 40 and older. Obstet Gynecol. 1996;87:917-922. [PubMed] [Google Scholar]

18. Jolly M, Sebire N, Harris J *et al*. The risks associated with pregnancy in women aged 35 years or older. Hum Reprod. 2000;15:2433-2437. [PubMed] [Google Scholar]

19. Cleary-Goldman J, Malone FD, Vidaver J *et al*. Impact of maternal age on obstetric outcome. Obstet Gynecol. 2005;105:983-990. [PubMed] [Google Scholar]

20. Schummers L, Hutcheon JA, Hernandez-Diaz S *et al*. Association of short interpregnancy interval with pregnancy outcomes according to maternal age. JAMA Intern Med. 2018;178:1661-1670. [PMC free article] [PubMed] [Google Scholar]

21. Sheen JJ, Wright JD, Goffman D *et al*. Maternal age and risk for adverse outcomes. Am J Obstet Gynecol. 2018;219:390.e1. [PubMed] [Google Scholar]

22. Zeitlin JA, Ancel PY, Saurel-Cubizolles MJ *et al*. Are risk factors the same for small for gestational age versus other preterm births? Am J Obstet Gynecol. 2001;185:208-215. [PubMed] [Google Scholar]

23. Paulson RJ, Boostanfar R, Saadat P *et al*. Pregnancy in the sixth decade of life: Obstetric outcomes in women of advanced reproductive age. JAMA. 2002;288:2320-2323. [PubMed] [Google Scholar]

24. Aliyu MH, Salihu HM, Wilson RE *et al*. The risk of intrapartum stillbirth among smokers of advanced maternal age. Arch Gynecol Obstet. 2008;278:39-45. [PubMed] [Google Scholar]

25. Fitzpatrick KE, Tuffnell D, Kurinczuk JJ *et al*. Pregnancy at very advanced maternal age: A UK population-based cohort study. BJOG. 2016;124:1097-1106. [PMC free article] [PubMed] [Google Scholar]

26. Hoyert DL, Miniño AM. Maternal mortality in the United States: Changes in coding, publication, and data release. National vital statistics reports. Hyattsville, MD: National Center for Health Statistics, 2020, 69(2). [PubMed] [Google Scholar]

27. Shipp TD, Zelop C, Repke JT *et al*. The association of maternal age and symptomatic uterine rupture during a trial of labor after prior cesarean delivery. Obstet Gynecol. 2002;99:585-588. [PubMed] [Google Scholar]

28. Callaghan WM, Berg CJ. Pregnancy-related mortality among women aged 35 years and older, United States, 1991-1997. Obstet Gynecol. 2003;102:1015-1021. [PubMed] [Google Scholar]

29. Chang J, Elam-Evans LD, Berg CJ *et al*. Pregnancy-related mortality surveillance - United States, 1991-1999. MMWR Surveill Summ. 2003;52:1-8. [PubMed] [Google Scholar]

30. Nybo Andersen AM, Wohlfahrt J, Christens P *et al*. Maternal age and fetal loss: Population-based register linkage study. BMJ. 2000;320:1708-1712 [PMC free article] [PubMed] [Google Scholar]

31. Farr SL, Schieve LA, Jamieson DJ. Pregnancy loss among pregnancies conceived through assisted reproductive technology, United States, 1999–2002. Am J Epidemiol. 2007;165:1380-1388. [PubMed] [Google Scholar]

32. Sandin S, Schendel D, Magnusson P *et al*. Autism risk associated with parental age and with increasing difference in age between the parents. Mol Psychiatry. 2016;21:693-700. [PMC free article] [PubMed] [Google Scholar]

33. Liu L, Franco S, Spyropoulos B *et al*. Irregular telomeres impair meiotic synapsis and recombination in mice. Proc Natl Acad Sci USA. 2004;101:6496-6501. [PMC free article] [PubMed] [Google Schola

34. Familiari A, Khalil A, Rizzo G, Odibo A, Vergani P, Buca D *et al*. Adverse intrapartum outcome in pregnancies complicated by small for gestational age and late fetal growth restriction undergoing induction of labor with Dinoprostone, Misoprostol or mechanical methods: a systematic review and meta- analysis. Eur J Obstet Gynecol Reprod Biol., 2020. https://doi.org/10.1016/j.ejogrb.2020.07.020

35. Karsdorp V, van Vugt J, van Geijn H, Kostense P, Arduim D, Montenegro N *et al*. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. Lancet. 1994;344(8938):1664-1668. https://doi.org/10.1016/s0140-6736(94)90457-x

36. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: diagnosis and management of fetal growth restriction. Am J Obstet Gynecol. 2020;223(4):B2-B17. https://doi.org/10.1016/j.ajog.2020.05.010

Chapter - 5

The Impact of Metformin in Pediatric Type-1 Diabetes Mellitus in Addition to Insulin Therapy

Author

Rohit Raina

MD Medicine, PDF Diabetology, Assistant Professor, Department of General Medicine, All India Institute of Medical Sciences, Bathinda, Punjab, India

Chapter - 5

The Impact of Metformin in Pediatric Type-1 Diabetes Mellitus in Addition to Insulin Therapy

Rohit Raina

Abstract

Background: Type 1 diabetes mellitus leads to significant cardiovascular risk through various mechanisms. Intensified insulin therapy is commonly required to achieve adequate glycemic control and reduce HbA1c. However, when insulin dose increases, it might increase insulin resistance and body weight, which directly affecting the cardiovascular profile.

Objective: We aim in this literature review to address the role of adding metformin to insulin therapy to limit the cardiovascular effect, insulin resistance and improve glycemic control in pediatric age.

Method: We searched in the PubMed database for relevant articles using the following Mesh words: Metformin - Type 1 diabetes mellitus, pediatrics - Cardiovascular risk.

Conclusion: Metformin was found to has promising cardiovascular protection when adding to insulin therapy. However, the impact of metformin in type 1 diabetes mellitus glycemic control is controversial, and further multi-systemic randomized clinical trials are recommended to address this issue.

Keywords: Metformin, Type 1 diabetes mellitus, Pediatrics, Cardiovascular risk, HbA1c, Glycemic control.

Introduction

Type 1 diabetes mellitus (T1DM) is a systemic autoimmune disease manifested by pancreatic beta-cells immune-mediated destruction resulting in severely reduced or completely absent insulin secretion [1-2]. In the absence of appropriate insulin secretion, glucagon levels might be elevated in the fasting and postprandial state [1], resulting in hypoglycemia [1-2]. T1DM is the most common chronic childhood metabolic disease that affects all body organs and is caused by a combination of genetic susceptibility and environmental determinants [2-3]. The prevalence of T1DM has increased across the last

decade [2]. Most T1DM patients have suboptimal glycemic control [2], and subsequently, intensive glycemic control might be warranted to reduce the risk of late diabetic complications; nevertheless, intensified insulin treatment also increases the risk of hypoglycemia and weight gain [1]. The latest might negatively alter the cardiovascular risk profile and may reduce adherence to treatment [1]. Therefore, the use of non-insulin additional pharmacotherapy has been recently an area of importance [2].

Moreover, targeting glycemic control in T1DM patients might increase the risk of hypoglycemia, especially when HbA1c approached target levels [4-5]. Furthermore, while insulin requirements might be increased to achieve optimal glycemic control, this might increase insulin resistance by weight gain, consequently escalating insulin dose requirements, elevating blood pressure and LDL-cholesterol levels [4-5]. Severe hypoglycemia has been reported in 13.9 and 12.5%, respectively, with a reported hypoglycemia-induced seizure or loss of consciousness in 11.8% among patients with HbA1c levels below 6.5% and 7% [5]. Importantly, glycemic variability itself is considered a hypoglycemia predictor, leading to poor glycemic control, poor patient satisfaction, diabetes burden, and poor compliance to treatment [5].

Based on the aforementioned above, the concept of adjunct non-insulin pharmacotherapy has been increasingly emerged to overcome these challenges and based on the nation that:

1) The addition of oral preparation to insulin might improve glycemic control;

2) The adjunct therapeutic agents might independently reduce diabetic complications [4].

Hence, the principle of adjunct therapy is to reduce insulin requirement, lower HbA1c without the risk of hypoglycemia, avoid weight gain, and directly reduce the risk of cardiovascular complications in order to improve life expectancy [4].

Diagnosis and types of diabetes mellitus in adulthood

The diagnostic criteria for diabetes mellitus in adulthood are similar to adult; mentioned in Table 1 [6]. However, the laboratory findings should be repeated if unequivocal hyperglycemia is absent [6]. The American Diabetes Association (ADA) recommended the use of blood glucose levels rather than HbA1c in T1DM diagnosis [6].

Overall, diabetes is classified into [6]:

- T1DM
- T2DM
- Gestational diabetes mellitus
- Specific types of diabetes mellitus secondary to other causes

In this article, T1DM management will be discussed, and other classes are beyond the scope of this literature review.

The target glycemic control in adulthood are summarized into the following [6]:

- HbA1c <7.5%
- Pre-meal blood glucose level 90 to 130 mg/dL
- Bedtime or overnight blood glucose level 90 to 150mg/dL

The goal of glycemic control must be individualized based on the risk of hypoglycemia, and higher targets might be needed if frequent or severe hypoglycemia were reported [6].

Table 1: Diagnostic criteria of diabetes mellitus

• HbA1c of at least 6.5% approved by the National Glycohemoglobin Standardization Program (NGSP) laboratory standardized to the Diabetes Control and Complication Trial (DCCT) assay
• Two-hour plasma glucose of at least 200mg/dL following an oral glucose tolerance test using a glucose load containing 75 g
• An 8 hours fasting plasma glucose level of at least 126mg/dL
• Presence of typical symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose of at least 200mg/dL

Discussion

Metformin is an antihyperglycemic agent that belongs to biguanide that reduces hepatic glucose output from the liver and enhances insulin sensitivity [7], as concentrated in the hepatic circulation [8]. Metformin works by inhibiting the complex-1 effect of the mitochondrial respiratory chain, resulted in regulating AMP-activated protein kinase (AMPK), particularly in muscle and liver [7-8]. Subsequently, this increased insulin-stimulated glucose uptake in skeletal muscles and adipocytes and reduced glucose output from the liver [7], leading to indirectly lowers circulatory insulin and glucose levels [8].

Additionally, metformin activates AMPK in the endothelium and smooth muscle; this likely explains the dependent and independent endothelium

vascular response following metformin administration in adults with T1DM and polycystic ovarian syndrome [7]. Also, it may explain the beneficial outcome of metformin on cardiovascular risk independently of its glucose lowering effect [7]. Besides, in T1DM, Gao-Fei ran et al. have found that metformin improves insulin resistance and inflammatory response through P53/RAP2A pathway [9]. Consequently, the P53/RAP pathway regulation was associated with improving the efficacy of metformin in the treatment of insulin-resistant [9].

The effect of metformin in type-1 diabetes mellitus

Recent interest has emerged in using metformin in T1DM to improve glycemic control and control weight gain in overweight teens [8]. Metformin use in T1DM patients was associated with decreased insulin dose, improve BMI and waist circumference in female participants [8]. While insulin is the mainstay therapy for T1DM patients, many other pharmacotherapies have been used or under investigation [10]. In a retrospective study conducted by Selvihan Beysel et al., the addition of metformin to insulin therapy in T1DM patients was associated with lower glucose concentrations, metabolic syndrome prevalence, and insulin requirement compared to insulin therapy alone after one year of treatment [11]. In addition, weight control was better in the metformin with insulin group than the insulin therapy alone [11].

Moreover, Melanie et al. have concluded in a double-blind, placebo-controlled clinical trial that adding metformin to insulin therapy in obese or overweight with T1DM improves whole-body and specifically muscle insulin resistance during a 13 weeks duration [12]. Nevertheless, the target hepatic insulin resistance needs alternative approaches in T1DM, obese or overweight youth [12]. Importantly, insulin resistance improvement secondary to metformin therapy was strongly linked to improved cardiovascular disease risk in adults and youth with T1DM [12]. Furthermore, Most US and UK guidelines recommended adding metformin to insulin therapy in overweight or obese adults with T1DM [13]. Similarly, these guidelines suggested that metformin not only improves insulin resistance but also provides potential or transit benefits on body weight and HbA1c [13].

On the other hand, metformin did not improve diabetic control among T1DM adults in a placebo-controlled randomized clinical trial and resulted in unfavorable gastrointestinal side effects [14]. However, metformin and insulin were associated with maintaining weight control and insulin requirement [14]. Likewise, James J et al. was concluded that adding metformin to insulin therapy does not lower HbA1c in poorly controlled T1DM [10]. Nonetheless,

adding metformin led to decrease insulin requirement, body weight, and LDL-cholesterol [10].

The effect of metformin on cardiovascular risk

Although hyperglycemia is the most common finding of T1DM, a consensus has demonstrated that patients with T1DM are also affected by intense insulin resistance [15]. In addition, insulin resistance in T1DM is more significant than expected compared to metabolic syndrome-related factors, such as obesity, hypertension, and dyslipidemia [15]. Interestingly, in the Coronary Artery Calcification in T1DM (CACT1) cohort study, adults with T1DM were found to have double insulin resistance compared to adults without T1DM who had various risk factors, including obesity and poor physical activity [15].

In T1DM, metformin improves the quality of life and reduces cardiovascular risk factors through weight loss and improving the lipid profile [16]. Bjornstad et al. found that metformin has promising cardiovascular protection in T1DM by reducing insulin sensitivity, BMI, and fat mass along with improving aortic and carotid vascular health over three months [17]. Moreover, reducing insulin resistance was not limited to obese patients [17]. This was supported by the REMOVAL double-blind, randomized, placebo-controlled trial [18]. The trial concluded that metformin might provide cardiovascular protection in the management of T1DM and possibly beneficial in reducing insulin dose requirements [18].

However, despite the previous promising metformin effect on CVD, the REMOVAL trial does not support the idea that metformin improves glycemic control in overweight/obese T1DM patients [18]. Furthermore, metformin was reported to improve vascular smooth muscle function over 12 months in overweight children with T1DM [19].

Safety consideration

Regarding metformin safety profile, the most commonly reported side effect is gastrointestinal events, such as abdominal pain, anorexia, diarrhea, nausea, taste disturbance, and vomiting [14, 20-21]. Rare side effects, such as erythema, lactic acidosis, pruritis, and urticaria, were reported [20]. Kidney function should be assessed before and after starting treatment [20]. Metformin should be used cautiously in patients with renal insufficiency, and a lower maximum daily dose is recommended for people with a glomerular filtration rate (GFR) of 30-59mL/min [20].

The most severe adverse effect is lactic acidosis, which carries a mortality rate of approximately 50% between 1960 and 2000, but it has decreased to

approximately 25% [21]. Metformin is contraindicated if GFR below 30mL/min and in acute kidney injury secondary to acute conditions, such as dehydration and severe infection [20]. Rarely, metformin use was associated with decreased vitamin-B12 absorption [20].

Conclusion

Type 1 diabetes mellitus is a chronic multi-systemic autoimmune disease that carries significant cardiovascular risk. Adequate management is mainly achieved by insulin therapy, but it adversely affects the total body weight and insulin resistance. Metformin has been shown to improve insulin resistance, decrease body weight, and improves lipid profile as well, particularly in overweight or obese patients, although no consensus yet about its efficacy in achieving glycemic control and reduce HbA1c. Further multi-systemic randomized clinical trial would be warranted to establish metformin efficacy on glycemic control and HbA1c.

References

1. Frandsen CS, Dejgaard TF, Madsbad S, Holst JJ. Non-insulin pharmacological therapies for treating type 1 diabetes. Expert Opin Pharmacother. 2018;19(9):947-960. doi: 10.1080/14656566.2018.1483339. PMID: 29991320.
2. Naciu AM, Pozzilli P. Novel blood glucose lowering therapies for managing type 1 diabetes in paediatric patients. Expert Opin Pharmacother. 2018;19(4):355-364. doi: 10.1080/14656566.2018.1441288. Epub 2018 Feb 20. PMID: 29460641.
3. Lunder M, Janić M, Japelj M, Juretič A, Janež A, Šabovič M *et al*. Empagliflozin on top of metformin treatment improves arterial function in patients with type 1 diabetes mellitus. Cardiovasc Diabetol. 2018;17(1):153. doi: 10.1186/s12933-018-0797-6. PMID: 30509271; PMCID: PMC6276165.
4. Livingstone R, Boyle JG, Petrie JR. REMOVAL Study Team. A new perspective on metformin therapy in type 1 diabetes. Diabetologia. 2017;60(9):1594-1600. doi: 10.1007/s00125-017-4364-6. Epub 2017 Aug 2. PMID: 28770327; PMCID: PMC5552844.
5. Wright LA, Hirsch IB. Non-insulin treatments for Type 1 diabetes: critical appraisal of the available evidence and insight into future directions. Diabet Med. 2019;36(6):665-678. doi: 10.1111/dme.13941. Epub 2019 Mar 27. PMID: 30801765.
6. Levesque C. Management of Diabetes in Children and Adolescents. Nurs

Clin North Am. 2017;52(4):589-603. doi: 10.1016/j.cnur.2017.07.008. Epub 2017 Oct 5. PMID: 29080580.

7. Anderson J, Peña AS, Sullivan T, Gent R, D'Arcy B, Olds T *et al*. Does metformin improve vascular health in children with type 1 diabetes? Protocol for a one year, double blind, randomised, placebo controlled trial. BMC Pediatr. 2013;13:108. doi: 10.1186/1471-2431-13-108. PMID: 23865839; PMCID: PMC3728146.

8. Thomas I, Gregg B. Metformin; A review of its history and future: from lilac to longevity. Pediatr Diabetes. 2017;18(1):10-16. doi: 10.1111/pedi.12473. PMID: 28052534.

9. Ren GF, Xiao LL, Ma XJ, Yan YS, Jiao PF. Metformin Decreases Insulin Resistance in Type 1 Diabetes Through Regulating p53 and RAP2A in vitro and in vivo. Drug Des Devel Ther. 2020;14:2381-2392. doi: 10.2147/DDDT.S249557. PMID: 32606605; PMCID: PMC7306576.

10. Chamberlain JJ, Kalyani RR, Leal S, Rhinehart AS, Shubrook JH, Skolnik N *et al*. Treatment of Type 1 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med. 2017;167(7):493-498. doi: 10.7326/M17-1259. Epub 2017 Sep 12. PMID: 28892816.

11. Beysel S, Unsal IO, Kizilgul M, Caliskan M, Ucan B, Cakal E *et al*. The effects of metformin in type 1 diabetes mellitus. BMC Endocr Disord. 2018;18(1):1. doi: 10.1186/s12902-017-0228-9. PMID: 29338714; PMCID: PMC5771191.

12. Cree-Green M, Bergman BC, Cengiz E, Fox LA, Hannon TS, Miller K *et al*. Metformin Improves Peripheral Insulin Sensitivity in Youth With Type 1 Diabetes. J Clin Endocrinol Metab. 2019;104(8):3265-3278. doi: 10.1210/jc.2019-00129. PMID: 30938764; PMCID: PMC6584133.

13. Standl E. Metformin in type 1 diabetes. Lancet Diabetes Endocrinol. 2017;5(8):567-569. doi: 10.1016/S2213-8587(17)30216-4. Epub 2017 Jun 11. PMID: 28615150.

14. Libman IM, Miller KM, DiMeglio LA, Bethin KE, Katz ML, Shah A *et al*. T1D Exchange Clinic Network Metformin RCT Study Group. Effect of Metformin Added to Insulin on Glycemic Control Among Overweight/Obese Adolescents with Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2015;314(21):2241-50. doi: 10.1001/jama.2015.16174. PMID: 26624824.

15. Snell-Bergeon JK. Diabetes: Cardiovascular benefits of metformin in T1DM. Nat Rev Endocrinol. 2017;13(10):565-566. doi: 10.1038/nrendo.2017.116. Epub 2017 Sep 12. PMID: 28895950.

16. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J *et al*. Effect of metformin on glycaemic control in patients with type 1 diabetes: A meta-analysis of randomized controlled trials. Diabetes Metab Res Rev. 2018;34(4):e2983. doi: 10.1002/dmrr.2983. Epub 2018 Feb 15. PMID: 29351716.

17. Bjornstad P, Schäfer M, Truong U, Cree-Green M, Pyle L, Baumgartner A *et al*. Metformin Improves Insulin Sensitivity and Vascular Health in Youth with Type 1 Diabetes Mellitus. Circulation. 2018;138(25):2895-2907. doi: 10.1161/CIRCULATIONAHA.118.035525. PMID: 30566007; PMCID: PMC6428045.

18. Petrie JR, Chaturvedi N, Ford I, Brouwers MCGJ, Greenlaw N, Tillin T *et al*. REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):597-609. doi: 10.1016/S2213-8587(17)30194-8. Epub 2017 Jun 11. Erratum in: Lancet Diabetes Endocrinol. 2017;5(8):e5. Erratum in: Lancet Diabetes Endocrinol. 2017;5(11):e7. PMID: 28615149; PMCID: PMC5641446.

19. Anderson JJA, Couper JJ, Giles LC, Leggett CE, Gent R, Coppin B *et al*. Effect of Metformin on Vascular Function in Children with Type 1 Diabetes: A 12-Month Randomized Controlled Trial. J Clin Endocrinol Metab. 2017;102(12):4448-4456. doi: 10.1210/jc.2017-00781. PMID: 29040598.

20. What role for metformin in type 1 diabetes? Drug Ther Bull. 2018;56(7):78-80. doi: 10.1136/dtb.2018.7.0645. PMID: 30008442.

21. Tan MH, Alquraini H, Mizokami-Stout K, MacEachern M. Metformin: From Research to Clinical Practice. Endocrinol Metab Clin North Am. 2016;45(4):819-843. doi: 10.1016/j.ecl.2016.06.008. Epub 2016 Oct 4. PMID: 27823607.

Indexing and Abstracting in Following Databases

1. Bowker: A ProQuest Affiliate

2. Crossref

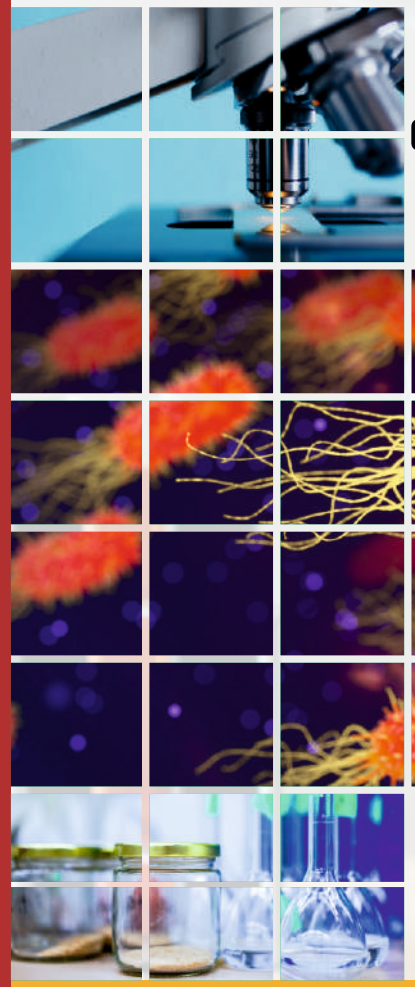
ISBN 9789358345599

₹ 702, US$ 16

Published by
Integrated Publications,
H. No. 3, Pocket - H34, Sector - 3, Rohini,
Delhi - 110085, India
Toll Free (India): 18001234070
Email: printintegrated@gmail.com

VOLUME - 3

Advanced Research in Medical Science & Technology



Chief Editor: Dr. Anil Meena

Integrated Publications
New Delhi

ARTIFICIAL INTELLIGENCE IN PHARMACEUTICAL TECHNOLOGY

Volume - 2

Editors

Dr. Akhil Sharma
Principal, R.J. College of Pharmacy, Raipur, Aligarh, Uttar Pradesh, India

Dr. Shaweta Sharma
Associate Professor, Galgotias University, Yamuna Expressway, Greater Noida, Uttar Pradesh, India

AkiNik Publications®
New Delhi

Published By: AkiNik Publications

AkiNik Publications
169, C-11, Sector - 3,
Rohini, Delhi-110085, India
Toll Free (India) – 18001234070
Phone No.: 9711224068, 9911215212
Website: www.akinik.com
Email: akinikbooks@gmail.com

Chief Editors: Dr. Akhil Sharma and Dr. Shaweta Sharma

Publication Year: 2023

Pages: 111

ISBN: 978-93-5570-893-9

Book DOI: https://doi.org/10.22271/ed.book.2427

Price: ₹ 721/-

Registration Details

- Printing Press License No.: F.1 (A-4) press 2016
- Trade Mark Registered Under
  - Class 16 (Regd. No.: 5070429)
  - Class 35 (Regd. No.: 5070426)
  - Class 41 (Regd. No.: 5070427)
  - Class 42 (Regd. No.: 5070428)

Contents

Chapter - 1
A Comprehensive Review on Past, Present and Future Scenario of Medical Devices in Healthcare Department

Authors

Bhimani Rushi K
B.Pharm Semester Seven Student, Smt. R.D. Gardi B. Pharmacy College, Nyara, Rajkot, Gujarat, India

Megha Gandhi
M. Pharm (Pharmaceutics) Assistant Professor, Smt. R.D. Gardi B. Pharmacy College, Nyara, Rajkot, Gujarat, India

Dr. Shital Faldu
Ph.D. (Pharmacy) Principal, Smt. R.D. Gardi B. Pharmacy College, Nyara, Rajkot, Gujarat, India

Chapter - 1

A Comprehensive Review on Past, Present and Future Scenario of Medical Devices in Healthcare Department

Bhimani Rushi K, Megha Gandhi and Dr. Shital Faldu

Abstract

Medical Device means any instrument, apparatus, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose. Medical devices are generally classified based on risks; the actual risk-based classification of the medical device depends upon its intended use and purpose. Development of an entirely new device typically begins with a concept by a physician or bioengineer for a solution to a medical problem. If the idea is determined to be workable and practical (proof of concept) an early design of the device, known as a prototype, will be built. A prototype device will undergo a cycle of preclinical testing, redesigning, preclinical testing of the redesign and so forth, until the design has been refined and tested to a point that it is ready for production and testing in humans. Preclinical animal tastings are conducted to provide reasonable evidence that novel technologies and therapies are safe and effective. When studying medical devices, clinical trials are not always required, and whether or not one will be conducted depends on a risk assessment. Post marketing surveillance is the practice of monitoring the safety of a medical device after it has been released on the market.

Keywords: Medical device, idea, discovery, prototype, preclinical research, clinical trials, regulatory review and decision, product launch, post marketing surveillance

1. Introduction

People have profited for several centuries from a variety of discoveries and advancements that have enhanced health, mostly in high-resource environments. Examples include the development of sewage and clean water systems, the identification of diseases and antibiotics and the elimination of smallpox.

The increased ability to forecast, prevent, diagnose, and treat numerous illnesses as well as to ameliorate functioning issues utilising medicines and technologies that were unfathomable just a few decades ago is linked to improvements in the health of many people. The most prevalent, most varied, and most often used medical products, such as drugs, vaccines, and gadgets, are those utilised in healthcare. Although accurate statistics are unavailable, generally accepted estimates place the number of primary medical device categories currently offered on the global market somewhere in the neighbourhood of 10,000. About 90 000 are added when all the various versions are included; some estimates put the amount as high as 1.5 million [1].

1.1 Prioritizing medical devices: Setting the scene

Following the global impact of the landmark report Priority medicines for Europe and the world [2] which proposed a specific research agenda leading to the creation of a public-private-partnership (PPP) and the success of the 'access to essential medicines' agenda in focusing the attention of the international community on the specific needs, problems, and challenges of this crucial public health area, it is now time for the international community to focus on an agenda to improve access to appropriate medical devices that adequately addresses global public health needs.

The concept of appropriate medical devices is relevant to high-, middle-, or low-income settings although each may be viewed from different ends of the spectrum. For example, the abundance of high-tech, actively marketed medical devices in high-income settings may mean that medical devices are chosen and used based on factors other than clinical and public health need.

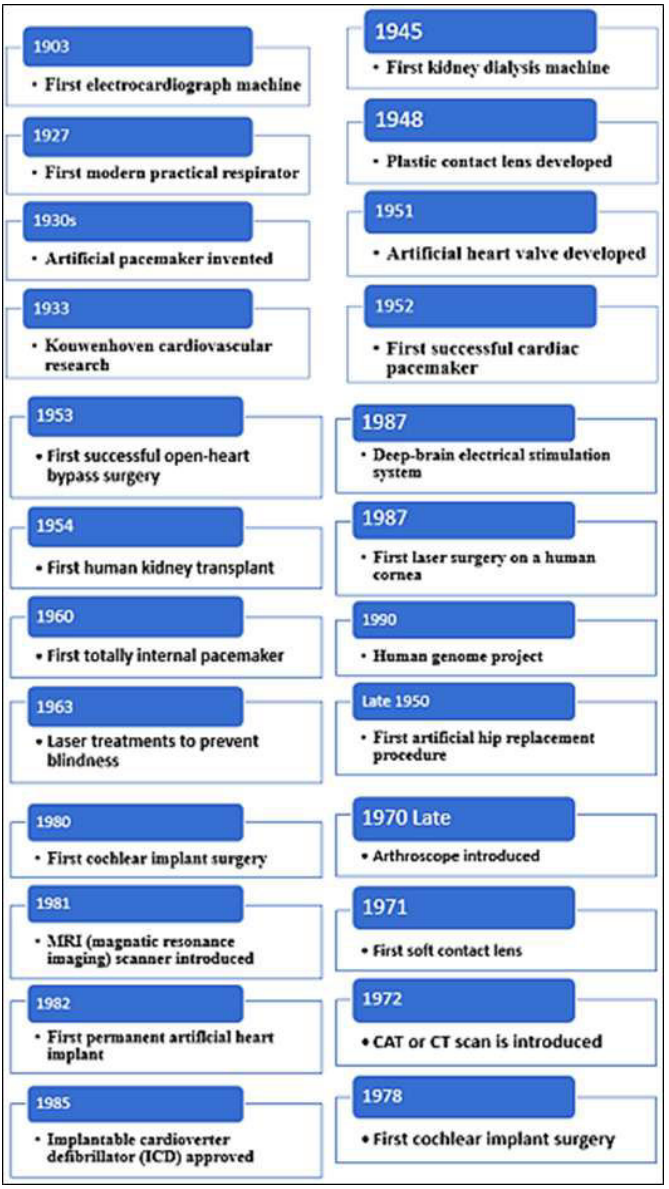
In low-income settings, medical devices may be available but not adapted to be effectively used in the local context; for example, they may not withstand hot and dusty climates or may not run on insufficient electricity supplies.

Countries with few resources frequently lack the funds and purchasing power to evaluate or address their numerous essential requirements. Typically, industry in high-resource settings has little interest in investing in medical device research and development that is required for low-resource nations and promises a low return on that investment [3].

The majority of high-resource nations prioritize medical research primarily on the basis of scientific and technological preferences, with little explicit consideration given to public health requirements [4].

Biomedical research contributes to development, equity, global security, the fight against poverty, scientific advancement and the discovery of solutions to health issues [5]. Medical device research, like similar areas of health research, does not focus on large populations worldwide. The needs of industrialized nations are the primary focus of most research activities [6].

2. Medical devices [7]



3. Past, Present and Future

Recent key trends

1980: Flood in the quantity of patient consideration clinical gadgets, especially high-goal imaging gadgets, outstandingly radiographic and fluoroscopic units. Frameworks for constant checking of cardiovascular boundaries-pulse, heart result and blood pressure-were becoming standard medical clinic apparatuses. Treatment was taken over by innovative advancement-ventilators, kidney dialysis machines and neonatal hatcheries were becoming typical [8].

1980s-2000: Most medical clinics in industrialized nations embraced modernized pivotal tomography (CT) scanners and attractive reverberation imaging (X-ray) units. Specialists, as well, could offer their patients a developing rundown of clinical gadgets to supplant body parts. Decision of clinical gadgets developed dramatically [9].

2000-2010: Mechanical technology turned into a truth of the clinical gadget world with defenders and adversaries [10].

Future trends

Smaller and less expensive robotic systems that allow high-precision surgery will continue to be developed, notably for orthopaedic and neurological procedures. Synergy and miniaturization will direct future innovation in medical device design, such as "smart medical capsules" [11, 12] Nanotechnology furthermore, genomics will cooperate to proceed with the ascent in customized care. Tissue-designed items will keep on arising out of the combination of various medical services related disciplines, for example, the natural sciences, nanotechnology, mental sciences, data innovation and material science [13, 14].

3.1 Past medical devices

1. Osteotome, 19th century

Fig 1: Osteotome

2. Trepan, 18th century

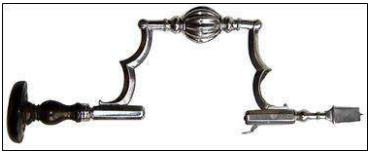


Fig 2: Trepan

3. Amputation saw

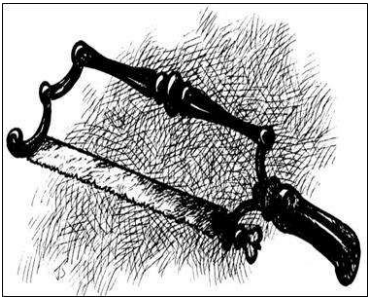


Fig 3: Amputation Saw

3.2 Present medical devices

Fig 4: Tongue depressor

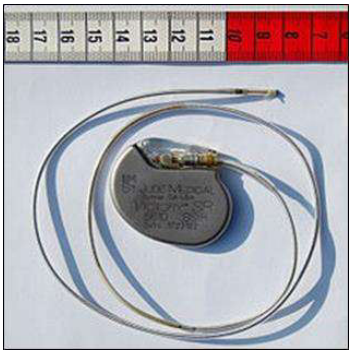


Fig 5: Artificial pacemaker

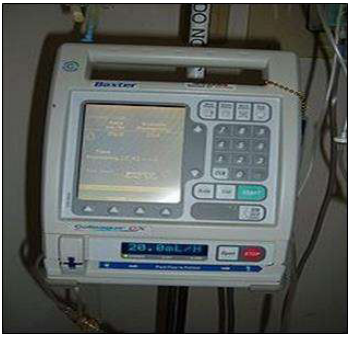


Fig 6: Infusion pump

3.3 Future medical devices

1. **Wearable watch**

Fig 7: Wearable medical devices

2. **Feather touch**

Fig 8: Feather Touch

3. **New medical technology and surgeries**

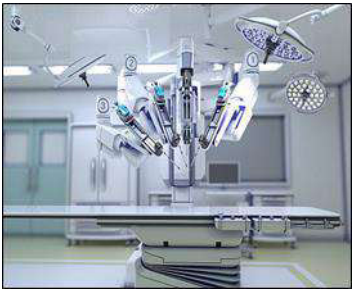


Fig 9: New medical Technology and surgeries

4. Pharmaceuticals and medical devices

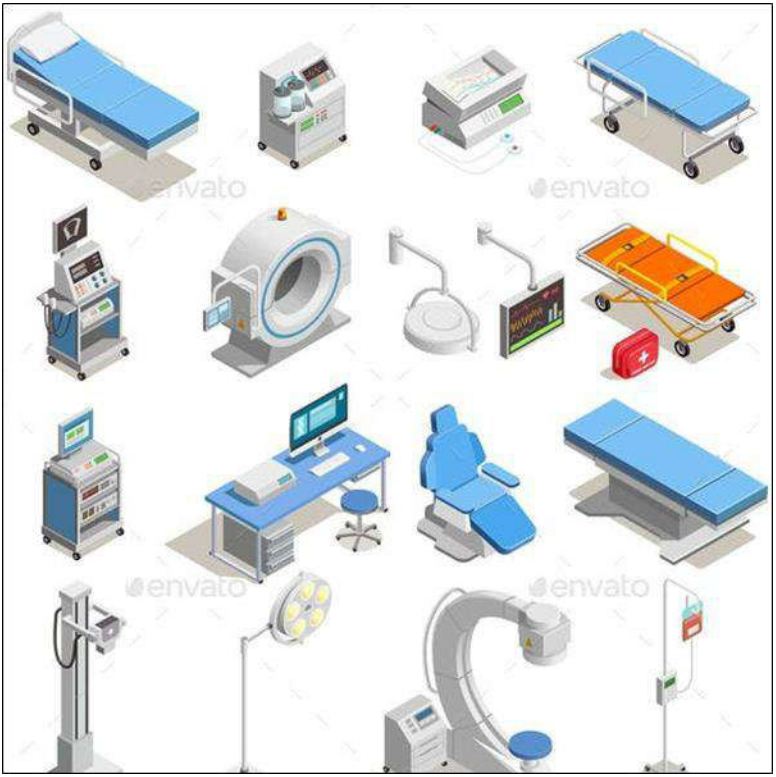


Fig 10: https://images.app.goo.gl/zdcbEu9iVBWhCsLX9

5. The medical device market

One of the most important and rapidly growing economic areas is the medical devise business. The global us$ 550 billion in 2021and is expected to reachus $850 billion by 2030 and growth rate of 5.5% during the forecast period 2022 to 2030 [15].

5.1 List of medical equipment manufacturers in India

Report highlights	Details
Market size	USD 850 Billion by 2030
Growth rate	CAGR of 5.5% From 2022 to 2030
Largest market	North America
Base year	2021
Forecast period	2022 to 2027
Segments covered	Product, Therapeutic Application, End User, Region

Regional scope	Asia Pacific, North America, Europe, Latin America, Middle East and Africa
Companies mentioned	DePuy Synthes, Medtronics Plc, Fesenius Medical Care, GE Healthcare, Philips Healthcare, Ethicon LLC, Siemens Healthineers, Stryker, Cardinal Health, Baxter International Inc., BD

5.2 World medical markets by sector

Medical Devices Companies in India	Year of Estd.	Market Value (Cr.)	Devices
Wipro GE Private Health Care	1945	16,720	Computed Tomography
Cure Spects Lasers Ltd.	1995	23	B-cure Laser for Personal use
Johari Digital Healthcare Ltd.	1979	500	Plastic injection molding
Maestros Medline Systems	1972	33	Maestro
Opto Circuits (India) Ltd.	1991	120	Exporter of oci medical equipment
Poly Medicure Ltd.	1995	6,503	Autofusion set
Becton Dickinson India Ltd.	1897	72.0B	Becton Dickinson
Siemens Healthcare Diagnostics	2015	255	Siemens acuson 3000 diagnostic ultrasound
India Medtronic Private Ltd.	1979	673	ENT equipment
Transasia Bio-Medicals	1979	2.33	Automated Laboratory Equipment
Hindustan Syringes and Medical Devices	1957	36.5	Plastic auto Disable syringes

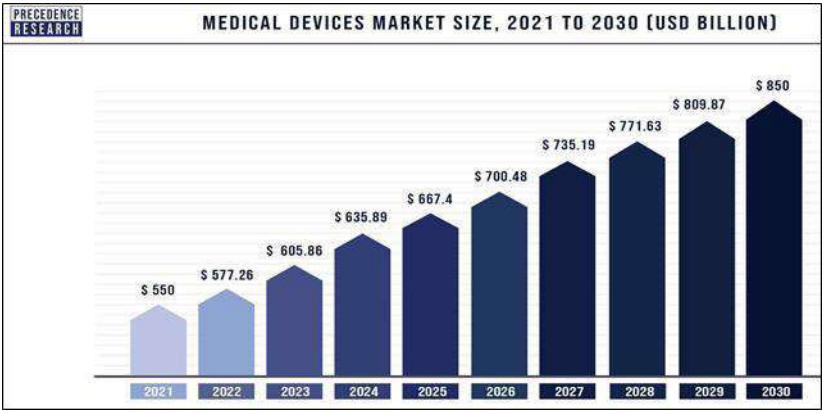


Fig 11: https://images.app.goo.gl/G d6brnjQCm762SCE7

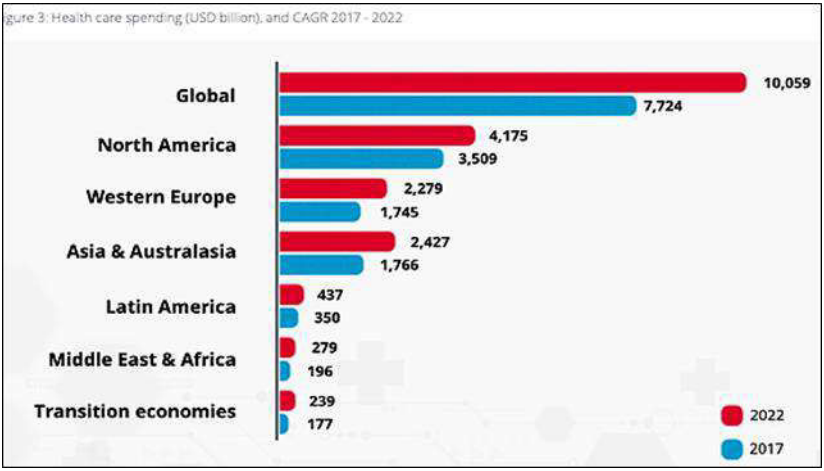


Fig 12: https://qph.fs.quoracdn.net/mainqimg9dd8c1e66a43e92ccb7cfd571aea88c8

6. Smart medical devices

6.1 What is smart medical devices

We referred to devices that are connected to the internet as "smart devices" in our blog post about IoT-based patient monitoring systems.

In our post about intelligent medical devices, we added "the ability to interact with users and other devices" to the definition of "smart devices".

We define "smart medical devices" as medical devices that can be manipulated by other devices or users who also have the ability to connect to the internet. We base our definition on this amalgamated idea.

A smart watch with a user-friendly interface that collects and uploads a patient's heart rate data to the cloud is an example of a "smart medical device [16]".

6.2 Smart medical devices market overview

At a CAGR of 23.5 percent, the global market for smart medical devices is anticipated to reach $23.5 billion by 2027.By 2021, 25% of broadband households in the United States had adopted this technology. The need to closely monitor chronic diseases like diabetes, asthma, COPD, etc. is the driving force behind the popularity of smart medical devices and restricted access to medical monitoring on-site as a result of the COVID-19 pandemic [17].

6.3 Smart medical devices: An all-around overview

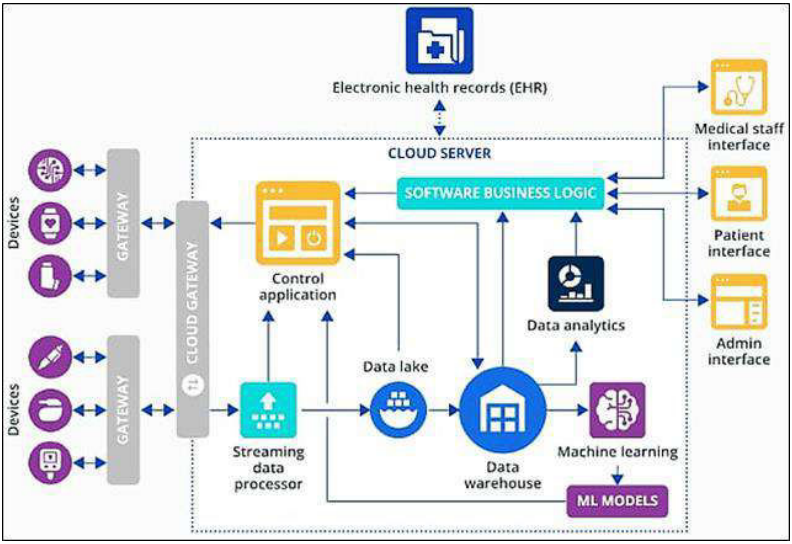


Fig 13: https://images.app.goo.gl/KPvD72T7BKC3BwQT6

6.4 Smart medical devices

1. Wearable smart asthma monitoring

According to the Centers for Disease Control and Prevention (CDC), 25 million Americans suffer from asthma, which is a chronic condition that causes an estimated 44,000 asthma attacks each day.

The majority of asthmatics don't realize they're having an attack until it's pretty advanced, which is not only unpleasant but also dangerous. It reduces the efficacy of treatments like medication and stopping the triggering activity.

Health Care Originals' ADAMM Intelligent Asthma Monitoring is a wearable technology that can predict an impending asthma attack before the wearer even notices the symptoms.

2. An AI-powered insulin pump

The 5-year-old son of Bryan Mazlish was given the diagnosis of Type 1 diabetes in 2011.Mazlish hacked his own insulin delivery system in 2014 because he was dissatisfied with the available insulin pumps. He began by making adjustments to a standard insulin pump and continuous glucose monitor. After that, he created an application and an algorithm to control the insulin dose.

Instead of simply responding to spikes in blood sugar, the algorithm is a metabolic simulation engine that anticipates how much insulin the patient will require and when they will require it. Preventing glucose spikes rather than treating them is much better for the patient's long-term health because they gradually damage organs.

Mazlish cofounded Bigfoot Biomedical later in 2014.Within two years, the company had partnerships with glucose monitoring companies and assets from a supplier of diabetes equipment.

At the Annual Diabetes Technology Meeting in 2017, Bigfoot presented data from a feasibility trial demonstrating their system's effectiveness in controlling Type 1 diabetes.

For their AI-driven insulin delivery system, the company received $37 million in Series B funding in December 2017. They are working on two products: the insulin pen Bigfoot Inject and the insulin pump Bigfoot Loop.

3. A smart drill

Similar to the smart toothbrush mentioned earlier, the SMART drill is significantly more complicated. The drill basically uses its calculations and senses of resistance, bone density, and other factors to suggest where and how to drill.

Surgeons can also receive real-time performance feedback from its screen. Surgeons, for instance, can use it to confirm that they have selected the appropriate screw depth or that they have utilized the appropriate number of screws; if they use too few screws, the object being screwed might fall out of place. Overuse of screws can impede healing [18].

7. An introduction to medical device innovation

Innovation in medical devices encompasses not only the creation of brand-new devices but also modifications to existing devices and clinical procedures or incremental enhancements thereof. It also refers to efforts to make devices that were made to be used in one setting, like a modern high-tech hospital, work in another, like a patient's home. The World Health Organization describes innovation as a "process cycle of three major phases that feed into one another: discovery, creation, and implementation [19].

Medical device innovation must demonstrate benefit to patient health. However, despite the technology's obvious benefits, it may be rejected simply because it is novel, poses a threat to existing practices, or has costs that outweigh its benefits [20].

The advancement of technology in health care is distinct from that in other industries. In the context of health care, among other things, emotional factors associated with health and illness and a widespread political commitment to provide people with the most recent medical technologies may influence technological development [21].

7.1 Applying non-medical innovation to health care

Many medical devices were initially developed using technologies developed in other fields rather than clinical research. Lasers, ultrasound, MRI, spectroscopy and information technology are examples of dual-use technologies. This phenomenon is known as "dual use". For instance, fundamental research on the structure of atoms led to the development of MRI, a non-invasive method for diagnosing injury to body organs caused by trauma, tumors, or infarction. Internet communication, shock wave technology (now used in lithotripsy), and devices created by the army for use in difficult field conditions are other examples of technologies that have been incorporated into health care. These devices can frequently serve as a model for the design of medical devices that are used in remote, low-resource settings [22].

8. Medical devices: Problems and possible solutions

Choosing medical devices

A transparent process based on information, reason, evidence, an assessment of public health needs, and a process for prioritizing are necessary for the complex process of selecting a medical device. Medical devices that are chosen without taking into account the need to improve public and individual health may be used improperly or not at all, wasting money. Both developed and developing nations suffer as a result of these factors. The Netherlands only performs 17 000 positron emission tomography (PET) scans annually, despite purchasing 24 scanners that can produce nearly three times as many. This may be an example of procurement without considering needs assessment, cost-effectiveness, priorities, or resource allocation [23].

Another illustration of excessive spending on unnecessary devices (and diagnostic procedures) is diagnostic imaging. According to the World Health Organization (WHO), high-tech diagnostic imaging is only required in 20% to 30% of medical cases where clinical examination alone is insufficient to make a correct diagnosis: Basic X-ray and/or ultrasound examinations can typically resolve between 80% and 90% of diagnostic problems in cases that require imaging. According to WHO's conclusion, "it will be difficult for health-care providers to contain the burgeoning costs" if demand is not properly managed through needs assessment, adequate procurement and other prerequisites [24].

8.1 Barriers to choosing medical devices

8.1.1 Lack of information

A perceived need that the medical device will satisfy is the driving force behind a purchase decision.

Therefore, information about the need and the extent to which a particular device or category of devices will satisfy that need will be necessary for a rational selection of a medical device.

Choosing devices that are likely to have a positive impact on one's health is clearly hampered by a lack of sufficient information at any stage of this process or by failing to conduct a rational and logical assessment of one's requirements.

According to a recent report, far too little money is spent on better understanding the relative advantages of various intervention options, and a significant portion of overall health care spending is spent on activities that do not improve health [25].

There is no evidence to support improved clinical outcomes over conventional radiation modalities for hospitals considering offering cutting-edge technology to their patients, such as expensive proton therapy, and no planned randomized controlled trials to make the necessary comparisons. The issue is made worse by the fact that older, more expensive radiotherapy systems can be had for one-fifth to one-thirty percent of the cost. Although physicians may advocate for the purchase of high-tech equipment, they do not have a complete understanding of its cost-effectiveness [26].

9. Conclusion

Traditional views of medical devices is higher used in medical field. Medical devices are used for diagnostic disease. Many medical devices higher used for cancer, diabetes and heart disease. This medical devices heavy high prize in market. This medical devices easy available Indian market. Wearble medical devices use see blood pressure, pulse, detected disease. Many of the medical devices used major roll of Covid-19 to detected covid. A medical device is an instrument apparatus, *in vitro* reagent, implant or other similar or related article, is intended for use in the diagnosis of disease or other conduction, or cure mitigation, treatment, or other prevention of disease or intended to affect the structure or any function of the body and which dose not achieve any of its primary intended purposes through its chemical action with in or on the body. Many scientists, doctors and biomedical engineers have a strong desire to improve public health and medical technology.

10. Future prospects

Innovation in both goods and services has significantly improved our lives. But innovation is crucial for survival of healthcare. The health of our next generation is directly impacted by innovation in this field. The difficulties and constraints we currently confront ought to serve as a foundation for future development. To expand the availability and accessibility of healthcare services outside Tier-1 cities, the main innovation trends in healthcare should contribute to the development of affordable medical devices. The choice now is between healthcare providers cutting corners in defense of an antiquated business model or rising to the occassion, innovating and unlocking the door to sustainable development.

11. References

1. Medical device regulations: global overview and guiding principles. Geneva, World Health Organization, 2003.
2. Kaplan W, Laing R. Priority medicines for Europe and the world. Geneva, World Health Organization, 2004. (WHO/EDM/PAR/2004.7)
3. Free MJ. Achieving appropriate design and widespread use of health care technologies in the developing world. Overcoming obstacles that impede the adaptation and diffusion of priority technologies for primary health care. International Journal of Gynecology and Obstetrics. 2004;85(1):S3-S13.
4. European Commission Directorate-General for Research Directorate. Responding to global challenges: the role of Europe and of international science and technology cooperation. Workshop Proceedings Brussels. European Communities, (EUR 23614 EN), 2007-2008 Oct. (http://ec.europa.eu/research/iscp/pdf/workshop_global_challenges_en.pdf, accessed 10 July 2010).
5. Daar AS, *et al*. Top ten biotechnologies for improving health in developing countries. Nature Genetics. 2002;32(2):229-232.
6. Monitoring financial flows for health research: Behind the global numbers. Geneva, Global Forum for Health Research, 2009.
7. Health technologies timeline: greatest engineering achievements of the 20th century. National Academy of engineering (http://www.greatachievements.org/?id=3824, accessed 10 July 2010).
8. Atles LR. A Practicum for biomedical engineering and technology management issues. Dubuque, Kendall Hunt Publishing, 2008.

9. Gaev J. Technology in health care. In: Dyro J, ed. Clinical engineering handbook. Burlington, Elsevier Academic Press, 2004, 342-345.

10. Butter M, *et al*. Robotics for healthcare. Final Report. European Commission, DG Information Society, 2008.

11. Kaplan W, *et al*. Future public health needs: commonalities and differences between high-and low-resource settings [Background Paper 8 of the Priority Medical Devices project]. Geneva, World Health Organization (http://whqlibdoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.8_eng.pdf).

12. Special report on health care technology. The Economist, 2009 April.

13. Geertsma RE, *et al*. New and emerging medical technologies: a horizon scan of opportunities and risks. National Institute for Public Health and the Environment (RIVM), 2007 (Report 360020002) (http:// www.rivm.nl/bibliotheek/rapporten/360020002.pdf, accessed 13 July 2010).

14. ECRI Institute. Computer-aided surgery: a GPS for the OR. Health Devices. 2009;38(7):206-218.

15. http://www.precedenceresearch.com/medical-devices-market10-09-2022

16. https://atltechnology.com/blog/smart-medical-devices/12-09-2022.

17. https://www.scnsoft.com/healthcare/medical-devices/smart#market-overview 14-09-2022.

18. https://blog.capterra.com/smart-medical-devices-that-are-changing-healthcare/18-09-2022.

19. Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG). The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPOA). Geneva, World Health Organization, 2008/2009.

20. Petkova H, *et al*. Barriers to innovation in the field of medical devices [Background Paper 6 of the Priority Medical Devices project]. Geneva, World Health Organization (http://whqlibdoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.6_eng.pdf)

21. Roberts E. Influences on innovation: extrapolations to biomedical technology. In: Roberts E, *et al.*, eds. biomedical innovation. Massachusetts, Massachusetts Institute of Technology Press, 1981.

22. Szpisjak DF, *et al*. Oxygen consumption of a pneumatically controlled ventilator in a field anesthesia machine. Anesthesia and Analgesia. 2008;107(6):1907-1911.

23. Klaver DL. Heel Veel PET-scanners (Many PET-scanners). Mediator, 2007, 18(2). (http://www.zonmw.nl/nl/organisatie/publicaties/mediator/archief/mediator-2007/mediator-2-2007/heel-veel-pet-scanners/, accessed 10 July 2010)

24. The role of medical devices and equipment in contemporary health care systems and services. World Health Organization. Technical discussion document for the Fifty-third Regional Committee for the Eastern Mediterranean, Agenda item, 2006 June, 7(b). (EM/RC53/Tech.Disc.2).

25. Feldman MD, *et al*. Who is responsible for evaluating the safety and effectiveness of medical devices? The role of independent technology assessment. Journal of General Internal Medicine. 2008;23(1):57-63.

26. Top 10 hospital technology issues: C-Suite watch list for and beyond. ECRI (Emergency Care Research Institute), 2009. (https://www.ecri.org/Forms/Pages/Top_10_Technologies.aspx, accessed 10 July 2010).

Chapter - 2
Design and Characterization of Clopidogrel Bisulfate Microspheres

Authors

K. Muni Raja Lakshmi
Department of Pharmaceutics, Sri Venkateswara College of Pharmaceutical Sciences, S.V. University, Tirupati, Andhra Pradesh, India

S. Poojitha
Department of Pharmaceutics, Sri Venkateswara College of Pharmaceutical Sciences, S.V. University, Tirupati, Andhra Pradesh, India

Chapter - 2

Design and Characterization of Clopidogrel Bisulfate Microspheres

K. Muni Raja Lakshmi and S. Poojitha

Abstract

The present research work is aimed to design and characterize clopidogrel bisulfate microspheres. Clopidogrel bisufate microspheres were prepared using polymers like HPMC K15M, EC and Carbopol 940 for controlled delivery. The prepared microspheres were evaluated for physico-chemical characteristics like drug interaction study (FTIR), surface morphology (SEM), Entrapment efficiency, drug content, *in vitro* dissolution studies and release kinetics. The regression (r^2) value of clopidogrel bisulphate was found to be 0.999 which was closed to unity indicates that the concentration range from 5-30µg/ml obeys beers lamberts law. The drug excipient compatibility studies showed that there are no interactions between the drug and excipients. SEM analysis showed that the surface area of Microspheres was spherical and found to be rigid in nature. All the formulations F1 to F8 has an average particle size in the range of 100-750 µm which indicates that the prepared microspheres are in micro size. Among all formulations, F8 formulation shows percentage drug entrapment efficiency of 96.92, drug content of 99.58 & percentage yield of 99.28, which indicates that increase in polymer concentration increases entrapment effectiveness. The F8 formulation shows microspheres had an optimum release at the end of 12^{th} hour with 99.92%. From the drug release kinetic studies it was observed that the Clopidogrel bisulphate microspheres exhibit Zero order drug release with super case II transport mechanism.

Keywords: Clopidogrel bisulphate, HPMC K15M, EC, Carbopol 940

Introduction

Platelets are anucleated discoid shape hematopoietic cells which have considerable roles in modulating hemostasis. Recent studies indicate that platelets are also involved in inflammation, infection, host response and even cancer. Platelets express and secrete adhesion molecules to accumulate in

damaged sites. Adhesion molecules favor adhesion of platelets to leukocytes and granulocytes. Furthermore, platelets secrete immune modulators which are chemotactic for neutrophils, monocytes and lymphocytes. Those interaction results in formation of platelet granulocyte or platelet-leukocyte aggregates which triggers further inflammation. Platelets are also involved in natural immunity because they can capture and engulf microbes. In addition; they prevent dissemination of bacteria by clot formation. Platelets are tiny blood cells that help your body form clots to stop bleeding. If one of your blood vessels gets damaged, it sends out signals to the platelets. The platelets then rush to the site of damage. They form a plug (clot) to fix the damage to prevent further loss of blood and damage. Platelets are made in your bone marrow along with your white and red blood cells. Once platelets are made and circulated into your bloodstream, they live for 8 to 10 days [1, 2].

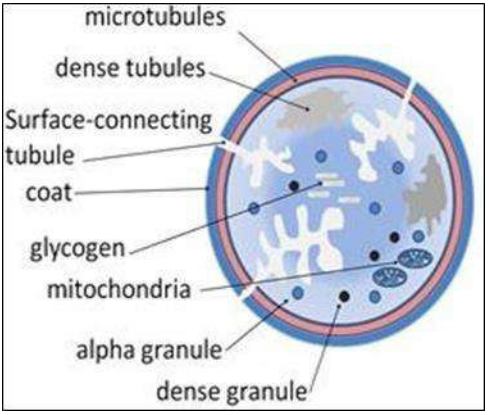
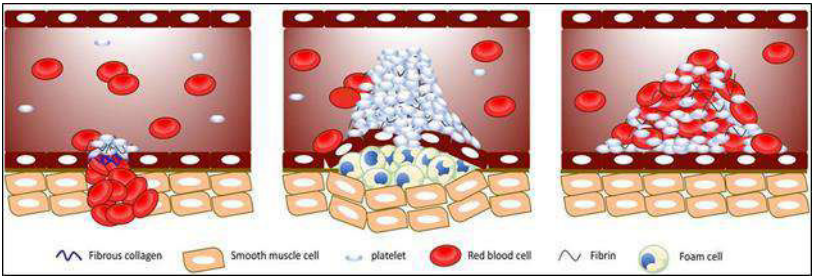


Fig 1: Schematic diagram of platelet

Role of platelets

Chronic or continued interaction of platelets with endothelial cells or WBCs can cause excessive immune stimulation or complex accumulation Excessive platelet-monocyte complex accumulation might be a finding of vascular diseases, for instance: Elevated level of monocyte platelet aggregates are accepted as early hallmark of MI acute myocardial infarction (AMI). Furthermore, circulating platelet-leukocyte aggregates (PLAs) might be a marker of sepsis. Additionally, aggregate formation may lead to atherosclerosis and platelets may facilitate it because granules contain proangiogenic proteins. The hemostatic system provides a natural balance between the coagulation and fibrinolysis [3, 4].



a) Hemostasis b) Arterial or athero (thrombosis) c) Venous thrombosis

Fig 2: The physiologic and pathophysiological role of platelets: Platelets participate inhemostasis to prevent blood loss by forming a haemostatic plug following a vascular insult

Almost 30% of the platelets are trapped in the spleen. Enlargement of spleen also called splenomegaly, affects all these vital functions. It traps and store too many platelets, which decrease the number of platelets in the circulation and cause thrombocytopenia. It is also caused by many diseases like inflammatory disease such as sarcodosis and rheumatoid arthritis, cancer such as leukemia and lymphoma (Hodgkin's disease), liver disease such as cirrhosis, Sclerosing cholangitis, Wilsons' disease, biliary atresia and cystic fibrosis, infiltrative disease such as Gaucher's disease, Niemann-pick disease, amyloidosis or glycogen storage disease. Other causes include Sickle cell splenic crisis, Banti's syndrome, Felty syndrome, trauma, such as sporting injury and cysts or abscesses. Vinyl chloride has been reported to cause thrombocytopenia in worker who has developed vinyl chloride induced hepatic fibrosis with esophageal varies and splenomegaly [5, 6].

Factors that can decrease platelet production include

Chemotherapy: Chemotherapy or radiation therapy is an important cause of the thrombocytopenia. Bone marrow suppression (myelosuppression) is a common side effect of chemotherapy it developed tumors in the bone marrow, which increase the chances of anemia, thrombocytopenia and neutropenia [7].

Alcohol consumption: People who abuse alcohol are at a high risk of hematological disorders. More than 80 grams of alcohol per day give toxic effects on bone marrow, red blood cells, white blood cells, platelets and also produced nutritional deficiency that impair the production and function of various blood cells [8].

Some other factor which decrease platelet production are:

- **Viral infection:** Chickenpox (varicella), Rubella, Hepatitis C, Epstein-Barr virus, HIVand parvovirus.
- Deficiency of vitamin B12 and folic acid.
- Condition like leukemia, lymphoma.
- **Medication:** Aspirin, Ibuprofen, thiazide diuretics.
- **Toxic chemical:** Arsenic, benzene and pesticide.

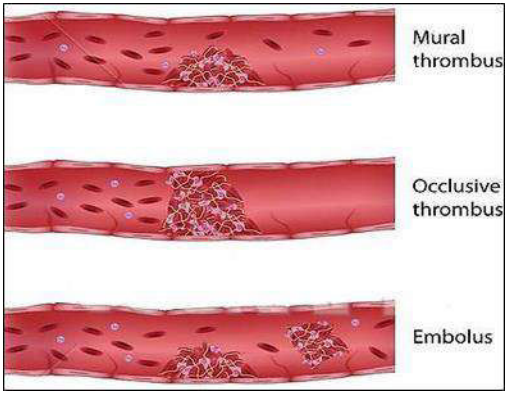


Fig 3: Types of thrombosis

Platelet adhesion

Once platelets are activated, when they come across injured endothelium cells, the von Willebrand factor (vWF) and fibrinogen will act as anchors to allow platelets to adhere onto the vessel wall. These molecules are released from the platelet themselves as a result of degranulation, a physiological change in the platelet's shape due to the secretion of the contentsof the dense granules and alpha granules. From the dense granules, serotonin and adenosine triphosphate are released [9].

Platelet aggregation

After platelets make contact with the focal point of the vascular injury, they begin to interact with each other to form a platelet aggregate. ADP can then catalyze the aggregation of platelets, allowing for fibrinogen to link two platelets together [10].

Platelet endothelium interaction, hemostasis and platelet aggregation

Platelets are completely different from endothelial cells and can interact in multiple ways when exposed to endothelial surface. These

interactions can be of cross talk over a distance also known as paracrine signaling via transient interactions or through receptor mediated cell-cell adhesion [11].

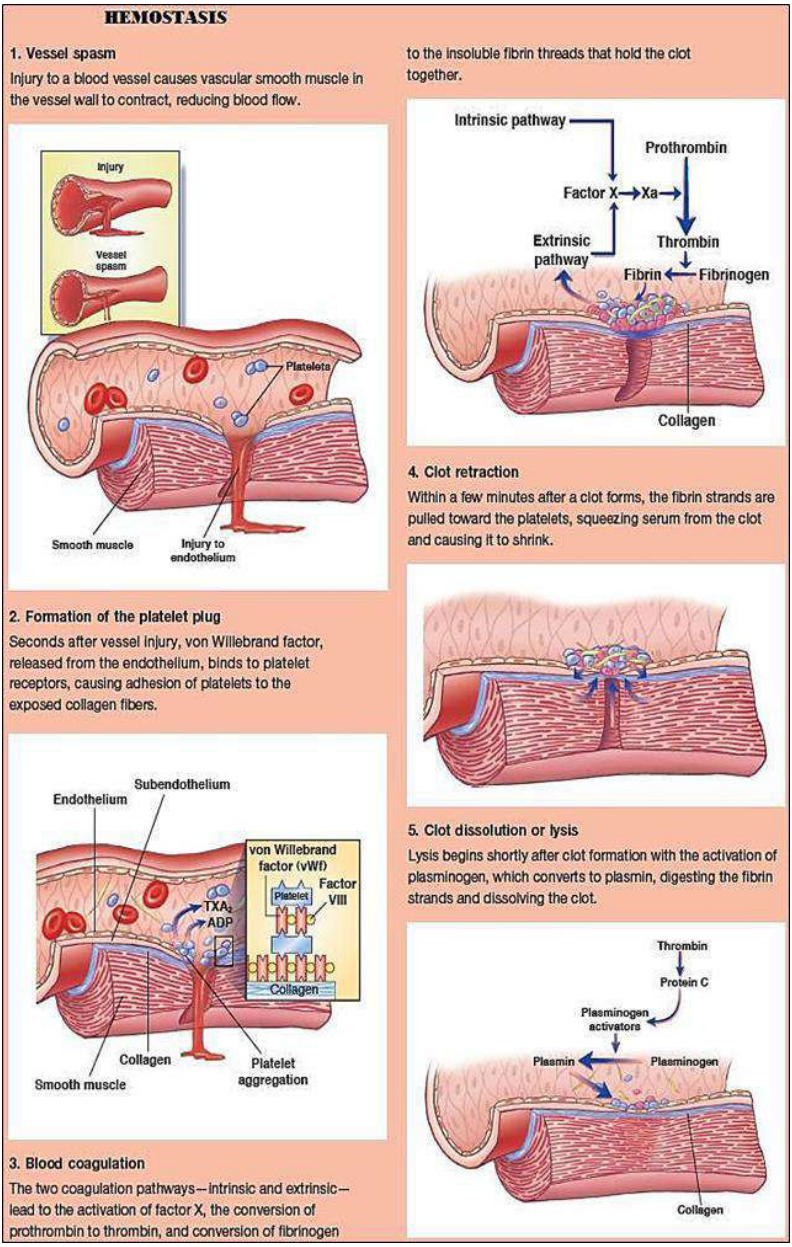


Fig 4: Process of hemostasis

Controlled drug delivery

One of essential issues of drug formulation is the controlled release of drugs, which can improve therapeutic efficacy by offering prolonged *in vivo* action, controlled blood concentration as well as tissue-targeted local release. A possible approach to the controlled and sustained release of drugs involves incorporation of drug molecules into the biodegradable polymer microspheres [12].

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant or cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. The release patterns of drug from both formulations traditional and controlled are given in Fig: 5.

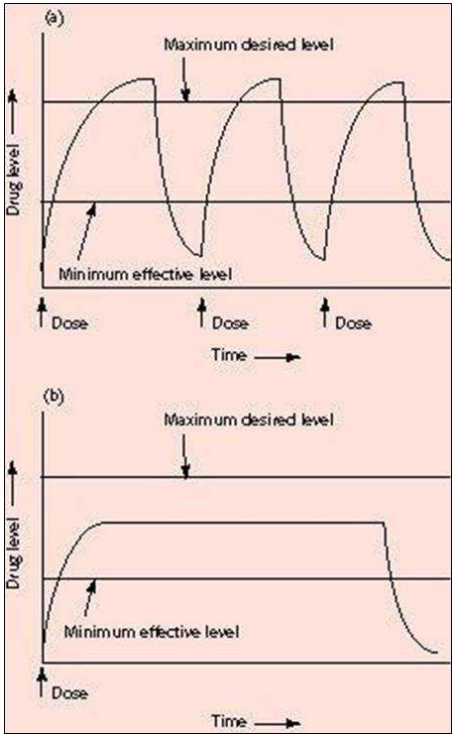


Fig 5: Drug levels in the blood with (a) traditional drug dosing (b) controlled drug dosing

Controlled release refers to the use of a delivery device with the objective of releasing the drug into the patient body at a predetermined rate, or at specific rimes or with specific release profiles. This could revolutionize the manner of medication and offer following advantages along with some disadvantages [13].

Table 1: Advantages and disadvantages

Advantages	Disadvantages
Reduction in dosing frequency	High cost
Reduced fluctuations in circulatory drug levels	Unpredictable or poor *in vitro-in vivo* Correlation
Avoidance of night patient compliance	Dose dumping
Increased patient compliance	Reduced potential for dosage adjustment
Mire uniform effect	Increased first pass clearance
Decreased side effects like reduced GI irritation	Poor systemic availability in general

Various characteristics of drug molecule that render it unsuitable for controlled releasedosing

- Narrow therapeutic index.
- Short/long limitation half-life.
- Poor absorption.
- Active absorption large doses.
- Low aqueous solubility.
- Extensive first pass metabolism.
- Incompatible pharmacological effects.
- Circulation time course.

Biodegradable polymers

For the past few decades, biodegradable polymers have been applied as carriers for controlled delivery of low molecular weight drugs as well as bioactive proteins. Biodegradable polymers, either synthetic or natural, are capable of being cleaved into biocompatible byproducts through chemical or enzyme-catalyzed hydrolysis. This biodegradable property makes it possible to implant them into the body without the need of subsequent removal by the surgical operation. Drugs formulated with these polymers can be released in a controlled manner, by which the drug concentration in the target site is maintained within the therapeutic window. The release rates of the drugs from biodegradable polymers can be controlled by a number of factors, such

as biodegradation kinetics of the polymers, physicochemical properties of the polymers and drugs· thermodynamic compatibility between the polymers and drugs, and the shape of the devices· Biodegradable polymer particles (e.g. microspheres, microcapsules, and nanoparticles) are highly useful because they can be administered to a variety of locations*in vivo* through a syringe needle. A variety of drugs, regardless of their molecular weights and water solubility, can be loaded into the biodegradable micro particles using different manufacturing techniques [14, 15].

Classes of biodegradable polymers Bio-degradable polymers may be classified based on the mechanism of release of the drug entrapped in it as under:

- Slow dissolution and erosion by hydrolysis.
- Water insoluble polymer undergoing hydrolysis, ionization or protonation of pendent group without undergoing backbone cleavage.
- Water insoluble polymer degrades to water soluble products by backbone cleavage.
- Bio-degradable polymers investigated for CDD
- Lactide/Glycolide polymers
- Polyanhydrides
- Poly-caprolactones.

Materials

Clopidogrel bisulphate was purchased from Glenmark Pharmaceuticals LTD, HPMC K 15M, Ethyl Cellulose was purchased from Spectrum pharmalabs Hyderabad, Carbopol 940 was obtained from Shreeji chemicals, Mumbai, Calcium Chloride, Sodium Alginate was purchased from SD Fine chemical Ltd., Mumbai.

Methods

Preformulation studies

Peformulation was defined as the phase of research and development process where physical, chemical and mechanical properties of a new drug substance were characterized alone and when combined with excipients, in order to develop a stable, safe and effective dosage form.

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of

physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of Preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced [16, 17].

Solubility

Solubility of Clopidogrel bisulphate was determined in pH 1.2 and pH 7.4 and pH 6.8 phosphate buffers

Solubility studies were performed by taking excess amount of Clopidogrel bisulphate in beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions are analyzed by spectrophotometrically [18].

Determination of UV spectrum of Clopidogrel bisulphate

10 mg of Clopidogrel bisulphate was dissolved in 10 ml of buffers so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and make up the volume to 10 ml using buffer to get the concentration of 100 µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using buffer to get the concentration of 10 µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm [19].

Calibration curve

Preparation of standard calibration curve of clopidogrel bisulphate in pH 1.2

Preparation of stock solution

10mg of Clopidogrel bisulphate was dissolved in 10ml of pH 1.2 buffers so as to get a stock solution of 1000 µg/ml concentration.

Preparation of standard solution

1ml of stock solution was diluted to 10 ml with pH 1.2 buffer in 10ml volumetric flask this gives aconcentration of 100µg/ml. Aliquot of standard drug solutions were prepared and transferred in to 100ml volumetric flask and were diluted up to the mark with pH 1.2 buffer. This gives the final concentration of 0.5, 1, 1.5, 2.0, 2.5, 3.0 µg/ml of Clopidogrel bisulphate respectively. The absorbances of the solution were measured against pH 1.2 as blank using UV visible spectrophotometer at 254 nm the absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve [20].

Drug-excipient compatibility studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation studies must generate the needed information [21].

FT-IR Studies

Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minimal (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards [22].

Formulation design

Preparation of clopidogrel bisulphate microspheres

Method used: Ionic Gelation Technique

Microspheres containing clopidogrel bisulphate were prepared by iontropic gelation method employing sodium alginate in combination with ethylcellulose calcium chloride HPMC K15M in different ratios. Sodium alginate was dissolved in the distilled water to form a homogenous polymer. The drug 1000 mg was added to the polymer dispersion containing sodium alginate with a stirring about 800 rpm. The resultant dispersion was then extruded through a syringe size no 18 needle and added drop wise into 100 ml calcium chloride solution 2.5 percentage w/v. to increase the beads mechanical strength they were left in the same solution for 60 min. the microspheres were collected by decantation and the product obtained was washed repeatedly and dried at 12hrs for 40 ºC [23].

Table 2: Formulation design for Clopidogrel bisulphate microspheres using different ratios of drug and polymers

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Clopidogrel Bisulphate (mg)	1000	1000	1000	1000	1000	1000	1000	1000
Sodium alginate (mg)	250	250	250	250	250	250	250	250
Carbopol 940 (mg)	250	500	--	--	--	--	--	--
HPMC K15M (mg)	--	--	250	500	--	--	250	500
Ethyl cellulose (mg)	--	--	--	--	250	500	250	250

Calcium Chloride (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Dis. Water (ml)	100	100	100	100	100	100	100	100
Drug: Polymer	1:0.5	1:0.75	1:0.5	1:0.75	1:0.5	1:0.75	1:0.75	1:1

Evaluation parameters of Clopidogrel bisulphate microspheres

Bulk density (Db)

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume [24]. Bulk density is expressed in gm/cc and is given by,

Db=M/Vo

Where, Db=Bulk density (gm/cc) M is the mass of powder (g) Vois the bulk volume of powder (cc)

Tapped density (Dt)

Ten grams of powder was introduced in to a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100times from a constant height and tapped volume was read [25]. It is expressed in gm/cc and is given by,

Dt = M/Vt

Where,

Dt = Tapped density (gm/cc) M is the mass of powder (g).

Vt is the tapped volume of powder (cc).

Carrs index

The compressibility index and the hausners ratio are determined by measuring both bulk volume and tapped volume of microspheres [26]. The percentage compressibility of microspheres was calculated according to equation given below.

$$\%\ \text{Compressibility Index} = tapped\ density - bulk\ density \div tapped\ density \times 100$$

Table 3: Relation between the Carr's index of powder and its flow characteristics

S. No.	Carrs index	Flow Properties
1.	5-12	Free flowing
2.	12-16	Good

3.	18-21	Fair
4.	23-35	Poor
5.	33-38	Very poor
6.	>40	Extremely poor

Hausner's Ratio

It is determined by comparing the ratio of the tapped density to the bulk density, which displaysthe granules flow behavior [27].

Hausner's Ratio = Tapped density/Bulk density.

Table 4: Relation between hausner's ratio and its flow properties

S. No.	Hausners ratio	Flow Property
1.	0-1.2	Free flowing
2.	1.1-1.6	Cohesive powder

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel [27].

The angle of repose was then calculated using the formula,

$\tan(\theta) = h \backslash r$

Where,

θ = Angle of repose.

h = Height of pile.

r = Radius of the base of the pile.

Percentage yield

Percentage practical yield of Clopidogrel bisulphate microspheres is calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Clopidogrel bisulphate microspheres recovered from each batch in relation to the sum of starting material. The percentage yield of prepared Clopidogrel bisulphate microspheres was determined by using the formula [27].

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Determination of Percentage Drug Entrapment (PDE)

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula [27]

$$\text{PDE} = \frac{\text{Practical drug loading}}{\text{theoretical drug loading}} \times 100$$

Practical drug content

Practical drug content was analyzed by using the following procedure, weighed amount of Clopidogrel bisulphate microspheres was dissolved in 100 ml of 6.8 pH Phosphate buffer. This solution was kept overnight for the complete dissolution of the Clopidogrel bisulphate microsphere in 6.8 pH Phosphate buffer. This solution was filtered and further diluted to make a conc of 10 µg/ml solution. The absorbance of the solutions was measured at 254 nm using double beam UV-Visible spectrophotometer against 6.8 pH Phosphate buffer solution as blank and calculated for the percentage of drug present in the sample [28].

Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry Clopidogrel bisulphate gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Clopidogrel bisulphate microspheres were taken by random scanning of the stub [28].

Particle size analysis

The size of the prepared microspheres was measured by the optical microscopy method using acalibrated stage micrometer [29]. Particle size was calculated by using equation.

$\lambda g = 10 \text{ X } [(ni \text{ x } \log xi)/N]$

λg is geometric mean diameter.

ni is number of particles in range.xi is midpoint of range.

N is the total number of particles.

All the experimental units were analyzed in triplicate (n=3).

***In vitro* dissolution studies**

The release rate of Clopidogrel bisulphate microspheres was determined by employing USP XXIII apparatus by rotating basket method. The dissolution test was performed using 900 ml of 6.8 pH Phosphate buffer, in 37±0.5 °C at 50rpm. Clopidogrel bisulphate microspheres were placed in a basket to avoid floating of microspheres. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were passed through whatman filter paper and the absorbance of these solutions was measured at 214 nm. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot. Data obtained was also subjected to kinetic treatment to understand release mechanism [30].

Drug kinetics

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t [30]. In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows.

- Cumulative percentage drug release vs. Time (zero order rate kinetics).
- Log cumulative percentage drug retained vs. Time (first order rate kinetics).
- Cumulative percentage drug release vs. √T (Higuchi's classical diffusion equation).
- Log of cumulative percentage drug release vs. log Time (Peppas exponential equation).

Results and Discussion

Preformulation studies

Table 5: Solubility study

Solvent	Concentration(mg/ml)
0.1N HCl	30.28±0.15

Distilled Water	0.914±0.23
6.8 pH Phosphatebuffer	0.31±0.45

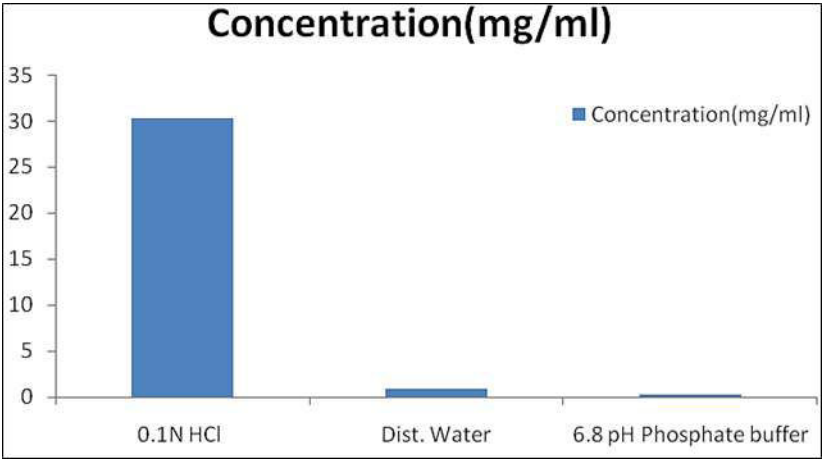


Fig 6: Solubility graph

Melting point

The melting point of clopidogrel bisulphate was found to be 199 ºC.

UV Spectrum of Clopidogrel bisulphate

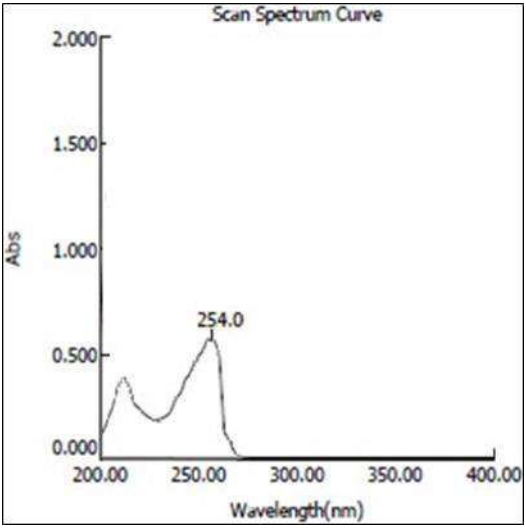


Fig 7: UV spectrum of Clopidogrel bisulphate

Standard calibration curve

Table 6: Standard calibration data of Clopidogrel bisulphate in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.182
10	0.321
15	0.466
20	0.625
25	0.768
30	0.942

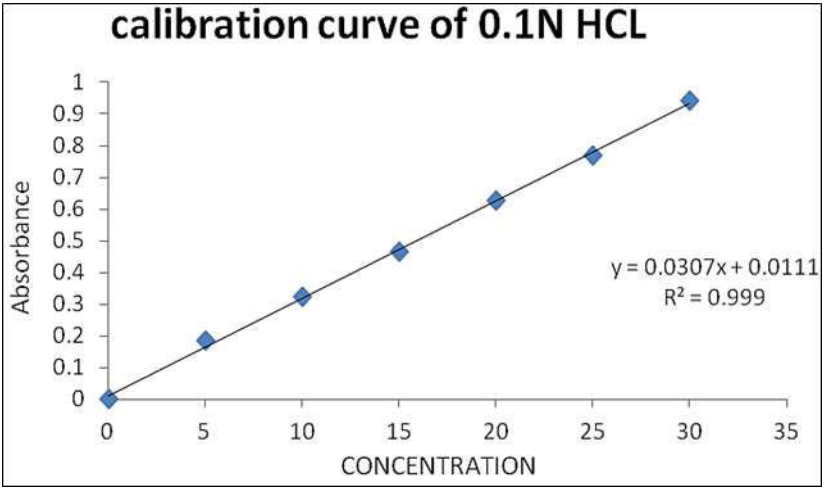


Fig 8: Standard calibration curve of clopidogrel bisulphate in 0.1N HCL

Evaluation of clopidogrel bisulphate microspheres

Drug polymer interaction (FTIR) study

From the spectra of Clopidogrel bisulphate, physical mixture of Clopidogrel bisulphate and polymer, Clopidogrel bisulphate microspheres and blank microspheres, it was observed that all characteristic peaks of Clopidogrel bisulphate were present in the combination spectrum, thus indicating compatibility of the Clopidogrel bisulphate and polymer. IR Spectra shown in Figures below.

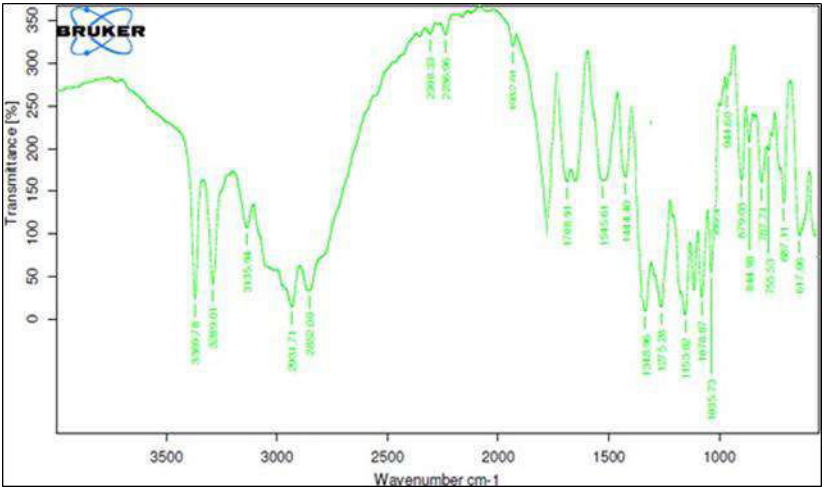


Fig 9: IR spectra of pure Clopidogrel bisulphate

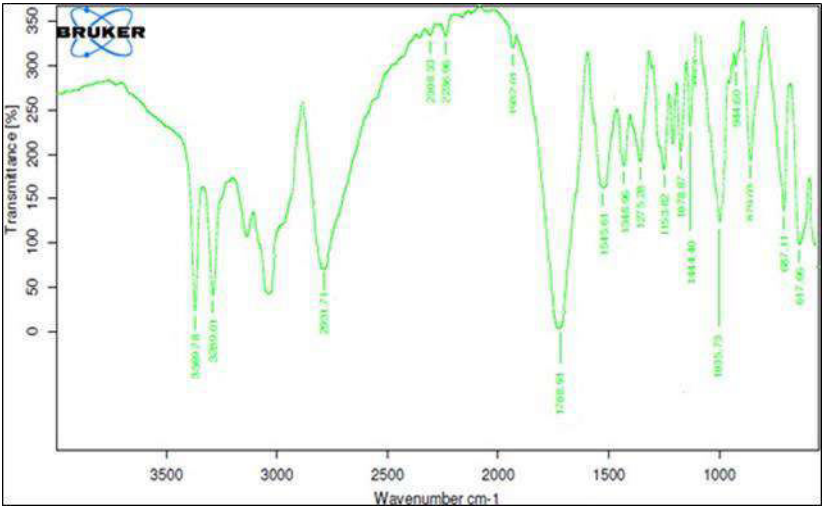


Fig 10: IR spectra of optimized formulation

Table 7: Interpretation of FTIR of clopidogrel bisulphate

Functionalgroups	Stretching/deformation	Pure drug (cm-1)	Drug + polymers (cm-1)
C=H	Stretching	1545.61	1545.61
CH3	Stretching	2931.71	2931.71
CH3	Deformation	1444.40	1444.40
C-H	Stretching	3300.78	3300.78

Surface morphology-Scanning Electron Microscopy (SEM)

Fig 11: SEM photographs of microspheres

Table 8: Determination of Average particle size

Formulation code	Average size (µm)
F1	600
F2	420
F3	320
F4	260
F5	100
F6	750
F7	600
F8	540

Table 9: Percentage drug entrapment efficiency, drug content, percentage yield

Formulation Code	Percentage Yield	Drug Content (%)	Entrapment Efficiency (%)
F1	70.64	90.10	89.16
F2	74.42	92.62	90.22
F3	79.19	94.62	93.78
F4	76.41	94.96	93.26
F5	84.62	98.83	97.68
F6	80.72	97.16	94.62
F7	84.74	98.72	96.29
F8	96.92	99.58	99.28

In vitro dissolution studies

Table 10: *In vitro* Release Data of Clopidogrel Bisulphate Microspheres

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	18.01	21.42	17.26	21.82	14.43	20.87	15.56	18.76
2	28.24	31.02	26.92	35.26	25.78	32.36	23.71	25.72
3	37.92	40.24	35.68	46.84	36.84	43.02	31.81	36.42
4	45.18	49.36	47.84	58.86	46.56	51.64	39.87	40.46
5	53.69	57.26	54.62	63.92	54.78	58.85	46.82	49.58
6	61.26	69.61	69.86	70.15	63.15	68.71	52.46	56.82
7	78.28	80.65	74.42	76.45	79.78	81.78	63.84	65.77
8	89.12	90.26	81.98	84.56	87.22	90.45	70.04	72.21
9	89.13	95.62	90.05	90.86	87.23	96.36	80.34	81.48
10	89.13	95.63	96.01	90.86	87.32	96.38	87.35	87.46
11	89.95	95.9	96.05	90.9	87.56	96.65	92.92	93.49
12	90.15	96.2	96.08	91.1	87.76	96.97	93.21	99.92

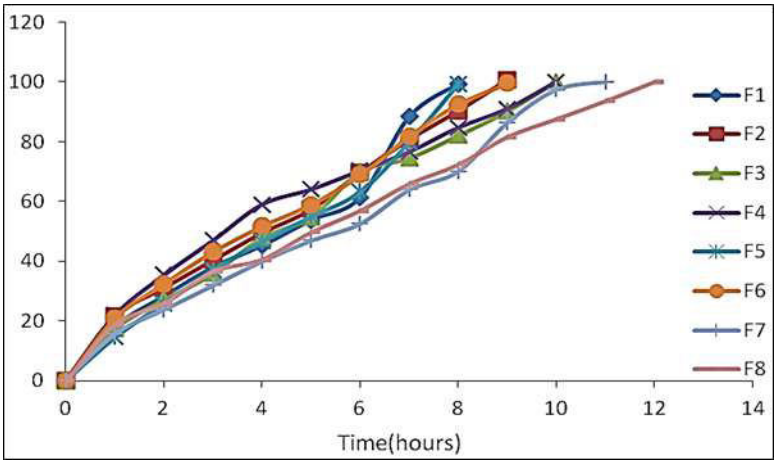


Fig 12: Percentage CDR Profile of Clopidogrel bisulphate microspheres F1-F8

Drug release kinetics studies

Zero order release

Fig 13: Zero order release profile of Clopidogrel bisulphate best formulation (F8)

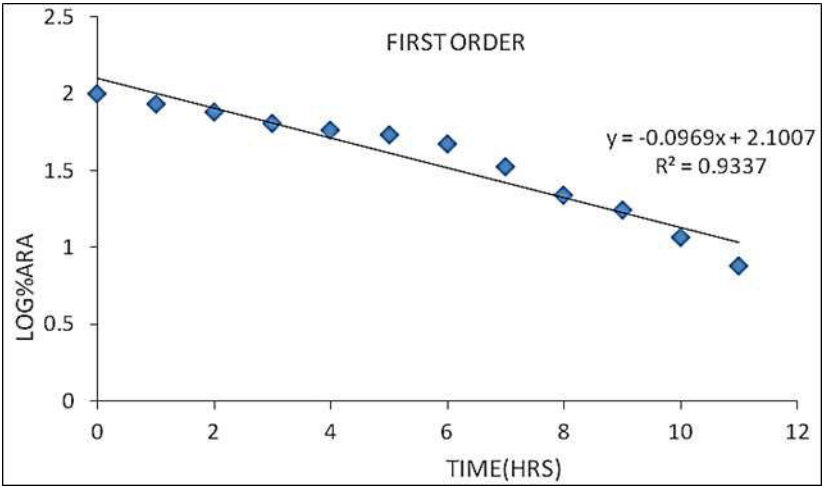


Fig 14: First order release profile of Clopidogrel bisulphate best formulation (F8)

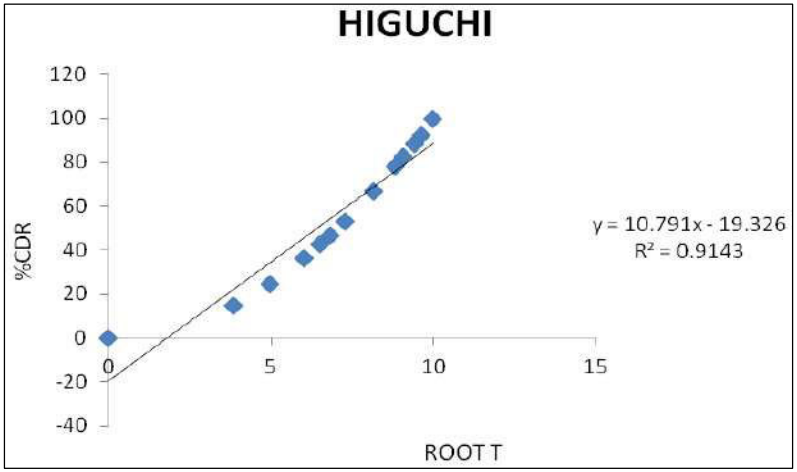


Fig 15: Higuchi release kinetics profile of Clopidogrel bisulphate best formulation (F8)

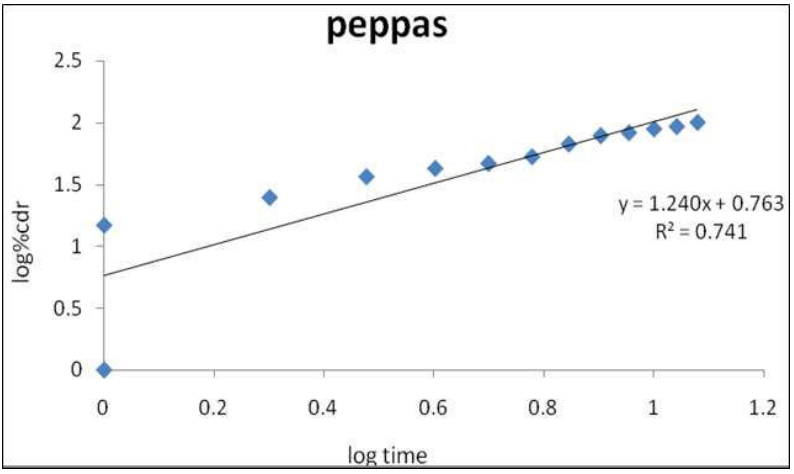


Fig 16: Peppas release kinetics profile of Clopidogrel bisulphate best formulation (F8)

Table 13: Regression co-efficient (r^2) values Clopidogrel bisulphate microspheres

Formulation	Zero order	First order	HiguchiMatrix	Peppas Plot	
				r^2 value	'n' value
F8	0.987	0.933	0.914	0.741	1.240

Discussion

Clopidogrel bisulphate was found to be having more solubility in 0.1N HCL than compared to 6.8 phosphate buffer and water. The maximum

absorbance of the Clopidogrel bisulphate was found to be at 254 nm. Hencethe Wavelength of 254 nm was selected for further analysis of drug.

From the calibration data given in table 6 & fig.8, it revealed that the regression (r^2) value was found to be 0.999 which was closed to unity indicates that the concentration range from 5-30 µg/ml obeys beers lamberts law.

From the drug excipient compatibility studies, FTIR it was revealed that there are no interactions between the pure drug (Clopidogrel bisulphate) and optimized formulation (Clopidogrel bisulphate + excipients) which indicates there are no in compatability.

From the results of SEM analysis it was observed that the surface area of Microspheres was spherical and found to be rigid in nature, due to the higher polymer concentration.

All the formulations F1 to F8 has an average particle size in the range of 100-750µm which indicates that the prepared microspheres are in micro size.

Among all formulations, F8 formulation shows the percentage drug entrapment efficiency, drug content and percentage yield of 96.92, 99.58 and 99.28 respectively. With an increase in polymer concentration there is an increase in entrapment effectiveness. The findings suggest that clopidogrel is distributed properly in micro spheres.

The results of the *in vitro* dissolution studies showed controlled release in a predictable manner. The F8 formulation shows microspheres had an optimum release at the end of 12^{th} hour with 99.92%.

From the drug release kinetic studies it was observed that the Clopidogrel bisulphate microspheres exhibit Zero order drug release with super case II transport mechanism.

Conclusion

Clopidogrel microspheres were prepared using different concentrations of sodium alginate, carbopol 940, HPMC K15M, Ethyl cellulose, Calcium Chloride. All the prepared formulations have drug entrapment efficiency of 96.92, drug content of 99.58 & percentage yield of 99.28. The *in vitro* dissolution studies shows that among all formulations F8 has highest drug release of 99.92% at 12 hours and followed Zero order drug release with super case II transport mechanism which proved that the prepared formulation showed controlled release for 12 hours.

References

1. Harris D, Fell JT, Sharma HL, Taylor DC. GI transit of potential bioadhesive formulations in man: a scintigraphic study. J Control Release. 1990;12(2):45-53.
2. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system. Int. J Pharm. Tech Research. 2009;1(3):623-633.
3. Longer MA, Ching HS, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery III: oral delivery of chlorothiazide using a bioadhesive polymer. J Pharm Sci. 1985;74:406-11.
4. Arshady R. Review: Biodegradable microcapsular drug delivery systems: man-facturing methodology, release control and targeting prospects. J Bioact Compat Pol. 1990;5:315.
5. Geng Y, Yuan W, Wu F. Formulating erythropoietin loaded sustained release PLGA microspheres without protein aggregation. J Control Release. 2008;130:259.
6. Leach KJP, Takahashi S, Mathiowitz E. Degradation of double-walled polymer microspheres of PLLA and P (CPP: SA) 20:80. II. *In-vivo* degradation, Biomaterials. 1998;19:19-81.
7. Cheung RY, Ying YM, Rauth AM. Biodegradable dextran-based microspheres for delivery of anticancer drug mitomycin C, Biomaterials. 2005;26:53-75.
8. Cho JC, Khang G, Choi HS. Preparation of biodegradable PLGA microspheres for sustained local anesthesia and their *in vitro* release behavior, Polymer (Korea). 2000;24:728.
9. Jong HP, Shin E, Sik Il A, Hyun HH, Cho MK, Soon HY, *et al*. Dextran/PLGA Double-Layered Microspheres for Sustained Release of Doxorubicin Tissue Engineering and Regenerative Medicine 2009;6(4~11):588-594.
10. Vyas SP, Khar RK. Essentials of Controlled Drug Delivery; c2002. p. 417-457.
11. Lisa Brannon-Peppas. Polymers in Controlled Drug Delivery Biomaterials; c1997.
12. Claude Farrugia. Gelatin nanoparticle production: an in-process study using size exclusion chromatography. Xjenza. 1997;2(1):15-20.

13. Amitava Ghosh, Udaya Kumar Nayak, Prasant Rout, Tanusree Nag, Partha Roy. Preparation, Evaluation and *in vitro- in vivo* Correlation (IVIVC) study of Lamivudine Loaded Microspheres. Research J Pharm and Tech. 2008;1(4):353-356.

14. Mathiowitz E, Kreitz MR, Brannon-Peppas L. Microencapsulation. Encyclopedia of Controlled Drug Delivery. New York, NY: John Wiley & Sons, Inc. 1999:493-546.

15. Limor Baruch, Marcelle Machluf. Alginate-chitosan complex coacervation for cell encapsulation: effect on mechanical properties and on long-term viability. J Biopolymers. 2006;82:570-579.

16. Alagusundaram M, Madhu Sudana Chetty C, Umashankari K. Microspheres as a novel drug delivery system. International Journal of Chem. Tech Research.

17. Capron AC, Locht C, Fracchia GN. (1994) Vaccine.12, 667; Edelman R. (1993) vaccine 11, 1361; Drews J. (1984) Immunostimulantien, Klin. Wochenscher.62, 254; Spier K.E. 1993;11:14-50.

18. Jae Hyung Park, Mingli Ye, Kinam Park. Biodegradable Polymers for Microencapsulation of Drugs Molecules. 2005;10:146-161.

19. Pekarek KJ, Jacob JS, Mathiowitz E. Double-walled polymer microspheres forcontrolled drug release. 1994;367:258-260.

20. Ulbrich K, Pechar M, Strohalm J, Subr V, Rihova B. Synthesis of biodegradablepolymers for controlled drug release. Ann NY Acad Sci. 1997;831:47.

21. Hejazi R, Amiji M. Chitosan-based gastrointestinal delivery systems. J Control Release. 2003;89:151-165.

22. Zhao Z, Wang J, Mao HQ Leong KW. Polyphosphoesters in drug and genedelivery. Adv Drug Delivery Rev. 2003;55:483-499.

23. Cicek H, Tuncel A, Tuncel M, Piskin E. Degradation and drug release characteristics of monosize polyethylcyanoacrylate microspheres. J Biomater Sci. Polym Ed. 1995;6:845-856.

24. Mi FL, Lin YM, Wu YB, Shyu SS, Tsa YH. Chitin/PLGA blend microspheres as a biodegradable drug-delivery system: phase-separation, degradation and release behavior. Biomaterials 2002;23:3257-3267.

25. Sawicki W, Lunio R. Compressibility of floating pellets with Verapamil hydrochloride coated with dispersion kollicoat SR 30 D. Eur. J Pharm Biopharm. 2005;60(1):153-7.

26. Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: Effect of some additives, hardening agent or coating on release behaviour of Metronidazole. Eur. J Pharm Sci. 2005;24(4):363-73.

27. Rao MR, Borate SG, Thanki KC, Ranpise AA, Parikh GN. Development and *in vitro* evaluation of floating Rosiglitazone maleate microspheres. Drug Dev. Ind. Pharmacy. 2009;35(7):834-42.

28. Kamila M, Nitamondal, Gosh L, Gupta B. Multiunit floating drug delivery system of Rosiglitazone maleate: Development, characterization, stastistical optimization of drug release and *in vivo* evaluation. AAPS Pharm Sci. Tech. 2009;10(3):887-99.

29. Senthilkumar SK, Jaykar B, Kavimani S. Formulation, Characterization and *In vitro* Evaluation of Floating Microsphere Containing Rabeprazole Sodium. JITPS 2010;1(6):274-82.

30. Barhate SD. Rupnar YS, Sonvane RM, Pawar KR, Rahane RD. Formulation and evaluation of floating microspheres of ketorolac trometamol. IJPRD. 2009;1(9):1-8.

Chapter - 3
Trending Role of Artificial Intelligence in Dental Radiology

Authors

Dr. Kriti Garg
Reader, Department of Oral Medicine and Radiology, Rama Dental College, Kanpur, Uttar Pradesh, India

Dr. Vishal Mehrotra
Professor and HoD, Department of Oral Medicine and Radiology, Rama Dental College, Kanpur, Uttar Pradesh, India

Dr. Sunita Pathak
Reader, Department of Oral Pathology and Microbiology, Rama Dental College, Kanpur, Uttar Pradesh, India

Dr. Ravi Seth
Reader, Department of Oral Pathology and Microbiology, Rama Dental College, Kanpur, Uttar Pradesh, India

Chapter - 3

Trending Role of Artificial Intelligence in Dental Radiology

Dr. Kriti Garg, Dr. Vishal Mehrotra, Dr. Sunita Pathak and Dr. Ravi Seth

Abstract

Artificial intelligence, which has been actively applied to a broad range of industries in recent years, is an active area of interest for many researchers. Since its first use for medical purposes in the 1960s, the concept of artificial intelligence has been especially appealing to health care, particularly radiology. With the development of ever more powerful computers from the 1990s to the present, various forms of artificial intelligence have found their way into different medical specialties most notably radiology, dermatology, ophthalmology, and pathology. Dentistry is no exception to this trend, and the applications of artificial intelligence are particularly promising in the field of oral and maxillofacial radiology. Convolutional neural networks have been used in recent Artificial intelligence research in oral maxillofacial radiology to do image classification, detection, segmentation, registration, generation, and refinement. Artificial intelligence systems in this field have been developed for the purposes of radiographic diagnosis, image analysis, forensic dentistry, and image quality improvement. Obtaining accurate and consistent data sets requires extensive amounts of data, which is a time-consuming process requiring the involvement of oral maxillofacial radiologists.

Keywords: Artificial intelligence, radiology, deep learning, dentistry.

Introduction

In the realm of health care, what previously appeared like science fiction is now a reality. Fast-evolving technology referred to as artificial intelligence (AI) enables machines to perform jobs that used to be carried out by humans. AI developments hint at potential health advantages like fewer complications during surgery, improved decision-making, higher quality of life, and less wasteful operations. When used in the disciplines of medicine and dentistry, AI can significantly increase the precision of diagnoses and transform patient care. Dentistry presently employs AI for a number of tasks, including the detection of typical and atypical structures, illness diagnosis, and treatment

outcome prediction. Additionally, AI is widely employed in dentistry laboratories and is becoming more prevalent in dental education. The overview that follows emphasizes AI's potential and current use in dentistry clinical practice. Artificial intelligence: What Is It? Artificial intelligence (AI), a subfield of computer science, aims to comprehend and create intelligent things, frequently in the form of software. It can be described as a series of actions intended to carry out a particular task. In the past, hand-written rules were used by artificially intelligent systems to complete the specific tasks they were designed to handle. Each task requires engineering, domain-specific knowledge, and manual system fine-tuning by subject-matter specialists. For instance, a system created to find lesions in medical imaging would search for lumps with an unusual color and a specific form. The system's fine-tuneable components might be a variety of colors for healthy tissue or the bare minimum lengths and widths of prospective lumps. Deep learning and machine learning are the fields of artificial intelligence that are currently most frequently applied in medicine.

What is artificial intelligence?

AI is a branch of computer science that aims to understand and build intelligent entities, often instantiated as software programs. It can be defined as a sequence of operations designed to perform a specific task. Historically, artificially intelligent systems applied hand-crafted rules to the specific tasks they were meant to solve. Each task required domain-specific knowledge, engineering, and manual fine-tuning of the system by subject-matter experts. For instance, a system designed to detect lesions in medical imaging might look for abnormally coloured lumps of a given shape. The fine-tunable parts of the system might be a range of healthy tissue colours or minimum lengths and widths for a potential lump. Nowadays, medicine most commonly uses a branch of AI called machine learning and, more recently, deep learning.

Machine learning (ML) is a branch of AI in which systems learn to perform intelligent tasks without a priori knowledge or hand-crafted rules. Instead, the systems identify patterns in examples from a large dataset, without human assistance. This is accomplished by defining an objective and optimizing the system’s tunable functions to reach it. In this process, known as training, an ML algorithm gains experience through exposure to random examples and gradual adjustments of the “tunables” toward the correct answer. As a result, the algorithm identifies patterns that it can then apply to new images. This technique is analogous to an adult showing several photos of cats to a child. The child eventually learns the patterns involved in recognizing a cat and identifying one in new images.

Deep learning (DL) is a sub-branch of ML wherein systems attempt to learn, not only a pattern, but also a hierarchy of composable patterns that build on each other. The combination and stacking of patterns create a “deep” system far more powerful than a plain, “shallow” one. For instance, a child does not recognize a cat in a single, indivisible step of pattern-matching; rather, the child first sees the edges of the object, a particular grouping of which defines a textured outline with simple shapes, such as eyes and ears. Among these components, larger groups such as heads and legs arise, and a particular grouping of these defines the whole cat. An extremely popular class of DL algorithms is the artificial neural network (ANN), a structure composed of many small communicating units called neurons organized in layers. A neural network is composed of an input layer, an output layer and hidden layers in between. It is possible to have 1 or a few hidden layers (shallow neural network) or multiple/many hidden layers (deep neural network, DNN). These layers are called hidden because their values are not pre-specified or visible to the outside. Their aim is to make it possible to build hierarchically on information retrieved from the visible input layer to compute the correct value of the visible output layer. The pattern of connections between neurons defines the particular neural network’s architecture, and the fine-tunable strengths of those connections are called the weights of the neural network. In medicine and dentistry, one of the most commonly used subclasses of ANN is the convolutional neural network (CNN). A CNN uses a special neuron connection architecture and the mathematical operation, convolution, to process digital signals such as sound, image, and video. CNNs use a sliding window to scan a small neighbourhood of inputs at a time, from left to right and top to bottom, to analyze a wider image or signal. They are extremely well adapted to the task of image classification and are the most-used algorithm for image recognition.

Artificial intelligence in dentistry

The field of dentistry has advanced significantly in recent years. Conventional dental care is being revolutionized thanks to new technological developments and diagnostic tools. One such development whose potential has just been realized is "artificial intelligence," a highly advanced system that can replicate the operation of the human brain. Artificial intelligence applications in dentistry could decrease costs, time, human expertise, and medical errors. Applications of AI in dental sciences include the management of head and neck illnesses, emergency dental care, differential diagnosis, imaging, and other dental specialties. While artificial intelligence by no means can replace the role of a dentist, it is of prime importance to be aware of the

possibilities to integrate this technology in the future. This can result in a rise in the standard of diagnosis and management of orofacial disorders.

Application of artificial intelligence in dentistry

- Regularizing appointments according to the convenience of the patients and dentists.
- Foreshadowing the patients and dentists about checkups whenever any genetic or lifestyle information indicates increased susceptibility to dental diseases.
- Managing the paperwork and insurance
- Supporting the clinical diagnosis and treatment planning
- Portending the dentist before every appointment about any allergies that the patient may have
- Making the dental healthcare provider vigilant about any relevant medical history
- Setting up regular reminders for patients who are on tobacco or smoking cessation programs.
- Providing emergency tele-assistance in cases of dental emergencies when the dental health care professional cannot be contacted.

Techniques of AI applied in oral medicine and radiology

- Artificial neural networks (ANN)
- Clinical Decision Support System (CDSS)
- Principal Component Analysis (PCA)
- Data Mining technique
- Fuzzy Logic
- Belief Merging
- Genetic Algorithms (GA)
- Probabilistic and General Regression Neural Network
- Dynamic Bayesian Networks
- Atlas based techniques

Artificial neural networks (ANN)

AI technology in the form of ANN has been widely applied in determining the level of cancerous activity that is aggressive, and it has remarkably assisted the development of original methods to anticipate the course of the disease

and prognosis, thereby offering prospective recommendations for treatment modalities. The design and operation of ANN closely resemble that of the brain. It is composed of perceptrons that functionally simulate the neurons. The basic concept in ANN is establishing a decision-making unit with interconnection of the perceptron units and this enables nonlinear analysis (Figure 1). There are two types of ANN. Among the most commonly utilized ANN formats are the multilayer perceptron (MLP). This represents a feed-forward network wherein a layer of input perceptrons connects to a number of hidden layers of perceptrons followed by an output layer. The MLP has been shown to be a well-grounded vehicle for exploring the predictive potential of biomarkers for oral cancer.

Clinical decision support system (CDSS)

CDSS are interactive computer programs, which are designed to help health professionals with decision-making tasks. The basic components of a CDSS include a dynamic knowledge base and an inferencing mechanism, implemented through medical logic modules based on a language such as Arden syntax (Fig 2). These systems use embedded clinical knowledge to analyze patient data and make decisions regarding diagnosis, prevention, and treatment of orofacial disorders. Additionally, CDSS may warn dentists about potentially hazardous conditions for a patient (drug allergies), or they may remind clinicians of routine tasks like more frequent screening for oral cancer in smokers, for periodontal disease in patients with diabetes, or even to use prophylactic antibiotics when necessary. The numerous applications, which can offer dentists more assistance, include patient education tools and radiography systems. This intelligent system has the potential to assist experts in making the final decision in the differential diagnosis of diseases when there are several viable alternatives as well as in multi-diagnosis when treating patients with multiple illnesses at the same time. It does this by ranking and weighting the relevant parameters. This system intelligently provides specialists with the necessary prognoses including the prediction of lesion's susceptibility to malignancy and proposes the necessary measures to the specialists. A clinical decision support system is used for the detection and diagnosis of oral cancer.

Principal component analysis (PCA)

The laser-induced fluorescence (LIF) spectroscopy and fluorescence imaging is a non-invasive diagnostic tool for differentiating normal and neoplastic oral tissues that involves illumination of tissue with monochromatic light and recording the fluorescence spectrum & utilize tissue fluorophores

(autofluorescence) or exogenous fluorophores and classification is made using both PCA and artificial neural network (ANN).

Advantages are

- Technique is fast,
- Uses cheap, portable equipment, and that can objectively evaluate in a community screening program
- Low-cost equipment like a LIF system can be acquired even by small clinics in rural areas.
- Examination with such equipment using certified calibration sets provided can reduce the chances of a pre-malignant/ malignant situation being missed

Data mining technique

The technique of finding patterns in huge data sets is computational. It takes data from a set and transforms it into a digestible structure for later usage. It is a component of the "knowledge discovery in databases" (KDD) method analysis stage. It includes the following processes: clustering, classification, regression, summarization, and association rule mining. Used to develop a novel approach to diagnosing and predicting the prognosis of oral cancer. The most straightforward algorithm for cancer diagnosis and prognosis is the genetic-based ID3 algorithm.

Fuzzy logic

Fuzzy logic is a superset of the conventional logic coined in 1965 and used in mathematics in the name of a “fuzzy” set. A fuzzy logic system (FLS) can be defined as the nonlinear mapping of an input data set to scalar output data. An important advantage that can stand alone in justifying the use of fuzzy logic in medicine is the ability of this machine algorithm to introduce into the process of decision linguistic terms, easier for human users to understand and communicate with. An FLS consists of four main parts: fuzzifier, rules, inference engine, and defuzzifier. Used for detection and diagnosis of oral cancer, prediction of oral cancer risk assessment, and diagnostic accuracy.

Belief merging

Belief merging looks at strategies for combining symbolic information, expressed in propositional logic, coming from different sources. Every source is coded as a set of propositional formulae and known as a belief base, where the group of belief bases in conjunction may be inconsistent; the strategies aim at obtaining a consistent belief base representing the group. In particular,

explains in detail the works on belief merging of propositional bases and logic-based merging with relevant strategies known as merging operators. Used in diagnosis of oral cancer.

Probabilistic and general regression neural network (PNN/GRNN)

(PNN/GRNN) models are helpful for the following decisions: To diagnose patients with malignancy and the type of malignancy based on demographic information, clinical symptoms, medical and personal history, and gross examination. To predict the stage and extent of oral cancer based on symptoms that are confirmed with the help of relevant tests and investigations. To predict the survivability of patients after appropriate treatments and follow-ups.

Artificial intelligence in the IMRT planning process dose prediction prior knowledge of the volumetric dose of a prospective patient undergoing radiotherapy would have a substantial impact on clinical workflows involved in IMRT treatment planning since it would provide dosimetric expectations which could be used to help identify outliers and planning cutoff criteria. Three main types of volumetric dose prediction techniques are:

1. **Atlas-based**

Atlas-based dosimetry relies on three sub-steps: the reduction of a set of imaging and contouring data into a subset of descriptive data points, the machine learning algorithm that relates the subset of descriptive data points to a corresponding patient, and a deformable image registration algorithm that warps a past dose volume to a novel patient geometry.

2. **Fully connected neural networks**

One alternative to atlas-based methods is to directly predict dose by learning a set of hierarchical features using artificial neural networks,

3. **Convolutional neural networks**

CNN-based architectures have been used to as an alternative to fully connected ANNs to predict volumetric information. While CNN-based dose prediction methods are still in the developmental stage, they tend to prevail in industry, and thus it is likely that these methods will also soon become common in volumetric dose prediction for head and neck IMR.

Planning support

IMRT planning is a lengthy process involving many iterations between the dosimetrist, physician, and treatment planning system.

1. Dosimetrist mimicking: An auxiliary program that mimics the treatment planning actions of a dosimetrist during the construction of an IMRT plan for a novel head and neck cancer patient.
2. Treatment planning system hyper-parameter optimization: Utilize hyper-parameter tuning algorithms to reduce the clinical burden of the treatment planning process through automation.
3. Normal tissue complication prediction: Mucositis is a common acute toxicity following IMRT. Using a random forest-based classifier, machine learning can accurately predict the probability of onset of mucositis from dose volume, spatial dose metrics, and clinical data in patients undergoing IMRT.

Genetic programming

By searching a population of candidate programs for a highly suited individual program, GP reinterpreted how existing machine learning algorithms solve problems. Numerous terminals and functions that are pertinent to the problem domain are present in this search area. Finding the program's fittest participants is how GP works. The Darwinian idea of survival and reproduction of the fittest, along with genetic operations throughout the process of evolution, notably mutation and crossover, are used by GP to produce populations of hundreds or thousands of computer programs. As a result, GP generally finds solutions to the issues that natural selection and genetic operations present. Used to determine the outlook for oral cancer.

Dynamic Bayesian networks

The dynamic Bayesian networks take into consideration time-series gene expression data collected at the follow-up study of patients that had or had not suffered a disease relapse. Based on that knowledge, to infer the corresponding dynamic Bayesian networks and subsequently conjecture about the causal relationships among genes within the same time slice and between consecutive time slices. This program aims to:

- Assess the prognosis of patients regarding oral cancer recurrence
- Provide important information about the underlying biological processes of the disease.

Artificial intelligence in oral radiology

The ability of CNNs to recognize and detect anatomical features has shown promise. As an illustration, some people have received training to recognize and classify teeth from periapical radiographs. In the detection and

identification of teeth, CNNs have shown a precision rate of 95.8-99.45%, closely matching the performance of clinical specialists, whose precision rate was 99.98%. CNNs have additionally been employed in the identification and treatment of dental cavities. Clinical diagnosis using radiographs alone, with sensitivity ranging from 19% to 94%, is significantly improved by this. Deep CNNs are one of the most effective methods employed in this field because of their speed and enormous potential for improving the sensitivity of dental caries diagnosis.

Applications of AI in oral radiology

- Interpretation of radiographic lesions and automated interpretation of dental radiographs
- Using the radiologist's work as data, AI may enable programs to identify details of individual radiologists' practice patterns and categorize them to create a sophisticated radiology report card.
- Caries detection: Logicon Caries Detector™ program is designed to assist dentists in the detection and characterization of proximal caries.
- Diagnosis of vertical root fractures on CBCT images of endodontically treated and intact teeth.
- To stage tooth development.
- Computer-based digital subtraction imaging.
- Computer-assisted image analysis is useful to visualize and evaluate the bone architecture directly from the dental panoramic radiograph.
- 3-dimensional orthodontics visualization using patient models and OPGs.
- Bone density evaluation to predict osteoporosis using OPGs.
- Automatic segmentation of mandibular canal.
- Forensic dental imaging: Personal Identification System Using Dental Panoramic Radiograph based on Metaheuristic Algorithm.
- Dental biometrics

Applications of AI orthodontics

ANNs offer a great deal of promise to support clinical decision-making. To provide patients with consistent results throughout orthodontic treatments, it is crucial to meticulously schedule treatments. The inclusion of tooth extractions in the orthodontic treatment plan is typical, nevertheless. Before beginning any irreversible operations, it is crucial to make the best clinical

decision possible. In individuals with malocclusion, an ANN was utilized to help identify whether tooth extraction was necessary before to orthodontic treatment. The four built ANNs demonstrated an accuracy of 80-93% in detecting whether extractions were required to treat patients' malocclusions while taking into account a number of clinical indices.

Applications of AI periodontics

According to the 1999 American Academy of Periodontology classification of periodontal disease, two clinical types of periodontitis are recognized: aggressive (AgP) and chronic (CP) forms. Because of the complex pathogenesis of the disease, no single clinical, microbiological, histopathological or genetic test or combination of them can discriminate AgP from CP patients. The ANN was 90–98% accurate in classifying patients as AgP or CP. The best overall prediction was made by an ANN that included monocyte, eosinophil, neutrophil counts and CD4+/CD8+ T-cell ratio as inputs. Various non-surgical and surgical methods have been devised for the treatment of periodontally compromised teeth (PCT) and supporting structures.

Despite improvements in therapeutic options, the process for detecting PCT and determining its prognosis has not much improved. The accuracy of clinical diagnostic and prognostic assessments is strongly dependent on empirical data. The accuracy of PCT diagnosis using the CNN algorithm was found to be 76.7-81.0%, while the accuracy of predicting the requirement for extraction was 73.4-82.8%. Premolars were more reliably identified as PCTs than molars in the study, which revealed a variation in accuracy across different tooth kinds. Premolars typically have a single root, whereas molars typically have two or three roots, making the anatomy of molars more complex and difficult for a CNN to read.

Applications of AI endodontics

Although mandibular molars tend to have similar root canal configurations, several atypical variations may occur. To minimize treatment failures related to morphological differences and to optimize the clinical outcomes of endodontic therapy, cone-beam computed tomography (CBCT) has become the gold standard. However, because of its higher dose of radiation compared with conventional radiographs, CBCT is not used systematically. To overcome such challenges, AI has been introduced to classify the given data using a CNN22 to determine whether the distal root of the first mandibular molar has one or more extra canals. Although the CNN had a relatively high accuracy of 86.9%, 20 several limitations exist regarding its clinical integration. The images must be segmented manually, which consumes a

considerable amount of time. Furthermore, the obtained images must be of adequate size and should focus on a small region to allow the system to concentrate on the object being studied while covering enough area to include pertinent information.

Applications of AI oral pathology

Because early detection often improves prognosis, oral lesion detection and diagnosis are vital in dentistry practises. It is crucial to obtain an accurate diagnosis and give the patient the proper therapy because some oral lesions might be malignant or precancerous in nature. In the process of diagnosing head and neck cancer lesions, CNN has proven to be a helpful tool. In contrast to specialists, who had specificity and accuracy of 83.2% and 82.9%, respectively, CNN exhibits excellent potential for identifying tumoral tissues in tissue samples or on radiographs, with values of 78-81.8% and 80-83.3%, respectively. One study used a CNN algorithm to distinguish between two important maxillary tumors with similar radiologic appearance but different clinical properties: ameloblastomas and keratocystic odontogenic tumours. The specificity and the accuracy of diagnosis by the algorithm were 81.8% and 83.3%, respectively, compared with those of clinical specialists at 81.1% and 83.2%. However, a more significant difference can be achieved in terms of diagnostic time: with the help of technology, specialists take an average of 23.1 minutes to reach a diagnosis, while CNN achieved similar results in 38 seconds.

Future perspectives

Radiological imaging has always been a crucial component of medical and dental care, from the early years of X-ray imaging in the 1890s to more recent developments in CT, MRI, and PET scanning. The quality, sensitivity, and resolution improvements in imaging systems now make it possible to distinguish very tiny variations in tissue densities. Even with trained eyes and some conventional AI techniques used in the clinic, these changes can occasionally be challenging to spot. Thus, these approaches fall short of imaging instruments' level of sophistication, but they nonetheless provide another reason to pursue this paradigm change toward stronger AI tools. Furthermore, we discover that deep learning algorithms scale with data, meaning that as more data are collected every day and with continuous research efforts, we expect to observe relative improvements in performance. This is in contrast to traditional methods based on predetermined features. All of these developments guarantee greater accuracy and fewer time- and energy-consuming repetitive chores.

Aligning research methodologies is crucial in accurately assessing the impact of AI on patient outcomes. In addition to the undeniable importance of reproducibility and generalizability, utilizing agreed-upon benchmarking data sets, performance metrics, standard imaging protocols, and reporting formats will level the experimentation field and enable unbiased indicators. It's also critical to remember that AI differs from human intelligence in many ways, and success in one activity does not always translate into success in others. Therefore, it is important to avoid overstating the potential of emerging AI techniques. The majority of cutting-edge developments in AI fall into the narrow AI category, where AI is taught for a single task and a single task only, with very few surpassing human intelligence. Despite the fact that such advancements are excellent at the bottom-up interpretation of sensory-perceptual input, they lack top-down, higher-level context knowledge and are unable to form associations in the same manner that a human brain does. It is clear that the sector is still developing and that instead of being overly excited about it, people should use reason and make thoughtful plans. It is also clear that radiologists won't be replaced by AI any time soon or even in the far future. As radiologists grow more technologically savvy and have access to better tools, their jobs will expand. As they contribute knowledge and monitor effectiveness, they are also expected to become important components of the AI training process. We anticipate that as AI develops and outperforms humans in various domains, it will become an important tool for education. In addition to monitoring results, human operators will attempt to understand their justification in order to validate them and possibly unearth previously unknown facts.

We discover that the most well-liked deep learning software platforms accessible today are open-source, in contrast to typical AI techniques locked within private commercial packages. This has encouraged innovation on an enormous scale and still does. AI initiatives are anticipated to switch from using processed medical pictures to using raw acquisition data in terms of data. Almost seldom are raw data down-sampled and optimized for viewers. When studies are performed by computers, this information loss and simplification can be avoided, but there are drawbacks such as impaired human validation and diminished interpretability. More signal is accessible for training as more data are produced. More noise is present, though. We anticipate that as time goes on, it will get harder to separate signal from noise. We anticipate a significant move towards unsupervised learning approaches to properly utilize the enormous archives of unlabelled data due to challenges in data curation and tagging.

Conclusion

The use of AI in dentistry has been demonstrated in numerous research, although dental practitioners still cannot be fully replaced by these systems. Instead, the usage of AI should be seen as a supplementary tool to support specialists and dentists. To guarantee that humans maintain the ability to oversee treatment and make knowledgeable judgments in dentistry, it is imperative to ensure that AI is integrated in a safe and controlled manner. The majority of institutions are currently unprepared for the challenge of successfully integrating AI into dentistry, which will require training in both dental and continuing education. AI is also essential to augmented reality (AR) and virtual reality (VR). In order to improve learning and surgical planning, a novel concept known as mixed reality combines elements of generative AI, VR, and AR into computer-superimposed information overlays. A future for AI in the healthcare system cannot be discounted given that several AI systems for various dentistry specialties are being researched and have achieved good first results. AI systems have the potential to be a valuable resource for oral health professionals.

References

1. Yu KH, Beam AL, Kohane IS. Artificial intelligence in healthcare. Nat Biomed Eng. 2018;2(10):719-31.
2. Russell SJ, Norvig P. Artificial intelligence: A modern approach. 3rd ed. Hoboken, N.J.: Prentice Hall, 2010.
3. Nielsen MA. Neural networks and deep learning. Determination Press; 2015. Available: http://neuralnetworksanddeeplearning.com/ (accessed 2021 April 16)
4. Zhang K, Wu J, Chen H, Lyu P. An effective teeth recognition method using label tree with cascade network structure. Comput Med Imaging Graph. 2018;68:61-70.
5. Tuzoff DV, Tuzova LN, Bornstein MM, Krasnov AS, Kharchenko MA, Nikolenko SI *et al*. Tooth detection and numbering in panoramic radiographs using convolutional neural networks. Dentomaxillofac Radiol. 2019;48(4):20180051.
6. Lee JH, Kim DH, Jeong SN, Choi SH. Detection and diagnosis of dental caries using a deep learning-based convolutional neural network algorithm. J Dent. 2018;77:106-11.

7. Bader JD, Shugars DA, Bonito AJ. Systematic reviews of selected dental caries diagnostic and management methods. J Dent Educ. 2001;65(10):960-8.

8. Xie X, Wang L, Wang A. Artificial neural network modelling for deciding if extractions are necessary prior to orthodontic treatment. Angle Orthod. 2010;80(2):262-6.

9. Jung SK, Kim TW. New approach for the diagnosis of extractions with neural network machine learning. Am J Orthod Dentofacial Orthop. 2016;149(1):127-33.

10. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol. 1999;4(1):1-6.

11. Armitage GC. Learned and unlearned concepts in periodontal diagnostics: a 50-year perspective. Periodontol 2000. 2013;62(1):20-36.

12. Papantonopoulos G, Takahashi K, Bountis T, Loos BG. Artificial neural networks for the diagnosis of aggressive periodontitis trained by immunologic parameters. PLoS One. 2014;9(3):e89757.

13. Papantonopoulos G, Takahashi K, Bountis T, Loos BG. Mathematical modeling suggests periodontitis behaves as a non-linear chaotic dynamical process. J Periodontol. 2013;84(10):e29-39.

14. Lee JH, Kim DH, Jegon SN, Choi SH. Diagnosis and prediction of periodontally compromised teeth using a deep learning-based convolutional neural network algorithm. J Periodontal Implant Sci. 2018;48(2):114-23.

15. Hiraiwa T, Ariji Y, Fukuda M, Kise Y, Nakata K, Katsumata A *et al*. A deep-learning artificial intelligence system for assessment of root morphology of the mandibular first molar on panoramic radiography. Dentomaxillofac Radiol. 2019;48(3):20180218.

16. Zhang X, Xiong S, Ma Y, Han T, Chen X, Wan F *et al*. A cone-beam computed tomographic study on mandibular first molars in a Chinese subpopulation. PLoS One. 2015;10(8):e0134919.

17. Xue Y, Zhang R, Deng Y, Chen K, Jiang T. A preliminary examination of the diagnostic value of deep learning in hip osteoarthritis. PLoS One. 2017;12(6):e0178992.

18. Wang X, Yang W, Weinreb J, Han J, Li Q, Kong X *et al*. Searching for prostate cancer by fully automated magnetic resonance imaging classification: deep learning versus non-deep learning. Sci Rep. 2017;7(1):15415.

19. Trebeschi S, van Griethuysen JJM, Lambregts DMJ, Lahaye MJ, Parmar C, Bakers FCH *et al*. Deep learning for fully-automated localization and segmentation of rectal cancer on multiparametric MR. Sci Rep. 2017;7(1):5301.

20. Halicek M, Lu G, Little JV, Wang X, Patel M, Griffith CC *et al*. Deep convolutional neural networks for classifying head and neck cancer using hyperspectral imaging. J Biomed Opt. 2017;22(6):60503.

21. Poedjiastoeti W, Suebnukarn S. Application of convolutional neural network in the diagnosis of jaw tumors. Healthc Inform Res. 2018;24(3):236-41.

22. Char DS, Shah NH, Magnus D. Implementing machine learning in healthcare - addressing ethical challenges. N Eng J Med. 2018;378(11):981-3.

23. He J, Baxter SL, Xu J, Xu J, Zhou X, Zhang K *et al*. The practical implementation of artificial intelligence technologies in medicine. Nat Med. 2019;25(1):30-6.

24. Software as medical device (SaMD). Maryland: United States Food & Drug Administration; 2018. Available: https://www.fda.gov/ medical-devices/digital-health/software-medical-device-samd (accessed 2023 July 7).

25. Redman TC. If your data is bad, your machine learning tools are useless. Harv Bus Rev. 2018;2 April. Available: https://hbr.org/2018/04/if-your-data-is-bad-your-machine-learning-tools-are-useless (accessed 2023 July 7).

26. Ferro AS, Nicholson K, Koka S. Innovative trends in implant dentistry training and education: a narrative review. J Clin Med. 2019;8(10):1618.

27. Nguyen TT, DMD, Larrivée N, Lee A, Bilaniuk O, Durand R *et al*. Use of Artificial Intelligence in Dentistry: Current Clinical Trends and Research Advances. J Can Dent Assoc. 2021;87:l7

28. Sherbet GV, Woo WL, Dlay S. Application of artificial intelligence-based technology in cancer management: a commentary on the deployment of artificial neural networks. Anticancer Res. 2018;38:6607-13.

29. Khanna S. Artificial intelligence: contemporary applications and future compass. Int Dent J. 2010;60:269-72.

30. Sudha Kamath D, Krishnax. Mahato D. Optical pathology using oral tissue fluorescence spectra: classification by principal component

analysis and k-means nearest neighbour analysis. J. Biomed. Opt. 2007;12:014028.

31. Kesavaraj G, Sukumaran S. A study on classification techniques in data mining, 2013 Fourth International Conference on Computing, Communications and Networking Technologies (ICCCNT), Tiruchengode, 2013, 1-7.

32. Scrobotă I, Băciuț G, Filip AG, Todor B, Blaga F, Băciuț MF *et al*. Application of Fuzzy Logic in Oral Cancer Risk Assessment. Iran J Public Health. 2017;46:612-619.

33. Sameem Abdul Kareem *et al*. An application of belief merging for the diagnosis of oral cancer. Applied Soft Computing. 2017; 61:1105-1112.

34. Sharma N, Om H. Usage of Probabilistic and General Regression Neural Network for Early Detection and Prevention of Oral Cancer. Scientific World Journal. 2015; 2015:234191

35. Karadaghy O, Shnayder Y, Kakarala K, Brant J, Shew M. Machine learning to predict occult nodal metastasis in early oral squamous cell carcinoma. Oral Oncol. 2019;92:20-25.

36. The application of artificial intelligence in the IMRT planning process for head and neck cancer. V. Kearney. Oral Oncol. 2018;87:111-116.

37. Babier Aaron, Boutilier Justin, Sharpe Michael, Mcniven Andrea, Chan Timothy. Inverse optimization of objective function weights for treatment planning using clinical dose-volume histograms. Physics in Medicine and Biology. 2018;12:56-59.

38. Tan MS, Tan JW, Chang S, Yap HJ, Abdul Kareem S, Zain RB *et al*. A genetic programming approach to oral cancer prognosis. Peer J 2016;4:e2482.

39. Kourou K, Rigas G, Exarchos KP, Papaloukas C, Fotiadis DI. Prediction of oral cancer recurrence using dynamic Bayesian networks. 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Orlando, FL, 2016, 5275-5278.

40. Artificial Intelligence in Dento-Maxillofacial Radiology. Anisha Yaji. *et al*. Acta Scientific Dental Sciences. 2019;3(1):116-121.

41. Shiraishi S, Moore KL. Knowledge-based prediction of three-dimensional dose distributions for external beam radiotherapy Med Phys. 2016;43:378-387.

42. Shiraishi S, Tan J, Olsen LA, Moore KL. Knowledge based prediction of plan quality metrics in intracranial stereotactic radiosurgery Med Phys. 2015;42:908-917.

43. Suganya B, David MP. Artificial intelligence in oral medicine and radiology-heralding a new era. International Journal of Contemporary Medical Research. 2020;7(12):L7-L11.

44. Kolarkodi SH, Alotaibi KZ. Artificial Intelligence in Diagnosis of Oral Diseases: A Systematic Review. J Contemp Dent Pract. 2023;24(1):61-68.

45. Khanagar SB, Al-ehaideb A, Maganur PC. Developments, application and performance of artificial intelligence in dentistry-A systematic review. Journal of Dental Sciences. 2021;16(1):508-522. Doi: 10.1016/j.jds.2020.06.019.

46. Steyerberg EW. Validation of prediction models. In: Steyerberg EW (Ed). Clinical prediction models: A practical approach to development, validation and updating. New York: Springer, 2010, 299-310.

47. Litjens G, Kooi T, Bejnordi BE. A survey on deep learning in medical image analysis. Med. Image Anal. 2017;42:60-88. DOI: 10.1016/j.media.2017.07.005

Chapter - 4
Artificial Intelligence in Psychiatry: The Way Forward

Authors

Rajnish Raj
Professor and Head, Department of Psychiatry, Government Medical College and Rajindra Hospital, Patiala, Punjab, India

Bhavneesh Saini
Senior Resident, Department of Psychiatry, Government Medical College and Rajindra Hospital, Patiala, Punjab, India

Chapter - 4

Artificial Intelligence in Psychiatry: The Way Forward

Rajnish Raj and Bhavneesh Saini

Abstract

The emerging field of artificial intelligence (AI) and its potential applications in psychiatry are being explored. This article provides an overview of AI technologies and their integration into psychiatric practice and discusses various benefits, challenges, and ethical considerations for its use in diagnosing and treating mental disorders. Additionally, it examines AI-driven interventions, such as chatbots and virtual therapists, and their impact on patient outcomes. Finally, this article explores future directions and potential limitations of AI in psychiatry.

Keywords: Artificial intelligence, attention deficit hyperkinetic disorder, autism, cyber security, post-traumatic stress disorder

Introduction

Artificial Intelligence (AI) refers to the development and application of computer systems that can perform tasks requiring human intelligence. Being a multidisciplinary field, it combines principles and techniques from computer science, mathematics, cognitive science and other related disciplines [1]. AI systems are designed such that they simulate human cognitive abilities, such as reasoning, problem-solving, learning, emotion, motivation and understanding of language. Such systems have the power to analyze vast datasets, recognize patterns and make decisions [2]. AI has made significant advancements in various fields, and psychiatry is no exception. With the increasing prevalence of mental health disorders worldwide, there is a growing need for innovative approaches to diagnosis, treatment, and monitoring. AI offers promising solutions by leveraging machine learning algorithms, natural language processing, and other AI techniques to assist psychiatrists and mental health professionals in improving therapeutic outcomes [3]. This article highlights the current and future applications of AI in psychiatry, highlighting its benefits, challenges and ethical considerations.

Common AIs used in healthcare

Early developments: AI in psychiatry and medicine traces its roots back 1970s-80s with the early applications of expert systems and rule-based reasoning [4]. Researchers explored the potential of computer algorithms to replicate decision-making processes. These systems focused primarily on knowledge representation and rule-based inference, aiming to assist in diagnosis. Commonly used AIs are as follows [5-8].

a) **Chatbots and Virtual agents:** Designed to interact with individuals and provide support, these devices can engage in conversations, offer emotional support and provide psycho-education and guidance. They can be accessed through messaging platforms, websites or mobile applications making mental health easily accessible.

b) **Wearable devices:** Equipped with sensors, these devices monitor physiological and behavioral health indicators. Smartwatches or fitness trackers can track parameters like heart rate, sleep patterns, physical activity, and stress levels. AI algorithms then provide insights into an individual's well-being based on the analyzed data.

c) **Smartphone applications:** AI-powered applications for mental health have gained popularity, especially post Covid-19. These often combine features like self-assessment, mood tracking, cognitive training exercises, meditation and mindfulness exercises, and personalized recommendations based on user data.

d) **Speech and Language analysis systems:** These analyze speech and language patterns and aid in diagnosing health conditions. These systems analyze speech characteristics, tone, and semantic content to detect signs of depression, anxiety, schizophrenia, etc. They may be integrated into phone calls, video conferences, or voice recordings to provide real-time analysis.

e) **Virtual Reality (VR) systems:** VR-based AI devices offer immersive environments for therapeutic interventions in psychiatry. By simulating real-world scenarios, these are used for exposure therapy, to confront and manage phobias, post-traumatic stress disorder (PTSD) and other conditions. AI can enhance the realism and adaptability of VR environments, tailoring the experience as desired.

Fig 1: Applications of mobile phone AI in psychiatric disorders [8]

Understanding artificial intelligence

AI is being increasingly used to assist in various aspects of mental healthcare. How these systems actually work, is based on some basic algorithms and procedural working, which are briefed as follows [9-14]:-

- **Machine learning algorithms:** These are employed to analyze large datasets and identify patterns, correlations, and predictive models. These algorithms are trained on diverse data sources such as electronic health records, genomics and even social media data.
- **Natural Language Processing (NLP):** NLP techniques are used to analyze and understand text-based data, including patient narratives, clinical notes, and social media posts. NLP algorithms can extract valuable information from unstructured text, assisting in diagnosing mental disorders, identifying risk factors, and monitoring progress.

- **Computer vision:** Computer vision techniques are utilized in the analysis of neuroimaging data, such as magnetic resonance imaging (MRI), functional MRI (fMRI) scans, etc. They can automatically detect and analyze brain structures, abnormalities, facial recognition, ocular responses and functional connectivity patterns, aiding in the diagnosis and monitoring of mental health disorders like autism, schizophrenia and dementia.
- **Predictive modeling:** AI can build predictive models that help identify individuals at risk of developing mental health conditions or predict treatment responses. These models generate personalized predictions and recommendations.
- **Data Integration and Multimodal fusion:** AI systems in psychiatry often involve the integration and fusion of diverse resources. These combine imaging data (MRI, fMRI, etc.), electronic health records, genetic information, imaging data, and patient-reported outcomes to generate a comprehensive understanding of an individual's status.
- **Deep learning:** Deep learning, a subset of machine learning, utilizes artificial neural networks with multiple layers to analyze complex data and extract intricate features. These have shown promise in tasks such as emotion recognition, sentiment analysis of text, and prediction of treatment response.
- **Clinical decision support systems:** AI can provide decision support systems for clinicians, offering evidence-based treatment recommendations, medication selection guidance, and risk assessment tools.
- **Data Privacy and Security:** As AI algorithms rely on sensitive patient data, ensuring data privacy and security is of utmost importance. Techniques such as secure data encryption, de-identification, and anonymity are employed to protect patient confidentiality and comply with privacy regulations. The recently proposed AI bill by the European Union is one step closer to the privacy protection of clients.

Uses of AI in the field of mental health

I. AI-Assisted diagnosis

a. **Risk assessment:** AI algorithms and techniques as described above can help identify patterns and risk factors associated with various

mental health conditions. By integrating genetic, environmental, and clinical data, AI models can help predict the likelihood of developing specific disorders, such as suicidal behaviors, depression, schizophrenia, or bipolar disorder [15].

b. **Early detection:** Using machine learning, AI can detect early signs of mental illness. AI's access to social media, online forums, smartphone usage patterns, wearable device data and electronic health records helps identify individuals at risk [9, 10]. Project Bi Affect is one such AI-run algorithm-based system that predicts depressive and manic episodes in bipolar affective disorder patients by analyzing keyboard metadata like variability in typing dynamics, mistakes, pauses and frequency of use of the backspace key [16]. AI has been used to predict psychotic disorders like schizophrenia using speech samples. Eder *et al*. used AI to predict the risk of mental health issues during Covid-19 times using factors like physical exercise, attachment anxiety, etc. [17].

c. **Diagnostic Support and improved accuracy:** AI algorithms can assist psychiatrists in making accurate diagnoses by analyzing symptoms, medical history and investigation data. Deep learning models can compare individual cases to a vast database of psychiatric information, aiding in differential diagnoses and reducing diagnostic errors like confirming ADHD in adults and also for the classification of ADHD subtypes [18]. Digital phenotyping (screen time, keyboard activity, and app usage) can be useful in depicting an accurate picture of an individual's mental state through digital behavior, rather than relying on self-report data [19].

II. Treatment interventions

a. **Treatment recommendations:** Based on already existing datasets, AI can model a treatment set, give a choice of medication and even predict its response. By considering a wide range of factors, AI algorithms can suggest optimal medication choices, dosages, and therapy approaches tailored to individual patients [20].

b. **Virtual therapeutic agents:** As mentioned earlier, AI-powered virtual agents or chatbots can provide patients with accessible and continuous support. These can communicate with lone patients, offer coping strategies, and provide psychoeducation and even basic counselling. It can modify its own responses based on real-time conversation. Examples include VR-based exposure therapy in

PTSD [21], Avatar therapy in the treatment of schizophrenia [22], text-based conversational agents for psycho-education [5], and 'Woebot' for reducing problematic substance use [23].

c. **Suicide Prevention and Crisis intervention:** AI-based systems can analyze cloud-based, online and offline information to identify the risk of self-harm and suicide. By detecting warning signs in real-time and alerting healthcare professionals or crisis helplines, AI technologies can contribute to timely interventions and potentially save lives [15].

d. **Bridging the treatment gap:** AI has the potential to address the shortage of mental health professionals by providing scalable and accessible interventions. With AI-driven tools, individuals in remote areas or those who face barriers to seeking in-person care can receive mental health support and interventions, reducing the treatment gap and increasing access to care [19].

e. **Decision support for clinicians:** Virtual or augmented reality agents act as decision support tools for clinicians. Some can even identify patients whose data has been lost from clinics. By integrating AI algorithms into clinical workflows, clinicians can access evidence-based guidelines to inform decision-making, medication selection, and drug monitoring [13].

f. **Drug repurposing:** Ashburn and Thor proposed a computational-based drug prediction strategy to help identify potential new therapies for rare and complex diseases. Similar therapies may also be included in mental disorders too [24].

g. **Mental health in special age groups**

- **Children and adolescents:** KASPAR is a child-sized humanoid robot that functions as a re-enforcer, provoker, mediator, trainer, prompter and diagnostic information provider for children with autism spectrum disorders [25].
- **Elderly:** Companion bots, Animal-like robots like 'PARO' have been used to serve as health-care assistants and respond to speech and movement with dynamic dialog. These have been found useful in reducing agitation, stress, and loneliness and in improving mood or social connections [26].

III. Remote mental health monitoring

Wearable devices and smartphone applications can collect continuous data like heart rate, blood pressure, oxygen saturation, ECG patterns, sleep

patterns, physical activity, and social interactions. AI algorithms can analyze this data to provide real-time feedback to friends, family and clinicians, enabling proactive interventions [8].

IV. Cybertherapy/E-therapy

AI may assist the therapist or act like one via video call/ voice call/ text/ other means. Five features of such communication have been defined by Suler [27]:

a. **Synchronous/Asynchronous communication:** Therapist and client interact via a digital interface at the same (e.g., audio-video conferencing) or at different times (e.g. WhatsApp)

b. **Text/Sensory communication:** Text means short messaging service/ text-based social networking applications like WhatsApp. Sensory involves audio-video conferencing.

c. **Imaginary/Real communication:** The whole cyberspace is filled with fantasy-based communities, the most recent being 'Meta' by Facebook where people may interact with self-made 'Avatars' in a virtual space.

d. **Automated/Interpersonal communication:** Programs including Chatbots and ChatGPT 4 may enhance psychotherapeutic alliance via guiding clients or providing personalized material on the disorders they are suffering from.

e. **Invisible/Present communication:** AI may be made to have a face or a body and be projected onto the real world using Augmented Reality like advanced holograms to aid in acceptability by clients.

Ways to conceptualize cybertherapy

a) Incorporating AI into pre-existing psychotherapy sessions.

b) New therapies like Chat-therapy.

c) Single integrated 'Cybertherapy' with both therapist and AI-assisted models to provide personalized care.

One of the ongoing projects on cybertherapy which utilizes the above approaches is VEPSY (Telemedicine and Portable Virtual Environment in Clinical Psychology) [28].

Table 1: Common AI modalities available in psychiatry [29, 30].

AI type	Specific soft/hardware	Intervention
VR	VR- based headsets	ERP in specific phobias and OCD

		Cognitive stimulation for ADHD Cognitive rehabilitation in Dementia
Interactive Games	Exergames CBT-based games Biofeedback games	Improve attention/concentration MCI Healthy aging Depression ERP
Robots	RoboThespian Paro (Japan)	Companionship Social skill training like in Autism
Online self-guided therapy	Multiple online modes available	Psychotherapy Biofeedback
Web-based interventions	Chatbots ChatGPT Woebots	Screening for disorders Evaluation & Diagnosis Primordial and primary prevention

Ethical considerations & challenges [31, 32]

a) **Data Privacy and Security:** The use of AI in psychiatry requires handling sensitive patient data. Proper measures must be in place to ensure data privacy, confidentiality, and protection against breaches or misuse.

b) **Algorithm Bias and Fairness:** Care must be taken to address potential biases in AI algorithms, ensuring fair and equitable outcomes across different populations and cultural contexts. Regular monitoring and auditing of AI systems can help identify and mitigate biases.

c) **Human-AI collaboration:** AI tools should be viewed as aids to enhance clinical decision-making rather than replace human psychiatrists. Maintaining a balance between the expertise of mental health professionals and the capabilities of AI is crucial to achieve optimal results.

d) **Forensic cyber-psychiatry:** Harmful usage of AI in psychiatry needs handling. Since the digitalization of the country, propelled even faster by restrictions induced by COVID-19, cybercrimes and misinformation are on the rise. Criminal use of AI in trolling, cyberbullying, cyberstalking, AI pornography, AI-produced novel designer drugs of abuse, etc., needs to be given attention and proper policies be framed. Unlike the European Union's AI Act, India lacks a 'data protection legislation specific to AI and relies on the IT Act 2000 and Rules 2021. A draft of Digital Personal Data Protection Bill 2022 however, has been proposed which will need the inclusion of the requisite measures.

Limitations [33-35]

1. **Human surveillance:** AI requires human input and review to be leveraged effectively. AI-based robots operate logically and lack empathy. Healthcare staff may notice necessary behavioral observations that can help diagnose or prevent missing out on several important details.
2. **Cultural factors:** Patient needs often extend beyond acute physical or mental conditions. AI systems may not be able to account for cultural factors and nuances that play an inevitable part in particular patients. Privacy also becomes an issue.
3. **Security risks:** Since AI is dependent on data networks; they are highly susceptible to security risks, including offensive content including racism and sexism. To sustain such technology, improved cyber security is required.
4. **Unemployment:** AI may help reduce costs and clinician burden, however, it also renders many jobs redundant and useless. A recent World Economic Forum report projected that AI may create up to 58 million jobs. However, about 75 million jobs may also be displaced. Heavy integration of AI across sectors will eliminate the need for repetitive human tasks, a major reason for displacement. Even if AI promises to improve healthcare and medicine, it is vital to consider the social, economic and humanitarian ramifications.
5. **Inaccuracies:** AI in medical services depends heavily on data available from the records and diagnoses of millions of persons. This creates a possibility that in cases with less data in terms of demographics, etiology, environmental risk factors, etc., a misdiagnosis is highly probable. AI needs to constantly evolve and improve upon the gaps in data. Also, specific populations, ethnicities and cultures may be excluded from the existing knowledge database while prescribing AI-based diagnosis and treatment.
6. **Methodological flaws in AI studies:** Research presented to us in journals has quality and methodological flaws inbuilt. Hence, it is important to take AI-based breakthroughs in psychiatric practice with a pinch of salt and devise responsible guidelines for use.
7. **Increased workload:** An article published in the New York Times in 2018 warned how technology and AI systems incorporated into healthcare may turn clinicians into clerical workers. It cited the

decrease of genuine human emotions towards patients, rather than relying heavily on electronic records and up-loadable paperwork, to maintain which one has to deprive oneself of emotions rather than turn into a desk clerk. Due to this, an increase in physician burnout while processing add-on information provided by the very AI designed to reduce burden.

8. **Special situations:** Patients expressing suicidal or homicidal ideas may require immediate human intervention, rather than the yet non-reaching AI interventions.
9. **Lack of 'human' touch:** Inability of AI to fully replicate the human empathic connection crucial to therapeutic relations.

Future of artificial intelligence [36]

a. **Artificial wisdom:** Current functioning of AI is limited, although advancements and broader applications are expected. It is not merely the 'intelligence' part that best caters to the technological needs of our society, but 'wisdom'. In this context, artificial wisdom is the need of the future. Its components should include one or more of the following:-

   - Pro-social behaviors like empathy and kindness.
   - Self-reflection as in re-assessment of diagnoses, or acknowledgment of previous errors.
   - Enthusiastic control, especially in situations like imminent suicide.
   - Patient perspective-taking.
   - Definitiveness in diagnosis and treatment.
   - Social prompting.

b. **Affective computing:** Analyzing facial expressions, voice tone, and physiological signals to assess an individual's emotional state. Integrating affective computing with AI algorithms will provide nuanced and personalized mental health interventions.

Conclusion

Artificial intelligence has the potential to revolutionize the field of psychiatry, offering valuable support in the diagnosis, treatment and monitoring of mental health disorders. While AI-based approaches hold significant promise, careful attention must be paid to ethical considerations and potential challenges. Collaborative efforts between mental health

professionals, researchers, and AI developers will be essential to harness its full potential, ultimately transforming patient care and outcomes in the field of mental health.

References

1. Amisha, Malik P, Pathania M, Rathaur VK. Overview of artificial intelligence in medicine. J Family Med Prim Care. 2019;8(7):2328-31. Doi: 10.4103/jfmpc.jfmpc_440_19. PMID: 31463251; PMCID: PMC6691444.
2. Bohr A, Memarzadeh K. The rise of artificial intelligence in healthcare applications. Artif Intell Healthcare, 2020, 25-60. Doi: 10.1016/B978-0-12-818438-7.00002-2. Epub 2020 Jun 26. PMCID: PMC7325854.
3. Davenport T, Kalakota R. The potential for artificial intelligence in healthcare. Future Healthc J. 2019;6(2):94-8. Doi: 10.7861/futurehosp.6-2-94. PMID: 31363513; PMCID: PMC6616181.
4. Kaul V, Enslin S, Gross SA. History of artificial intelligence in medicine. Gastrointest Endosc. 2020;92(4):807-12. Doi: 10.1016/j.gie.2020.06.040
5. Vaidyam AN, Wisniewski H, Halamka JD, Kashavan MS, Torous JB. Chatbots and Conversational Agents in Mental Health: A Review of the Psychiatric Landscape. Can J Psychiatry. 2019;64(7):456-64. Doi: 10.1177/0706743719828977
6. Servan-Schreiber D. Artificial intelligence and schizophrenic speech analysis. J Nerv Ment Dis. 1994;182(4):220-1. https://pubmed.ncbi.nlm.nih.gov/10678319/
7. Kim S, Kim E. The Use of Virtual Reality in Psychiatry: A Review. Soa Chongsonyon Chongsin Uihak. 2020;31(1):26-32. Doi: 10.5765/jkacap.190037. PMID: 32612410; PMCID: PMC7324842.
8. Boonstra TW, Nicholas J, Wong QJ, Shaw F, Townsend S, Christensen H. Using Mobile Phone Sensor Technology for Mental Health Research: Integrated Analysis to Identify Hidden Challenges and Potential Solutions. J Med Internet Res. 2018;20(7):e10-131. Doi: 10.2196/10131
9. Squires M, Tao X, Elangovan S, Gururajan R, Zhou X, Acharya UR, *et al*. Deep learning and machine learning in psychiatry: a survey of current progress in depression detection, diagnosis and treatment. Brain Inform. 2023;10(1):10. Doi: 10.1186/s40708-023-00188-6. PMID: 37093301; PMCID: PMC10123592.

10. Jiang Z, Luskus M, Seyedi S, Griner EL, Rad AB, Clifford GD, *et al*. Utilizing computer vision for facial behavior analysis in schizophrenia studies: A systematic review. PLoS One. 2022;17(4):e0266828. doi:10.1371/journal.pone.0266828

11. Hashemi J, Tepper M, Vallin Spina T, Esler A, Morellas V, Papanikolopoulos N, *et al*. Computer vision tools for low-cost and non-invasive measurement of autism-related behaviors in infants. Autism Res Treat., 2014, 935-686. Doi: 10.1155/2014/935686

12. Jacobs GR, Voineskos AN, Hawco C, Stefanik L, Forde NJ, Dickie EW, *et al*. Integration of brain and behavior measures for identification of data-driven groups cutting across children with ASD, ADHD, or OCD. Neuropsychopharmacology. 2021;46(3):643-53. Doi: 10.1038/s41386-020-00902-6

13. Tutun S, Johnson ME, Ahmed A, Albizri A, Irgil S, Yesilkaya I, *et al*. An AI-based Decision Support System for Predicting Mental Health Disorders. Inf. Syst. Front. 2023;25(3):1261-76. Doi: 10.1007/s10796-022-10282-5

14. Meszaros J, Minari J, Huys I. The future regulation of artificial intelligence systems in healthcare services and medical research in the European Union. Front Genet. 2022;13:927721. doi:10.3389/fgene.2022.927721

15. Khan NZ, Javed MA. Use of Artificial Intelligence-Based Strategies for Assessing Suicidal Behavior and Mental Illness: A Literature Review. Cureus. 2022;14(7):e27225. doi: 10.7759/cureus.27225. PMID: 36035036; PMCID: PMC9400551.

16. Zulueta J, Piscitello A, Rasic M, Easter R, Babu P, Langenecker SA, *et al*. Predicting Mood Disturbance Severity with Mobile Phone Keystroke Metadata: A BiAffect Digital Phenotyping Study. J Med Internet Res. 2018;20(7):e241. doi:10.2196/jmir.9775

17. Eder SJ, Steryl D, Stefanczyk MM, Pieniak M, Molina JM, Pesout O, *et al*. Predicting fear and perceived health during the COVID-19 pandemic using machine learning: A cross-national longitudinal study. PLoS ONE. 2021;16(3):e0247997. doi:10.1371/journal.pone.0247997

18. Tenev A, Markovska-Simoska S, Kocarev L, Pop-Jordanov J, Muller A, Candrian G. Machine learning approach for classification of ADHD adults. Int J Psychophysiol. 2014;93(1):162-6. doi:10.1016/j.ijpsycho.2013.01.008

19. Prakash J, Chaudhury S, Chatterjee K. Digital phenotyping in psychiatry: When mental health goes binary. Ind Psychiatry J. 2021;30(2):191-2. Doi: 10.4103/ipj.ipj_223_21.

20. Ceskova E, Silhan P. From Personalized Medicine to Precision Psychiatry? Neuropsychiatr Dis Treat. 2021;17:3663-8. Doi: 10.2147/NDT.S337814.

21. Heo S, Park JH. Effects of Virtual Reality-Based Graded Exposure Therapy on PTSD Symptoms: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2022;19(23):15911. doi:10.3390/ijerph192315911

22. Aali G, Kariotis T, Shokraneh F. Avatar Therapy for people with schizophrenia or related disorders. Cochrane Database Syst. Rev. 2020;5(5):CD01-1898. Doi: 10.1002/14651858.CD011898.pub2

23. Prochaska JJ, Vogel EA, Chieng A, Kendra M, Baiocchi M, Pajarito S, *et al*. A Therapeutic Relational Agent for Reducing Problematic Substance Use (Woebot): Development and Usability Study. J Med Internet Res. 2021;23(3):e24-850. doi:10.2196/24850

24. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov. 2004;3(8):673-83. Doi: 10.1038/nrd1468

25. Wood LJ, Zaraki A, Robins B, Dautenhahn K. Developing Kaspar: A Humanoid Robot for Children with Autism. Int J Soc Robot. 2021;13(3):491-508. Doi: 10.1007/s12369-019-00563-6

26. Yu R, Hui E, Lee J, Poon D, Ng A, Sit K, *et al*. Use of a therapeutic, socially assistive Pet Robot (PARO) in improving mood and stimulating social interaction and communication for people with dementia: study protocol for a randomized controlled trial. JMIR Res. Protoc. 2015;4(2):e45. Doi: 10.2196/resprot.4189

27. Suler JR. Psychotherapy in Cyberspace: A 5-dimensional model of online and computer-mediated psychotherapy. Cyberpsychol Behav. 2000;3(2):151-9. DOI: 10.1089/109493100315996

28. Riva G, Botella C, Castelnuovo G, Gaggioli A, Mantovani F, Molinari E. Cybertherapy in practice: the VEPSY updated project. Stud Health Technol. Inform. 2004;99:3-14. https://pubmed.ncbi.nlm.nih.gov/15295143/

29. AI-Therapy. Computers and Therapy [Internet]. 2023 [cited 2023 Jun 26]. Available from: https://www.ai-therapy.com/articles/computers-and-therapy/

30. Fleming TM, Bavin L, Stasiak K, Hermansson-Webb E, Merry SN, Cheek C, *et al*. Serious games and gamification for mental health: Current status and promising directions. Front Psychiatry. 2017;7:215. Doi: 10.3389/fpsyt.2016.00215.

31. Gerke S, Minssen T, Cohen G. Ethical and legal challenges of artificial intelligence-driven healthcare. Artificial Intelligence in Healthcare, 2020, 295-336. Doi: 10.1016/B978-0-12-818438-7.00012-5.

32. Bhave S, Gawande S, editors. Cyberpsychiatry. New Delhi (IN): Jaypee Publications; 2023, 226.

33. Montemayor C, Halpern J, Fairweather A. In principle obstacles for empathic AI: why we can't replace human empathy in healthcare. AI Soc. 2022;37(4):1353-9. Doi: 10.1007/s00146-021-01230-z

34. World Economic Forum. The future of jobs report 2018. Geneva (SZ): WEF; c2018.

35. Verghese A. How technologies can turn doctors into clerical workers. NY Times; c2023.

36. Jeste DV, Graham SA, Nguyen TT, Depp CA, Lee EE, Kim HC. Beyond artificial intelligence: exploring artificial wisdom. Int. Psychogeriatr. 2020;32(8):993-1001. Doi: 10.1017/S1041610220000927

Chapter - 5
Drug Discovery and Drug Development with Artificial Intelligence

Authors

Dr. Narender Boggula
Associate Professor, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India

S. Raja Shekhar
Associate Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy, Chowdariguda, Ghatkesar, Medchal, Telangana, India

Marati Kavitha
Assistant Professor, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad, Telangana, India

Aravinda Nalla
Assistant Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy, Chowdariguda, Ghatkesar, Medchal, Telangana, India

Dr. G. Umarani
Associate Professor, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad, Telangana, India

Chapter - 5

Drug Discovery and Drug Development with Artificial Intelligence

Dr. Narender Boggula, S. Raja Shekhar, Marati Kavitha, Aravinda Nalla and Dr. G. Umarani

Abstract

As expenditure on drug development increases exponentially, the overall drug discovery process requires a sustainable revolution. Since artificial intelligence (AI) is leading the fourth industrial revolution, AI can be considered as a viable solution for unstable drug research and development. Generally, AI is applied to fields with sufficient data such as computer vision and natural language processing, but there are many efforts to revolutionize the existing drug discovery process by applying AI. Artificial intelligence (AI) is becoming more widely adopted in the pharmaceutical industry, creating both excitement and questions about its potential and long-term success. In recent years, a plethora of companies-ranging from large pharmaceuticals to startups – have set expectations of AI as a panacea that will revolutionize the industry. While the thought of AI as such is an appealing one, it is not realistic. This review provides a comprehensive, organized summary of the recent research trends in AI-guided drug discovery process including target identification, Hit identification, ADMET prediction, lead optimization, and drug repositioning. The main data sources in each field are also summarized in this review. In addition, an in-depth analysis of the remaining challenges and limitations will be provided, and proposals for promising future directions in each of the aforementioned areas. The increasing relevance of AI in drug discovery and development is reflected by the growing number of start-up companies specialized in this field, the growing number of collaborations from pharma with AI platforms, and the high number of articles and reviews reporting current applications, their success and limitations. In this chapter, we focused on the recent data-driven based research trends of the fields that are effectively cost reducible with AI. This review will address the stages of drug discovery and development in which the application of AI and ML modelling has altered the traditional development of drugs.

Keywords: Artificial intelligence, drug discovery, drug repositioning, machine learning, hit identification

Introduction

Six to seven % of global gross domestic product (8.5 to 9 trillion US$) is spent on healthcare annually and bringing a new medicine to market costs well over $1 billion and can take up to 14 years. Success in drug development (defined as phase I clinical trials to drug approval) is very low across all therapeutic categories worldwide with, for example, 97% of the cancer drugs failing during clinical trials. This makes investments risky and inflates the price of approved drugs to compensate for all the failures.

According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person". This new approach allows physicians and researchers to increase accuracy in predicting disease treatment and prevention strategies that will work for particular groups of people. This approach contrasts with the "one-size-fits-all" approach, more widely used until relatively recently, in which the strategies mentioned above are developed with the average person in mind, regardless of differences between individuals.

The opportunity for the creation of new treatments offered by precision medicine generates at the same time great difficulties in the development of new methodologies. For this reason, in recent years a large amount of biomedical data has been generated, coming from very diverse sources: from small individual laboratories to large international initiatives. These data, known mostly as omic data (genomic, proteomic, metabolomic, pharmacogenomic, etc.), are an inexhaustible source of information for the scientific community, which allows stratifying patients, obtaining specific diagnoses or generating new treatments.

Artificial Intelligence (AI) has recently started to gear-up its application in various sectors of the society with the pharmaceutical industry as a front-runner beneficiary. This review highlights the impactful use of AI in diverse areas of the pharmaceutical sectors *viz*., drug discovery and development, drug repurposing, improving pharmaceutical productivity, etc. to name a few, thus reducing the human workload as well as achieving targets in a short period. The stages in the discovery of new drugs were illustrated in the Figure 1.

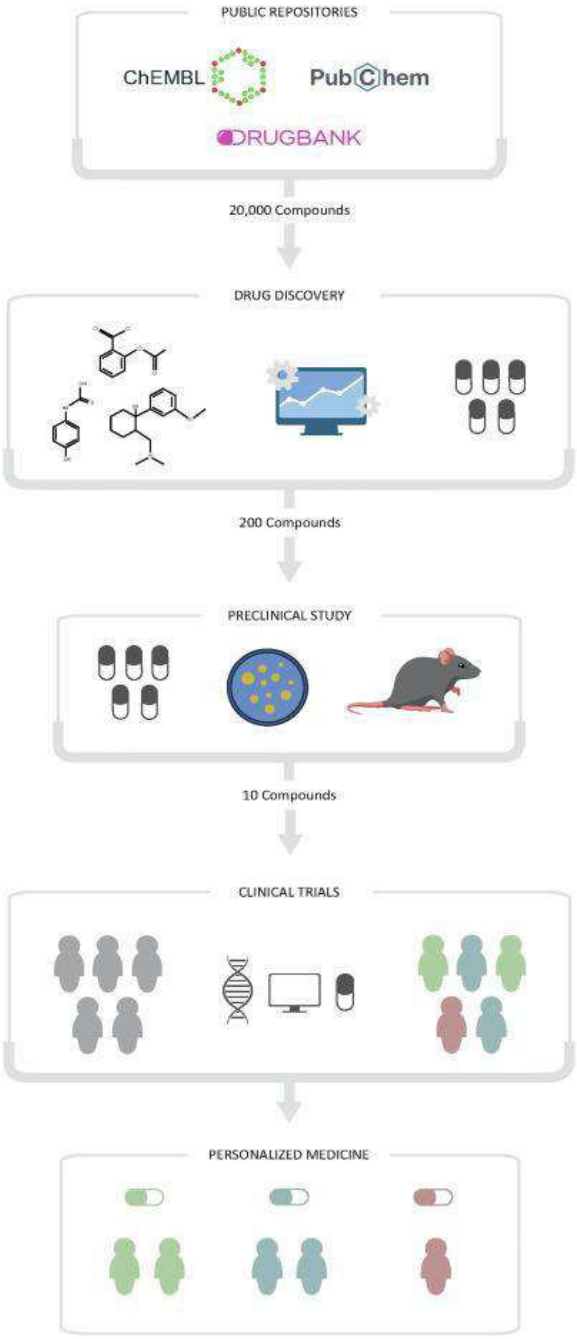


Fig 1: Stages in the discovery of new drugs in the context of precision medicine

A drug discovery pipeline will usually consist of several stages as given in the Figure 2. In target-based discovery, the first step is to identify novel targets, with evidence of association to disease, from a large space of proteins (an organism's proteome). Potentially interacting molecules are identified by high throughput screening of compound libraries against these targets. Compounds will be optimized for favourable drug properties, tested in pre-clinical and clinical trials, and given FDA approval in the ideal case. All stages of the drug discovery pipeline could benefit from AI, for example, generative models for the design of new synthetic molecules, reinforcement learning (RL) to optimize properties of molecules in a particular direction, GNNs to predict drug-disease associations, drug-repurposing, and the response to a drug. Natural language processing (NLP) could be used to find drugs by mining the scientific literature and to automate FDA approval steps.

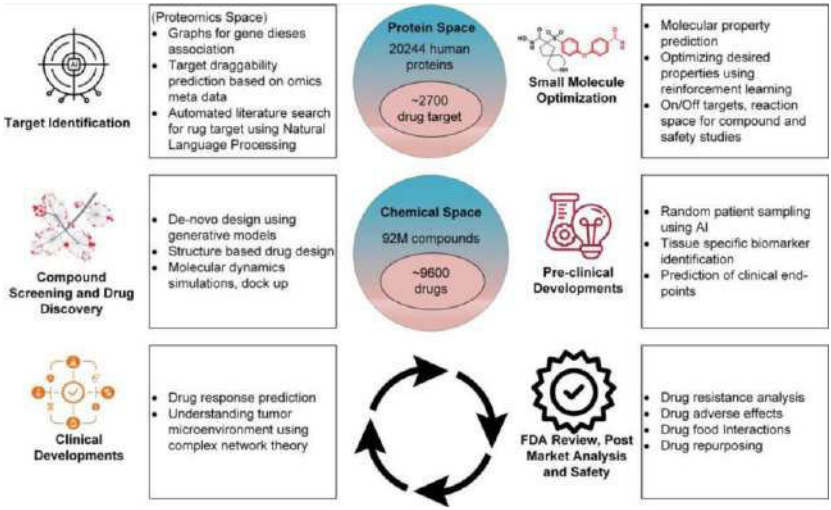


Fig 2: Applications of AI in drug discovery

Artificial Intelligence (AI) has emerged as a transformative force in various fields, and drug development is no exception. Over the years, the pharmaceutical industry has faced numerous challenges in discovering and developing new drugs, including high costs, lengthy timelines, and a high failure rate in clinical trials. AI has the potential to revolutionize drug development by significantly improving the efficiency, accuracy, and success rates of the process.

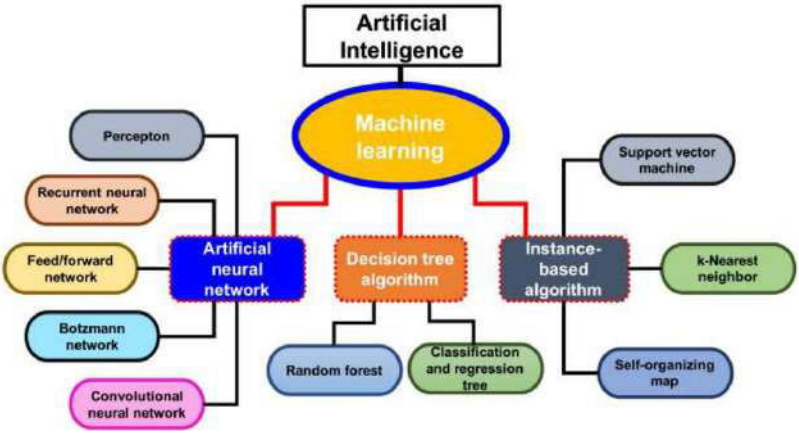


Fig 3: Method domains of AI in drug discovery

AI refers to the simulation of human intelligence in machines, enabling them to perform tasks that typically require human cognitive abilities. In drug development, AI leverages advanced algorithms, machine learning, and big data analytics to analyze vast amounts of biological, chemical, and clinical data. This approach allows researchers and scientists to gain valuable insights and make more informed decisions throughout the drug discovery and development pipeline.

Artificial Intelligence (AI) is revolutionizing the field of drug discovery, offering innovative solutions to the challenges faced by pharmaceutical researchers and scientists. Traditional drug discovery processes are time-consuming, expensive, and often result in a high rate of failure. AI-driven technologies have the potential to transform this landscape by accelerating the identification of potential drug candidates and streamlining the development process.

In drug discovery, AI leverages advanced algorithms, machine learning, and big data analysis to analyze vast amounts of biological, chemical, and clinical data. This enables researchers to uncover hidden patterns, relationships, and insights that may not be apparent through traditional methods. AI's ability to process and interpret complex data sets at an unprecedented scale and speed has the potential to significantly impact the efficiency and success rate of drug discovery.

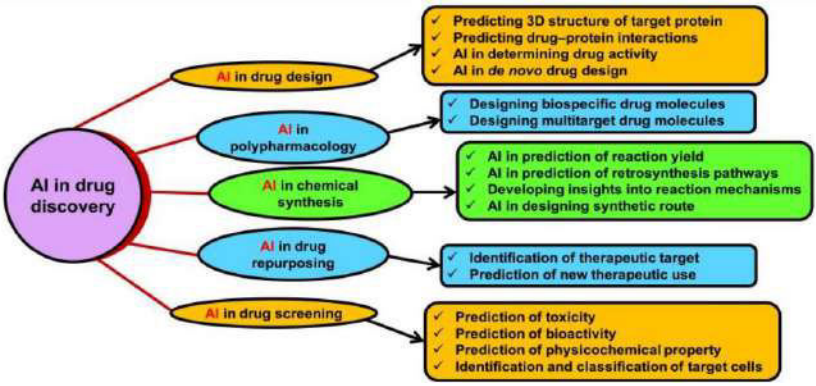


Fig 4: Role of AI in drug discovery

AI-networks and tools

AI involves several method domains, such as reasoning, knowledge representation, solution search, and, among them, a fundamental paradigm of machine learning (ML). ML uses algorithms that can recognize patterns within a set of data that has been further classified. A subfield of the ML is deep learning (DL), which engages artificial neural networks (ANNs). These comprise a set of interconnected sophisticated computing elements involving 'perceptons' analogous to human biological neurons, mimicking the transmission of electrical impulses in the human brain. ANNs constitute a set of nodes, each receiving a separate input, ultimately converting them to output, either singly or multi-linked using algorithms to solve problems. ANNs involve various types, including multilayer perceptron (MLP) networks, recurrent neural networks (RNNs), and convolutional neural networks (CNNs), which utilize either supervised or unsupervised training procedures.

Below Table 1 shows number of available compounds in each repository and its usability.

Table 1: Top public repositories with chemistry used in machine learning model training

Database	No. of compounds	Usability	Link
DrugBank	14K	Drug discovery	https://go.drugbank.com/
PubChem	110M	Computational chemistry	https://pubchem.ncbi.nlm.nih.gov/
ChEMBL	2.1M	Drug discovery	https://www.ebi.ac.uk/chembl/
ZINC	750M	Virtual screening	https://zinc.docking.org/

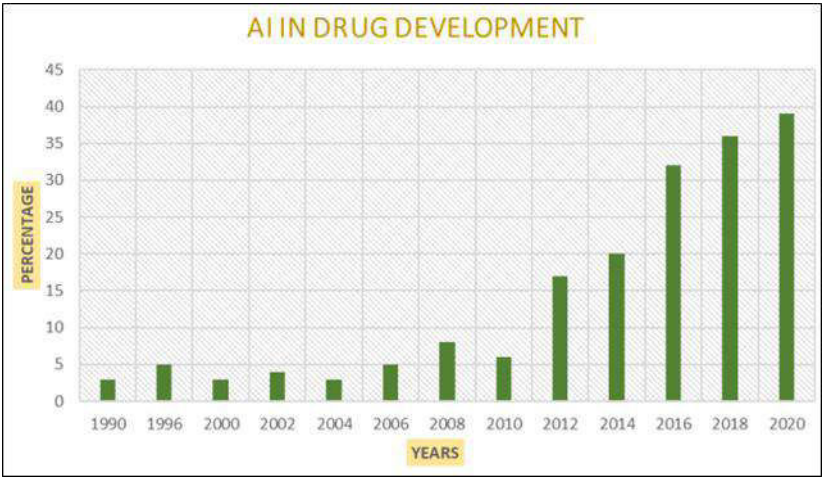


Fig 5: AI in drug development

AI and its potential for use in drug discovery

The use of artificial intelligence (AI) in medicinal chemistry has gained significant attention in recent years as a potential means of revolutionizing the pharmaceutical industry. Drug discovery, the process of identifying and developing new medications, is a complex and time-consuming endeavour that traditionally relies on labour-intensive techniques, such as trial-and-error experimentation and high-throughput screening. However, AI techniques such as machine learning (ML) and natural language processing offer the potential to accelerate and improve this process by enabling more efficient and accurate analysis of large amounts of data. The successful use of deep learning (DL) to predict the efficacy of drug compounds with high accuracy has been described recently.

AI-based methods have also been able to predict the toxicity of drug candidates. These and other research efforts have highlighted the capacity of AI to improve the efficiency and effectiveness of drug discovery processes. However, the use of AI in developing new bioactive compounds is not without challenges and limitations. Ethical considerations must be taken into account, and further research is needed to fully understand the advantages and limitations of AI in this area. Despite these challenges, AI is expected to significantly contribute to the development of new medications and therapies in the next few years.

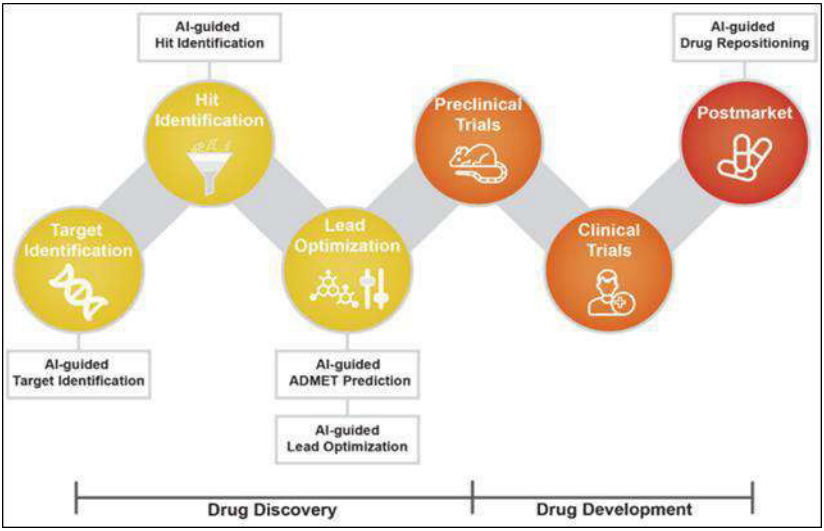


Fig 6: Overall process of drug discovery and development

AI guided hit identification

Identifying drug-target interactions is one of the crucial steps in preclinical drug discovery. Desired effects of the drugs depend on the interaction between the drug and selected target, while the possibility of side effects and drug repositioning can also come from interactions between proteins that are not targeted during drug development. However, it is difficult to search the entire chemical space of compounds for druggable target proteins by experiments, as approved drugs are very sparse. Fortunately, data of compounds, drugs, proteins, and their bioactivities accumulate fast, which enables data-driven computation models to identify hits from vast chemical space. Therefore, many computational models to identify drug-target interaction and estimate binding affinities have been developed to leverage the efficiency of the early stages in drug development, which also has the advantage of delivering novel drug candidates. There are three main categories of computational methods for hit identification, as shown in Figure 7; structure-based methods, ligand-based methods, and chemogenomic methods concentrating on protein structure, ligand structure, and their data, respectively.

AI guided ADMET prediction

One of the big challenges in drug discovery is optimizing pharmacokinetic properties such as absorption, distribution, metabolism, excretion, and toxicity (ADMET). Therefore, the early assessment of

compounds' ADMET properties is needed to guide the subsequent drug discovery steps efficiently. For decades, both pharmaceutical industries and academia have been attracted to in silico ADMET property prediction, because of the accumulation of bioactivity and property data and sophisticated machine learning methods. In this section, we focus on the recent trend of ADMET property prediction by introducing the various ADMET related properties and the characteristics of current studies. A concise summary of this section is shown in Figure 8.

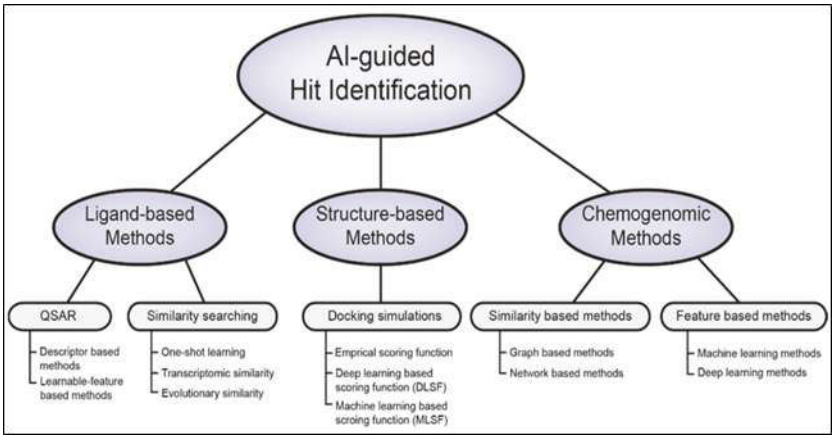


Fig 7: AI guided hit identification

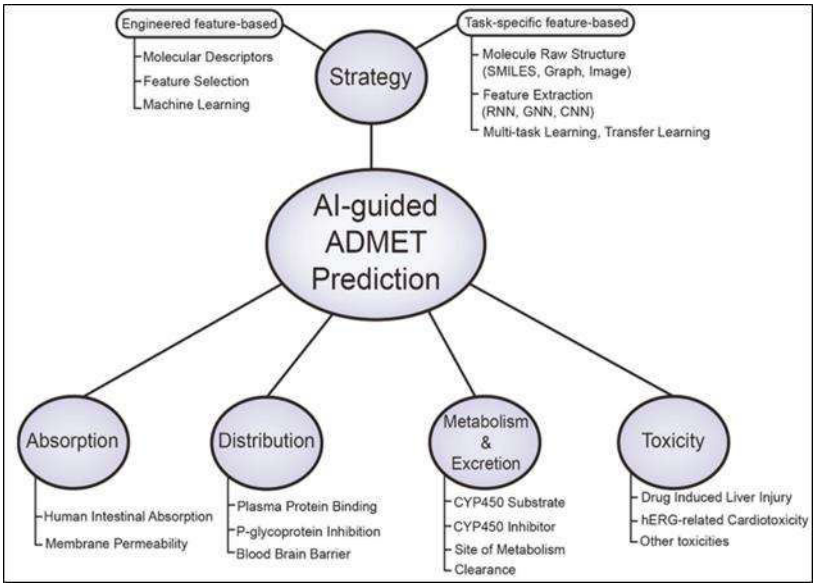


Fig 8: AI guided ADMET prediction

AI-guided lead optimization

Finding a molecule that has the desired pharmacological properties or has activity against biological targets can be described by the metaphor "finding a needle in a haystack". Specifically, researchers estimate the chemical space of synthesizable compounds to comprise approximately 1030-1060 possibilities, whereas the number of compounds registered in Chemical Abstracts Service has only reached about 160 million to date. Fully enumerating this vast space will require too much resource and computing power. Thus, computer-aided de novo drug design has been an active research area for the past 10 to 20 years.

The demand for in silico technologies or AI applications in pharmaceutical development research has increased and will continue to do so, due to a need for accurate prediction of pharmacokinetics/ADMET (Absorption, Distribution, Metabolism and Toxicity, as shown in Figure 8) of hit compounds, as pharmacokinetics as well as toxicity need to be assessed to prevent the failure of candidate drug in a later stage of drug development. The pharmacokinetics of a molecule can be predicted and modelled in relation to the target protein's 3-D structure, through various methods like molecule docking, dynamics simulation, quantum mechanisms as well as PBPK (Quantitative-activity relationship and physiologically based pharmacokinetic) modelling.

AI-guided drug repositioning

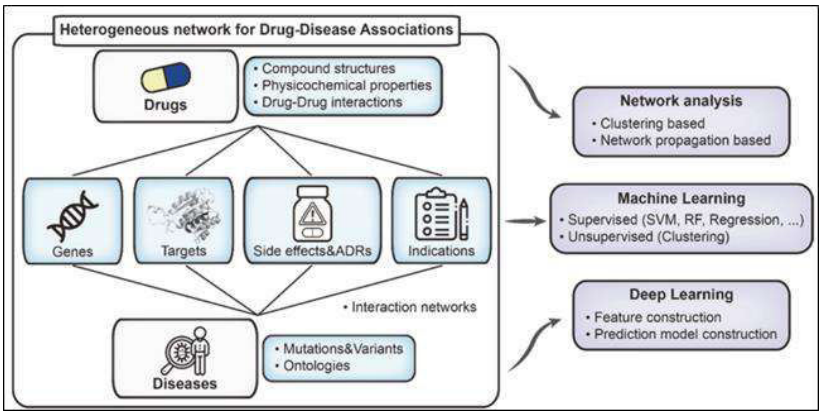


Fig 9: Data types and applied methods in drug repositioning

Drug repositioning, also known as drug repurposing, is the process of finding new indications of drugs. This approach is based on approved drugs or tested compounds and uses information about their known pharmacology.

Therefore, drug repositioning has an advantage as it significantly reduces the time and cost than traditional de novo drug discovery approaches. Previously, most of the drug repositioning has been serendipitous. For example, sildenafil, which was developed in 1989 and used to treat angina, was found to treat erectile dysfunction, and was named Viagra.

In the case of thalidomide, it was first developed for morning sickness but resulted in severe birth defects with malformation of the limbs, and was withdrawn from the market. Several years later, researchers discovered the anti-angiogenesis effect of thalidomide and further used it to treat multiple myeloma and leprosy. Table 5 shows more successful drug repositioning examples, most of which were discovered using the understanding of the pharmacology of each drug. Although drug repositioning is an essential approach in drug development, the identification of drugs through experiments remains a challenge. However, several data-driven computational approaches have been developed. Here, we review various data types used for drug repositioning and recent computational approaches have been developed.

Artificial intelligence in drug discovery

The vast chemical space, comprising $>10^{60}$ molecules, fosters the development of a large number of drug molecules. However, the lack of advanced technologies limits the drug development process, making it a time-consuming and expensive task, which can be addressed by using AI. AI can recognize hit and lead compounds, and provide a quicker validation of the drug target and optimization of the drug structure design. Despite its advantages, AI faces some significant data challenges, such as the scale, growth, diversity, and uncertainty of the data. The data sets available for drug development in pharmaceutical companies can involve millions of compounds and traditional ML tools might not be able to deal with these types of data. Quantitative structure-activity relationship (QSAR)-based computational model can quickly predict large numbers of compounds or simple physicochemical parameters, such as log P or log D. However, these models are some ways from the predictions of complex biological properties, such as the efficacy and adverse effects of compounds.

In addition, QSAR-based models also face problems such as small training sets, experimental data error in training sets, and lack of experimental validations. To overcome these challenges, recently developed AI approaches, such as DL and relevant modeling studies, can be implemented for safety and efficacy evaluations of drug molecules based on big data modeling and analysis. In 2012, Merck supported a QSAR ML challenge to observe the

advantages of DL in the drug discovery process in the pharmaceutical industry. DL models showed significant predictivity compared with traditional ML approaches for absorption, distribution, metabolism, excretion, and toxicity (ADMET) data sets of drug candidates.

The virtual chemical space is enormous and suggests a geographical map of molecules by illustrating the distributions of molecules and their properties. The idea behind the illustration of chemical space is to collect positional information about molecules within the space to search for bioactive compounds and, thus, virtual screening (VS) helps to select appropriate molecules for further testing. Several chemical spaces are open access, including Pubchem, Chembank, Drugbank and ChemDB. Numerous in silico methods to virtual screen compounds from virtual chemical spaces along with structure and ligand-based approaches, provide a better profile analysis, faster elimination of nonlead compounds and selection of drug molecules, with reduced expenditure. Drug design algorithms, such as coulomb matrices and molecular fingerprint recognition, consider the physical, chemical, and toxicological profiles to select a lead compound.

Various parameters, such as predictive models, the similarity of molecules, the molecule generation process, and the application of in silico approaches can be used to predict the desired chemical structure of a compound. Another approach applied a multi objective automated replacement algorithm to optimize the potency profile of a cyclin-dependent kinase-2 inhibitor by assessing its shape similarity, biochemical activity, and physicochemical properties. QSAR modelling tools have been utilized for the identification of potential drug candidates and have evolved into AI-based QSAR approaches, such as linear discriminant analysis (LDA), support vector machines (SVMs), random forest (RF) and decision trees, which can be applied to speed up QSAR analysis.

QSAR/QSPR and structure-based modeming with artificial intelligence

Quantitative structure-activity/property relationship (QSAR/QSPR) modelling has come a long way since its inception more than 50 years ago [16]. The impact of these computational models on drug discovery is undeniable, evidenced by the successful prediction of biological activity and pharmacokinetic parameters, *viz*. absorption, distribution, metabolism, excretion and toxicity (ADMET). For ligand-based QSAR/QSPR modelling, the structural features of molecules (e.g. as pharmacophore distribution, physicochemical properties and functional groups) are commonly converted into machine-readable numbers using the so-called molecular descriptor. The

spectrum of hand-crafted molecular descriptors is wide, aiming to capture a variety of aspects of the underlying chemical structure. In general, QSAR/QSPR approaches have transitioned from the use of simpler models, such as linear regression and k-nearest neighbours, toward more universally applicable machine learning techniques, such as support vector machines (SVM) and gradient boosting methods (GBM), aiming to address more complex and potentially nonlinear relationships between the chemical structure and its physicochemical/biological properties, often at the expenses of interpretability.

Deep learning is not a new technique. Artificial neural networks in chemoinformatics had their first heyday in the 1990s when many of the current concepts were pioneered, including deep and adaptive network architectures, self-organizing maps, recurrent systems for sequence and time-series analysis, and autoencoders. However, deep networks had their final breakthrough arguably after their success in the Merck Molecular Activity Challenge in 2012. While there is some controversy as to whether the latter type of models is superior performance-wise to other approaches (e. g. gradient boosting machines) when using the same set of descriptors, deep learning methods offer several advantages. Arguably, the most important one is that deep networks can perform automatic feature extraction during the training procedure. Graph neural networks (also referred to as message-passing approaches) and recurrent neural networks in particular, are able to generate internal context-specific representations of molecular structures. In the specific case of graph neural networks, this is achieved by learning latent atom and bond representations during the training process. Therefore, deep learning approaches are promising for modelling tasks for which classical descriptors had not been initially engineered. Examples include the modelling of peptides, macrocycles and proteolysis-targeting chimeras (PROTACs).

Another potential advantage of deep architectures is their applicability to multitask learning, which aims to find a common internal representation that is useful for a set of related endpoints (not to be confused with multioutput learning which does not explicitly exploit related information between the tasks to be learned). As drug discovery is a multiparameter optimization challenge, multitask learning might make more efficient use of correlated data in common scenarios where the entirety of a molecular library is not exhaustively tested on all endpoints of interest, and without the need for prior imputation. The idea of multi-output QSAR modelling, aiming to relate a set of predefined chemical descriptors to observable endpoints, had been explored before the rise of popularity of deep learning approaches. Despite the promise

of multitask learning, to date, only modest performance improvements over single-task models have been reported.

A well-known drawback of deep learning is its poor performance in medium-to-low data scenarios. Some chemogenomic-based approaches might provide further insight in these scenarios by exploiting additional genomic or biological interactome data sources. In addition, recent advances in 'few-shot' learning (i.e., a set of approaches that can use prior knowledge to obtain better generalization when data is scarce) and meta-learning (i.e., a family of methods that aims to develop a set of learnable parameters that can quickly adapt to new, unseen tasks) hold promise in mitigating some of these issues. Along those lines, purely data-driven approaches for molecular property predictions are, in contrast to techniques that are (fully or partially) physics-based, fundamentally limited in their ability to extrapolate and make reliable predictions for unseen compound classes. Physics inspired machine learning approaches and additional active learning strategies (i.e., approaches where the model has a role in requesting specific training data for improved generalization) provide additional tools to overcome these limitations. The success of these strategies, will furthermore critically depend on how well their specific implementations cope with data sparsity, given that suitable sources that would allow for efficient data imputation are often scarce.

A well-known drawback of deep learning is its poor performance in medium-to-low data scenarios. Some chemogenomic-based approaches might provide further insight in these scenarios by exploiting additional genomic or biological interactome data sources. In addition, recent advances in 'few-shot' learning (i.e., a set of approaches that can use prior knowledge to obtain better generalization when data is scarce) and meta-learning (i.e., a family of methods that aims to develop a set of learnable parameters that can quickly adapt to new, unseen tasks) hold promise in mitigating some of these issues. Along those lines, purely data-driven approaches for molecular property predictions are, in contrast to techniques that are (fully or partially) physics-based, fundamentally limited in their ability to extrapolate and make reliable predictions for unseen compound classes. Physics inspired machine learning approaches and additional active learning strategies (i.e., approaches where the model has a role in requesting specific training data for improved generalization) provide additional tools to overcome these limitations. The success of these strategies, will furthermore critically depend on how well their specific implementations cope with data sparsity, given that suitable sources that would allow for efficient data imputation are often scarce.

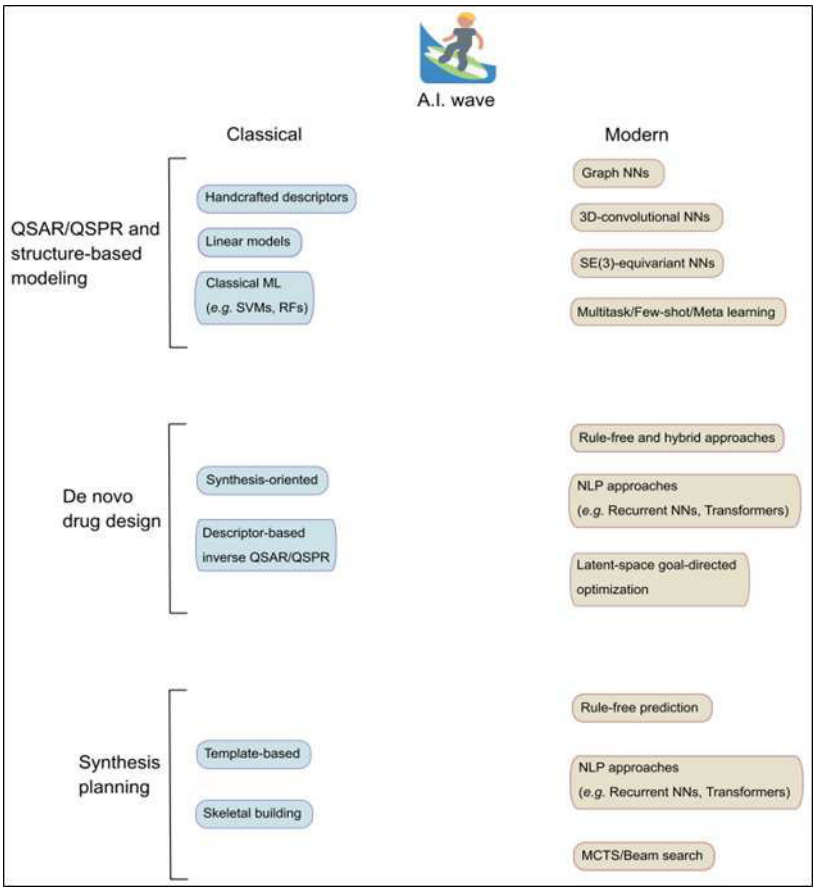


Fig 10: Schematic diagram of the transition between classical and modern methodologies for some relevant problems in drug discovery, such as QSAR/QSPR modelling, de novo drug design, and synthesis planning. Abbreviations: ML, machine learning; SVM, support vector machine; RF, random forest; QSAR/QSPR, quantitative structure-activity/property relationship; NN, neural network; SE(3), special Euclidean group in three-dimensions; NLP, natural language processing; MCTS, Monte Carlo tree search

General drug discovery reviews

Many existing papers have covered the general aspects of drug discovery and related concepts, such as chemical space, VS (virtual screening) and HTS (high-throughput screening), optimal properties for drug candidates, QSAR, target prediction, and computer-aided drug design. Besides, one prominent challenge in drug discovery is that molecular properties can be highly sensitive to minor structural changes. This is also known as the activity cliffs (ACs),

where pairs of structurally similar molecules exhibit significantly different activities. We strongly recommend the readers (especially those new to drug discovery) refer to these reviews for a better understanding on drug discovery and recognition of potential pitfalls.

The impact of AI on the drug discovery process and potential cost savings

Another key application of AI in drug discovery is the design of novel compounds with specific properties and activities. Traditional methods often rely on the identification and modification of existing compounds, which can be a slow and labour-intensive process. AI-based approaches, on the other hand, can enable the rapid and efficient design of novel compounds with desirable properties and activities. For example, a deep learning (DL) algorithm has recently been trained on a dataset of known drug compounds and their corresponding properties, to propose new therapeutic molecules with desirable characteristics such as solubility and activity, demonstrating the potential of these methods for the rapid and efficient design of new drug candidates.

Recently, DeepMind has made a significant contribution to the field of AI research with the development of AlphaFold, a revolutionary software platform for advancing our understanding of biology. It is a powerful algorithm that uses protein sequence data and AI to predict the proteins' corresponding three-dimensional structures. This advance in structural biology is expected to revolutionize personalized medicine and drug discovery. AlphaFold represents a significant step forward in the use of AI in structural biology and life sciences in general.

ML techniques and molecular dynamics (MD) simulations are currently being used in the field of de novo drug design to improve efficiency and accuracy. The technique of combining these methodologies is being explored to take advantage of the synergies between them [20]. The use of interpretable machine learning (IML) and DL methods is also contributing to this effort. By leveraging the power of AI and MD, researchers are able to design drugs more effectively and efficiently than ever before.

Pre-clinical and clinical development

Predicting possible responses to a drug is a critical step in a drug design pipeline. Similarity or feature-based machine learning methods can be used to predict the response of a drug on individual cells and the efficacy of a drug-target interaction by binding affinity or free energy of binding. Similarity methods assume that similar drugs act on similar targets, while feature-based methods find individual features of drugs and targets and feed the drug-target

feature vector to the classifier. Deep learning-based methods, such as DeepConv-DTI and DeepAffinity are examples methods, where the embedding of drugs and targets are learned using convolution and attention mechanism.

AI-based techniques can assist in selecting potential patients for pre-clinical trials by identifying relevant human-disease bio-markers and anticipating potential toxic or unnecessary side effects and by filtering a high dimensional set of clinical variables to select a cohort of patients. AI can also help in predicting the outcome of clinical trials well ahead of the actual trial minimizing the chance of any harmful effect on patients.

FDA approval and post market analysis

Natural Language Processing (NLP) can be used to mine scientific literature to report adverse effects, such as toxicity, of a drug or resistance to it and prepare automated evaluations for regulatory (FDA) approval or a patent application. NLP-based sentiment analysis methods can be used to recommend drugs. Prediction of likely sales of a product by machine learning-based systems could help pharmaceutical companies optimize their business resources.

Future scope

AI algorithms learn on data, and the availability of databases for training determines the quality of the outcomes. Drug design presents a number of difficult difficulties in terms of information selection, data modelling, classification, prediction, and optimization, all of which encourage the development and use of specialised AI systems. Artificial intelligence is being used to detect links between patterns of genetic variants and expression profiles and clinical and other phenotypes, as well as to create predictive fingerprints of disease states, progression, and therapeutic intervention outcomes. CTS studies employ computational simulation approaches on selected populations to evaluate alternative trial designs before investing money in the real clinical trial.

Limitations of the current methods in drug discovery

Currently, medicinal chemistry methods rely heavily on a hit-and-miss approach and large-scale testing techniques. These techniques involve examining large numbers of potential drug compounds, in order to identify those with the desired properties. However, these methods can be slow, costly, and often yield results with low accuracy. In addition, they can be limited by the availability of suitable test compounds and the difficulty of accurately predicting their behaviour in the body.

Different algorithms based on AI, including supervised and unsupervised learning methods, reinforcement, and evolutionary or rule-based algorithms, can potentially contribute to solving these problems. These methods are typically based on the analysis of large amounts of data that can be exploited in different ways. For instance, the efficacy and toxicity of new drug compounds can be predicted using these approaches, with greater accuracy and efficiency than when using traditional methods. Furthermore, AI-based algorithms can also be employed to identify new targets for drug development, such as the specific proteins or genetic pathways involved in diseases. This can expand the scope of drug discovery beyond the limitations of more conventional approaches and may eventually lead to the development of novel and more effective medications. Thus, while traditional methods of pharmaceutical research have been relatively successful in the past, they are limited by their reliance on trial-and-error experimentation and their inability to accurately predict the behaviour of new potential bioactive compounds. AI-based approaches, on the other hand, have the ability to improve the efficiency and accuracy of drug discovery processes and can lead to the development of more effective medications.

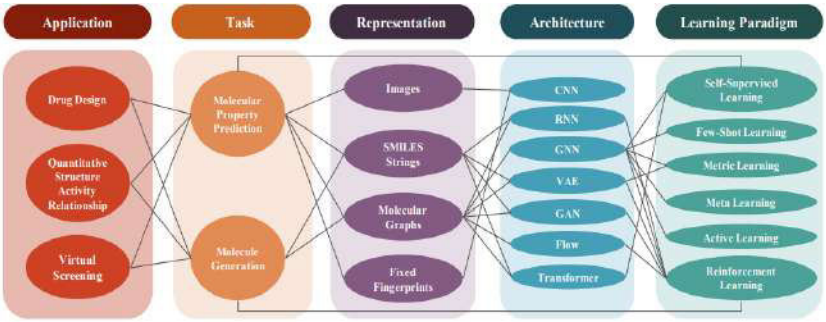


Fig 11: Applications and Techniques of AI in Drug Discovery. The applications of AI in small-molecule drug discovery include virtual screening, quantitative structure-activity relationship and drug design, which can be reduced to two major tasks: molecular property prediction and molecule generation. Small molecules can be represented by fixed fingerprints, molecular graphs, simplified molecular input entry system (SMILES) strings, and images. Various model architectures have been applied on each representation format, including convolutional neural networks (CNN), recurrent neural networks (RNN), graph neural networks (GNN), variational autoencoders (VAE), generative adversarial networks (GAN), normalizing flow models and transformers. Still, challenges exist for the low-data molecular property prediction and goal-directed molecule generation

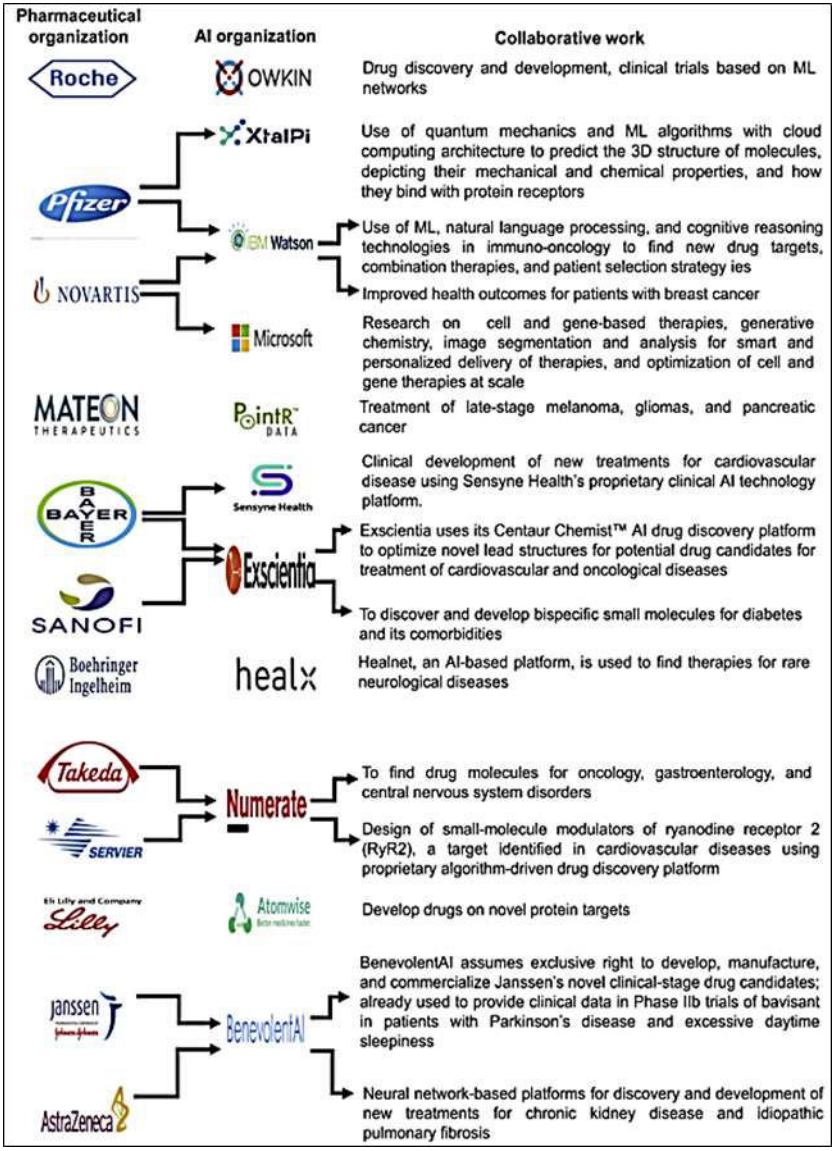


Fig 12: Examples of some AI based applications

Conclusion

In the context of drug discovery, full comprehensibility of deep learning models may be hard to achieve, although the provided predictions can still prove useful to the practitioner. When striving for interpretations that match the human intuition, it will be crucial to carefully devise a set of control

experiments to validate the machine-driven hypotheses and increase their reliability and objectivity. In conclusion, AI has the potential to revolutionize the drug discovery process, offering improved efficiency and accuracy, accelerated drug development, and the capacity for the development of more effective and personalized treatments. However, the successful application of AI in drug discovery is dependent on the availability of high-quality data, the addressing of ethical concerns, and the recognition of the limitations of AI-based approaches.

Recent developments in AI, including the use of data augmentation, explainable AI and the integration of AI with traditional experimental methods, offer promising strategies for overcoming the challenges and limitations of AI in the context of drug discovery. The growing levels of interest and attention from researchers, pharmaceutical companies, and regulatory agencies, combined with the potential benefits of AI, make this an exciting and promising area of research, with the potential to transform the drug discovery process.

AI technology can be applied to a wide range of applications. The widely used AI algorithms, particularly deep learning-based algorithms, were primarily developed in the fields of computer vision, natural language processing, and acoustic signal processing. However, because of the reasons here, applying fancy AI techniques to the drug discovery process is quite challenging. First, the drug discovery process is very complicated and it involves specialized knowledge in a variety of fields (biology, chemistry, and medicine; among others). Second, the drug discovery process requires compelling evidence for decision making because it directly affects public health and the pharmaceutical industry's net profits. Nevertheless, many researchers proved the fact that the future of drug discovery with AI technology is obviously promising by their tremendous efforts that are covered in this review. Still, the discrepancy between the two domains is a big hurdle. Therefore, AI experts and other domain experts will need to collaborate closely to develop 'drug discovery-specific' AI technology for real advances in the current drug discovery. AI experts will need to understand the characteristics of drug discovery data and make an effort to develop appropriate and interpretable algorithms that can explain the modes of action, to provide evidence for further decision making. Other domain experts will need to generate biological and chemical data with minimal experimental errors and store them in unified platforms for further improvements to the AI systems. However, the most important thing for both groups is to be open to working together and actively communicating to construct a concrete

framework for a new revolution in drug discovery. We hope this review provides a good starting point for closing this gap.

The promise made by AI for the future are better drugs, discovered and delivered faster. It should also be noted that in the case of drug design, basic properties of the molecules, for example, bonding, quantum and physicochemical properties, are not the only aspects to be taken into account. Medicines may have multiple biological targets and effects, and their efficiency depend on several factors such as bioavailability, effect of formulation and administration, as well as individual genetic profiles of patients.

The newfound interest in explainable AI, with methodologies such as feature attribution, instance-based molecular counterfactual explanation, and uncertainty estimation, will increase the acceptance of AI-supported drug discovery. The development and validation of these techniques will require further interdisciplinary research. Special consideration will also be given to approaches that can exploit information in low-data regimes, such as transfer learning, as well as multi-task and meta-learning. The barriers against learning and prospectively applying deep learning approaches have been greatly lowered for interested practitioners in the last few years. The current trend suggests that these methods will be increasingly accessible in the foreseeable future, with the continued development of general high-level research and deployment software packages, as well as comprehensible documentation.

References

1. Dias DA, Urban S, Roessner U. A historical overview of natural products in drug discovery. Metabolites. 2012;2(2):303-333.
2. DiMasi JA, HG Grabowski, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J. Health Econ. 2016;47:20-33.
3. Samuel AL. Machine learning. The Technology Review. 1959;62(1):42-45.
4. Jeon J, Nim S, Teyra J, Datti A, Wrana JL, Sidhu SS *et al*. A systematic approach to identify novel cancer drug targets using machine learning, inhibitor design and high-throughput screening. Genome Medicine. 2014;6(7):1-18.
5. Johnson JI, Decker S, Zaharevitz D, Rubinstein LV, Venditti JM, Schepartz S *et al*. Relationships between drug activity in NCI preclinical *in vitro* and *in vivo* models and early clinical trials. British Journal of Cancer. 2001;84(10):1424-1431.

6. Badillo S, Banfai B, Birzele F, Davydov II, Hutchinson L, Kam-Thong T *et al*. An Introduction to Machine Learning. Clinical pharmacology and therapeutics. 2020;107(4):871-885.
7. Mak KK, Pichika MR. Artificial intelligence in drug development: present status and future prospects. Drug Discovery Today. 2019;24(3):773-780.
8. Angermueller C, Pärnamaa T, Parts L, Stegle O. Deep learning for computational biology. Molecular Systems Biology. 2016;12(7):878.
9. Segall DM. Multi-parameter optimization: identifying high quality compounds with a balance of properties. Current Pharmaceutical Design. 2012;18(9):1292.
10. Niyati Shah, Mamta Kumari, Piyushkumar Sadhu, Chitrali Talele. Artificial Intelligence in Pharma Industry - A Review. Asian Journal of Pharmaceutics. 2023;17(2):173-178.
11. Awol AK, Kumari M, Lan K, Lingam M. Application of Artificial Intelligence and Machine Learning in Drug Discovery and Development. Journal of Drug Delivery and Therapeutics. 2023;13(1):151-158.
12. Wei JN, Duvenaud D, Aspuru-Guzik A. Neural networks for the prediction of organic chemistry reactions. ACS Cent Sci. 2016;2(10):725-732.
13. Sharma M, Chaudhary PR, Mudgal A, Nautiyal A, Tangri S. Review on Artificial Intelligence in Medicine. J Young Pharm. 2023;15(1):1-6.
14. Yang X. Concepts of artificial intelligence for computer-assisted drug discovery. Chem. Rev. 2019;119:10520-10594.
15. Schneider G. Automating drug discovery. Nat. Rev. Drug Discov. 2017;17:97-113.
16. Ramesh A. Artificial intelligence in medicine. Ann. R. Coll. Surg. Engl. 2004;86:334-338.
17. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G *et al*. Applications of machine learning in drug discovery and development. Nat. Rev. Drug Disc. 2019;18:463-477.
18. More Swati K. Artificial Intelligence: Review and Wide Applications in Pharmaceuticals. International Journal of Science and Research. 2022;11(6):487-490.
19. Mishra BB, Tiwari VK. Natural products: an evolving role in future drug discovery. Eur. J Med. Chem. 2011;46(10):4769-4807.

20. Nisha Kalayil V, Shona D'souza S, Showkhiya Khan Y, Pallavi Paul. Artificial Intelligence in Pharmacy Drug Design. Asian J Pharm Clin Res. 2022;15(4):21-27.

21. Singh B, Mal G, Gautam SK, Mukesh M. Computer-aided drug discovery. In: Advances in Animal Biotechnology. Cham: Springer, 2019, 471-81.

22. Batool M, Ahmad B, Choi S. A structure-based drug discovery paradigm. Int. J Mol. Sci. 2019;20(11):27-83.

23. Mandal S, Moudgil M, Mandal SK. Rational drug design. Eur. J Pharmacol. 2009;625(1-3):90-100.

24. Sliwoski G, Kothiwale S, Meiler J, Lowe EW. Computational Methods in Drug Discovery, Pharmacological Reviews. 2013;66(1):334-395.

25. Mater AC, Coote ML. Deep learning in chemistry. J Chem. Inform. Model. 2019;59(6):2545-2559.

26. Schmidhuber J. Deep learning in neural networks: an overview. Neural Netw. 2015;61:85-117.

27. Ch Krishnaveni, Swarupa Arvapalli, Sharma JVC, Divya K. Artificial Intelligence in Pharma Industry- A Review. International Journal of Innovative Pharmaceutical Sciences and Research. 2019;7(10):37-50.

28. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. Adv. Neural. Inf. Process. Syst. 2012;25:1097-1105.

29. Lillicrap TP, Santoro A, Marris L, Akerman CJ, Hinton G. Backpropagation and the brain. Nat. Rev. Neurosci. 2020;21(6):335-346.

30. Duch W, Swaminathan K, Meller J. Artificial intelligence approaches for rational drug design and discovery. Curr Pharm Des. 2007;13:1497-1508.

31. Roshan Kumar, Purabi Saha. A Review on Artificial Intelligence and Machine Learning to Improve Cancer Management and Drug Discovery. International Journal for Research in Applied Sciences and Biotechnology. 2022;9(3):149-156.

32. Anjila Isani I, Ambika Nagarbhadiya D, Gauri Tatewar N. The Concept of Artificial Intelligence in Pharmaceutical Industry. International Journal for Research Trends and Innovation. 2023;8(4):820-824.

33. Ferrero E, Dunham I, Sanseau P. In silico prediction of novel therapeutic targets using gene-disease association data. J Transl Med. 2017;15(1):182.

34. Winkel P. Artificial intelligence within the chemical laboratory. Ann Biol Clin (Paris). 1994;52(4):277-282.

35. Bajorath J, Kearnes S, Walters WP, Georg GI, Wang S. The Future Is Now: Artificial Intelligence in Drug Discovery. Journal of Medicinal Chemistry. 2019;62(11):5249.

36. Gupta R, Srivastava D, Sahu M, Tiwari S, Ambasta RK, Kumar P *et al*. Artificial intelligence to deep learning: Machine intelligence approach for drug discovery. Mol. Divers. 2021;25:1315-1360.

37. Bajorath J, Kearnes S, Walters WP, Meanwell NA, Georg GI, Wang S, *et al*. Artificial Intelligence in Drug Discovery: Into the Great Wide Open. J Med Chem. 2020;63(16):8651-8652.

38. Struble TJ, Alvarez JC, Brown SP, Chytil M, Cisar J, Desjarlais RL, *et al*. Current and future roles of artificial intelligence in medicinal chemistry synthesis. J Med Chem. 2020;63:8667-8882.

39. Hessler G, Baringhaus KH. Artificial Intelligence in Drug Design. Molecules. 2018;23(10):2520.

40. Staszak M, Staszak K, Wieszczycka K, Bajek A, Roszkowski K, Tylkowski B, *et al*. Machine learning in drug design: Use of artificial intelligence to explore the chemical structure-biological activity relationship. WIREs Comput. Mol. Sci. 2022;12:e15-68.

41. Green CP, Engkvist O, Pairaudeau G. The convergence of artificial intelligence and chemistry for improved drug discovery. Future Med Chem. 2018;10(22):2573-2576.

42. Silver D, Schrittwieser J, Simonyan K. Mastering the game of Go without human knowledge. Nature. 2017;550(7676):354-359.

43. Zhang L, Tan J, Han D, Zhu H. From machine learning to deep learning: progress in machine intelligence for rational drug discovery. Drug Discov Today. 2017;22(11):1680-1685.

44. Brown N, Ertl P, Lewis R, Luksch T, Reker D, Schneider N, *et al*. Artificial intelligence in chemistry and drug design, J Comput Aided Mol. Des. 2020;34(7):709-715.

45. Kellici T, Ntountaniotis D, Vrontaki E, *et al*. Rational drug design paradigms: the odyssey for designing better drugs. Comb. Chem. High Throughput Screen. 2015;18(3):238-256.

46. Baltos JA, Paoletta S, Nguyen AT, Gregory KJ, Tosh DK, Christopoulos A *et al*. Structure activity analysis of biased agonism at the human adenosine A3 receptor. Molecular Pharmacology. 2016;90(1):12-22.

47. Huang K, Fu T, Glass LM, Zitnik M, Xiao C, Sun J *et al*. Deeppurpose: a deep learning library for drug-target interaction prediction. Bioinformatics. 2020;36(22-23):5545-5547.

48. Lavecchia A. Machine-learning approaches in drug discovery: methods and applications. Drug Discovery Today. 2015;20(3):318-331.

49. Ganesh Parkhe, Trupti Thange. A Review: Artificial Intelligence in Drug Discovery and Development. International Journal of Research Publication and Reviews. 2022;3(7):501-510.

50. Russel S, Dewey D, Tegmark M. Research priorities for robust and beneficial artificial intelligence. AI Mag. 2015;36(4):105-114.

51. Chen Y, Argentinis JE, Weber G. Ibm watson: how cognitive computing can be applied to big data challenges in life sciences research. Clinical Therapeutics. 2016;38(4):688-701.

52. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. Smote: Synthetic minority over-sampling technique. J. Art. Intell. Res. 2002;16:321-357.

53. Jaganathan K, Panagiotopoulou SK, McRae JF, Darbandi SF, Knowles D, Li YI *et al*. Predicting splicing from primary sequence with deep learning. Cell. 2019;176(3):535-548.

54. Weber M, Beutter M, Weking J, Böhm M, Krcmar H. AI Startup Business Models. Bus Inf. Syst. Eng. 2022;64:91-109.

55. Parvathaneni M, Awol AK, Kumari M, Lan K, Lingam M. Application of Artificial Intelligence and Machine Learning in Drug Discovery and Development. Journal of Drug Delivery and Therapeutics. 2023;13(1):151-158.

56. Jagiello K, Grzonkowska M, Swirog M, Ahmed L, Rasulev B, Avramopoulos A *et al*. Advantages and limitations of classic and 3D QSAR approaches in nano-QSAR studies based on biological activity of fullerene derivatives. J Nanopart Res. 2016;18(9):256.

57. Mendenhall J, Meiler J. Improving quantitative structure–activity relationship models using artificial neural networks trained with dropout. J Computer-aided Mol Design. 2016;30(2):177-189.

Indexing and Abstracting in Following Databases

1. Bowker: A ProQuest Affiliate

2. Crossref

ISBN 9789355708939

₹ 721, US $16

Published by
AkiNik Publications®
169, C-11, Sector - 3, Rohini,
Delhi - 110085, India
Toll Free (India): 18001234070
Email: akinikbooks@gmail.com

Peer Reviewed & Refereed

ARTIFICIAL INTELLIGENCE IN PHARMACEUTICAL TECHNOLOGY

Volume 2

Editors
Dr. Akhil Sharma
Dr. Shaweta Sharma

AKINIK PUBLICATIONS™
NEW DELHI

RESEARCH TRENDS IN PHARMACEUTICAL SCIENCES (VOLUME -II)

Editor
Dr. Rahul Trivedi
Professor
Department of Pharmacy,
Sumandeep Vidyapeeth, Deemed to be University,
Posts: Pipariya, Taluka: Waghodiya
Vadodara, Gujarat

SOUTH ASIAN
ACADEMIC PUBLICATIONS

Published By:
South Asian Academic Publications
3-37, Dirisavancha, Kanigiri, Prakasm District
Andhra Pradesh-523445 India
Phone No. -9441545787, 9959049730
Email- saapbooks@gmail.com

Editor: Dr. Rahul Trivedi

Publication Year: 2023

Pages: 73

ISBN: 978-93-92153-88-4

Price: Rs. 499 INR/-

INDEX

CHAPTER 1

REGENERATIVE MEDICINE

Mr. Sunil Kardani
Associate Professor, Department of Pharmacy
Sumandeep Vidyapeeth Deemed to be University
Vadodara 391 760, Gujarat, India

Rajesh Hadia, Ghanshyam Parmar
Nirmal Shah, Dipti Gohil
Rahul Trivedi, Sunil Baile
Rajesh Maheshwari
Department of Pharmacy
Sumandeep Vidyapeeth Deemed to be University
Vadodara 391760, Gujarat.

Abstract

Regenerative Medicine, a transformative field at the intersection of biology, engineering, and clinical practice, holds unprecedented promise for revolutionizing healthcare. This abstract provides a concise overview of the key facets within this burgeoning discipline. The core principles encompass the utilization of stem cells, sourced from diverse origins, and the intricate design of biomaterial scaffolds in tissue engineering. The integration of these elements forms the foundation for innovative therapeutic approaches, spanning cell therapy, gene therapy, and tissue engineering applications. Within the realm of disease treatment, Regenerative Medicine emerges as a potent force against a spectrum of medical challenges. From cardiovascular diseases to neurological disorders and orthopedic conditions, its applications are manifold, offering novel avenues for restoring function and ameliorating debilitating conditions. However, the field is not without its complexities and ethical considerations. Immunogenicity, safety concerns, and the ethical implications of stem cell research pose significant hurdles

that necessitate careful navigation. Navigating the regulatory landscape is imperative for the translation of regenerative therapies from the laboratory to the clinic. This abstract touch upon the guidelines set forth by regulatory bodies, such as the FDA, and explores the international regulatory framework governing these revolutionary treatments. Looking forward, the abstract discusses the future perspectives of Regenerative Medicine, including the integration of emerging technologies, collaboration with artificial intelligence, and the potential for groundbreaking advancements. This abstract aims to encapsulate the dynamic landscape of Regenerative Medicine, offering a glimpse into its transformative potential and the challenges that accompany its pursuit

Keywords: *Regenerative Medicine, Tissue Engineering Applications, Ethical Considerations, Regulatory Landscape*

Introduction

Regenerative Medicine involves harnessing the body's natural healing mechanisms to restore or replace damaged tissues and organs, utilizing advanced biomedical technologies [1]. Regenerative Medicine is a multidisciplinary field at the crossroads of biology, engineering, and clinical practice, focusing on the development of innovative therapeutic strategies for tissue and organ repair [2]. Regenerative Medicine encompasses the application of stem cells, tissue engineering, and gene therapies to promote healing, regeneration, and functional restoration of damaged tissues [3]. Regenerative Medicine is a transformative approach seeking to create bioartificial organs, repair tissues, and address chronic diseases by manipulating cellular and molecular processes [4]. Regenerative Medicine is an evolving field aiming to revolutionize healthcare through personalized treatment strategies, utilizing the body's regenerative potential and cutting edge technologies [5]. Regenerative Medicine stands at the forefront of biomedical innovation, representing a paradigm shift in healthcare by harnessing the intrinsic biological processes of the human body to restore,

replace, or regenerate damaged tissues and organs. This multidisciplinary field integrates principles from biology, engineering, and clinical practice to develop cutting edge therapeutic strategies with unprecedented potential for revolutionizing medical treatment. At its core, Regenerative Medicine employs a variety of approaches, including stem cell therapy, gene therapy, and tissue engineering, to facilitate the repair and regeneration of tissues. Stem cells, with their remarkable capacity for self renewal and differentiation, play a pivotal role in these regenerative processes. The intricate design of biomaterial scaffolds further enhances the potential of tissue engineering applications, providing a supportive framework for cell growth and tissue regeneration.

1. Historical Overview of Regenerative Medicine

Regenerative Medicine has emerged as a revolutionary field, drawing from a rich historical tapestry that intertwines scientific discoveries, medical breakthroughs, and technological advancements. The roots of this transformative discipline can be traced back to pivotal moments in medical history.

- **Cellular Foundations:** The groundwork for Regenerative Medicine was laid with the discovery of stem cells. James Till and Ernest McCulloch's groundbreaking work in the early 1960s identified the existence of hematopoietic stem cells, providing a crucial understanding of the regenerative potential inherent in certain cells [6].
- **Birth of Tissue Engineering:** The term "tissue engineering" was coined by Robert Langer and Joseph P. Vacanti in the 1980s. Their vision of creating functional tissues outside the body laid the foundation

for tissue engineering, a cornerstone of Regenerative Medicine.

- **First Successful Transplants:** The late 20th century witnessed the first successful organ transplants, marking a significant stride in Regenerative Medicine. The pioneering efforts of surgeons like Thomas Starzl, who performed the first liver transplant in 1967 [7], highlighted the potential for replacing damaged organs.
- **Stem Cell Revolution:** The isolation of human embryonic stem cells by James Thomson in 1998 [8], opened new frontiers for Regenerative Medicine. This discovery provided researchers with a potent tool for studying development and the potential to generate various cell types for therapeutic applications.
- **Clinical Milestones:** The 21st century saw Regenerative Medicine transitioning from laboratories to clinical settings. Notable milestones include the approval of the first stem cell based therapy, GraftJacket, for chronic wounds in 2003 [9], and the advent of induced pluripotent stem cells (iPSCs) by Shinya Yamanaka in 2006 [10], offering a way to reprogram adult cells into a pluripotent state.

2. Importance of Regenerative Medicine in Modern Medicine

Regenerative Medicine has emerged as a transformative force in modern healthcare, offering innovative solutions for treating a myriad of medical conditions. Its significance lies in the potential to harness the body's own regenerative capabilities and leverage advanced technologies to address previously incurable diseases and conditions.

- **Personalized Treatment Approaches:** Regenerative Medicine facilitates the development of personalized treatment strategies. By utilizing a patient's own cells or tissues, therapies can be tailored to individual genetic and immunological profiles, reducing the risk of rejection and enhancing treatment efficacy.
- **Treatment of Chronic Diseases:** The field holds immense promise for the treatment of chronic diseases that have traditionally posed significant therapeutic challenges. Cardiovascular diseases, neurodegenerative disorders, and autoimmune conditions are among the many ailments that could benefit from regenerative approaches.
- **Reduced Reliance on Organ Transplants:** As an alternative to traditional organ transplants, Regenerative Medicine aims to create functional tissues and organs in the laboratory. This could mitigate the shortage of donor organs and alleviate the complexities associated with organ transplantation, such as rejection and the need for immunosuppressive drugs [11].
- **Innovative Therapies for Injuries and Trauma:** Regenerative Medicine offers novel solutions for repairing and regenerating tissues damaged by injuries or trauma. From spinal cord injuries to severe burns, regenerative approaches hold the potential to restore functionality and improve the quality of life for patients [12].
- **Advancements in Stem Cell Therapy:** Stem cell therapy, a key component of Regenerative Medicine, has shown promise in treating a variety of conditions. The versatility of stem cells allows for the regeneration

of different cell types, making them invaluable in addressing degenerative diseases and tissue damage.

- **Economic and Social Impact:** The implementation of regenerative therapies could have profound economic and social implications. By reducing the burden of chronic diseases and improving patient outcomes, Regenerative Medicine has the potential to enhance productivity, decrease healthcare costs, and improve overall societal well being [13].

3. Basic Principles of Regenerative Medicine

Regenerative Medicine operates on fundamental principles grounded in biology, engineering, and clinical practice to harness the body's natural healing mechanisms for therapeutic purposes. The intricate interplay of these principles forms the foundation of this transformative field.

- **Stem Cells:** Central to Regenerative Medicine is the utilization of stem cells, which possess unique properties of self renewal and differentiation. The seminal work of James Till and Ernest McCulloch laid the groundwork by identifying hematopoietic stem cells in the 1960s. Stem cells can be sourced from various tissues, including embryonic, induced pluripotent, and adult tissues, providing a versatile toolkit for therapeutic applications.
- **Tissue Engineering:** Tissue engineering involves the design and fabrication of biological substitutes using a combination of cells, biomaterials, and biochemical factors. The pioneering work of Robert Langer and Joseph P. Vacanti in the 1980s marked the inception of tissue engineering. Biomaterial scaffolds play a critical role in supporting cell growth and facilitating tissue regeneration [14].

- **Biomaterials:** The selection of appropriate biomaterials is crucial for the success of regenerative therapies. Biomaterials serve as scaffolds that mimic the extracellular matrix, providing a supportive environment for cell attachment, proliferation, and differentiation [15]. Advances in biomaterial science contribute significantly to the development of effective regenerative strategies.
- **Cell Therapy:** Cell therapy involves the transplantation or manipulation of cells to restore or replace damaged tissues. Stem cell therapy is a subset of cell therapy, wherein stem cells are employed to promote tissue regeneration. This approach holds promise for treating a wide range of diseases, including degenerative conditions and injuries.
- **Gene Therapy:** Gene therapy aims to modify or introduce genetic material into cells to treat or prevent diseases. The advent of technologies like CRISPR/Cas9 has revolutionized gene editing [16], opening new possibilities for precisely engineering cells to enhance their regenerative potential.

4. Regenerative Therapies

Regenerative therapies represent a revolutionary approach in medicine, aiming to restore or replace damaged tissues and organs by harnessing the body's natural regenerative capabilities. This category of therapies encompasses diverse strategies, including cell therapy, gene therapy, and tissue engineering applications.

- **Cell Therapy:** Cell therapy involves the transplantation or infusion of cells into a patient to restore or improve tissue function. Stem cells, with their unique ability to differentiate into various cell

types, are central to cell based regenerative therapies. For example, mesenchymal stem cells have shown promise in treating conditions such as osteoarthritis and autoimmune disorders. Clinical trials employing cell therapy continue to expand, exploring their potential in diverse medical fields.

- **Gene Therapy:** Gene therapy seeks to treat or prevent diseases by introducing, removing, or modifying genetic material within a patient's cells. Recent advances, particularly with CRISPR/Cas9 technology, enable precise gene editing. In the context of regenerative medicine, gene therapy holds promise for addressing genetic disorders, enhancing the regenerative potential of cells, and correcting malfunctioning genes [17].
- **Tissue Engineering Applications:** Tissue engineering combines cells, biomaterials, and biochemical factors to create functional tissues or organs in the laboratory. The integration of engineered tissues into the body aims to restore normal function. Notable applications include the development of artificial skin for burn victims [18], and the creation of bioartificial organs, such as the bioartificial pancreas for diabetes treatment [19].
- **Organ Transplants:** While traditional organ transplantation is not a new concept, advancements in regenerative medicine have the potential to transform this field. Decellularization techniques, where donor organs are stripped of their cells, leaving behind a scaffold, pave the way for creating bioartificial organs. This approach aims to overcome the challenges of organ shortages and transplant rejection.

5. Applications of Regenerative Medicine in Disease Treatment

Regenerative Medicine holds tremendous potential for revolutionizing disease treatment by offering innovative approaches to repair, replace, or regenerate damaged tissues and organs. This transformative field has shown promising applications across a spectrum of medical challenges, demonstrating its versatility and efficacy.

- **Cardiovascular Diseases:** Regenerative Medicine offers new avenues for treating cardiovascular diseases, such as myocardial infarction. Stem cell therapy has been investigated for its ability to regenerate cardiac tissue and improve heart function [20]. Clinical trials have explored the transplantation of stem cells to enhance vascularization and repair damaged heart tissue [21].
- **Neurological Disorders:** The treatment of neurological disorders, including Parkinson's disease and spinal cord injuries, benefits from regenerative strategies. Stem cells, particularly neural stem cells and induced pluripotent stem cells, hold promise for replacing damaged neural tissues [22]. Research focuses on stimulating neurogenesis and enhancing functional recovery in the central nervous system [23].
- **Orthopedic Conditions:** Regenerative Medicine plays a crucial role in orthopedic applications, particularly in the treatment of musculoskeletal disorders. Mesenchymal stem cells have been investigated for their potential in promoting bone and cartilage regeneration, offering alternatives to traditional treatments for conditions like osteoarthritis and fractures.

- **Autoimmune Diseases:** In the realm of autoimmune diseases, where the immune system attacks healthy tissues, regenerative approaches aim to modulate immune responses. Mesenchymal stem cells have demonstrated immunomodulatory properties, holding potential for treating conditions like rheumatoid arthritis and multiple sclerosis [24]. Gene therapies targeting specific immune responses are also being explored [25].
- **Diabetes:** Regenerative strategies are being explored for diabetes treatment, aiming to restore insulin producing beta cells. Islet transplantation, combined with tissue engineering approaches, seeks to create bioartificial pancreases for long term diabetes management [26].

Conclusion

Regenerative Medicine stands as a groundbreaking force at the forefront of biomedical innovation, offering a transformative paradigm in healthcare. This multidisciplinary field, converging biology, engineering, and clinical practice, holds unprecedented promise for revolutionizing medical treatment. The core principles of Regenerative Medicine, encompassing stem cell therapy, gene therapy, and tissue engineering, converge to facilitate the repair and regeneration of tissues. Stem cells, with their remarkable capacity for self renewal and differentiation, play a pivotal role in driving regenerative processes. The integration of biomaterial scaffolds further enhances the potential of tissue engineering applications, providing a supportive framework for cell growth and tissue regeneration. To comprehensively define Regenerative Medicine, it is crucial to delve into the scientific literature, as evidenced by the foundational works highlighted

in this overview. As we navigate the dynamic landscape of Regenerative Medicine, its historical evolution, basic principles, and diverse applications underscore its transformative potential. The field's significance extends beyond scientific and clinical realms, addressing ethical considerations, regulatory landscapes, and future perspectives that will shape the trajectory of healthcare. Through collaboration with emerging technologies and the integration of artificial intelligence, Regenerative Medicine offers a glimpse into a future where innovative therapies may redefine the boundaries of medical possibility.

Acknowledgement

The authors whole heartedly convey their sincere gratitude to Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara for their support to carry out the work.

Conflicts of Interest

None

References

1. Mason, C., & Dunnill, P. (2008). A brief definition of regenerative medicine. Regenerative Medicine, 3(1), 1-5.
2. Trounson, A., & McDonald, C. (2015). Stem Cell Therapies in Clinical Trials: Progress and Challenges. Cell Stem Cell, 17(1), 11-22.
3. Atala, A., Bauer, S. B., Soker, S., Yoo, J. J., & Retik, A. B. (2006). Tissue engineered autologous bladders for patients needing cystoplasty. The Lancet, 367(9518), 1241-1246.

4. Langer, R., & Vacanti, J. P. (1993). Tissue engineering. Science, 260(5110), 920-926.
5. Caplan, A. I., & Correa, D. (2011). The MSC: an injury drugstore. Cell Stem Cell, 9(1), 11-15.
6. McCulloch, E. A., & Till, J. E. (1960). The radiation sensitivity of normal mouse bone marrow cells, determined by quantitative marrow transplantation into irradiated mice. Radiation Research, 13(1), 115-125.
7. Starzl, T. E., Marchioro, T. L., & Vonkaulla, K. N. (1967). Homotransplantation of the liver in humans. Surgical Gynecology and Obstetrics, 124(2), 301-306.
8. Thomson, J. A., Itskovitz Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S., & Jones, J. M. (1998). Embryonic stem cell lines derived from human blastocysts. Science, 282(5391), 1145-1147.
9. Treadwell, T., & Schwartz, Z. (2003). Graftjacket® as an effective allograft alternative in the closure of myelomeningocele defects: A report of 3 cases. Journal of Pediatric Surgery, 38(6), E2.
10. Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell, 126(4), 663-676
11. Ott, H. C., Matthiesen, T. S., Goh, S. K., Black, L. D., Kren, S. M., Netoff, T. I., & Taylor, D. A. (2008). Perfusion decellularized matrix: using nature's platform to engineer a bioartificial heart. Nature Medicine, 14(2), 213-221.
12. Hwang, N. S., Varghese, S., Zhang, Z., Elisseeff, J. (2006). Chondrogenic differentiation of human embryonic stem cell derived cells in arginine glycine

aspartate modified hydrogels. Tissue Engineering, 12(9), 2695-2706.

13. Draper, J. S., Pigott, C., Thomson, J. A., Andrews, P. W. (2002). Surface antigens of human embryonic stem cells: changes upon differentiation in culture. Journal of Anatomy, 200(3), 249-258.
14. Elisseeff, J., Puleo, C., Yang, F., Sharma, B., & Seliktar, D. (2005). Design of a Bioartificial Pancreas. Organogenesis, 2(3), 129-140.
15. Ratner, B. D., Hoffman, A. S., Schoen, F. J., & Lemons, J. E. (Eds.). (2004). Biomaterials Science: An Introduction to Materials in Medicine. Elsevier Academic Press.
16. Doudna, J. A., & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR Cas9. Science, 346(6213), 1258096
17. Gaj, T., Gersbach, C. A., & Barbas, C. F. (2013). ZFN, TALEN, and CRISPR/Cas based methods for genome engineering. Trends in Biotechnology, 31(7), 397-405.
18. Yannas, I. V., & Burke, J. F. (1980). Design of an artificial skin. Journal of Biomedical Materials Research, 14(1), 65-81.
19. Orive, G., Emerich, D. F., Khademhosseini, A., & Matsumoto, S. (2018). Engineering Bioartificial Pancreas for Type 1 Diabetes. Endocrine Reviews, 39(6), 688-725.
20. Bolli, R., Chugh, A. R., D'Amario, D., Loughran, J. H., Stoddard, M. F., Ikram, S., & Anversa, P. (2011). Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. The Lancet, 378(9806), 1847-1857.

21. Hare, J. M., Fishman, J. E., Gerstenblith, G., DiFede Velazquez, D. L., Zambrano, J. P., Suncion, V. Y., & Heldman, A. W. (2012). Comparison of allogeneic vs autologous bone marrow–derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the Poseidon randomized trial. JAMA, 308(22), 2369-2379.
22. Lindvall, O., & Kokaia, Z. (2006). Stem cells in human neurodegenerative disorders-time for clinical translation? Journal of Clinical Investigation, 116(5), 1186-1194.
23. Tetzlaff, W., Okon, E. B., Karimi Abdolrezaee, S., Hill, C. E., Sparling, J. S., Plemel, J. R., & Kwon, B. K. (2011). A systematic review of cellular transplantation therapies for spinal cord injury. Journal of Neurotrauma, 28(8), 1611-1682.
24. English, K., & Mahon, B. P. (2011). Allogeneic mesenchymal stem cells: agents of immune modulation. Journal of Cellular Biochemistry, 112(8), 1963-1968.
25. Chandran, S., & Compston, A. (2011). Neural stem cells as a potential source of oligodendrocytes for myelin repair. Journal of Neuropathology & Experimental Neurology, 70(9), 708-717.
26. Kroon, E., Martinson, L. A., Kadoya, K., Bang, A. G., Kelly, O. G., Eliazer, S., & Melton, D. A. (2008). Pancreatic endoderm derived from human embryonic stem cells generates glucose responsive insulin secreting cells in vivo. Nature Biotechnology, 26(4), 443-452.

CHAPTER 2

INNOVATION UNLEASHED: A DEEP DIVE INTO ADVANCES IN CHEMICAL RESEARCH

Bharat Pandey
Department of Chemistry
S.B.S. Govt.P.G. College, Rudrapur
U.S. Nagar, Uttarakhand, India

Kamal K Pande
Department of Chemistry
Govt. P.G. College, Bazpur
U.S. Nagar, Uttarakhand, India

Lata Pande
Department of Food and Nutrition
D.S.B. Campus Kumaon University
Nainital, Uttarakhand, India

Abstract

Chemical research is at the forefront of driving innovation and advancements across various scientific disciplines. "Innovation Unleashed" is a comprehensive exploration of the latest breakthroughs and developments in the field of chemical research. This deep dive into the world of chemical research aims to shed light on the transformative power of chemistry and its impact on society.

Introduction

Innovation is the driving force behind progress and growth in every aspect of our lives. It fuels advancements, shapes industries, and propels societies forward. In this chapter, we will explore the concept of innovation, its

significance, and how it can be fostered to create a better future for all.

Understanding Innovation:

Innovation can be described as the process of turning novel ideas into valuable products, services, or processes. It involves the application of creativity, knowledge, and critical thinking to solve problems and meet evolving needs. Innovation is not limited to any specific field, industry, or individual, and it can manifest in various forms – from incremental improvements to groundbreaking breakthroughs.

The Significance of Innovation:

Innovation plays a crucial role in driving economic growth, enhancing productivity, and improving the quality of life. It empowers businesses to stay competitive, adapt to changing market dynamics, and create new opportunities. Moreover, innovation has the potential to address societal challenges, such as sustainability, healthcare, education, and poverty, by introducing transformative solutions.

Fostering a Culture of Innovation:

Creating an environment that nurtures and encourages innovation is essential for organizations, communities, and individuals alike. Here are some key factors that contribute to fostering a culture of innovation:

1. Embrace a Growth Mindset: Cultivate a mindset that sees failures as learning opportunities and encourages continuous improvement.
2. Encourage Collaboration: Foster a collaborative work environment that encourages diverse perspectives, interdisciplinary collaboration, and knowledge sharing.

3. Promote Creativity: Provide the necessary resources, time, and freedom for individuals to explore their creativity and generate new ideas.
4. Emphasize Experimentation: Encourage a culture of experimentation and risk-taking, where individuals are supported in trying new approaches and learning from both successes and failures.
5. Support Lifelong Learning: Promote continuous learning and skill development to stay updated with the latest trends and technologies.
6. Embrace Diversity and Inclusion: Embrace diversity in all its forms, as it brings together different backgrounds, experiences, and perspectives, which can lead to more innovative solutions.
7. Foster Open Communication: Establish an open and transparent communication channel that encourages the exchange of ideas, feedback, and constructive criticism.
8. Provide Resources: Ensure access to necessary resources, such as funding, technology, and mentorship, to support the implementation of innovative ideas.

Innovations Transforming Our World:

The impact of innovation can be seen in various fields, from healthcare and transportation to communication and energy. Here are some noteworthy examples of recent innovations:

1. Artificial Intelligence (AI) and Machine Learning: AI has revolutionized industries by enabling automation, data analysis, and predictive modeling, leading to improved efficiency and decision-making.

2. Renewable Energy: Advances in renewable energy technologies, such as solar and wind power, have paved the way for a cleaner and more sustainable future.
3. Healthcare Breakthroughs: Innovations in medical technology, precision medicine, and telehealth have transformed healthcare, improving patient outcomes and accessibility to medical services.
4. Internet of Things (IoT): The IoT has connected devices and enabled the collection and analysis of vast amounts of data, leading to smarter and more efficient systems in sectors like transportation, agriculture, and manufacturing.

Conclusion

Innovation is a catalyst for progress and a key driver of positive change. By fostering a culture of innovation and embracing new ideas, we can unlock the potential for solving complex problems, driving economic growth, and improving the quality of life for individuals and communities worldwide. Embracing innovation is not just about advancing technology but also about embracing creativity, collaboration, and continuous improvement. Together, let us embrace innovation and shape a better future for all.

References

1. Christensen, C. M. (2013). The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail. Harvard Business Review Press.
2. Dyer, J., Gregersen, H., & Christensen, C. M. (2011). The Innovator's DNA: Mastering the Five Skills of Disruptive Innovators. Harvard Business Review Press.

3. Brown, T. (2009). Change by Design: How Design Thinking Transforms Organizations and Inspires Innovation. HarperBusiness.
4. Pink, D. H. (2009). Drive: The Surprising Truth About What Motivates Us. Riverhead Books.
5. Kelley, T., & Kelley, D. (2013). Creative Confidence: Unleashing the Creative Potential Within Us All. Crown Business.
6. Rothaermel, F. T. (2017). Strategic Management: Concepts and Cases: Competitiveness and Globalization. McGraw-Hill Education.
7. Chesbrough, H. (2010). Open Innovation: The New Imperative for Creating and Profiting from Technology. Harvard Business Review Press.
8. Tidd, J., Bessant, J., & Pavitt, K. (2013). Managing Innovation: Integrating Technological, Market, and Organizational Change. Wiley.
9. West, M. A. (2002). Sparkling Fountains or Stagnant Ponds: An Integrative Model of Creativity and Innovation Implementation in Work Groups. Applied Psychology: An International Review, 51(3), 355-387.
10. Gassmann, O., & Frankenberger, K. (2017). The Business Model Navigator: 55 Models That Will Revolutionize Your Business. Pearson.
11. Rogers, E. M. (2010). Diffusion of Innovations. Simon and Schuster.
12. Govindarajan, V., & Trimble, C. (2012). Reverse Innovation: Create Far From Home, Win Everywhere. Harvard Business Review Press.
13. Hargadon, A. B. (2003). How Breakthroughs Happen: The Surprising Truth About How Companies Innovate. Harvard Business Review Press.

14. Johnson, S. (2010). Where Good Ideas Come From: The Natural History of Innovation. Riverhead Books.
15. Tushman, M. L., & O'Reilly III, C. A. (2002). Winning Through Innovation: A Practical Guide to Leading Organizational Change and Renewal. Harvard Business Review Press.
16. Nonaka, I., & Takeuchi, H. (2011). The Knowledge-Creating Company: How Japanese Companies Create the Dynamics of Innovation. Oxford University Press.
17. Bessant, J., & Tidd, J. (2015). Innovation and Entrepreneurship. John Wiley & Sons.
18. von Stamm, B. (2008). Managing Innovation, Design and Creativity. John Wiley & Sons.
19. Christensen, C. M., & Raynor, M. E. (2003). The Innovator's Solution: Creating and Sustaining Successful Growth. Harvard Business Review Press.
20. Sawhney, M., Wolcott, R. C., &Arroniz, I. (2006). The 12 Different Ways for Companies to Innovate. MIT Sloan Management Review, 47(3), 75-81.

CHAPTER 3

GENOMICS IN THE BREAST CANCER

Dr. Narender Boggula
Associate Professor
CMR College of Pharmacy, Kandlakoya
Medchal, Hyderabad, Telangana, India

Dr. Ganesh Akula
Associate Professor
Sri Ranganayaka Swamy College of Pharmacy
Ramancha, Chinna Kodur, Siddipet, Telangana, India

Korapati Rama Rao
Assistant Professor
Sultan-ul-Uloom College of Pharmacy
Mount Pleasant, Banjara Hills, Hyderabad, Telangana, India

Aravinda Nalla
Assistant Professor
Nalla Narasimha Reddy Education Society's Group of Institutions
School of Pharmacy, Chowdariguda, Ghatkesar, Medchal, Telangana, India

Abstract

Cancer is a socioeconomical burden in any nation. Out of that, breast cancer is identified as the most common malignancy worldwide among women irrespective of age. As women are an important segment in a community, the weakening of their strength toward the development of a nation is a critical problem in each nation. Breast cancer remains a major health issue in the world with 1.7 million new cases in 2012 worldwide. It is the second cause of death from cancer in western countries. Metastatic breast cancer, which is uncommon at the time of disease onset, variably impacts patients throughout the course of their disease. Both the molecular

profiles and diverse genomic pathways vary in the development and progression of metastatic breast cancer. Genomics have started to modify the treatment of breast cancer, and the developments should become more and more significant, especially in the present era of treatment personalization and with the implementation of new technologies. With molecular signatures, genomics enabled a de-escalation of chemotherapy and personalized treatments of localized forms of estrogen-dependent breast cancers. Genomics can also make a real contribution to constitutional genetics, so as to identify mutations in a panel of candidate genes. In this review, we will discuss the contributions of genomics applied to the treatment of breast cancer, whether already validated contributions or possible future applications linked to research data. Genomic abnormalities in breast cancer have been described according to diverse conceptual frameworks, including histologic subtypes, clinical molecular subtypes, intrinsic DNA, RNA, and epigenetic profiles, and activated molecular pathways. Specific genomic alterations have been found in primary breast cancer involving driver mutations that result in tumorigenesis. Genomics have started to modify the treatment of breast cancer, and the developments should become more and more significant, especially in the present era of treatment personalization and with the implementation of new technologies. In this review, we will discuss the contributions of genomics applied to the treatment of breast cancer.

Keywords: *Genomic, breast cancer, histological classification, human epidermal growth factor receptor.*

Introduction

Cancer is a disease whose development is at least partially driven by germline and/or somatic genetic alterations located on oncogenes or tumour suppressor genes. Thanks to the advent of next-generation sequencing (NGS), DNA analyses have shown that the genomic drivers of cancer can differ between patients. This observation led to the development of cancer precision medicine, in which a comprehensive genomic profile is generated in each patient and a targeted therapy is given accordingly (1-3).

The development of next-generation sequencing (NGS) technologies allows, today, to profile the mutational landscape of tumours with reasonable times and costs. This translated, in the clinical setting, into the development of molecular screening programs mainly for patients with advanced disease resistant to standard therapies, with the aim of improving outcomes by means of new targeted therapies. Implementation of clinical genomics assessments in the clinical trial setting, while being a great opportunity to understand the disease's biology, raises the challenges of data interpretation and their practical applicability. As illustration, nowadays there is no guidance to select genomic alterations in patients with metastatic breast cancer (mBC) and, unfortunately, matching an actionable event with a targeted therapy does not always translate into the expected clinical benefit (4,5).

Breast cancer is the second leading cause of cancer deaths among women. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Early diagnosis of breast cancer is one of the best approaches to prevent this disease. In some developed countries, the 5-year relative survival rate of breast cancer patients is above 80% due to early prevention. In the recent decade, great progress has been made in the understanding of breast cancer as well as in the development of preventative methods. The pathogenesis and tumor drug-resistant mechanisms are revealed by discovering breast cancer stem cells, and many genes are found related to breast cancer(6-8).

Breast cancer remains one of the leading causes of cancer death in women, despite significant improvements in survival over the past 25 years. One of the greatest challenges faced by clinicians and researchers in this field is that breast cancer is

not a single entity, but rather a heterogeneous group of several subtypes displaying distinct differences in biological and clinical behaviour. A primary aim in cancer management is to tailor clinical decisions to the individual, based on a detailed understanding of the molecular profile of the tumour and the likely clinical outcome of the individual's disease. This progress will facilitate personalised treatment approaches that are more targeted, have superior efficacy and are associated with less toxicity. Our increased knowledge of the genomic aberrations underlying human breast cancers, and the molecular processes that are disrupted, are key to understanding the diversity of the disease and achieving the aims of personalised medicine. Over the past decade, the development of high-throughput technologies to study genetic, epigenetic and proteomic changes has allowed for rapid progress in our understanding of the complexity of breast cancer biology. Here, we review recent advances that have led to the integration of information on the genomic and transcriptomic landscapes of breast cancers to refine the molecular classification of the disease (9-11).

There are schematically three main histologic types of breast cancer (Figure 1): i) estrogen-dependent breast cancers expressing the estradiol receptor (ER) and treated with a panel of drugs that target the estradiol receptor pathway; ii) breast cancers overexpressing the human epidermal growth factor receptor 2 (HER2) oncoprotein and treated with anti-HER2-based chemotherapies, the first anti-HER2 being a therapeutic monoclonal antibody, trastuzumab; and iii) "triple negative" breast cancers which lack the expression of the estradiol receptor, the progesterone receptor, and HER2. There are still no targeted therapies for triple-negative breast cancers, which have a high metastatic potential, and consequently a bad prognosis (12,13).

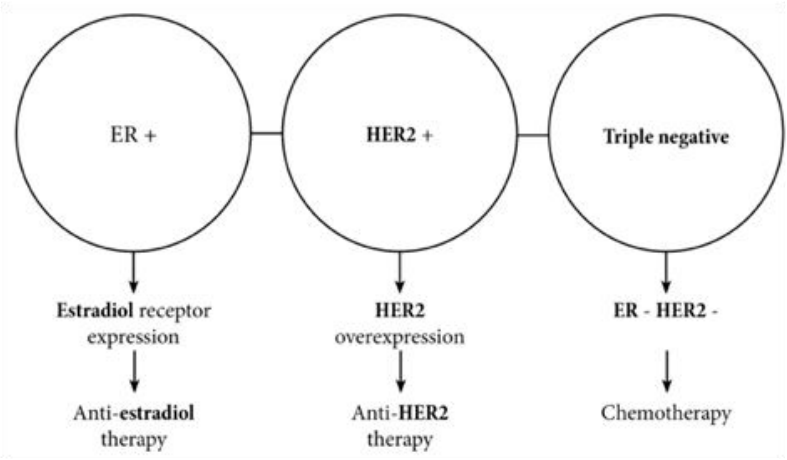


Figure 1: Histological classification

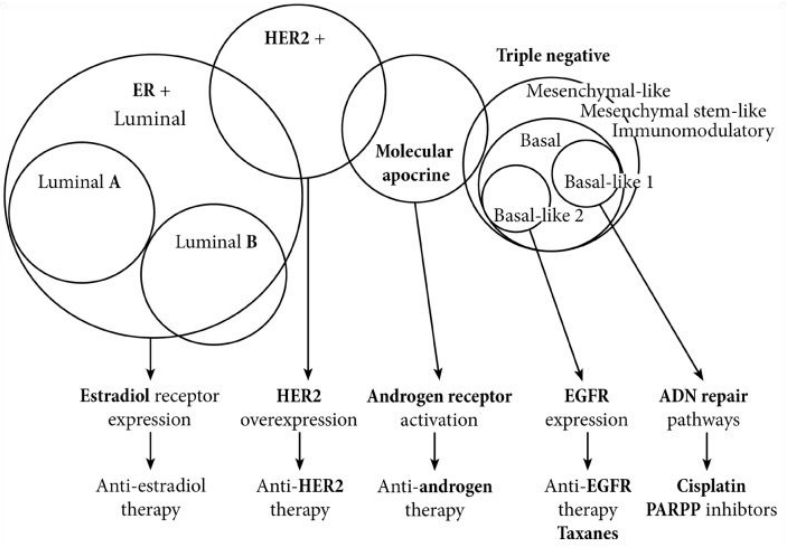


Figure 2: Molecular classifications

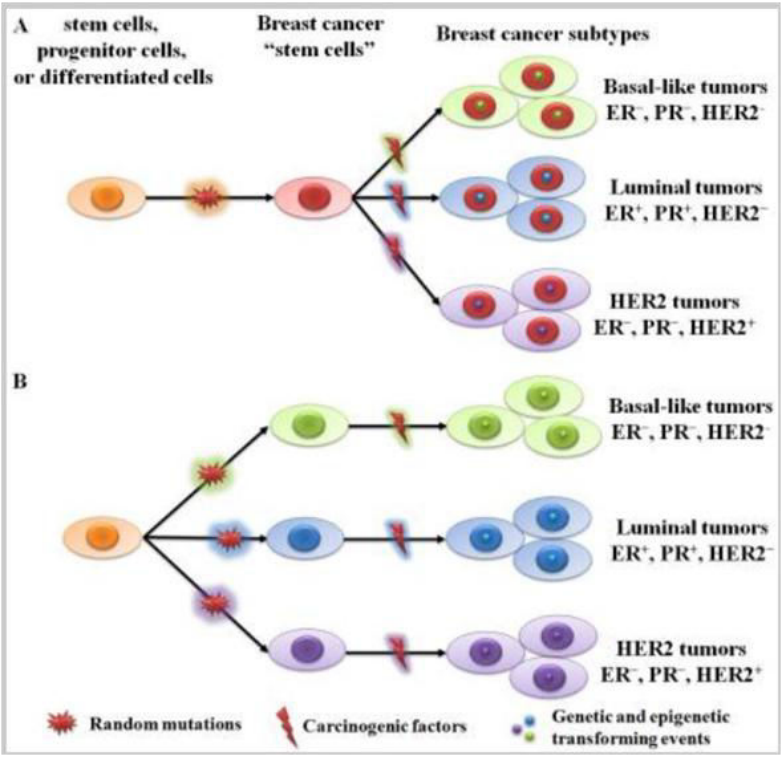


Figure 3: Two hypothetical theories of breast cancer initiation and progression. (A) All subtypes of tumour are derived from the same stem cells or progenitor cells. Different tumor phenotypes are then determined by subtype-specific transforming events. (B) Each tumour subtype is initiated from a single cell type (stem cell, progenitor cell or differentiated cell). Random mutations can gradually accumulate in any breast cells, leading to their transformation into tumour cells when an adequate no. of mutations have accumulated.

In conjunction with histopathological assessment, the standard evaluation of breast cancer for clinical purposes involves IHC characterisation of ER, PR and HER2 status.

Hormone receptor-positive breast cancers account for around 75–80% of all cases and standardised IHC assays for the routine testing of ER and PR are used to guide the selection of patients for hormonal-based therapies. HER2 represents the only additional predictive marker currently in routine use. Approximately 10–15% of breast cancers have HER2 overexpression and/or amplification with around half of these co-expressing hormone receptors. These patients are selected for anti-HER2 based therapies, including the humanised monoclonal HER2 antibody, trastuzumab, which targets the extracellular domain of the HER2 receptor. The remaining 10–15% of breast cancers are defined by hormone receptor and HER2 negativity (i.e., triple negative cancers), which represent a key clinical entity given their lack of therapeutic options. While the current classification of human breast tumours has been fundamental for prognostic and predictive evaluation, there remain a number of important limitations. First, considerable variation in response to therapy and clinical outcome still exists, even for tumours with apparent similarities in clinical and pathological characteristics. Second, this classification continues to provide limited insight into the complex underlying biology and the molecular pathways driving the disease in different subtypes (14-17).

Risk factors of breast cancer

Because breast cancer is a complex illness, various hereditary and nongenetic variables predispose to malignancy. Several risk factors for breast cancer have been discovered in epidemiologic investigations. Only around 10% of all breast cancer instances are caused by hereditary factors, whereas the remaining 90% are caused by nongenetic causes.

Breast cancer is caused by a complex combination of environmental and hereditary factors.

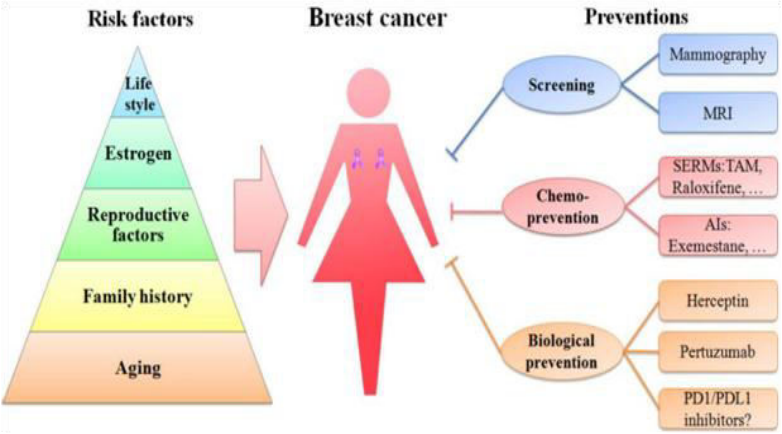


Figure 4: Risk factors

Nongenetic Risk Factors

Female breast cancer risk is affected by the reproductive history. The hormonal background also influences the course of the disease. The female reproductive hormones such as estrogens, progesterone, and prolactin have a major impact on breast cancer and control postnatal mammary gland development. Most of the hormonal risk factors are associated with estrogen hormone. Prolonged exposure to estrogen is known to be associated with elevated levels of breast cancer risk. Factors such as early age at menarche, late onset of menopause, long menstrual history, nulliparity, recent use of postmenopausal hormone therapy or oral contraceptives, late age at first birth, and obesity are considered as hormonal risk factors. There are a number of nonhormonal risk factors associated with the development of breast cancer, which are indirectly attached to modulate the estrogen exposure, such as

age at exposure to ionizing radiation, alcohol consumption, and dietary factors.

The metastatic process ends after a series of sequential steps have been completed. If tumor cells have already invaded the surrounding host tissue, they can spread to lymphatic or blood vessels and other organs and tissues. The cancer cells distribute throughout the body via blood and lymphatic veins. Angiogenesis and proliferation occur when tumor cells are in cell cycle arrest, preventing tumor cells from entering the target organ's parenchyma. Both apoptosis and immunosuppression must be avoided. If these phases successfully spread cancer, there may be "metastases of metastases". In its early stages, breast cancer can damage the auxiliary lymph nodes, lungs, bones, brain, liver, and peritoneum. BC that has spread to the bones is a regular occurrence. The metastatic spread of breast cancer tumours to the bones is approximately 67 percent. Breast tumours with luminal B (79%) and luminal A (70%) are more likely to metastasize to the bones, whereas HER2+ and TNBC (basal-like) have 60% and 40% chances, respectively. Breast cancer metastases are often found in the liver, auxiliary lymph nodes, and lungs. In about 37% of instances, advanced BC will spread to the liver and lungs, and 30-50% will spread to the auxiliary lymph nodes(18-21).

TNBC with HER2+ liver metastases are less common than luminal breast cancer. TNBC has a 35% likelihood of metastasizing to the liver, while HER2+ has a 45% chance. TNBC has a higher risk of angiogenesis and infection of auxiliary lymph nodes than other subtypes. Luminal A and B had a reduced likelihood of metastasis in the lungs (25-30%) than TNBC and HER2+ (45-35%). Metastases to the liver, lungs, or brain can substantially reduce a patient's survival time. Metastases to other organs affect 12.6 percent of cancer

patients. TNBC and HER2+ breast tumours reported more metastases in this metastatic zone (25-30%) than Luminal A and Luminal B (5-15%). Less common metastatic locations include the mammary internal chain lymph nodes (10-40%), contralateral breast (6%), and supraclavicular lymph nodes (1-4%).

Pathophysiology

Breast cancer is a malignant tumor that starts in the cells of the breast. Like other cancers, there are several factors that can raise the risk of getting breast cancer. Damage to the DNA and genetic mutations can lead to breast cancer have been experimentally linked to estrogen exposure. Some individuals inherit defects in the DNA and genes like the BRCA1, BRCA2 and P53 among others. Those with a family history of ovarian or breast cancer thus are at an increased risk of breast cancer. The immune system normally seeks out cancer cells and cells with damaged DNA and destroys them. Breast cancer may be a result of failure of such an effective immune defence and surveillance. These are several signalling systems of growth factors and other mediators that interact between stromal cells and epithelial cells. Disrupting these may lead to breast cancer as well.

Etiology

Identifying factors associated with an increased incidence of breast cancer development is important in general health screening for women. Risk factors for breast cancer can be divided into 7 broad categories:

- Age: The age-adjusted incidence of breast cancer continues to increase with the advancing age of the female population.
- Gender: Most breast cancers occur in women.

- Personal history of breast cancer: A history of cancer in one breast increases the likelihood of a second primary cancer in the contralateral breast.
- Histologic risk factors: Histologic abnormalities diagnosed by breast biopsy constitute an important category of breast cancer risk factors. These abnormalities include lobular carcinoma in situ (LCIS) and proliferative changes with atypia.
- The family history of breast cancer and genetic risk factors: First-degree relatives of patients with breast cancer have a 2-fold to 3-fold excess risk for developing the disease. Five percent to 10% of all breast cancer cases are due to genetic factors, but they may account for 25% of cases in women younger than 30 years. BRCA1 and BRCA2 are the 2 most important genes responsible for increased breast cancer susceptibility.
- Reproductive risk factors: Reproductive milestones that increase a woman's lifetime estrogen exposure are thought to increase her breast cancer risk. These include the onset of menarche before 12 years of age, first live childbirth after age 30 years, nulliparity, and menopause after age 55 years.
- Exogenous hormone use: Therapeutic or supplemental estrogen and progesterone are taken for various conditions, with the two most common scenarios being contraception in premenopausal women and hormone replacement therapy in postmenopausal women(22-24).

Genes related to breast cancer

Lots of genes have been identified in relation to breast cancer. Mutations and abnormal amplification of both

oncogenes and anti-oncogenes play key roles in the processes of tumor initiation and progression.

BRCA1

BRCA1 is a versatile protein that links DNA damage sensing and DDR effectors. BRCA1 interacts with tumour suppressors, DNA repair proteins and cell cycle regulators through its various functional domains and thereby has diverse roles in multiple DNA repair pathways (particularly HR, NHEJ and single-strand annealing (SSA)) and in checkpoint regulation. BRCA1 contains an amino-terminal RING domain that has E3 ubiquitin ligase activity (which catalyses protein ubiquitylation) and a BRCT domain that facilitates phospho-protein binding. Many inherited cancer-associated BRCA1 mutations have been found within the RING and BRCT domains, indicating that both domains are involved in suppressing breast and ovarian cancer.

BRCA2

In contrast to the multifunctional activities of BRCA1, the primary function of BRCA2 is in HR (homologous recombination). BRCA2 mediates the recruitment of the recombinase RAD51 to DSBs; RAD51 recruitment is not only essential for HR but is also responsible for the tumour-suppressive function of this repair process. BRCA2 contains a DNA-binding domain (DBD) that binds single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) and eight BRC repeats that bind RAD51. The DBD contains five components: a 190-amino-acid α-helical domain, three oligonucleotide binding (OB) folds that are ssDNA-binding modules, and a tower domain (TD) that protrudes from OB2 and binds dsDNA. The helical domain, OB1 and OB2 also associate with

deleted in split-hand/split-foot syndrome (DSS1), which has been linked to BRCA2 protein stabilization (25).

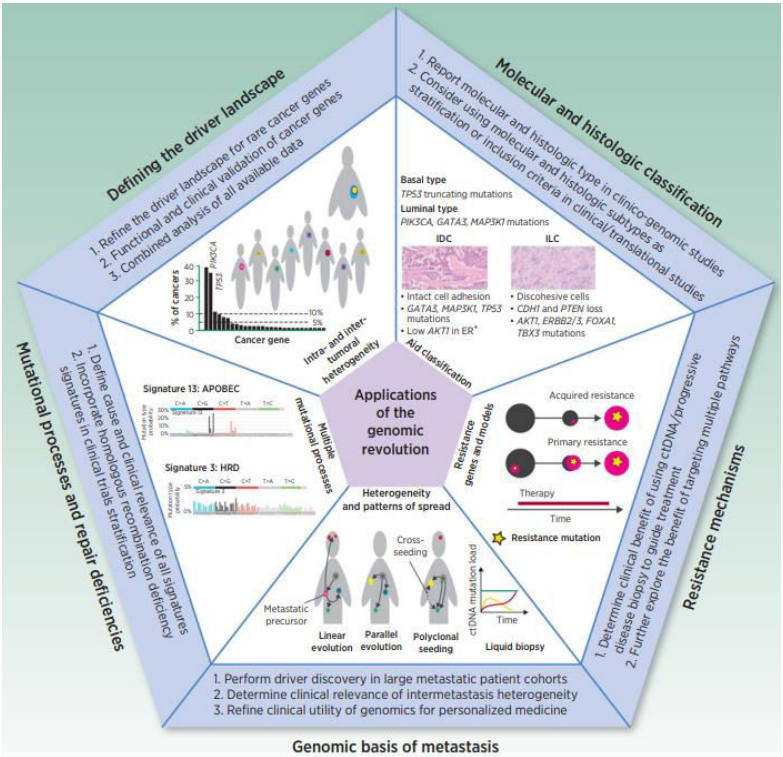


Figure 5: Applications of the genomic revolution in breast cancer. Each of the five segments represents an application of the genomic revolution, main findings are pictured within the inner, white panel, and outstanding challenges are summarized in the outer, blue panel. Histologic subtypes: invasive ductal cancer (IDC) and invasive lobular cancer (ILC).

Table 1: Gene panel tests used for therapeutic decision of localized breast cancers (26)

Signature	Number of genes	Clinical application	Risk category
MammaPrint	70	N−, ER+ or ER− Estimates relapse risk	Low and high
OncotypeDX	21	ER+, HER2−, N− Estimates chemotherapy benefit and relapse risk during hormonotherapy	Low, intermediate and high
EndoPredict	11	ER+, HER2−, N− or N+ Predicts local and metastatic relapse during hormonotherapy	Low and high
Prosigna (PAM50)	50	ER+/N− and N+ treated by hormonotherapy Predicts 10-year metastasis-free survival	Low, intermediate and high
Breast Cancer Index	5 and 2 genes ratio	ER+/N− and N+ treated by hormonotherapy Predicts 10-year metastasis-free survival	Low and high
Rotterdam	76	ER+, N− Predicts relapse under treatment with tamoxifen	Low and high

BluePrint	80	Discriminates sub-types with different level of sensitivity to adjuvant treatment	Not applicable

N: Node status in TNM classification; ER: Estradiol Receptor; RT-PCR: Reverse Transcription-Polymerase Chain Reaction.

HER2

Human epidermal growth factor receptor 2, also known as *c-erbB-2*, is an important oncogene in breast cancer and located on the long arm of human chromosome 17 (17q12). The homologene in mice is *Neu*, which was first identified in 3-methylcholanthrene induced rat neuroblastoma cells. The expression of *HER2* gene is activated mainly through the gene amplification and re-arrangement. HER2 protein is an epidermal growth factor receptor (EGFR) of tyrosine kinase family and form heterodimers with other ligand-bound EGFR family members such as Her3 and Her4, thus to activate downstream signaling pathways. Knockout of *HER2* in mouse models disrupts normal mammary duct formation. Overexpression of HER2, which is detected in about 20% of primary breast cancers, increases the number of cancer stem cells by PTEN/Akt/mTORC1 signaling, and indicates poor clinical outcomes.

Epidermal Growth Factor Receptor (EGFR)

EGFR, also known as *c-erbB-1* or *Her1* in humans, is located on the short arm of chromosome 7 (7p12). The EGFR protein is a cell surface glycoprotein of tyrosine kinase family and is activated by binding to EGF, TGF-α, amphiregulin, betacellulin and so on. The downstream signaling pathways of EGFR including PI3K, Ras-Raf-MAPK and JNK are triggered to promote cell proliferation, cell invasion,

angiogenesis and to protect cells against apoptosis. Overexpression of EGFR is found in more than 30% of cases of the inflammatory breast cancer (IBC), a very aggressive subtype of breast cancer. Patients with *EGFR*-positive IBC have a poorer prognosis than those with *EGFR*-negative tumours. More than half of triple-negative breast cancer (TNBC) cases, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) expression and HER2 amplification, also have EGFR overexpression. Therefore, targeting the EGFR pathway might be a promising therapy for these malignant tumours.

c-Myc

This gene is located on the long arm of chromosome 8 (8q24) and encodes for the Myc protein, a transcription factor containing the bHLH/LZ (basic Helix-Loop-Helix Leucine Zipper) domain. Genome-wide screening shows that 15% of all genes are regulated by the Myc protein mainly through binding on the E-box consensus (CACGTG) and recruiting histoneacetyl transferases (HATs) or DNA methyltransferases. Some of the Myc-regulated genes such as *MTA1, hTERT* and *PEG10* play vital roles in breast cancer initiation and progression. The over expression of c-Myc is predominantly observed in the high-grade, invasive stage of breast carcinomas, while no c-Myc amplification is detected in the benign tissues (27,28).

Changes in transcription of ER, its co-regulators, epigenomic, and post-translational modifications in ER, genetic polymorphisms affecting pharmacokinetics of anti-hormone drugs that affect ER expression, mutations in ER pathway that affect its activity along with therapy induced genomic aberrations may favour endocrine resistance (Figure 6). Owing to the complexity of ER biology in cancer, an

integrative analysis of multiplatform data that can evaluate wellness trajectories during the course of treatment is necessary in identifying more mechanisms, and newer targets to combat endocrine resistance.

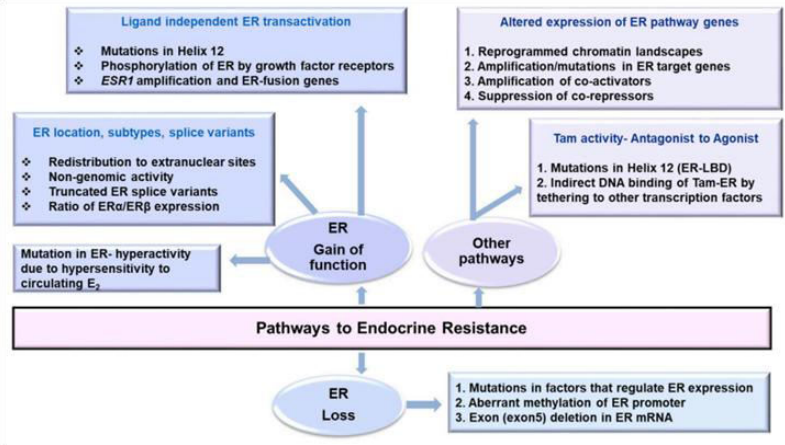


Figure 6: Pathways that may lead to endocrine resistance in breast cancer

NGS Assays of Cancer Samples

The application of NGS technologies to the characterization of human tumours has provided unprecedented opportunities to understand the biological basis of different cancer types, develop targeted therapies and interventions, discover genomic biomarkers of drug response and resistance, and to guide clinical decision-making regarding the treatment of patients. Furthermore, the versatility of NGS assays in addition to the diversity of upstream sample preparation methodologies has enabled the characterization of cancer genomes, transcriptomes, and epigenomes. NGS can reveal sequence mutations, small insertions and deletions, copy number alterations, structural rearrangements, and loss of heterozygosity in tumour DNA

samples. Sequencing of tumour-derived RNA enables the identification of differentially expressed genes, gene fusions, small RNAs, aberrantly spliced isoforms, and allele-specific expression patterns. Chemical modifications of DNA and/or histones, and changes in higher-order chromatin structure can also be mapped with increasing levels of precision. The algorithmic analysis of data from multiple NGS-based assays, in addition to the intrinsic genetic complexity of cancer, poses a major challenge to the clinical interpretation of NGS data(29).

Identifying Genomic Mechanisms of Resistance to Treatment

Changes in sub clonal structure have been demonstrated across treatment interventions using cytotoxic and endocrine therapy and targeted therapies. Several genomic mechanisms of resistance to various therapies have recently been uncovered, with mutations in ESR1, the gene encoding the ER, being the most described and studied in the context of endocrine resistance. Mutations cluster in the ligand-binding domain of ESR1 and activate ER in the absence of the estrogen ligand. These mutations have been detected almost exclusively in the context of prior endocrine therapy, typically with aromatase inhibitors, and more frequently where sensitivity to prior endocrine therapy was observed, suggesting that these mutations are associated with acquired, but not primary, endocrine resistance. A recent large-scale initiative, the Metastatic Breast Cancer Project, characterized over 140 metastatic biopsies from endocrine therapy–treated patients and identified several acquired mutations, in addition to ESR1, that may be involved in endocrine resistance, including AKT1, ERBB2, KRAS, and RB1 alterations(30).

Significantly Mutated Genes Versus Background Mutations in Breast Cancer

Sequencing of DNA and RNA from tumours by using massively parallel sequencing with a capture or other sequence selection approach (exomes or candidate genes) or unbiased 'whole genome' approach has become a standard research tool now that the technology has been extensively commercialized. One objective of cancer sequencing studies is to identify genes that have undergone somatic mutations, which contribute to malignant transformation. Genes that accumulate somatic mutations at a higher than stochastic rate are referred to as 'significantly mutated genes' (SMGs) and are considered likely drivers of malignant progression. In breast cancer, there is a dramatic difference in the SMG list between luminal-type breast cancer and basal-like breast cancer. In The Cancer Genome Atlas (TCGA) breast cancer data, at least 20 SMGs were observed in luminal type A, eight in luminal-type B, but only three in basallike breast cancer. This is not because luminal breast cancer genomes are more complex than those of basal-like breast cancer; in fact, the opposite is true. Basal-like breast cancer genomes are often so complex that it has proven difficult to identify the causal events by using mutation recurrence statistics. Furthermore, structural rearrangements (large-scale chromosomal deletions, amplifications, inversions, and translocations) are likely to play a particularly critical role in basal-like breast cancer, and the complete delineation of these events requires whole genome sequencing, which is technically demanding and expensive(31,32).

The genomic structure of breast cancer reveals underlying DNA repair defects

Aside from the focus on the identification of individual genes that are repetitively disrupted in breast cancer, a more broad-based analysis of breast cancer genome structures has led to a paradigm shift in the way we view pathogenesis. The standard multistep model of carcinogenesis postulates that mutations accumulate gradually, one at a time, in a process of Darwinian selection in which individual mutant-bearing clones effectively compete with normal cells and other clones within the tumor through the acquisition of the ability to transform, invade, metastasize, and evade drug treatment. However, it was recently demonstrated that multiple mutations can arise over a very short period wherein multiple chromosomal breaks that occurred during a single catastrophic cell division event are (rarely) viably repaired, reshuffling the genome in a way that rapidly triggers transformation though the simultaneous oncogene amplifications and tumor suppressor gene deletions in the vicinity of the multiple translocations that ensue (chromothripsis).

Chemoresistance is a critical concern in the treatment of breast cancer. It is difficult to understand their chemoresistance mechanisms. More effective therapies are desperately needed to combat medication resistance and improve current therapy regimens. The issue can be addressed using novel pharmacological agents and carriers, as well as a combination of therapies. Other new medications, such as gene therapy and immune-based therapies, are being tested to see if they can overcome drug resistance (33-35).

HER2 and ESR1 mutations as examples of novel druggable targets

The utility of detailed preclinical work on potentially druggable genes is nicely illustrated by the study of HER2 mutations in breast cancer. Data from eight breast cancer genome-sequencing studies identified 25 patients with HER2 somatic mutations without HER2 amplification. Thirteen HER2 mutations were functionally characterized by using in vitro kinase assays, protein structure analysis, cell culture, and xenograft experiments. The results showed that the investigational drug neratinib, an irreversible HER2 inhibitor, rather than lapatinib, an approved HER2 kinase inhibitor, was a better approach for clinical studies since some of the recurrent mutations were naturally lapatinib resistant. This is a result that simple drug somatic mutation matching software would not have revealed. Currently, patients with advanced HER2 mutation-positive tumours are being enrolled into a single-agent study of neratinib. Point mutations in the estradiol-binding domain of the estrogen receptor gene (ESR1) are emerging as a potent cause of acquired endocrine therapy resistance. Although there are no drugs that specifically target these mutations, alternative endocrine therapies may be effective in this setting and this possibility will soon be addressed in clinical trials(36-38).

Patient-derived xenografts as genomic models for breast cancer

A major criticism of standard cell lines as a model for human breast cancer is that they are essentially disconnected from the individuals from whom they were derived. Without knowledge of the progenitor tumor genome as a reference point and no knowledge of the clinical characteristics of the patient who donated the tissue, it is uncertain what the cell

lines actually model from an individual patient perspective and to what degree genetic drift has occurred after prolonged in vitro culture. These limitations likely contribute to the poor predictive utility of cell line panels in drug development. An alternative preclinical model for drug optimization and target validation is the patient-derived xenograft (PDX) approach. Detailed information covering the continuum from specimen acquisition to development of patient-derived xenografts has been presented and reviewed elsewhere. In brief, a biopsy-sized sample of primary or metastatic tumor is transferred directly into an immunodeficient mouse by orthotopic or subcutaneous implantation. Once tumor engraftment has occurred, RNA and DNA sequencing or chip-based analysis is employed to compare the patient tumor to the PDX. PDXs maintain fidelity to the patient tumor based on molecular subtypes, mutational spectrum, copy number variations, gene expression profiles, and histopathology(39-41).

Future Areas of Research

Proteomics as the next step in the annotation of the breast cancer genome

A fundamental problem in the study of cancer genomics at the level of DNA and RNA is that conclusions regarding pathway activation are indirect since proteins, not nucleic acids, execute these functions. Thus, when signaling and biology are discussed, it is through inference from signal transduction databases that may or may not have been conducted in the relevant biological context and that may or may not be correct. Informatics approaches generate hypotheses, not conclusions. The reverse phase protein array (RPPA) is one answer to the problem of efficiently tracking protein levels and phosphorylation events. Here, tumor protein extracts from many tumours are spotted into slides

and probed with highly quality-controlled antibodies. Unfortunately, the generation of RPPA-quality antibodies is technically challenging; in particular, the number of phosphosite-specific antibodies is very limited. Therefore, mass spectrometry is being developed to examine the protein biochemistry of the cancer cells in less biased ways by direct protein sequencing and mass analysis to determine post-translational modifications. Next-generation proteomic technologies are poised to provide deep information on tumor proteomes and on post-translational modifications of all types. When combined with genomic data, proteomics may enable a deep understanding of complex mechanisms that regulate gene function and dysfunction in cancer. These objectives are being realized by the National Cancer Institute Clinical Proteomic Tumor Analysis Consortium, which is applying standardized proteome analysis platforms to analyze tumor tissues from the TCGA program as well as unique cell and xenograft models and other tissue collections, all of which are accompanied by rich genomic datasets (42-44).

In this domain of constitutional genetics, many questions remain unanswered, particularly the translational value of identifying mutations of unknown significance in genes of low to moderate penetrance. The contributions of Genome-Wide Association Studies (GWAS) have not been very great. To date, more than sixty GWAS have been conducted on breast cancer samples. A meta-analysis of these GWAS identified 84 loci of interest possibly associated with an increased risk of breast cancer. Numerous low penetrance variants have been identified, without validating their functional significance. One of these variants concerns the oncogene FGFR2 (fibroblast growth factor receptor 2), the FGFR2 protein being overexpressed in 5% of breast cancers. This variant corresponds to a single nucleotide polymorphism

(SNP) that affects the binding site of FGFR2, thus activating the downstream signaling pathway in a ligand-independent manner. It is necessary to address the potential benefit of targeting FGFR2 for therapeutic purpose. Another SNP, in the 8q24 region, participates in regulating MYC oncogene transcription which is distant from this SNP by more than 300 kb. Most GWAS studies suggest that mutations in low penetrance genes could partially explain genetic predisposition to breast cancer, even though their functional significance remains unclear.

Conclusion

Multiple layers of evaluation combining clinical information regarding pathways underpinning particular groups will be used in the future of breast cancer categorization, with various consequences for the rationale development of targeted treatments. As we obtain a greater understanding of breast cancer's heterogeneity, it is evident that thousands more individuals must be investigated in order to properly understand the therapeutic consequences of novel and uncommon subgroups of the disease. Furthermore, more advanced model systems, both in vitro and in vivo, will be required to examine the molecular complexity of this heterogeneity, including the use of xenograft tumours grown directly from source clinical material. Finally, genomics-based tests are increasingly being used as a component of evidence-based diagnosis that can influence cancer care.

The use of clinical genomics in cancer care is gaining traction as the utility of the assays increases. As might be imagined in this rapidly progressing field, several genomic applications are currently under active development and might further expand the clinical utility of genomic assays in the future. A prime example involves the development and

extension of assays designed to profile DNA isolated from samples obtained using minimally invasive procedures, such as sampling of blood plasma or other bodily fluids (sputum, urine, or cerebrospinal fluid). Liquid biopsy sampling takes advantage of the fact that cell death in actively growing tumours leads to the release of tumour cell-derived DNA into the circulation and into other fluids that come into contact with organs. Cell-free DNA (cfDNA) collected in this fashion might be used for tumour mutation profiling, genomic monitoring of response to therapy, and identifying emerging mechanisms of resistance to therapy, thereby providing highly sensitive and specific indicators to guide clinical care and decision-making processes.

More work has to be done to keep up-to-date this classification, and it is planned to update this ranking on an annual basis. It is imperative that the scientific community shares all results, even and especially the negative ones, in order to improve knowledge in precision and personalized cancer medicine.

Great enthusiasm accompanied the initial years of the genomic revolution as a flood of novel insights into the breast cancer genome were presented in quick succession. We now have a clearer idea not only of the potential clinical applications of genomics but also of the scale and nature of the challenges that must be surmounted to bring maximum benefit to breast cancer patients. It is clear that delivering personalized breast cancer treatments to all patients in the future will only be possible if we focus on collaborative and integrative approaches now.

References

1. HanahanD, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144:646–674.
2. Liu, J. et al. An integrated TCGA pan-cancer clinical data resource to drive high-quality survival outcome analytics. Cell. 2018; 173:400–416.
3. Yates, L. R. et al. The European Society for Medical Oncology (ESMO) Precision Medicine Glossary. Ann. Oncol. 2018; 29:30–35.
4. Arnedos, M. et al. Precision medicine for metastatic breast cancer-limitations and solutions. Nat. Rev. Clin. Oncol. 2015; 12:693–704.
5. Gennari, A. et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann. Oncol. 2021; 32:1475–1495.
6. Andre F, Bachelot T, Commo F et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). Lancet Oncol. 2014; 15(3): 267–274.
7. Massard C, Michiels S, Ferte C et al. High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: results of the MOSCATO 01 trial. Cancer Discov. 2017; 7(6):586–595.
8. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med. 2011; 62:233–47.
9. Higgins MJ, Baselga J. Targeted therapies for breast cancer. J Clin Invest. 2011; 121:3797–3803.
10. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010; 363:1938–48.

11. Dawson SJ, Provenzano E, Caldas C. Triple negative breast cancers: clinical and prognostic implications. Eur J Cancer. 2009; 45(Suppl 1):27–40.
12. AM, Weber BL. Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst. 2000;92(14):1126–1135.
13. Brisken C, O'Malley B. Hormone action in the mammary gland. Cold Spring Harb Perspect Biol. 2010;2(12):a003178.
14. Roman M, Sakshaug S, Graff-Iversen S, et al. Postmenopausal hormone therapy and the risk of breast cancer in Norway. Int J Cancer. 2016;138(3):584–593.
15. Newcomb PA, Trentham-Dietz A, Hampton JM, et al. Late age at first full term birth is strongly associated with lobular breast cancer. Cancer. 2011;117(9):1946–1956.
16. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res. 2005;7(1):21–32.
17. Ji X, Lu Y, Tian H, Meng X, Wei M, Cho WC. Chemoresistance mechanisms of breast cancer and their countermeasures. Biomed Pharmacother. 2019;114:108800.
18. Tufail M. Genome editing: an essential technology for cancer treatment. Medicine in Omics. 2022;4:100015.
19. Majidpoor J, Mortezaee K. Steps in metastasis: an updated review. Med Oncol. 2021;38:1–17.
20. Welch DR, Hurst DR. Defining the hallmarks of metastasis. Cancer Res. 2019;79:3011–3027.
21. Brown M, Assen FP, Leithner A, Abe J, Schachner H, Asfour G, Bago-Horvath Z, Stein J, Uhrin P, Sixt M. Lymph node blood vessels provide exit routes for

metastatic tumor cell dissemination in mice. Science. 2018;359:1408–1411.
22. Fidler IJ, Gersten DM, Hart IR. The biology of cancer invasion and metastasis. Adv Cancer Res. 1978;28:149–250.
23. Talmadge JE, Fidler IJ. AACR centennial series: the biology of cancer metastasis: historical perspective. Cancer Res. 2010;70:5649–5669.
24. Watanabe Y, Anan K. The decision to perform or omit sentinel lymph node biopsy during mastectomy for ductal carcinoma in situ should be tailored in accordance with preoperative findings. Breast Cancer. 2019; 26(2):261-262.
25. Rakha EA, Green AR. Molecular classification of breast cancer: what the pathologist needs to know. Pathology. 2017; 49:111–119.
26. Rocque GB, Williams CP, Kenzik KM, Jackson BE, Azuero A, Halilova KI, Ingram SA, Pisu M, Forero A, Bhatia S. Concordance with NCCN treatment guidelines: Relations with health care utilization, cost, and mortality in breast cancer patients with secondary metastasis. Cancer. 2018; 124(21):4231-4240.
27. Huen MS, Sy SM, Chen J. BRCA1 and its toolbox for the maintenance of genome integrity. Nature Rev Mol Cell Biol. 2010; 11:138–148.
28. Deng CX, Brodie SG. Roles of BRCA1 and its interacting proteins. Bioessays. 2000; 22:728–737.
29. Yang H, et al. BRCA2 function in DNA binding and recombination from a BRCA2-DSS1-ssDNA structure. Science. 2002;297:1837–1848.
30. Kristensen CN, Bystol KM, Li B, Serrano L, Brenneman MA. Depletion of DSS1 protein disables homologous

recombinational repair in human cells. Mutat Res. 2010;694:60–64.
31. Miller CA, Gindin Y, Lu C, Griffith OL, Griffith M, Shen D, et al. Aromatase inhibition remodels the clonal architecture of estrogen-receptor-positive breast cancers. Nat Commun. 2016;7:12498.
32. Yates LR, Gerstung M, Knappskog S, Desmedt C, Gundem G, Van Loo P, et al. Subclonal diversification of primary breast cancer revealed by multiregion sequencing. Nat Med. 2015;21:751–759.
33. Balko JM, Giltnane JM, Wang K, Schwarz LJ, Young CD, Cook RS, et al. Molecular profiling of the residual disease of triple-negative breast cancers after neoadjuvant chemotherapy identifies actionable therapeutic targets. Cancer Discov. 2014;4:232–245.
34. Ng CK, Martelotto LG, Gauthier A, Wen HC, Piscuoglio S, Lim RS, et al. Intra-tumor genetic heterogeneity and alternative driver genetic alterations in breast cancers with heterogeneous HER2 gene amplification. Genome Biol. 2015; 16:107.
35. Lucy R. Yates, Christine Desmedt. Translational Genomics: Practical Applications of the Genomic Revolution in Breast Cancer. Clin Cancer Res. 2017; 23(11):2630–2639.
36. Sgroi DC. Preinvasive breast cancer. Annu Rev Pathol. 2010; 5:193–221.
37. Masuda H, Baggerly KA, Wang Y, Zhang Y, Gonzalez-Angulo AM, Meric-Bernstam F, Valero V, Lehmann BD, Pietenpol JA, Hortobagyi GN, Symmans WF, Ueno NT. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res. 2013; 19:5533-5540.

38. Wooster R, Bignell G, Lancaster J. et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378(6559):789–792.
39. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature. 2012;481(7381):287–294.
40. Jiang Q, Greenberg RA. Deciphering the BRCA1 Tumor Suppressor Network. J Biol Chem. 2015;290(29):17724–17732.
41. Kreso A, Dick JE. Evolution of the cancer stem cell model. Cell Stem Cell. 2014;14(3):275–291.
42. Pleasance ED, Cheetham RK, Stephens PJ, McBride DJ, Humphray SJ, Greenman CD, Varela I et al. A comprehensive catalogue of somatic mutations from a human cancer genome. Nature. 2010; 463:191–196.
43. Rodrigo Goncalves, Wayne A Warner, Jingqin Luo, Matthew J Ellis. New concepts in breast cancer genomics and genetics. Breast Cancer Research. 2014; 16:460.
44. Ellis MJ, Gillette M, Carr SA, Paulovich AG, Smith RD, Rodland KK, Townsend RR, Kinsinger C, Mesri M, Rodriguez H, Liebler DC, Clinical Proteomic Tumor Analysis Consortium (CPTAC): Connecting genomic alterations to cancer biology with proteomics: the NCI Clinical Proteomic Tumor Analysis Consortium. Cancer Discov. 2013; 3:1108–1112.

CHAPTER 4

TURMERIC (*CURCUMA LONGA*): EXPLORING ITS MULTIFACETED BIOLOGICAL ACTIVITIES

Rajesh A. Maheshwari, Dhanya B. Sen
Rahul Trivedi, Avinash K. Seth &
Ashim Kumar Sen
Department of Pharmacy
Sumandeep Vidyapeeth Deemed to be University
Piparia, Vadodara, Gujarat, India

Hiren R. Chaudhary
Nootan Pharmacy College, Faculty of Pharmacy
Sankalchand Patel University, Visnagar, Gujarat, India

Abstract

This review delves into the extensive history and versatile applications of turmeric, with a specific focus on its active compound, curcumin. With a medicinal legacy dating back 4,000 years, turmeric has played a vital role in traditional healing practices, notably in Ayurveda. Over the last 25 years, nearly 3,000 studies have highlighted turmeric's increasing recognition in modern medicine. Curcumin, constituting 0.3-5.4% of raw turmeric, is the key therapeutic component, and studies have explored its diverse biological activities, including antioxidant, anti-inflammatory, anticancer, hepatoprotective, cardioprotective, and antidepressant effects. Turmeric and curcumin show promise in addressing various diseases in contemporary medicine. The review emphasizes turmeric's antioxidant properties, reducing oxidative stress and its anti-inflammatory effects, particularly in joint-related conditions. Curcumin's anti-cancer potential, demonstrated through apoptosis induction, and its hepatoprotective effects in liver injury studies are discussed. The cardioprotective impact of

turmeric, linked to its vasorelaxant effects and preventive influence on cardiovascular diseases, is explored. The antidepressant activity of turmeric and curcumin is highlighted, showcasing their efficacy in mitigating neurochemical changes induced by swim stress in mice. Long-term curcumin administration significantly impacts neurotransmitter levels in the hippocampus and frontal cortex of male albino rats, indicating potent antidepressant effects. In summary, this chapter underscores the extensive therapeutic potential of turmeric and curcumin, offering a comprehensive overview of their applications in various health concerns. Ongoing research into the molecular mechanisms behind these effects emphasizes the dynamic nature of turmeric's role in modern medicine.

Keywords: *Turmeric, curcumin, antioxidant, anti-inflammatory, anticancer, hepatoprotective*

Introduction

Throughout the entirety of human history, individuals have harnessed natural plant products for diverse purposes. These plants, having evolved alongside animal life for billions of years, generate a broad spectrum of natural substances. As secondary metabolites produced by higher plants, tens of thousands of these compounds serve as innate defenses against infections and illnesses. Intriguingly, a substantial proportion of these natural compounds demonstrate biological or pharmacological activity, presenting promising opportunities for application in pharmaceutical drug design and discovery. Medications derived from plants have consistently held a significant position in medical practices across a range of societies, spanning both ancient and modern eras.[1-3] The Traditional Indian Healthcare System, Ayurveda, addresses a range of ailments, including cancer, predominantly using medicines or formulations sourced from plants. Among the at least 877 small-molecule medications introduced worldwide from 1981 to 2002, the majority (61%) are derived from natural sources.[4] *Curcuma longa*, popularly known as turmeric (family: Zingiberaceae), a plant with a

history of approximately 4,000 years of medicinal use, plays a dual role in Southeast Asia, particularly India. Beyond its prominence as a key spice, it is employed in medicinal and religious ceremonies. The vibrant yellow hue of turmeric has led to its colloquial designation as "Indian saffron." The nearly 3,000 studies conducted in the last 25 years underscore the growing recognition within modern medicine of the significance of turmeric.[5] Curcumin, also known as diferuloylmethane, along with other volatile oils like tumerone, atlantone, and zingiberone, constitute the key components of turmeric. Additional ingredients include resins, proteins, and carbohydrates. Among these, curcumin, the extensively studied active ingredient, constitutes 0.3-5.4% of raw turmeric. The vibrant golden-yellow pigment of turmeric is attributed to its active compounds, the most notable being curcumin.[6] Curcumin is responsible for many of its therapeutic properties. Numerous studies have explored the diverse biological activities of curcumin, including its free radical scavenger, inflammation-reducing effect, cancer-fighting effect, antiproliferative, antidiabetic, lipid lowering effect, anti-thrombotic, hepatoprotective, anti-diarrheal, carminative, diuretic, antirheumatic, antihypertensive, antibacterial, antiviral, larvicidal, insecticidal, antivenomous, and antityrosinase effects, among others.[7-9] Therefore, both turmeric and curcumin possess the potential for advancement in modern medicine for addressing a variety of diseases. Extensive research has focused on exploring the molecular mechanisms behind these effects, and ongoing investigations are actively pursuing this line of inquiry.

The Traditional Medicinal Use of Turmeric

Turmeric boasts a long and storied history in traditional medicine, spanning millennia. Employed for its therapeutic

advantages since ancient times, this vibrant spice is renowned for its efficacy in addressing diverse health concerns. It often holds a pivotal role in traditional healing practices, underscoring its cultural importance and widespread recognition for its medicinal value across various societies. Several effects of turmeric were discussed in this context:

Antioxidant Activity

Turmeric showcased its antioxidant capabilities by diminishing oxidative stress in animals. In an experiment, rats deficient in retinol were fed a diet containing 0.1% turmeric for three weeks, resulting in a notable reduction in lipid peroxidation rates in the liver (22.6%), kidney (24.1%), spleen, and brain (31.4%).[10] The ingestion of a nutritional amount of turmeric extract orally exhibited a decrease in vulnerability to oxidation in laboratory conditions for both liver microsomes and erythrocyte membranes. In rabbits subjected to a high-fat diet, the administration of turmeric hydroalcoholic extract at a dosage of 1.66 mg/kg of body weight resulted in significantly lower oxidation levels in erythrocyte membranes compared to those in control animals. Furthermore, liver microsomes showed decreased levels of hydroperoxides and thiobarbituric acid-reactive substances.[11] Curcumin boosts its effectiveness as an antioxidant by neutralizing different reactive oxygen species (ROS) such as hydrogen peroxide, superoxide, and nitric oxide (NO) radicals, and by inhibiting lipid peroxidation.[12] Furthermore, it seems that turmeric has the potential to mitigate oxidative stress associated with diabetes. In diabetic rats, an AIN93 diet supplemented with 0.5% turmeric demonstrated a reduction in oxidative stress by preventing elevated levels of protein carbonyls and thiobarbituric acid-reactive substances. Additionally, it reversed changes in antioxidant enzyme activities without

affecting the hyperglycemic condition.[13,14] Turmeric appeared to mitigate osmotic stress, particularly noteworthy for its ability to hinder the aggregation and insolubilization of lens proteins induced by hyperglycemia. This implies that turmeric may either delay or prevent the onset of cataracts.15 Moreover, curcumin has the capacity to elevate glutathione (GSH) levels by upregulating the messenger RNAs (mRNAs) of glutathione transferase. Furthermore, curcumin can inhibit ROS-producing enzymes such as LOX, COX, and xanthine oxidase. Its lipophilic nature positions curcumin as a chain-breaking antioxidant, capable of scavenging peroxyl radicals.[16] The meta-analysis encompassed four studies, comprising three double-blind and one single-blind investigation. The overall participant count comprised 308 individuals, with males accounting for 40%, and the average age of participants being 27.60 ± 3.79 years. Over an average supplementation period of 67 days, with a daily curcumin dosage of 645 mg, the findings suggested a trend towards a reduction in malondialdehyde (MDA) concentration and a significant elevation in total antioxidant capacity (TAC). In conclusion, pure curcumin exhibits potential in lowering MDA levels and augmenting overall antioxidant capacity.[17]

Anti-Inflammatory Activity

Turmeric possesses antiarthritic qualities by averting joint inflammation and the deterioration of periarticular joints. In vivo administration of turmeric extract impeded the localized activation of NF-κB and the expression of genes regulated by NF-κB associated with joint degradation and inflammation. These genes encompass the receptor activator of NF-κB ligand (RANKL), COX-2, and chemokines. Additionally, turmeric prevented the formation of periarticular osteoclasts in rats, as well as the levels of PGE2 in the joints and the infiltration of

inflammatory cells.[18] On the flip side, given that oxidative stress is recognized as a catalyst for persistent inflammation, there is a growing association between antioxidant molecules and their inflammation reducing capabilities. Curcumin, in this context, can influence the expression of NF-κB. The initiation of the NF-κB pathway results in the generation of pro-inflammatory cytokines like TNF-α and interleukins, triggering supplementary pro-inflammatory signaling pathways. Moreover, curcumin's activation of the Nrf2 pathway has the potential to alleviate both oxidative stress and swelling. The COX 1 and 2 converts arachidonic acid into prostaglandins and thromboxanes. Specifically, the activation of COX-2, prompted by various cytokines and tumor promoters, is closely associated with both swelling and carcinogenesis. Numerous studies have provided evidence that curcumin has the ability to hinder the elevation of COX-2 gene expression. [19] Turmeric significantly suppressed carrageenan-initiated edema in rats, and its water extracts demonstrated greater efficacy than its alcohol extracts. Additionally, when administered intraperitoneally, turmeric extract proved more effective in reducing edema compared to hydrocortisone.[20,21] The discovery revealed that curcumin not only inhibited the release of steroidal hormones but also impeded the metabolism of arachidonic acid, cyclooxygenase, lipoxygenase, nuclear factor-kB, and cytokines (TNF-α and ILs). Beyond its potent antioxidant capabilities, curcumin has demonstrated the ability to induce uncoupling of oxidative phosphorylation and stabilize the lysosomal membrane, factors contributing to its inflammation lowering effects. In various animal studies, an effective anti-inflammatory activity was observed within a dosage range of 100-200 mg/kg body weight, with minimal reported side effects on human systems.[22] The anti-inflammatory efficacy of naturally

occurring curcumin analogs from turmeric, including feruloyl, 4-hydroxy cinnamoyl methane (FHM), and bis(4-hydroxy cinnamoyl) methane (BHM), was evaluated using carrageenan-induced rat paw edema. These analogs were compared with phenylbutazone (PB) and sodium curcumin (NaC). FHM emerged as the most potent among the three curcumin analogs studied. The dose-dependent pattern of anti-inflammatory effects in curcumin analogs was evident up to a dosage of 30 mg/kg, but an elevated dose of 60 mg/kg led to a decline in anti-inflammatory activity. Phenylbutazone (PB) displayed a dose-dependent effect within the range of 10-100 mg/kg. Sodium curcuminate (NaC) robustly and progressively inhibited contractions induced by nicotine, Ach, 5-HT, histamine, and $Bacl_2$ on isolated guinea pig ileum. In an isolated rabbit intestine, NaC also diminished both tone and pendular movements. The influence of NaC on contractions induced by nicotine in the isolated guinea pig ileum and the reduction in the resting tone of the rabbit intestine demonstrated similarities to the effects of non-steroidal anti-inflammatory drugs.[23] In their investigation of the anti-neuroinflammatory effects of curcumin, researchers utilized lipoteichoic acid (LTA)-stimulated BV-2 microglial cells. Curcumin exhibited inhibitory effects on inflammatory cytokines, including TNF-α, PGE2, and NO in LTA-persuaded microglial cells. Additionally, curcumin prevented the LTA-induced expression of COX-2 and iNOS. Mechanistic studies indicated that curcumin hindered NF-κB translocation and the phosphorylation of MAPK, including ERK, p38, and Akt, in LTA-induced microglial cells. Furthermore, curcumin induced the expression of Nrf-2 and hemeoxygenase-1 (HO-1) in microglial cells. The inhibitory outcome of curcumin on the release of inflammatory mediators in LTA-stimulated microglial cells was reversed by the inhibition of HO-1. In

conclusion, these findings propose that curcumin might serve as a therapeutic intervention for the management of neurodegenerative diseases by effectively suppressing neuro-inflammatory responses.[24]

Anticancer Effect

Curcumin has the ability to initiate apoptosis in cancer cells via a mechanism dependent on p53. Recognized as a crucial tumor suppressor protein, p53 plays a role in regulating cell division, programmed cell death, and responses to DNA damage.[25] Ethanol-derived turmeric extract demonstrated distinct effects on Ehlrich ascitic carcinoma cells and murine lymphocytes. Turmeric induced the breakdown of plasma membranes and the formation of cytoplasmic blebs in tumor cells, while simultaneously enhancing the viability and blastogenesis of lymphocytes. This suggests that turmeric has dual effects, inducing apoptosis and inhibition in tumor cells, while also serving as a supportive agent for lymphocytes.[26] A comparative examination of the antitumor characteristics of extracts derived from herbaceous plants such as *Gossypium barbadense* and *Ricinus communis*, in contrast to those from edible plants like *Curcuma longa* and *Ficus carica*, revealed that extracts from the edible plants exhibited more potent antitumorigenic properties. Consequently, edible plants demonstrating in vivo antitumor actions may serve as secure sources of antitumor compounds.[27] In a prior investigation, it was observed that curcumin has the potential to hinder IL-6-induced STAT-3 phosphorylation and the nuclear translocation of STAT-3 in patients with multiple myeloma. Additionally, curcumin exhibited the capability to impede the migration, invasion, and proliferation of retinoblastoma cells while promoting apoptosis. The antitumor effects were

attributed to the up-regulation of miR-99a, resulting in the suppression of the JAK/STAT pathway.[28]

Hepatoprotective Effect

Reports indicate that turmeric possesses hepatoprotective properties. In rats with liver damage persuaded by D-galactosamine, diets supplemented with turmeric extract were observed to mitigate the increased levels of ALT, AST, and LDH.[29] The administration of a 5% turmeric extract was shown to mitigate the increases in serum levels of bilirubin, cholesterol, AST, ALT, and ALP persuaded by CCl4 in mice.[30] In Sprague-Dawley rats experiencing similar hepatotoxicity, the administration of 200 mg/kg curcumin led to increased hepatic GSH and decreased lipid peroxidase levels. Additionally, it resulted in reduced activities of both AST and ALT.[31] The administration of curcumin in Sprague-Dawley rats subjected to CCl4- initiated hepatic fibrosis demonstrated a comprehensive strategy for mitigating liver fibrosis. This encompassed a reduction in extracellular matrix overproduction in hepatic stellate cells (HSCs), disruption of the PDGF-R)/ERK and mammalian target of rapamycin (mTOR) pathways, activation of PPAR-γ, upregulation of phosphatase and tensin homolog (PTEN) and microRNA-29b (miR-29b) expression, and downregulation of cannabinoid receptors type 1 and DNA methyltransferase 3b. Collectively, these mechanisms collaborated to alleviate liver fibrosis in the experimental model.[32,33] Both low-dose and high-dose curcumin treatments in a rat model of fulminant hepatic failure (FHF) resulted in higher survival rates compared to the thioacetamide (TAA) alone group. The low-dose curcumin group exhibited reduced levels of blood ammonia, hepatic necroinflammation, and biochemical markers for liver injury compared to TAA controls, with further reductions observed

in the high-dose group. Curcumin treatment also decreased TAA-induced elevated levels of thiobarbituric acid-reactive substances in the liver, prevented NFκB from binding to the nucleus, and reduced iNOS expression. In general, curcumin enhanced survival and alleviated hepatocellular damage, necroinflammation of liver, oxidative stress, NFκB binding and iNOS expression, indicating its potential as a hepato-protective agent.[34]

Cardioprotective Effect

The yellow powder derived from turmeric is widely recognized for its robust vasorelaxant effects and its ability to alleviate the atherogenic characteristics of cholesterol. A study revealed that incorporating turmeric into the diet of animals enhanced the vasorelaxant responses to substances such as acetylcholine, adenosine, and isoproterenol, which are known to promote blood vessel relaxation.[35] Moreover, curcumin, as demonstrated in a study by Yao et al. (2016), exerts a preventive influence on cardiovascular diseases by diminishing the expression of the angiotensin II type 1 receptor. This effect is achieved by reducing the binding capability of the AT1R gene promoter in conjunction with specificity protein 1.[36] Studies have shown that curcumin has the potential to alleviate chronic heart failure by increasing the activity of ASK1, JNK, and p38 MAPK.[37] Excessive use of Doxorubicin (Dox) resulted in cardiomyopathy characterized by elevated biomarker levels and an antioxidant deficit. However, pre-treatment with curcumin significantly mitigated the toxicity induced by Dox. Curcumin effectively normalized biochemical parameters (AST, ALT, and ALP) and reduced elevated biomarker enzymes (CPK and LDH). Additionally, curcumin decreased the elevated level of MDA in cardiac tissue while increasing depleted levels of GSH,

SOD, and CAT.[38] Curcumin triggers the activation of Nrf2, a pivotal molecular target, leading to the induction of HO-1. This activation is accountable for the cytoprotective and inflammation lowering effects in the face of oxidative stress.[39] The study employed a model of myocardial injury caused by ischemia and reperfusion to investigate the impact of turmeric on cardiac function and myocardial apoptosis. Administering 100 mg/kg of turmeric for one month demonstrated substantial cardioprotection and improved functional recovery, attributed to a reduction in cell death.[40]

Antidepressant activity

The reductions in 5-HIAA, serotonin, noradrenaline, and dopamine levels brought on by the swim stress, along with a decline in serotonin turnover were considerably mitigated by the ethanolic extract of turmeric. Furthermore, the extract successfully countered the rises in cortisol and serum corticotropin-releasing factor that swim stress induced, controlling the neuroendocrine and neurochemical systems in mice.[41] A different study found that giving mice aqueous turmeric extracts (140–560 mg/kg) abridged their immobility in the forced swimming and tail suspension test. Interestingly, at a dose of 560 mg/kg, turmeric's antidepressant effects were more powerful than fluoxetine's. Brain MAO-A activity was significantly inhibited by the extracts at lower doses, and brain MAO-B activity was inhibited at higher doses. On the other hand, fluoxetine merely demonstrated a propensity to reduce MAO-A and MAO-B effect in the animal brains. These results suggest that there are particular antidepressant properties of turmeric in vivo.[42] Curcumin treatment over an extended period of time markedly increased the levels of noradrenaline, 3,4-dihydroxyphenylacetic acid, serotonin, and 5-hydroxyindoleacetic acid in the hippocampus region of

male albino rats. Additionally, curcumin restored the normal levels of dopamine, noradrenaline, and 5-hydroxyindoleacetic acid in the frontal cortex of these rats. Collectively, these findings indicate that curcumin possesses potent antidepressant effects in male albino rats.[43]

Conclusion

In conclusion, the extensive historical use of plant-derived compounds, particularly the well-studied turmeric and its active component curcumin, underscores their diverse biological and pharmacological activities. Traditional medical systems like Ayurveda have employed turmeric for millennia, and modern research has delved into its therapeutic potential. The review emphasizes curcumin's multifaceted benefits, ranging from antioxidant and anti-inflammatory properties to its potential as an anticancer, hepatoprotective, and cardioprotective agent. The inflammation lowering and free radical scavenger qualities of turmeric, particularly in the context of joint-related conditions, are highlighted. Furthermore, curcumin's ability to inhibit joint inflammation and prevent the formation of periarticular osteoclasts underscores its potential in addressing inflammatory joint issues. The anticancer properties of curcumin, including its role in inducing apoptosis in cancer cells through p53 regulation, are discussed. Additionally, curcumin's hepatoprotective effects in the context of liver injury and its potential to prevent cardiovascular diseases, demonstrated through vasorelaxant effects, contribute to its versatile therapeutic profile. The review also acknowledges the antidepressant properties of turmeric and curcumin, as evidenced by their capacity to mitigate stress-induced neurochemical alterations. Animal studies have provided insights into the mechanisms underlying these antidepressant

effects, emphasizing the potential advantages for mental well-being. The overall assessment is that curcumin and turmeric exhibit significant therapeutic potential across a spectrum of medical issues. Ongoing research into the molecular mechanisms further underscores the dynamic role of turmeric in modern medicine, suggesting that it may continue to be a valuable source of medicinal compounds for various health applications.

References

1. Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981− 2002. Journal of Natural Products. 2003;66(7):1022-37.
2. Butler MS. The role of natural product chemistry in drug discovery. Journal of Natural Products. 2004;67(12):2141-53.
3. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life sciences. 2005;78(5):431-41.
4. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. Journal of Natural Products. 2007;70(3):461-77.
5. Prasad S, Aggarwal BB. Turmeric, the golden spice. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. 2011.
6. Akram M, Shahab-Uddin AA, Usmanghani KH, Hannan AB, Mohiuddin E, Asif M. *Curcuma longa* and curcumin: a review article. Romanian Journal of Biology-Plant Biology. 2010;55(2):65-70.
7. Wilson B, Abraham G, Manju VS, Mathew M, Vimala B, Sundaresan S et al. Antimicrobial activity of *Curcuma zedoaria* and *Curcuma malabarica* tubers. Journal of Ethnopharmacology. 2005; 99(1):147-51.

8. Reanmongkol W, Subhadhirasakul S, Khaisombat N, Fuengnawakit P, Jantasila S, Khamjun A. Investigation the antinociceptive, antipyretic and anti-inflammatory activities of *Curcuma aeruginosa* Roxb. extracts in experimental animals. Songklanakarin Journal of Science and Technology. 2006;28(5):999-1008.
9. Sharifi-Rad J, Rayess YE, Rizk AA, Sadaka C, Zgheib R, Zam W et al. Turmeric and its major compound curcumin on health: bioactive effects and safety profiles for food, pharmaceutical, biotechnological and medicinal applications. Frontiers in Pharmacology. 2020;11:1021.
10. Kaul S, Krishnakantha TP. Influence of retinol deficiency and curcumin/turmeric feeding on tissue microsomal membrane lipid peroxidation and fatty acids in rats. Molecular and Cellular Biochemistry. 1997;175:43-8.
11. Mesa MD, Aguilera CM, Ramírez-Tortosa CL, Ramírez-Tortosa MC, Quiles JL, Baró L et al. Oral administration of a turmeric extract inhibits erythrocyte and liver microsome membrane oxidation in rabbits fed with an atherogenic diet. Nutrition. 2003;19(9):800-4.
12. Ak T, Gülçin I. Antioxidant and radical scavenging properties of curcumin. Chemico-Biological Interactions. 2008;174(1):27-37.
13. Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant Foods for Human Nutrition. 2002;57:41-52.
14. Suryanarayana1ABCDE P, Satyanarayana1BCDE A, Balakrishna2ACDE N, Kumar3BCDE PU, Reddy1ACDEFG GB. Effect of turmeric and curcumin on oxidative stress and antioxidant enzymes in

streptozotocin-induced diabetic rat. Medical Science Monitor. 2007;13(12):292.

15. Suryanarayana P, Saraswat M, Mrudula T, Krishna TP, Krishnaswamy K, Reddy GB. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. Investigative Ophthalmology & Visual Science. 2005;46(6):2092-9.
16. Indira Priyadarsini K, MAITY DK, Naik GH, Sudheer Kumar M, Unnikrishnan MK, Satav JG et al. Role of phenolic OH and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. Free Radical Biology & Medicine. 2003;35(5):475-84.
17. Jakubczyk K, Drużga A, Katarzyna J, Skonieczna-Żydecka K. Antioxidant potential of curcumin—A meta-analysis of randomized clinical trials. Antioxidants. 2020;9(11):1092.
18. Funk JL, Frye JB, Oyarzo JN, Kuscuoglu N, Wilson J, McCaffrey G, Stafford G, Chen G, Lantz RC, Jolad SD, Sólyom AM. Efficacy and mechanism of action of turmeric supplements in the treatment of experimental arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2006;54(11):3452-64.
19. Yang H, Huang S, Wei Y, Cao S, Pi C, Feng T, Liang J, Zhao L, Ren G. Curcumin enhances the anticancer effect of 5-fluorouracil against gastric cancer through down-regulation of COX-2 and NF-κB signaling pathways. Journal of Cancer. 2017;8(18):3697.
20. Yegnanarayan R, Saraf AP, Balwani JH. Comparison of anti-inflammatory activity of various extracts of *Curcuma longa* (Linn). The Indian Journal of Medical Research. 1976;64(4):601-8.

21. Ghatak N, Basu N. Sodium curcuminate as an effective anti-inflammatoryagent. Indian Journal of Experimental Biology. 1972;10:235–6.
22. Kohli K, Ali J, Ansari MJ, Raheman Z. Curcumin: a natural antiinflammatory agent. Indian Journal of Pharmacology. 2005;37(3):141.
23. Rao TS, Basu N, Siddiqui HH. Anti-inflammatory activity of curcumin analogues. Indian Journal of Medical Research. 1982:75:574-8.
24. Yu Y, Shen Q, Lai Y, Park SY, Ou X, Lin D, Jin M, Zhang W. Anti-inflammatory effects of curcumin in microglial cells. Frontiers in Pharmacology. 2018;9:386.
25. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, Xie M, Zhang Q, McMichael JF, Wyczalkowski MA, Leiserson MD. Mutational landscape and significance across 12 major cancer types. Nature. 2013;502(7471):333-9.
26. Chakravarty AK, Yasmin H. Alcoholic turmeric extract simultaneously activating murine lymphocytes and inducing apoptosis of Ehlrich ascitic carcinoma cells. International Immunopharmacology. 2005;5(10): 1574-81.
27. Amara AA, El-Masry MH, Bogdady HH. Plant crude extracts could be the solution: extracts showing in vivo antitumorigenic activity. Pakistan Journal of Pharmaceutical Sciences. 2008;21(2): 159-71
28. Shanmugam MK, Rane G, Kanchi MM, Arfuso F, Chinnathambi A, Zayed ME, Alharbi SA, Tan BK, Kumar AP, Sethi G. The multifaceted role of curcumin in cancer prevention and treatment. Molecules. 2015;20(2):2728-69.

29. Miyakoshi M, Yamaguchi Y, Takagaki R. et al. Hepatoprotective effect of sesquiterpenes in turmeric. Biofactors. 2004;21:167–70.
30. Deshpande UR, Gadre SG, Raste AS, Pillai D, Bhide SV, Samuel AM. Protective effect of turmeric (*Curcuma longa* L.) extract on carbon tetrachloride-induced liver damage in rats. Indian Journal of Experimental Biology. 1998;36(6):573-7.
31. Lee HY, Kim SW, Lee GH, Choi MK, Jung HW, Kim YJ et al. Turmeric extract and its active compound, curcumin, protect against chronic CCl 4-induced liver damage by enhancing antioxidation. BMC Complementary and Alternative Medicine. 2016;16:1-9.
32. Chen N, Geng Q, Zheng J, He S, Huo X, Sun X. Suppression of the TGF-β/Smad signaling pathway and inhibition of hepatic stellate cell proliferation play a role in the hepatoprotective effects of curcumin against alcohol-induced hepatic fibrosis. International Journal Of Molecular Medicine. 2014;34(4):1110-6.
33. Zhang F, Zhang Z, Chen L, Kong D, Zhang X, Lu C, Lu Y, Zheng S. Curcumin attenuates angiogenesis in liver fibrosis and inhibits angiogenic properties of hepatic stellate cells. Journal of Cellular and Molecular Medicine. 2014;18(7):1392-406.
34. Shapiro H, Ashkenazi M, Weizman N, Shahmurov M, Aeed H, Bruck R. Curcumin ameliorates acute thioacetamide-induced hepatotoxicity. Journal of Gastroenterology and Hepatology. 2006;21(2):358-66.
35. Ashraf MZ, Hussain ME, Fahim M. Antiatherosclerotic effects of dietary supplementations of garlic and turmeric: Restoration of endothelial function in rats. Life sciences. 2005;77(8):837-57.

36. Yao Y, Wang W, Li M, Ren H, Chen C, Wang J, Wang WE, Yang J, Zeng C. Curcumin exerts its anti-hypertensive effect by down-regulating the AT1 receptor in vascular smooth muscle cells. Scientific reports. 2016;6(1):25579.
37. Cao Q, Zhang J, Gao L, Zhang Y, Dai M, Bao M. Dickkopf-3 upregulation mediates the cardioprotective effects of curcumin on chronic heart failure. Molecular Medicine Reports. 2018; 17(5): 7249-57.
38. Swamy AV, Gulliaya S, Thippeswamy A, Koti BC, Manjula DV. Cardioprotective effect of curcumin against doxorubicin-induced myocardial toxicity in albino rats. Indian Journal of Pharmacology. 2012;44(1):73.
39. Pittala V, Vanella L, Salerno L, Romeo G, Marrazzo A, Di Giacomo C, Sorrenti V. Effects of polyphenolic derivatives on heme oxygenase-system in metabolic dysfunctions. Current Medicinal Chemistry. 2018;25(13):1577-95.
40. Mohanty I, Arya DS, Gupta SK. Effect of *Curcuma longa* and *Ocimum sanctum* on myocardial apoptosis in experimentally induced myocardial ischemic-reperfusion injury. BMC Complementary and Alternative Medicine. 2006;6:1-2.
41. Xia X, Cheng G, Pan Y, Xia ZH, Kong LD. Behavioral, neurochemical and neuroendocrine effects of the ethanolic extract from *Curcuma longa* L. in the mouse forced swimming test. Journal of Ethnopharmacology. 2007;110(2):356-63.
42. Yu ZF, Kong LD, Chen Y. Antidepressant activity of aqueous extracts *of Curcuma longa* in mice. Journal of Ethnopharmacology. 2002;83(1-2):161-5.

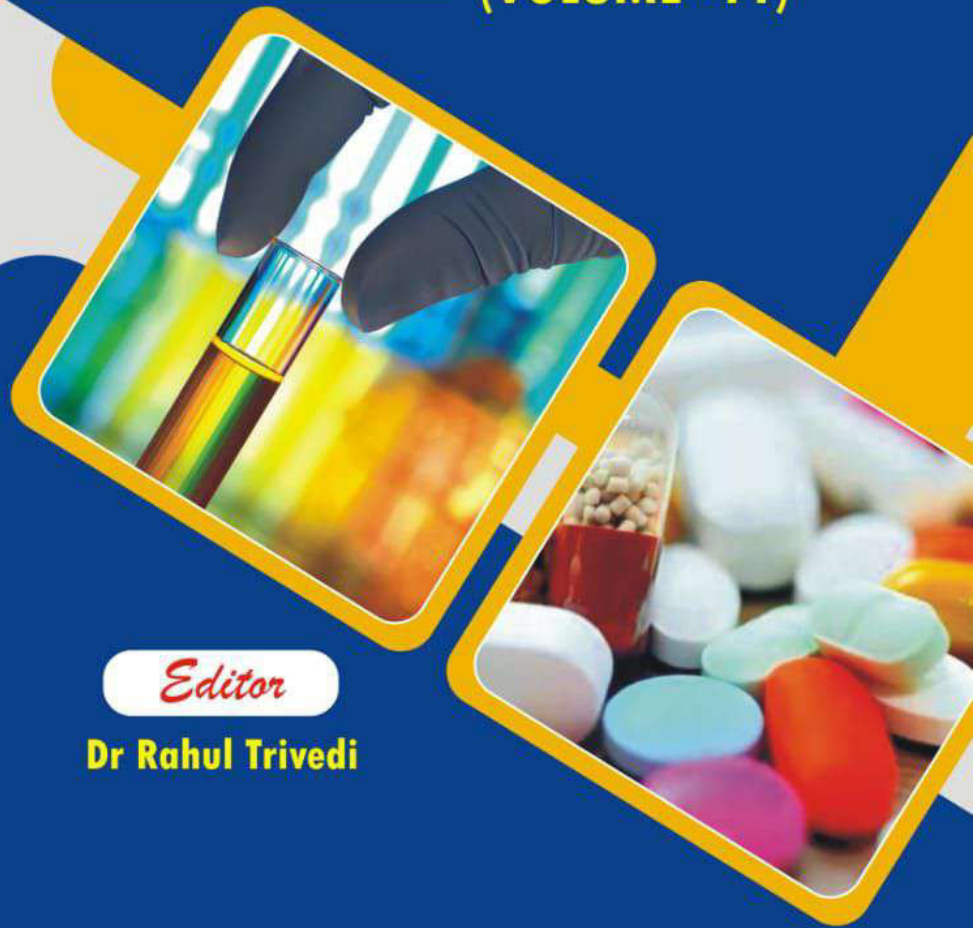
43. Chang XR, Wang L, Li J, Wu DS. Analysis of anti-depressant potential of curcumin against depression induced male albino wistar rats. Brain Research. 2016; 1642:219-25.

South Asian Academic Publications
3-37, Dirisavancha, Kanigiri, Prakasm District
Andhra Pradesh-523445 India
Email- saapbooks@gmail.com
http://www.saap.org.in/

ISBN 939215388-0
9 789392 153884

RESEARCH TRENDS IN PHARMACEUTICAL SCIENCES

(VOLUME -11)



Editor
Dr Rahul Trivedi

ADVANCED STUDIES IN MULTIDISCIPLINARY RESEARCH

Volume - 7

Chief Editor

Dr. Suprita Jha
Associate Professor, Department of English, Mata Sundri College,
University of Delhi, Delhi, India

Bright Sky Publications ™
New Delhi

Published By: Bright Sky Publications

Bright Sky Publications
Office No 3, 1st Floor,
Pocket - H34, SEC-3,
Rohini, Delhi, 110085, India
Phone: +91-9911215212, +91-9999779515
Email: brightskypublications@gmail.com

Chief Editor: Dr. Suprita Jha

Publication Year: 2024

Pages: 173

ISBN: 978-81-968309-2-2

Price: ₹ 769/-

Contents

Chapter - 1
Development of Women Entrepreneurship through Handicrafts from Natural Fibres

Authors

Priyanka Borah
Research Scholar, Department of Textiles and Apparel Designing, College of Community Science, Assam Agricultural University, Jorhat, Assam, India

Dr. Rickey Rani Boruah
Assistant Professor, Department of Textiles and Apparel Designing, College of Community Science, Assam Agricultural University, Jorhat, Assam, India

Momita Konwar
Assistant Professor, Department of Textiles and Apparel Designing, College of Community Science, Assam Agricultural University, Jorhat, Assam, India

Chapter - 1

Development of Women Entrepreneurship through Handicrafts from Natural Fibres

Priyanka Borah, Dr. Rickey Rani Boruah and Momita Konwar

Abstract

Rural women are endowed with an invaluable talent for weaving masterpieces on textiles. Traditional cultural perception believed that women's role were restricted to the four walls of the house. However, in modern times, with economic reforms, there is a transitional trend that is observed in terms of women's participation in economic growth and women's participation in business entities. Handcrafted items are characterized as items made frequently with the utilization of basic tools and are aesthetic or customary in nature. This chapter aims briefly to describe the role of women in handicraft production from the easily available natural fibres for generating their income or uplifting their lives.

Keywords: Entrepreneurship, handicrafts, natural fibre, women empowerment

Introduction

Entrepreneurship is one of the most important inputs towards the economic development of the country. An entrepreneur is a leader in the business who seeks out new ideas, thoughts and technologies and implements them to promote economic development. An entrepreneur can be regarded as a person, who has the creativity skill and motivation to set up a business or innovativeness of his own and who always looks for high achievements. They are the catalyst for social transformation and work for the common well-being. They look for opportunities, identify them and seize them primarily for economic gains. The entrepreneur is usually a sole proprietor, a partner, or the one, who owns the majority of shares in an integrated enterprise (Dhaliwal, 2016).

Industrial development, entrepreneurship abilities and competencies of an individual are the foundations for the nation's economic development. When understanding the importance of entrepreneurship, there are several factors that need to be taken into consideration. Entrepreneurial development involves

the implementation of various procedures, functions and activities that are associated with perceiving opportunities and the formation of the organizations to pursue them. Entrepreneurs experience several opportunities and challenges within the course of pursuance of their goals and objectives (Kapur, 2018). Entrepreneurial orientation consists of three dimensions such as innovativeness, proactiveness and risk-taking (Arzubiaga *et al.* 2018). Entrepreneurship is one of the significant components of the economic growth of a country. For women, there could be many influencing factors such as education, family business, friend's inspiration, and an intention to make themselves financially stable in the future by taking on entrepreneurship as a career (Jabeen *et al.,* 2018).

Women entrepreneurship

The growth of a nation depends primarily on its human resources, both men and women of working age. They serve as the foundation for the nation's economic growth. Women's power is an important segment and forms a big workforce group which cannot be isolated from the economic development of any nation. Over time, women entrepreneurship has been a growing factor in promoting economic growth and employment creation. Equality among men and women is essential for the development of a society which can be possible through the economic independence of women (Mohandas, 2016). Women have the role of the foundation of society. If women are empowered economically and financially, they can prove themselves as change-makers by providing education facilities to their children, improving the living standard of the family members (Negi *et al.,* 2016).

Women Entrepreneurs may be defined as the women or a group of women, who recruit, organise and manage a business enterprise. The government of India has defined women entrepreneurs as an enterprise maintained and regulated by a woman having a minimum financial interest of 51 per cent of the capital and giving at least 51 per cent of employment produced in the enterprise to women. The development of women entrepreneurs and their involvement in the national economy is quite noticeable in India. Women entrepreneurs need to be acclaimed for their increased utilisation of modern technology, increased investments, finding a niche in the export market, forming a considerable occupation for others, and setting the trend for other women entrepreneurs within the organised sector (Fazalbhoy, 2014). In the last two decades, an increasing number of Indian women have entered the field of entrepreneurship and also have rendered their immense contribution to changing the face of business of today both, accurately and symbolically (Kapur, 2018).

Female entrepreneurs not only contribute to employment creation and economic growth through their increased participation but also add the diversity and quality of entrepreneurship in the economic process (Jong, 2013 & OECD, 2016). Women are engaged in various activities like sewing, embroidery, knitting, crocheting, rally-quilt etc. They do embroidery on bedsheets, veils, cushion covers, table covers, shirts, pillow covers, scarves, mantel covers etc. to get an opportunity to generate income. They make bed sheets, cushion covers, shawls, rugs, bags, scenery decorations, wall hangers, shoes, sofa backs, table covers, clothes, jewellery etc. and start taking part in the household economy by making these handicrafts (Mohyuddin *et al.* 2012).

Entrepreneurship development among women can be considered as a possible approach to the economic empowerment of women. A woman entrepreneur is economically more powerful than a mere worker because ownership not only confers control over assets but also gives her the freedom to make decisions. Through entrepreneurship development, women will not only generate income for themselves but will generate employment for other women in the locality. This will also uplift social status significantly. This will have a multiplier effect on the generation of income and poverty alleviation. It is said that education can be a source of income for a boy, but education to a girl can be the source of education for the entire family. Therefore, women are particularly skilled at weaving delicate designs onto textiles. They effortlessly infuse their creativity into weaving colourful pieces for near and dear ones (Mishra and Mohapatra, 2019).

Entrepreneurship has served to be enormously beneficial and helpful for the women of the country. It has turned them into self-sustaining individuals. Entrepreneurship has become more prevalent not only amongst the women in urban areas but also in rural areas. Farming and agriculture have never been looked upon as an enterprise, therefore the concept of entrepreneurship in agriculture and allied activities is quite recent. Entrepreneurship is stated to be an act of business ownership and business creation that empowers women economically, increases their cost-effective strength as well as standing within the society (Kapur, 2018).

Women are not a burden or an impediment to development; rather, they have become one of the potential assets under construction. One way to increase women's empowerment is to create small and medium-sized businesses to absorb the labour of unemployed women. In addition to lowering the unemployment rate, these women's expertise or skills could be enhanced (Setyaningsih *et al.*, 2012). Creative industries are one of the activities that, in addition to increasing women's empowerment, can improve society's economic system (Gbgindonesia, 2011). The key components of the

empowerment process include education and capacity building. Educated woman plays an important role in family decision-making. Education, employment as well as earnings increase financial independence of a woman, therefore they are regarded as powerful means of empowerment (Gholipour *et al.,* 2010).

With the fast-changing world and rapidly changing times, women have acquired a distinct position for themselves in society. There has been an increase in the number of women, who are educated and aware. Women in India have developed considerable awareness amongst themselves to be self-employed and self-reliant. Within society, women have stepped out from the limitations of their homes and have engraved a position for themselves in various fields (Kapur, 2018).

Entrepreneurship is the driver of growth. It aids in the development of inventive businesses that serve as a foundation for boosting a country's competitiveness. Women entrepreneurs in the developing world make a large and often unrecognized contribution to their country's economic development. They contribute significantly to the growth of emerging market economies around the world by employing others, offering valuable services. Many women in India cannot take up regular, full-time jobs due to certain unavoidable circumstances such as looking after their children, household requirements and so forth. Due to these conditions, entrepreneurship is turning out to be the best way for them to carve a position for themselves (Sharma, 2013).

The subject of women's entrepreneurship covers both the status of women in society and the role of entrepreneurship in that same society. Women entrepreneurs experience many impediments, especially in marketing their products, in addition, they have to take care of the family responsibilities (Fazalbhoy, 2014). Women are seen making a notable involvement in economic and business advancement. When they are socially and economically equipped, they become a powerful force for change (Rehman *et al.,* 2017).

The foremost self-evident advantage of craftsmanship generation is the generation of income. Production of handicrafts uplifts women’s feelings of self-esteem and freedom. It permits open doors for innovative self-sufficiency and articulation and uplifts the status and roles of women inside their networks. Besides, as women are more likely to contribute their cash to their children than men, the production of crafts permits women to upgrade positive social change in their communities (Shealy, 2011).

Role of handicraft in women empowerment

Handicrafts are, by definition, traditional. People make these to use in their daily lives by using their primitive instruments, their hands. It should be noted that most handicrafts have aesthetic and artistic value (Sultana, 2012).

Handicraft goods are those made by artisans either by hand or such types of hand tools. Handiwork is one of the chief export sections of certain countries like Indonesia and Bangladesh. Handicraft goods will more entirely support enriching productivity that will ultimately raise economic growth, which will be accomplished easily believing to warrant women's financial empowerment (Spreitzer, 1996). Handiworks are traditional by nature and using their primitive implements, individuals create these to practice in their day-to-day lives. It should be recognized that most of the time handiworks have an aesthetic outlook and creative significance (Sultana *et al.,* 2010).

A handcraft is an extensive variety of work where useful and decorative goods are produced entirely by hand or by using only elementary tools. It is sometimes more precisely referred to as an artisanal handicraft or handmade. It refers to a variety of artistic and design activities that include creating things with one's hands and ability, including work with fabrics, mouldable and stiff materials, paper, and plant fibres (Gouda and Manju, 2018).

Handicraft goods are simply made by the aptitude of the hand possessed by the maker and it involves centuries of evolutionary tradition. Handicrafts in the rural and the urban regions serve as a technique for survival among the low-paid social class and on such grounds ought to be a fully equipped financial sector. Handicrafts also have cultural and social importance to many as they are mostly produced using indigenous plants. Subsequently, indigenous information assumes a pivotal role in the aptitudes required for the creation and protection of these items as most of them depend on indigenous abilities and are produced using locally-accessible resources (Bano *et al.,* 2021).

The handicrafts sector plays a noteworthy and significant job in the nation’s economy. In rural and urban areas, this sector provides employment opportunities to many craft persons and produces generous foreign exchange for the nation while preserving and promoting its cultural heritage. Crafted works have incredible potential as they hold the key for supporting not just the millions of working craftsmen spread all over the country, but also the undeniably enormous number of new contestants in the crafts industry. Currently, handicrafts contribute greatly to the generation of employment and exports. Besides, the high business potential in this area is financially

significant, involving the purpose of low capital venture, a high proportion of significant worth expansion, and potential for outside trade income (Dar & Parrey, 2013).

Women's economic empowerment can be defined as a process in which women's lives are shifted from a condition where they have less and limited power to experiencing more advanced power through control over assets and resources (Hunt and Samman, 2016). Empowerment can be defined as growth in the ability of people to make deliberate life choices in circumstances where this capacity was previously invalidated (Kabeer, 2011). Female home industry workers show multiple 'burden' roles, and flexible working hours, but no special education related to working. For the development of a small home-based enterprise, the creation of a framework for empowering poor women and a more effective gender mainstreaming strategy are needed (Susanti and Masudah, 2017).

Women's empowerment is defined in two ways, including empowerment as a goal and empowerment as a process. Empowerment is not merely a product; rather it is an ongoing process that could not be considered as a final goal. It is an ongoing process that enables the powerless to have control over their social and economic circumstances in their lives (Bano *et al.,* 2021).

Women's empowerment in India is carried out by forming self-help groups to pave the way for women's independence. Self-help groups can create jobs, increase income, strengthen purchasing power, reduce costs, and increase business convenience (Datta & Gailey 2012, Paramanandam & Packirisamy 2015, Datta 2015, Brody *et al.* 2016).

Use of natural fibre in handicraft

The different forms of natural fibres include grass, bamboo, shola pith, cane, jute, leaves and so forth. There is use of these natural fibres in the production of various items such as mats, baskets, brooms, rooftops, clothing, hats, sticks, canes and so forth. These items are meant for daily use, and make provision of shelter and income to most of the individuals throughout the country. Most of the women who belong to the socio-economically backward sections of society are engaged in natural fibre weaving to produce objects for daily use. Many industries survive on the production of materials from jute (Jena, 2010).

A fibre is a thin, hair-like portion of a plant or animal's tissue or other substance that has a very small diameter and a length. A fibre is a material which is several hundred times as long as its thickness (Rhetso and Aomi, 2016). Natural fibres are the foundation of the eco-fashion movement, which

aims to produce clothes that is sustainable from creation to disposal. Natural fibres have intrinsic properties such as mechanical strength, low weight and healthier to the wearer which has made them particularly attractive (Annapoorani, 2018). Natural fibre is abundant and more affordable in comparison with synthetic fibre specifically with lower density and energy requirements, renewability, no skin irritation, higher strength-to-weight ratio, higher aspect ratio length to diameter (L/D) of around 100, and higher strength and elasticity modulus, showing great potential as glass, carbon, or other synthetic fibre replacements. In addition, these benefits have led to the use of natural fibre for human needs as well as for industrial raw materials such as textiles, pulp and paper, accessories, bio-composites, and crafts (Karimah *et al.,* 2021).

Today utility of natural fibres is increasing at a global level due to the growing concern for the environment. The low cost and good mechanical properties of natural fibres increase their use in producing different handicraft items (Ortega *et al.,* 2016).

Animal, plant, and mineral fibres are the constituents of natural fibre. Protein and cellulose respectively, are the principal components of animal and plant fibres. Furthermore, the fibre plant is divided into stems, leaves, seeds, xylem, bark, and fruit. These fibres come from primary or secondary meristematic tissue depending on the species. Rice, bamboo, corn stem, wheat, and bagasse are also included in the stem fibre. Examples of fruit fibres include oil palm and coconut, while leaf fibres include abaca, pineapple, sisal, and agave. Furthermore, examples of seed fibres include wider, kapok, and cotton. Bark fibres are Roselle, jute, hibiscus, abaca, soybean fibre, and ramie, while animal fibres include wool, silk, bird fibre, hair, and collagen fibres. Asbestos, carbon, and glass are examples of mineral fibres (Sari *et al.,* 2020).

With the increasing environmental awareness and the growing importance of eco-friendly fabrics, products made of natural fibres have been recognised for their good qualities and now its application is increasing in making different handicraft products to generate the income of rural women.

Value-added products from natural fibre

Natural fibre has multifaceted uses in preparing many value-added products of handicraft items such as table mats, bags, wall hangings and other fancy articles, ropes, craft paper, etc. Natural fibre is a material that may be converted into filaments, thread, or even rope and is derived from plants and animals. They exist in hair-like materials which are interrupted filaments or in distinct elongated pieces. They can be utilised as one of the components in

creating a part or a finished product. Natural fibres are also famous for their excellent properties such as low density, high specific strength and effectual costing (Khalil *et al.,* 2012).

Natural fibre composites are used for building products such as panels, door shutters, and roofing sheets and it is used alone or in combination with other materials. In China, bagasse is used for making particle boards. The handicrafts of bamboo are one of the oldest crafts better known to man. It is universally performed across several Indian regions. India is a fashionable source of bamboo materials, and therefore the Indian artisans had observed to provide beautiful utility articles. In recent years, cane and bamboo are also used to make a wide variety of decorative items. In India, thousands of people are employed full-time in the bamboo cane craft. Additionally, these artisans work on decorative items. The use of bamboo products is wide from boxes, chairs, teapots, baskets, handbags, etc. (Verma *et al.,* 2012). Thailand uses Thai wood fibre for hardboard making hardboards. The Philippians use coir and banana stalks for particle boards (Khalil *et al*., 2012). Many cottage industries in South India use banana fibre for making different handicraft products. In some parts of the world like Japan and Nepal, this plant is used for making textile materials and accessories (Vigneswaran *et al.,* 2015).

Some automobile industries like Audi, BMW, Fiat, Ford, Mitsubishi, Renault, and Volvo have been using natural fibre for their different parts (Bledkzi *et al.,* 2006). Natural fibres are used in the packaging industry (Hirvikrpi *et al.,* 2011) and are degradable (Johansson *et al.,* 2012). Due to their poor moisture resistance and low mechanical properties, natural fibres are primarily utilised in interior and non-structural applications (Dittenber *et al.,* 2012). Natural fibres are used for making ropes, dusters, seed pots etc. After processing natural fibres to yarn forms fabrics can be constructed in different weave structures. Diversified products like coats, kurti, ties, and upholstery items can be made depending on the properties of fibres (Bhuyan and Gogoi, 2020).

Conclusion

The chapter aimed to present the role of women entrepreneurs through handicrafts from natural fibres. The women are empowering themselves with the skill of handicrafts which paved the way for the stabilized social status of women in society. It strongly approved the women's economic and social position and they are the source of change in terms of motivation, inspiration, and encouragement to the other women in the society. The skill of handicrafts helps rural women as a source of income and provides financial support for their families.

References

1. Annapoorani SG. Sustainable Textile Fibres. Editors: Subramanian Senthilkannan Muthu, 2018. DOI: 10.1007/978-981-10-8578-9_1. Pp: 1-30.
2. Arzubiaga U, Kotlar J, Massis A, Maseda A. Entrepreneurial orientation and innovation in family SMEs: Unveiling the actual impact of the Board of Directors. J. Bus. Ventur. 2018;33:455-469.
3. Bano S, Farid N, Ashfaq A, Mas'udah S. Uplifting the socio-economic empowerment of women through handicraft industry, 2021, Pp. 367-379. https://doi.org/10.20473/mkp.V34I42021.
4. Bhuyan S, Gogoi N. Natural Fibers: Innovative Sustainable and Eco-Friendly. International Journal of Current Microbiology and Applied Sciences. 2020;9(7):1004-1011. https://doi.org/10.20546/ijcmas.2020.907.118
5. Bledzki AK, Farukand O, Sperber VE. Macromol. Mater. Eng. 2006;291:449-457.
6. Brody C, Hoop T, Vojtkova M, Warnock R, Dunbar M, Murthy P, *et al.,* Can self-help group programs improve women's empowerment? A systematic review. Journal of Development Effectiveness. 2016;9(1):15-40. https://doi.org/10.1080/19439342.2016.1206607.
7. Dar MA, Parrey AH. Socio-economic potential of handicraft industry in Jammu and Kashmir: Opportunities and challenges. Journal of Research in Management & Technology. 2013;2:20-28.
8. Datta PB, Gailey R. Empowering women through social entrepreneurship: Case study of a women's cooperative in India. Entrepreneurship Theory and Practice. 2012;36(3):569-587. https://doi.org/10.1111/j.1540-6520.2012.00505.x.
9. Datta U. Socio-economic impacts of JEEViKA: A large-scale self-help group project in Bihar, India. World Development. 2015;68:1-18. https://doi.org/10.1016/j.worlddev.2014.11.013.
10. Dhaliwal A. Role of Entrepreneurship in Economic Development. International Journal of scientific research and management. 2016;4(6):4262-4269.
11. Dittenber DB, GangaRao HV. Critical review of recent publications on use of natural composites in infrastructure. Compos Appl Sci Manuf. 2012;43(8):1419-e29.

12. Fazalbhoy S. Women Entrepreneurship as the Way for Economic Development. Annual Research Journal of Symbiosis Centre for Management Studies. 2014;2(1):117-127.
13. Gbgindonesia. Services, Indonessia creative industries, global business guide, 2011.
14. Gholipour A, Rahimian A, Mirzamani A, Zehtabi M. Impact model of women's empowerment. International Business Research. 2010;3(1):57-65.
15. Gouda H, Manju H. The role of handicrafts and souvenir industry in women empowerment: a study in Karnataka state. International Journal of Scientific Research, 2018, 7(3). ISSN No 2277 – 8179.
16. Hirvikorpi T, Vaha M, Nissi J, Nikkola, Harlin A, Karppinen M. Surt coating biotechnology. 2011;2005:5088-5092
17. Hunt A, Samman E. Women's economic empowerment navigating enablers and constraints. ODI Development Progress, 2016. https://cdn.odi.org/media/documents/10683.
18. Jabeen F, Friesen HL, Ghoudi K. Quality of work life of Emirati women and its influence on job satisfaction and turnover intention. Journal of Organizational Change Management. 2018;31(2):352-370. https://doi.org/10.1108/jocm-01-2017-0016.
19. Jena PK. Indian Handicrafts in Globalization Times: An Analysis of Global Local Dynamics. Interdisciplinary Description of Complex Systems. 2010;8(2):119-137.
20. Johansson C, Bras J, Mondragon T, Nechita P, Plackett D. Bioresource. 2012;7:2506.
21. Jong D. Women's entrepreneurship in the EU. Library of the European Parliament, 2013. https://eige.europa.eu/docs/2041_LDM_BRI(2013)130517_REV1_EN.pdf
22. Kabeer N. Between affiliation and autonomy: Navigating pathways of women's empowerment and gender justice in rural Bangladesh. Development and Change. 2011;42(2):499-528.
23. Kapur R. The Importance of Entrepreneurship in India, 2018. https://www.researchgate.net/publication/323825716

24. Karimaha A, Muhammad R, Munawar S, Adi D, Ismadi R, Subiyanto B, *et al.,* A review on natural fibres for development of eco-friendly bio-composite: characteristics, and utilizations. Journal of Materials Research and Technology. 2021;13:2442-2458.

25. Khalil A, Amouzgar HPS, Jawaid M, Hassaan A, Ahmed F, Hadiyana A, *et al*., Bioenergy. J. Biobased Mater. 2012;6:299-308.

26. Mishra SS, Mohanpatra AKD. Women entrepreneurship in handloom sector: Prospects and challenges. Alochana Chakra Journal, 2019. ISSN No. 2231-3990.

27. Mohandas K. A study of women entrepreneurs and women empowerment in the textile and garment units in Kerala. IJARIIE. 2016;1(4):C-1357.

28. Mohyuddin A, Chaudhry HR, Ambreen M. Contribution of women in economic activities in rural Baluchistan: World system analysis at micro level in anthropological perspective. Academic Research International. 2012;3(2):548-556.

29. Negi M, Rani A, Singh A. New prospects for women empowerment through value addition of remnant fabrics with Aipan applique. Indian Research Journal of Extension Education. 2016;16(3):84-88.

30. OECD. Entrepreneurship at a Glance. Paris: OECD Publishing Paris, 2016. http://dx.doi. org/10.1787/entrepreneur_aag-2016-en.

31. Ortega Z, Moron M, Monzon MD, Badallo P, Paz R. Production of banana fibre yarns for technical textile reinforced composites. Materials. 2016;9(5):370.

32. Paramanandam DA, Packirisamy P. An empirical study on the impact of micro enterprises on women empowerment. Journal of Enterprising Communities: People and Places in the Global Economy. 2015;9(4):298-314. https://doi.org/10.1108/jec-08-2014-0017.

33. Rehman F, Ali RN, Aziz A, Iqbal A. Potential of cottage industry in Azad Kashmir and the role of female entrepreneurship. Journal of Political Studies. 2017;24(1):1-15.

34. Rhetso VK, Aomi VK. Skill development in banana and pineapple fibre extraction and utilization, 2016, Pp. 49-52.

35. Sari NH, Fajrin J, Suteja, Fudholi A. Characterisation of swell ability and compressive and impact strength properties of corn husk fibre composites. Composites Communications. 2020;18:49-54.

36. Setyaningsih S, Ruchita CP, Ummu H, Ilma NR. Women Empowerment through Creative Industry: A Case Study. Procedia Economics and Finance. 2012;4:213-222. https://doi.org/10.1016/S2212-5671(12)00336-X.

37. Sharma Y. Women Entrepreneur in India. IOSR Journal of Business and Management. 2013;15(3):9-14.

38. Shealy S. Her hands: Images of craftswomen in Uganda, Bolivia and India. Consilience. 2011;6(1):291-319.

39. Spreitzer GM. Social structural characteristics of psychological empowerment. Academy of Management Journal. 1996;39(2):483-504.

40. Sultana A. Promoting Women's Entrepreneurship through SME: Growth and Development in the context of Bangladesh. IOSR Journal of Business and Management. 2012;4(1):18-29.

41. Sultana B, Zaaba ZB, Umemoto K. Women's Empowerment through the Development of Micro Entrepreneurship in Rural Bangladesh. Soc Sci. 2010;5(1):1-9.

42. Susanti E, Mas'udah S. Women's empowerment model in home-based industries in East Java Province, Indonesia. Masyarakat, Kebudayaandan Politik. 2017;30(4):353-366. http://dx.doi.org/10.20473/mkp.V30I42017.353-366

43. Verma D, Gope PC, Maheswari MK, Sharma RK. Bagasse Fibre Composites-A Review. J Mater. Environ. Sci. 2012;3(6):1079-1092.

44. Vigneswaran C, Pavithra V, Gayathri V, Mythili K. Banana fibre: Scope and value added product development. J Textile Apparel Technol. Mgt. 2015;9(2):1-7.

Chapter - 2
Does the Quality of Life of Workers Improve after Migration? Evidence from Goa

Author

Rajesh V. Shetgaokar
Assistant Professor, M.E.S College of Arts and Commerce,
Zuarinagar, Goa, India

Chapter - 2

Does The Quality of Life of Workers Improve after Migration? Evidence from Goa

Rajesh V. Shetgaokar

Abstract

The paper examines the issue of internal migration in Goa. The main objective of the paper was to highlight the quality of life of migrant workers in Goa. The study is based on primary data collected from 350 migrant workers in North and South Goa. The result of the logistic regression model shows that the quality of life of migrant workers is lower compared to the local workers. In addition, the majority of migrant workers were young and migrated in search of higher wages and a better quality of life. The study also found that the wealth of migrant workers was significantly lower than that of native workers. The regression coefficients for the number of days worked was negative, indicating that migrant workers receive a lower number of days worked per year. We conclude that the large number of young people moving to other states shows that India's employment generating initiatives have failed. It means that the cumulative causation process, which is having an impact on the various states, is causing the difference between the states to widen with time. Therefore, it is essential from a policy perspective that migration does not have a detrimental influence on regions that are already experiencing backwardness. It is imperative that adequate air, lighting, drinking water, and sanitary facilities be provided for them.

Keywords: Migration, migrants workers, local workers, age, assets, working days.

Introduction

Employee migration is a human phenomenon with deep historical roots and broad ramifications. Migrations have an economic origin and subsequent socio-political and cultural repercussions. Throughout India, social structures and patterns of development are the fundamental drivers of migration. The fundamental driving force for migration is uneven development. The

differences between regionally and among uniquely created socioeconomic strata are brought to it. The majority of migrants are landless, impoverished people from lower castes, indigenous groups, and economically underdeveloped areas. The unfavourable distress factors push them to the urban centers with the intent of saving a part of their income. But they are often exploited by the middlemen and other agents. The vulnerable sections of migrants are women and children.

Migrants are very often subjected to new social and living conditions in their new settlements. The right to reside and settle in any area of Indian territory is guaranteed by Article 19(1)(e) of the charter, subject to reasonable restrictions in the benefit of the general public or the safety of any scheduled tribe. However, people who migrate for work face significant challenges such as:

i) Lack of social security and health benefits and poor implementation of the minimum protection standards regulation.

ii) A loss of portability of country-provided benefits, particularly food provided through the public distribution system (PDS).

iii) A loss of access to affordable housing and basic amenities in urban areas.

According to the 2011 census, Goa has a population of 14.58 lakh people, 18.5% of whom are immigrants from other states. About 1.35 lakh people moved to Goa from other states in 2011, and since then, the population has been increasing. Although these employees are mostly employed in the hotel, tourism, and construction industries, they have a sizable presence in almost every other sector in the state. The majority of inter-state migrant workers lack adequate housing and are forced to live in unsanitary neighborhoods without adequate sanitation and safe drinking water, which contributes to the spread of communicable diseases and other social problems in society. The inter-state migration, aside from the neighboring states of West Bengal, Bihar, Orissa, Chhattisgarh, and Jharkhand are the dominant migrant labours force in state's job sector. Reports have shown, these individuals work for a meager wage and make up the least privileged corporations in the labour market. The criminal protection envisioned by the Interstate Migrant Workmen (law of Employment and Conditions of Service) Act, 1979 is not available to them because they are not employed through a contractor or intermediary.

There are many reasons why migration is increasing in Goa. Workers from other states moved to Goa in pursuit of higher pay and better living

conditions due to the high wages. Rapid industrialisation and the ensuing growth of the tourism sector led to a rise in technical and white-collar occupations. In addition, due to unexpected growth in a variety of unrelated areas, such as production and home-based businesses, the influx of migrants labour have been increasing in recent years. Further, boom in construction industry and flourishing service sector had provided a vast employment opportunity for migrants labour. Besides, Goa is one of the more prosperous states, with a per capita income of Rs.49, 673, the highest in the country. These also provide incentives for migrants to influx in Goa, as migrant's population who are largely marginalized are fascinated by high living standard in state.

Review of literature

The studies on impact of migration are sparse in Goa. This make even difficult to trace the effect of migrations on Goan economy and its positive and adverse effect. However, various studies have highlighted the issues of migration, its causes, its beneficial and negative effect on society. Shamna and Baiju (2016) use a qualitative tool to gauge satisfaction with their working and living conditions. The issues that immigrant employees confront include wages, employment, living conditions, working conditions, health-related concerns, and social security benefits. Rajan & Suneetha (2015) found that migrant labourers in the southern Indian state of Kerala face daily hardships such as a fight for a better living wage and better working circumstances. They put up with the sweat and labour because those who come to India from other regions of the country promise them a brighter future. Using information from the Indian Census, Viswanathan and Kumar (2012) investigate the three-way interaction between climate variability, agricultural productivity, and internal migration in India at the state and district levels. With respect to the per capita net state domestic product, the interstate outmigration rate has an elasticity of about (-) 0.75. Korra (2011) looked into the characteristics of both temporary and long-term migration. The majority of short-term migrants, it was found, relocated to metropolitan and other rich rural areas in search of work. Permanent migration is more common among female migrants seeking better opportunities. According to Mahapatro (2010), migration studies should place more emphasis on the impact of economic factors in determining female migration, rather than just family and employment reasons. The data show that throughout time, the labour participation rate of female migrants increased in rural-urban migration relative to female non-migrants. According to Bhagat (2010), the percentage of the workforce, per capita income, and the share of the state's

gross domestic product produced by industries other than agriculture were all significantly positively connected with both in-migration and out-migration rates. However, state-level analysis did not discover a significant link between poverty and a rise in out-migration. Mehta (1996) assessed the volume of high-skilled immigration from India before identifying two of its effects on the domestic economy. Remittances sent home have surged as a result of high-skilled migration; at the moment, India is the world's top beneficiary of remittances. The nation's deficits have diminished as a result of the accessibility of these remittances. Prabhat (2007) looks into the nature of development gaps and interstate migration in India. The Composite Development Index was calculated using 14 socioeconomic indicators. It is discovered that the net migration rate and interstate disparities are connected. The relationship between these differences and net male migration rate is stronger. Based on an analysis of the empirical data, Haan (1999) draws the conclusion that it may not be able to draw broad conclusions about the traits of migrants or the impacts of migration on overall development, inequality, or poverty. Population mobility should be encouraged by policies, and options for enhancing its benefits should be investigated.

Given the dearth of research in this field, we concentrate on three key elements in our paper. First, we aim to provide a evidence of state which are contributing maximum to migration in Goa. Second, to understand the socio-economic profile of migrants labours in Goa. Third, to determine the quality of life migrants enjoys when compared to local workers. We have used simple statistical tools such as averages, parentages'. Further, we have provided a result using logit regression model. The study is analytical and descriptive in nature. Separate structured interview schedules for migrant workers, local workers, and employers were used to obtain primary data. A total of 350 migrant labourers were taken into account: in North Goa 200 workers were selected and in South Goa, 150.

Analyses and interpretations

We began our analysed by providing a demographic profile of the respondents. The results are presented in Table 1.

Table 1: Demographic profiles of the respondents

Variables	Category	Number of Respondents	Percentages
Age	Up to 25	160	45.71
	26-35	120	34.28
	Above 35	70	20.01
Total		**350**	**100**

Gender	Male	275	78.57
	Female	75	21.43
Total		**350**	**100**
Marital Status	Single	210	60.00
	Married	140	40.00
Total		**350**	**100**
Number of dependent family members	01-03	130	37.14
	03-05	120	34.28
	More than 5	100	28.75
Total		**350**	**100**
Area	Rural	280	80.00
	Urban	70	20.00
Total		**350**	**100**
Education	Primary	160	45.71
	Secondary	80	22.85
	Higher Secondary	60	17.14
	Graduate	50	14.28
Total		**350**	**100**

Source: Author calculations based on Primary Data

The migrant population of Goa is described in various fascinating ways in the demographic profile. Table 1 shows that the age group between 25 and 35 years old, which is followed by the age group under 25 years old, accounts for the largest proportion of migrant workers (45.71 percent) and (34.28 percent). Additionally, around 21.01 percent of the migrating population is above the age of 35. (20.01 percent). The classification based on gender reveals that males migrate at a higher rate (78.57 percent) than females (21.43 percent). Further, we discovered in our sample study that migration is higher among single people (60%) than it is among married people (about 40%). The number of family members who are dependent on the migrants' labour is another fascinating feature of the demographic profile analysis. According to our research, 37.14 percent of migrant workers have 1 to 3 family members who are dependent on them. The percentage of migrant workers who had dependent family members in the age groups of 3 to 5 and more than 5 was followed by 34.28 and 28.75 percent, respectively. The data also demonstrates that the majority of migrants come from rural areas (80%), while only around 20% of migrants come from urban areas, which is consistent with migration theory, which states that this is where the rural-urban migration typically occurs.

We have also broken down migrant labour by state of origin. According to the census from 2011, we chose these states for our study since there is a large migration rate to Goa from these states. Additionally, these states score poorly on economic development metrics such the HDI, PCI, or HPI.

Table 2: Migrant labour by state of origin

States	Total number of respondents	Percentage
Bihar	46	13.14
Assam	28	08.00
Jharkhand	14	04.00
Uttar Pradesh	43	12.28
Orissa	12	03.42
Bengal	24	12.00
Karnataka	145	41.42
Chattisghad	38	10.85

Source: Primary Data

The study's findings indicate that the state of Goa experiences a maximum inflow of migration of about 41% from Karnataka. Such high-level migrations can be explained by two different factors. First off, Karnataka is a neighboring state to Goa and has excellent transportation options. Second, it is convenient for immigrants to quickly pick up Goan languages and culture. The largest influx of migrants after Karnataka comes from Bihar (13.14 percent), next from Uttar Pradesh (12.28 percent), West Bengal (12.28 percent), Assam (08 percent), Jharkhand (4 percent), and Orissa (03.42 percent).

We also looked at the source of information regarding job information for migrants in our investigation. We have identified a number of factors that could serve as informational resources for migrants travelling to Goa. The recognised sources of employment openings were agents, close relatives, social networks, and other people. Table 3 contains the findings from the sources of information about the job opportunity.

Table 3: Source of knowledge about job opportunity

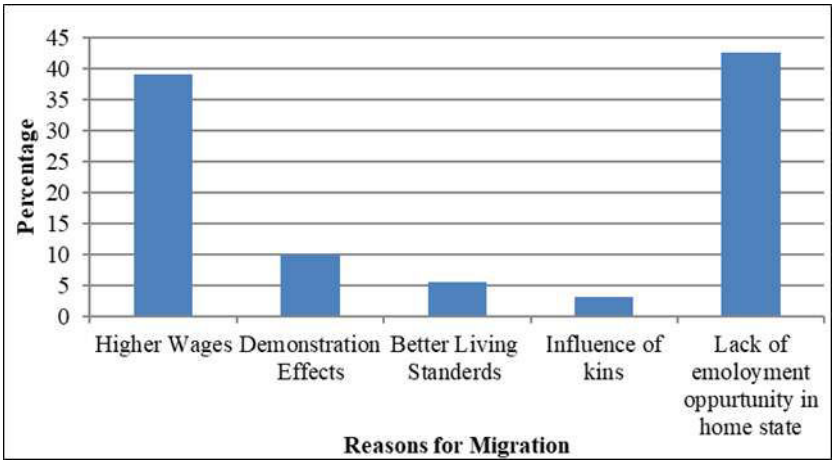
Source of Knowledge	Number of Respondents	Percentage
Social Network	174	49.79
Agents	45	12.85
Relatives and close Kin	67	19.14
Media	34	09.71
others	10	2.85

Total	250	100

Source: Primary data

According to the analysis, the majority of the migrant workers were aware of job openings via their social networks. We discovered that 49.79% of migrants learn about job openings in Goa using social networks. Following this were family members and close friends (19.14%), agencies (12.85%), the media (09.71%), and other sources at roughly 2.85 percent.

We also looked at the reasons why people migrate to Goa as labourers, which was an interesting topic. We identify a number of them, including improved living conditions, higher earnings, the demonstration effect, the absence of employment possibilities in the home state, and the influence of friends and family. The outcome is shown in Figure 1 below.



Source: Primary Data

Fig 1: Reasons for migrations from domicile state

The higher incomes that draw a lot of migrants to Goa, as seen in Figure 1, are the main drivers of migration. According to our research, almost 39.14% of migrants moved to Goa in search of jobs with greater pay. Theoretical and empirical literature both strongly supports this and is in line with a priori predictions. Additionally, the dearth of employment possibilities in their home states is a contributing factor in the significant migration to Goa. We discovered that this aspect affected migrant workers' decisions by about 42.34 percent. We also discovered that migrations from the domicile state to Goa were significantly influenced by the demonstration effect. We discovered that the demonstration effect causes about 10% of migrants to relocate to Goa.

The quality of life of migrant workers is then understood by calculating the logistic regression. A dummy variable that represents different forms of labour is used as the dependent variable in the study. The dummy variable is programmed to indicate 1 if they are migrant workers and 0 if they are local workers. In the logistic regression model, six significant variables that are connected to the workers' quality of lives were used as independent variables. Age, assets possessed, job, salaries, working days, and living expenditures were some of the factors in the model. Except for working days and living expenditures, all independent variables were changed to dummy variables. In our approach, we treat the number of working days and daily living costs as continuous variables. We have presented the summery of the logistic regression in Table 4.

Table 4: Coefficients of final logistic regression model

Step	-2 log likelihood	Cox & snell R square	Nagelkerke R square
13	34.326	0.804	0.947

Source: Authors Calculation based on primary

According to the model summary of logistic regression, Cox and Snell's R square is 0.814, meaning that the six variables kept in the final regression model account for 70.4% of the variation in the status of being a migrant or local laborer. According to Nagelkerke R Square, 94.7 percent of the variation is covered by the independent variables that were kept. According to the findings, the six variables account for nearly 80% of the difference in laborers' status as either migrants or locals.

We now proceed to calculate the logistic regression model's coefficient. Table 5 includes the coefficient and associated attributes.

Table 5: Result of logistic regression model's coefficient

Variables	B	S.E.	Wald	df	Sig.
Age	6.51	3.647	3.199	1	0.034
Assets held	-7.764	3.267	5.671	1	0.017
Employment, Wages	-15.291	4.285	12.73	1	0.002
Wages per day	-4.039	5.567	4.56	1	0.001
Working days	-9.876	6.897	8.984	1	0.000
Living Expenses	-6.564	8.987	8.576	1	0.000

Sources: Author calculation based on primary data

At a significance level of 5%, the coefficient of all the variables is significant. The Wald results and Stanford errors show that the model is well-fitted, highly effective, and consistently reliable. We can now move on

to the result estimations. The final regression model's results showed that the dummy variables' coefficients for the age are positive. The conclusion that follows is that migrant workers are generally younger than local workers. Since the coefficient is largest in this age group, the proportions of migrant workers are substantially larger in the youngest age range of up to 25 years. Although they have a negative coefficient, the asset variables are quite important. It indicates that, in comparison to local workers, migratory labourers have fewer assets. There are two plausible explanations for this. Due to Goa's significantly higher rent costs, the labour force of migrants must first spend a larger portion of their salary on accommodation. Second, the migrant workers send the money to their home state because they are staying outside of their hometown and away from their relatives. Positive regression coefficients for the dummy variables denoting daily wages as the kind of employment show that migrant workers are, on average, paid daily wages. Compared to migrants, local labourers were found to have a higher percentage of contract jobs. In our model, the pay coefficient comes out to be negative but significant. This demonstrates that the average wage for migrant workers was lower than the wage for local workers by 4%. It is clear from the outcome that migrant workers make comparably less money than local workers. Workday and living expense variables are treated as continuous variables. These variables' regression coefficients are found to be negative, indicating that migrant employees receive a lesser number of working days annually. The regression coefficient demonstrates that overseas employees work nine fewer days per month than domestic employees. Meanwhile, migrant workers' living costs are significantly lower (6%) than those of native labourers. This may be primarily because, in comparison to local labour, the majority of migrant workers do not spend their money on entertainment and other leisure pursuits.

Our research has several implications. First off, the enormous number of young people leaving other states demonstrates the failure of India's employment generation policies. Second, it implies that the gap between the states is growing over time due to the cumulative causation process, which is affecting the different states. Third, it is abundantly obvious from the data that the majority of the states have failed to offer youth job possibilities, which has led to population migration and the establishment of firms in other states. Fourth, although migrants move with the purpose of earning higher pay and increasing their quality of life, the quality of their work life is lower to that of local workers. Finally, excessive migration might result in social, economic, and unemployment issues in the receiving state.

Conclusion

Migration has been a significant human activity for centuries, driven by the desire for better economic opportunities and safer environments. These movements significantly impact the lives of migrants and their communities, enhancing their prospects and those of their offspring. However, migration also has a significant impact on society, particularly in regions already experiencing backwardness. To prevent negative effects, it is crucial to improve the quality of life in these regions, ensuring they have suitable sanitary, drinking, and lighting conditions. Additionally, the potential impact on host communities' infrastructure and resources must be considered. Investments in healthcare, education, and transportation sectors are essential to ensure better living conditions for both natives and immigrants. Policies should also promote social cohesiveness and reduce conflicts, encouraging integration and cultural interaction between immigrants and host communities.

References

1. Bhagat RB. Internal Migration in India: Are the Underclass More Mobile? 26th IUSSP General Population Conference held in Morocco, 2009.
2. Mahapatro SR. Patterns and Determinants of Female Migration in India: Insights from Census, ISBN 978-81-7791-102-2, The Institute for Social and Economic Change, Bangalore, 2010.
3. Mehta GS. Employment Structure and Earnings of Migrant Workers in Urban Economy, Manpower Journal. 1996;XXXI(4):29-41.
4. Prabhat Kumar. Linkage between Internal migration and regional Development-A case of India, M.Phil. Dissertation in Applied Economics, Centre for Development Studies, Trivandrum, 2007.
5. Shamna TC, Baiju KC. The emerging issues of immigrant labourers in the Construction sector of Kerala, Indian Journal of Economics and Development, 2016, 4(2).
6. Vijay Korra. Short Duration Migration in India: An Appraisal from Census 2001, Working Paper No. 442, Centre for Development Studies, Thiruvananthapuram, 2011.

Chapter - 3
Development of Assamese Motifs in Woven Fabric for Construction of Hand-Woven Kurti

Authors

Dr. Syeda Sahnaz Yasmin
Ph.D., Department of Textiles and Apparel Designing, College of Community Science, Assam Agricultural University, Jorhat, Assam, India

Dr. Rickey Rani Boruah
Assistant Professor, Department of Textiles and Apparel Designing, College of Community Science, Assam Agricultural University, Jorhat, Assam, India

Chapter - 3

Development of Assamese Motifs in Woven Fabric for Construction of Hand-Woven Kurti

Dr. Syeda Sahnaz Yasmin and Dr. Rickey Rani Boruah

Abstract

Handloom weaving is the richest traditions of Assam made from different materials and by using a variety of techniques. The tradition of textile production has been handed down from generation to generation among different communities and the historical antecedents provide substance to the contemporary practice. It is amply evident that handloom weaving is an integral part of the life and tradition of the indigenous weavers. The traditional skill of the indigenous weavers including their deep perception of beauty in color and design is a high order which has achieves acclaim in and outside the country. However, this items are generally found limited to the traditional items. In view of the present market demand need for product diversification has become an important issue of consideration. This study was an attempt for preserving the handloom heritage for the livelihood of weavers by developing woven kurtis with suitable Assamese motifs in the center panel.

Keywords: Assam, motifs, center panel, handloom weaving, kurti

Introduction

Weaving as a handicraft, has a vital place in Assamese society that both tradition and financial side are inter-linked to it. The tradition of textile production has been handed down from generation to generation among different communities and the historical antecedents provide substance to the contemporary practice. It is amply evident that weaving is an essential part of the rural culture and economy of Assam. Borah (1994).

Textiles constructed with beautiful eye catching designs in the family looms is a prestigious and possession for every Assamese lady. As a matter of fact, textiles and designs constructed in handlooms not only have monetary importance but also represent a sentiment which is established in the community customs. Teron, R. and Borthakur (2012).

Design is most effective when it is 'indegenious' or uncommon and astonishing. The arrangement of the motif is considered as design in a pattern, whether it is spaced broadly or narrowly on the ground, in well-ordered or actually at random, or in rows that form stripes. Designing is an innovative process that depends upon the skills of the designer to combine aesthetic sensibility with a solid knowledge of the technology. Chandler (2011). The artistic process often arises with different art methods to draw ideas for the finished product. Conventionally, sketches of woven textile designs were transformed onto special forms of graph paper called point papers, which were used by the weavers for weaving the fabric design. Mazumder, L. (1987)

The traditional skill of the indigenous weavers including their deep perception of beauty in color and design is a high order which has achieves acclaim in and outside the country. However, this items are generally found limited to the traditional items. In view of the present market demand need for product diversification has become an important issue of consideration. All through the world ethnic cultures are under risk from the forces of upgrading and globalization. Handloom weaving of Assam is also fronting the same problematic. Knowledge of incorporating conventionally used design and motifs as these are fast vanishing; even weaving in back-strap loom is restrained to only a few senior women. Bearing in mind the declining trend in textile culture of Assam, it was felt essential to take measure for maintaining the handloom heritage for the livelihood of weavers by developing woven kurtis with suitable Assamese motifs in the center panel with the following objectives.

1) Development of motifs.
2) Preparation of drafting, peg plan and tie-up of the motifs for the development of woven kurtis.

Materials and Methods

The study was conducted in the year 2018 at Jorhat district of Assam. The research was started with the collection of Assamese hand woven motifs from various sources. Motifs were collected from both primary as well as secondary sources. Internet, magazines, sanekis, and books were used for the study and through personal visit, information's were collected from weavers of Assam. Thirty (30) designs for center panels were developed with some suitable motifs by using Reach Tex Software in the computer. From the developed thirty center panel designs, seven (7) center panel designs were selected randomly in consultation with the members of Advisory Committee.

Selected designs were woven in the Kurti material for which drafting pegplan and tieups of the motifs were prepared.

Results and Discussion

Collection of motifs

Assamese motifs were collected from various primary and secondary sources such as internet, magazines, sanekis, books and through personal visit to collect information's from weavers of Assam.

Development of motifs

From the collected motifs nine motifs were selected and developed in Reach Tex Cad for the development of center panel design

Documentation of motifs used in center panel design

Objects of nature constitute the main source of inspiration for motifs and designs used in the ornamentation of textiles in Assam. The textile motifs of Assam are more stylized than naturalistic. (Mazumdar, L. 2013).

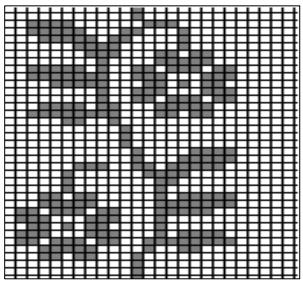
Motifs used in center panels were documented digitally. Documented motifs were shown as Fig 1.

Details of the selected motifs

Details of the selected motifs are given below.

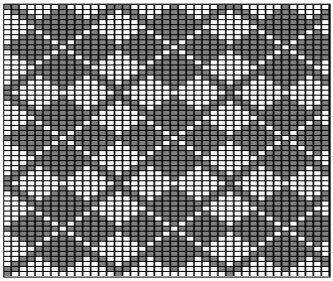
Motif 1: Babori (Flower)

Dutta (1991) stated that Babori phul is a common floral motif which has been derived from babori xaak in Assamese and has been named as Annual chrysanthemum in English occupies a vital place in the textile design of Assam. In the present study the babori flower motif has arranged in creepers and therefore it is named as babori lata. The investigator has used the motif in the vertical stripes form for the center panel design of the Kurti. Numbers of picks used for developing the motif were seventeen and ends were eighteen.



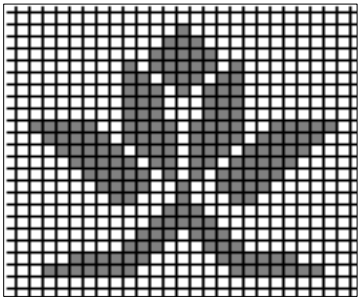
Motif 2: Golpota (NeckPiece)

Sharma (2014) reports that Golpota is a type of traditional Assamese necklace which wedged around the neck. Varities of designs in stylish floral form are adorned in it.There are two types of golpotas that were customary since ancient periods Rotnomoy Golpota and Guliya Golpota. Assam has a rich collection of traditional jewelry. Adoption of art, crafts and materials stuffs in the socio-cultural life of the Assamese peoples for ornamenting the textile. The motif has wonderful unity, orderliness, harmony of line, the symmetry of form and shape. Such design is classified under geometric design. In the present study, the investigator has used the Golpota motif vertically as all over design for the center panel of the kurti. Numbers of picks used in the motif were sixteen and ends were fifteen.



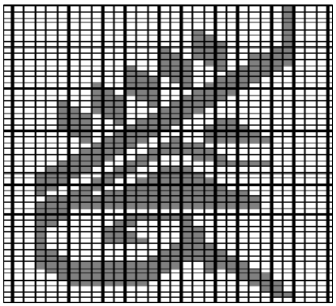
Motif 3: Padum (Lotus)

Gogoi (1985) stated that Padum is a floral motif and is known as Lotus in English. It offers infinite opportunity for decoration of the textiles. Simplest and smallest formation with well-defined petals of flowers are establish in the textile designs of Assam. Padum (Lotus) is traditionally used in fabrics of religious importance also. In the present study the motif was used alternately along with the geometric motif named Barfi for the center panel design of the kurti. Numbers of picks used in the motif were twenty one and ends were also twenty one.



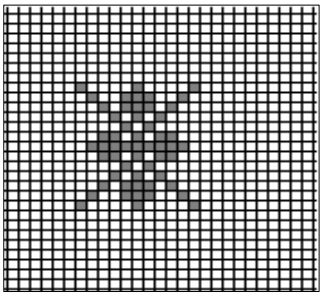
Motif 4: Dhekia

Mazumdar (2013) stated that Dhekia is a vegetable fern and found in varieties of annual weeds and herbs grow commonly in the rural domiciles. Dhekia motif also depicted in the textile designs. Even these have captured the imagination of the women and they have suitably adopted the motif on their looms. The power of observation and tremendous capability of the indigenous weavers to render objects of nature into textiles motifs has contributed towards the enrichment of the textile tradition of Assam. In the study the motif has been arranged in the vertical stripes form in the center of the kurti as a center panel design. Numbers of picks used in the motif were fifty-four and ends were twenty-three.



Motif 5: Mokora

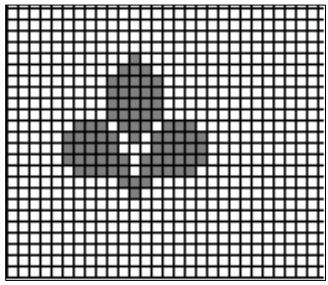
Chetia (1992) mentioned that Mokora is an Assamese motif which is also known as Spider in English. It is a structural motif and used in stylised form in the Assamese textiles. In the study the motif has arranged in the vertical stripes form in the center of the kurti as a center panel design. Number of pick used in the motif were thirteen and ends were eleven.



Motif 6: Pankota

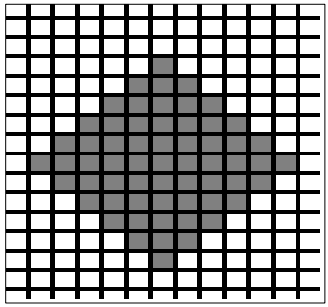
Mazumdar (2013) stated that Pankota is a common motif used in the textiles of Assam. It is a betel leaf in stylized and geometric forms, used

either individually as buta or as a element in the design. In the present research work, the motif has been used alternately along with the kalka motif and has been arranged in such a way that the spaces between the kalkas and pankota are maintained uniformly along with two border design. The whole design is arranged at the center of the kurti as a center panel design. Numbers of picks were thirteen and ends were thirteen.



Motif 7: Barfi

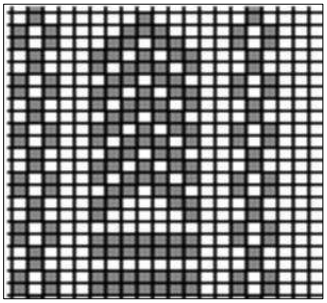
Kalita (1998) stated that Barfi is a geometrical motif resembles the shape of a diamond. In the textiles of Assam, it has been used independently or in arrangement with the other motifs widely and since the historic times. It is commonly used by the local weaver in their textiles. In the study it has been used along with the padum motif for constructing the center panel design. Numbers of picks were eleven and ends were eleven.



Motif 8: Kech basa

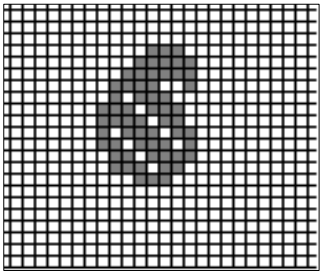
1. Kalita (1998) described that Kech basa is a geometric pattern used at the edge of the design as a corner design. Ribbed pattern is used in arrangement of bands and lines with different colours is called kech basa or stripes design. It is cast-off on the edge of Riha. Riha is an significant item of bridal outfit on marriage ceremonies. Currently, this design is altered and is used in chadar also. This design is adopted from the tribal textile designs done on the loin loom. The investigator has used the motif in the vertical stripes

form for developing the center panel design of the kurti. Numbers of picks used in the motif were twenty-four and ends were twenty.



Motif 9: Kalka

Mazumdar (2013) reports that Kalka is also known as paisley, the commonly and traditionally used motif in Indian as well as Assamese textiles. It is a mango shaped motif with curved ornate top. Another name by which it is known is mogor. The kalka design was probably adopted from the old Gomcheng and Kingkhap which were often lavishly adorned with kalkas. Conventionally, here, in Assam, the kalka is applied in the edge of a chadar. However, various sizes of kalkas are used individually as buta or as a unit in the border design. In the present research work, the motif has been arranged in such a way that the spaces between the kalkas and pankota are maintained uniformly along with two border design. The whole design is arranged at the center of the kurti as a center panel design. Numbers of picks used were twelve and ends were eight.



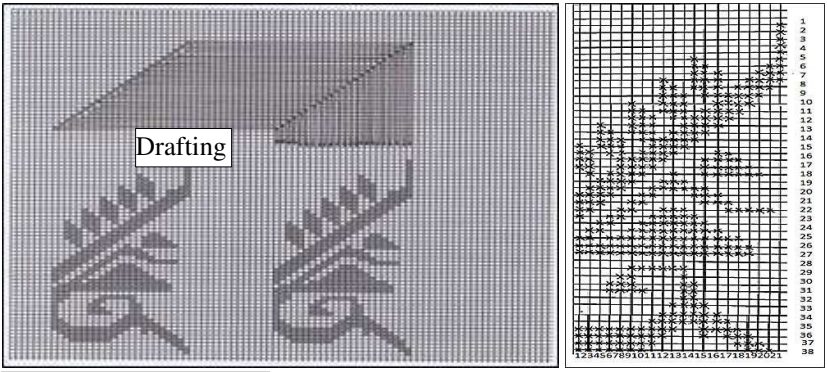
Development of designs for Kurti using Assamese motifs

The collected Assamese motifs were used to developed woven designs for Kurti. The placement of motifs was done on center panel of the kurti. The investigator developed thirty (30) designs for center panels. Out of which seven designs were selected in consultation with the major Advisory for the construction of the Kurti material.

Preparation of drafting, peg plans and tie up of the designs

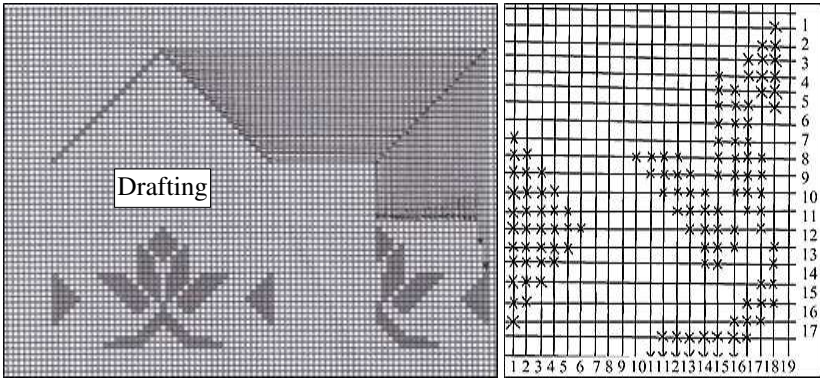
The investigator had developed the drafting, peg plans and ties up of the selected motifs for the study by using REACH Tex Software and were presented below (Fig 1 to 11).

Drafting and Pegplan **Tie-ups**



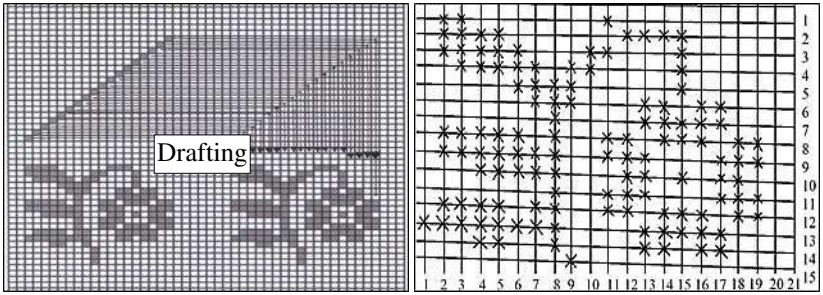
Peg plan Straight Drafting

Fig 1: Drafting, Peg plan an Tie-up of Dhekia motif



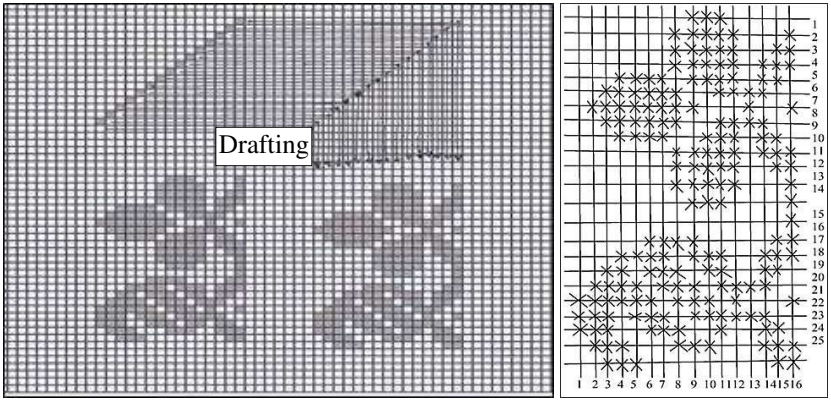
Peg plan pointed drafting

Fig 2: Drafting, Peg plan an Tie-up of Podum and Barfi motifs



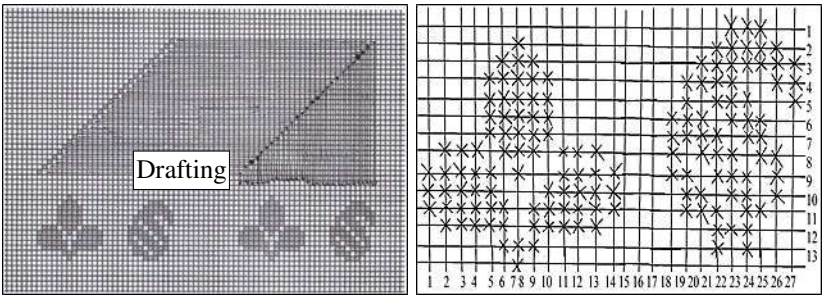
Peg plan Straight Drafting

Fig 3: Drafting, Peg plan an Tie-up of Babori motif



Peg plan straight drafting

Fig 4: Drafting, Peg plan an Tie-up of Kalka and Pankota motifs for border



Peg plan straight drafting

Fig 5: Drafting, Peg plan an Tie-up of Kalka and Pankota motifs

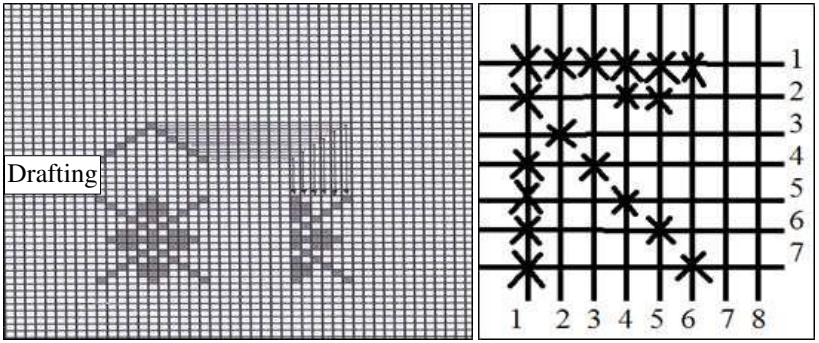


Fig 6: Drafting, Peg plan an Tie-up of Mokora motif

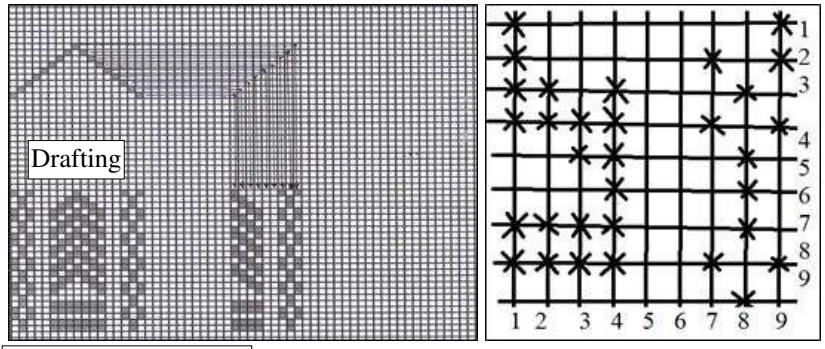


Fig 7: Drafting, Peg plan an Tie-up of Kechbasa motif

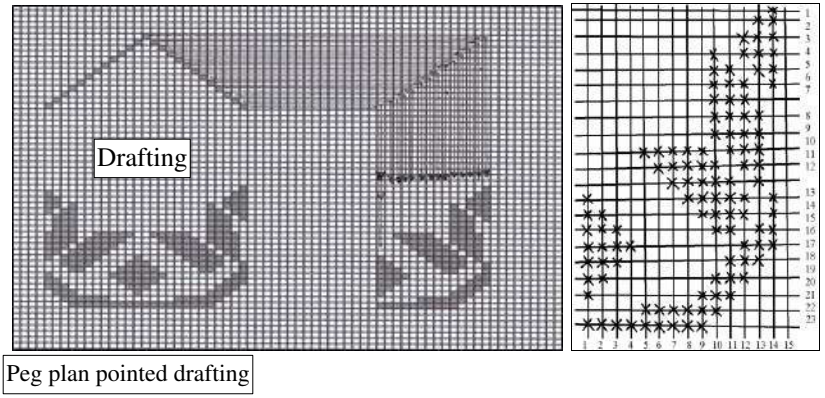


Fig 8: Drafting, Peg plan an Tie-up of Padum and Barfi motifs border

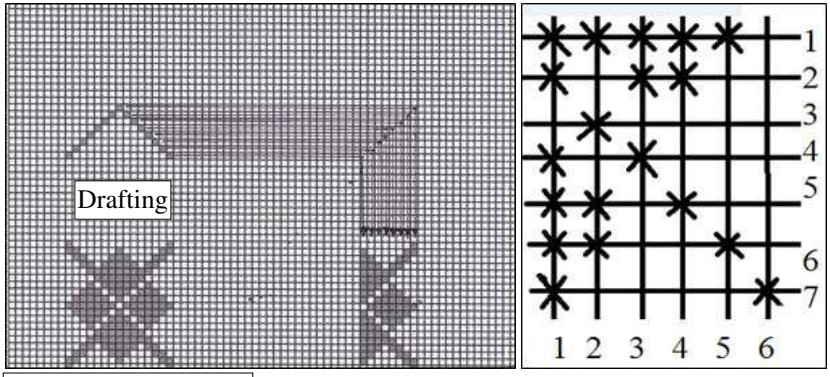


Fig 9: Drafting, Peg plan an Tie-up of Golpota motif

Selection of yarns for weaving

For the purpose of the study, the investigator had collected different types of yarns of different count number available in the Jorhat district of Assam. Out of them, Polyester yarn locally called Padmini yarn of Count number 60/2 was selected for the weaving of the kurti material.

Selection of colour for kurti and center panels

The investigator had collected different coloured Padmini yarns from Jorhat district of Assam for the study. The collected yarns were paired to get the best combination suitable for kurti and center panel. Out of them navy blue and red coloured yarns were selected for kurti and center panels respectively.

Weaving of the fabric for selected kurtis with center panel designs

The woven fabrics were developed for the selected seven (7) center panel designs for construction of kurtis. The center panel designs were woven horizontally on the loom along with the kurti material. Plain weave was used to construct the fabric and extra weft yarns were used for the construction of the center panel design and width of the center panel is six inches which is constant for all the kurtis.

Construction particulars of woven fabrics were shown as Table 1.

Table 1: Details of the woven fabric were shown in table 1

Yarns	Yarn count	Weave	Types of loom	Reed no.	Cloth width
Padmini (Polyester yarn)	60/2	Plain weave	Fly-shuttle	48	48 inch

Documentation of the woven center panel design

Constructed woven fabric with the center panel design were shown as Fig 10.

			
Design 1	**Design 2**	**Design 3**	**Design 4**
			
Design 5	**Design 6**	**Design 7**	

Conclusion

This type of study will helps in discovering and popularizing the textile motifs of Assam and also preserving the handloom tradition by enabling the sustainability of Assamese hand-woven motifs in Kurtis which helps to diversify the designs and also commercialize the handloom products in different forms and prevent them from going into extinction for the livelihood of weavers.From the findings it can be concluded that it is possible to developed new and interesting designs using woven motifs of Assam to meet the excessive demands of contemporary designs in apparel fields. This study will help the designers for creating more innovative ideas and explore the Assamese motifs in other states also and it will also help the motivates people to come up with an indigenous work, which indirectly help in upgrading the art and craft of Assam as well as India.

References

1. Borah J. Designing and Construction Kurtas from Hand woven Textiles of Assam. Unpublished M.Sc. (H.Sc.) Thesis, Assam Agricultural University, Jorhat, 1994, 133.
2. Chandler D. Jacquard Weaves. Retrieved 8 November, 2011, From http://www.bookdepository.co.uk

3. Teron R, Borthakur SK. Biological motifs and designs on traditional costumes among Karbis of Assam, Indian Journal of Traditional Knowledge, 2012, 11(2).
4. Mazumder L. Traditional Textile of Assam, A study of an indigenous craft with reference to continuity of change, Unpublished Ph.D. thesis, Assam Agricultural University, Jorhat, 1987, 168-216.
5. Mazumdar L. Textile Tradition of Assam, an empirical study, Publisher Bhabani Books, Guwahati, Assam, 2013, 122-135.
6. Dutta L. Handloom Industry in Assam. Unpublished Ph.D. Thesis, Guwahati University, 1991, 112-118.
7. Sharma M, Mishra S. Designing on Khadi Kurtis by using Fasteners. IOSR J. Humanities and Social Science. (IOSR-JHSS). 2014;19(7):132-137.
8. Gogoi A. A comparative study of some Historical Textile Design and Symbolism of Decorative Motifs in textiles of North-East India. Unpublished Ph.D. thesis (Home science), M.S. University, Baroda, 1985.
9. Chetia S. A study on Handloom Textiles of an indigenous craft with reference to continuity of change, Unpublished Ph.D. thesis, Assam Agricultural University, Jorhat, 1992, 156.
10. Kalita RC. Sualkuchir tat silpar itihash, in Hingkhap. Edited by Bhrigu Ram Das. Sualkuchi: Assam Samabai Reshom Pratisthan Ltd., 1998, 7-13.

Chapter - 4
Comfort Properties of Kenaf and Ramie Blended Fabrics

Author

Dr. Ankita Kakoty
Department of Textiles & Apparel Designing, Faculty of Community Science, AAU, Jorhat, Assam, India

Chapter - 4

Comfort Properties of Kenaf and Ramie Blended Fabrics

Dr. Ankita Kakoty

Abstract

Clothing comfort, being a fundamental and universal need for consumers, may be defined as a pleasant state of physiological, psychological and physical harmony between a human being and the environment. The demands from fabrics have changed with the developments in textile technology and the rise of people's living standards. Now the requirement is not only style and durability, but also clothing comfort. To fulfill sustainability need of today's comfort conscious consumers, an attempt has been made by evaluating the properties of fabrics which were compared under drape-coefficient, thermal conductivity, Wicking height and air-permeability of controlled and blended fabrics. Ramie blended fabrics showed better result in many cases thus we compare the present work with an aim for analyzing comfort properties of fabric.

Intensive growth of world population indicates the need of making clothing fabrics that comply with the requirements of a large number of consumers. Due to continuous changing preference, product diversification becomes one of the crucial issues for a visible economic activity. The topic leaves many opportunities for various researchers especially when it covers the comfort of clothing fabric.

Keywords: Flax, appearance, luster, drape-coefficient, wicking height, air permeability, thermal conductivity

Introduction

Clothing comfort is an important phenomenon nowadays and has drawn attention of many of the textile research worker. Probably many researchers have carried out extensive work on the fabric handle properties. The ease of body motion and the load generated in the fabric during body movement are obviously related to the fabric handle properties. The clothing comfort may be related to the smoothness, ability to drape, roughness, permeable etc. (Darin 1982) [1].

Methodology

The comfort properties of the fabric were analysed by different methods

Air permeability ($cm^3/cm^2/sec$)

Air permeability is defined as the volume of air measured in cubic centimeter passed per second through $1cm^2$ of the fabric at a pressure of 1cm of water.

All the samples were tested as directed by ASTM D-737 test method.

Drape-coefficient (%)

Drape is the ability of a fabric to assume a graceful appearance in us. Fabric drape may be explained as the extent to which a fabric deforms when it is allowed to hang under its own weight.

Drape co-efficient was calculated by using the formula:

$$F = \frac{As\text{-}Ad}{(AD\text{-}Ad)} \times 100$$

Where,

AD = The area of the specimen.

Ad = The area of the supporting disk.

As = The actual projected area of the specimen.

Drape co-efficient F was the ratio of the projected area of the draped specimen to its undraped area, after deduction of the area of the supporting disk (Booth, 1968).

Wicking height (cm)

Miller Tyomkin (1984) pointed out that spontaneous uptake of liquid in a fabric has always been called wicking, also stated that when a porous material such as fabric is placed in contact with a liquid, spontaneous uptake of liquid may occur.

The height reached (at a constant time of 2 minutes) by the water in the fabric above the water level in the reservoir of distilled water was measured and recorded (Booth, 1968).

Thermal conductivity

(ASTM: D 1518-1985)

Thermal conductivity was tested using apparatus. The apparatus gives

the value of thermal insulation in CLO units and can give test temperatures of upto 50 °C [3].

Results and Discussion

Drape co-efficient (%) of controlled and blended fabrics

The drape co-efficient of plain weave blended fabrics were systematically analysed and the data were recorded in the Table 1.

Drape is the ability of fabric to hang in graceful fold. Fabric drape is the extent to which a fabric will deform, when it is allowed to hang under its own weight. It is largely affected by the yarn twist. The drape coefficient expresses the drapability of the fabric, and the higher the value of drape coefficient, the poorer its drapability (Shinkle, 1970) [4].

Table 1 illustrated the drape coefficient and wicking height of controlled and blended fabrics. It was depicted that among the controlled fabrics, highest drape co- efficient (75%) was recorded in controlled kenaf and least was observed in controlled ramie (60%). And in case of blend proportion 75:25 kenaf: ramie shows highest drape coefficient followed by 50:50 kenaf: ramie (60%) and 25: 75 kenaf: ramie (60%).

Drapability of fabric is a combined effect of several factors such as stiffness, flexural rigidity, weight, thickness etc. Stiffness, an attribute of fabric hand is one of the most important factors determining draping quality of fabric e.g. soft fabric drapes closer to the body forming ripples whereas stiff fabric drapes away from the body (Hatch, 1999) [5].

Table 1: Drape co-efficient of controlled and blended fabrics

Fabric	Drape co-efficient (%)
Controlled fabrics	
Kenaf	75
Ramie	60
Blended fabrics	
Kenaf: Ramie	
75:25	65
50:50	60
25:75	60
SED±	0.36
CD (0.05)	0.75

The results were mean of five observations.

Wicking height (cm) of the fabrics

From Table 2 it was seen that among the controlled fabrics maximum wicking height was observed in controlled ramie fabric in warp (6.45 cm) and weft (6.39cm) direction and minimum was recorded in controlled kenaf fabric in warp (4.14 cm) and weft way (4.09 cm). Among the blended fabrics 25:75 kenaf: ramie showed maximum wicking height warp (6.29 cm) and weft (6.20 cm) and least was seen in 75: 25 kenaf: ramie warp (5.62 cm) and weft (5.56 cm) followed by 50:50 kenaf: ramie blend proportion warp (5.75 cm) and weft (5.54 cm).

It could be in inferred from the Table 2 that wickability is more in controlled ramie because ramie fibers has better absorbancy than other cellulosic fiber because of its porous sieve that makes it even better absorbency and it is also crystalline in nature. So wicking height is good in controlled ramie fabrics.

Table 2: Wicking height of controlled and blended fabrics

Fabric (%)	**Wicking height (cm)**	
	Warp	**Weft**
Controlled fabric		
Kenaf	1.14	0.90
Ramie	1.45	0.39
Blended fabric		
Kenaf: Ramie		
75:25	0.62	0.56
50:50	0.75	0.54
25:75	1.29	1.20
SED±	0.3	0.34
CD (0.05)	0.02	0.21

The results were mean of five observations

Air permeability for controlled and blended fabric

Air permeability measures how easily air is passed through fabrics. It indicates the weather resistant and water-proof fabric. The main influences on air-permeability are the density of the material and its structure.

In Table 3 it was observed that in case of controlled fabric air permeability is highest in controlled ramie because of the porous sieve of ramie i.e. (63.89 cm^3) followed by controlled kenaf (59.44cm^3). In case of blended proportion 25: 75 kenaf: ramie shows highest air permeability (63.33 cm^3) followed by 50:50 kenaf: ramie (61.67 cm^3) and 75:25 kenaf: ramie (59.44 cm^3).

Table 3: Air permeability for controlled and blended fabrics

Fabric	Air permeability ($cm^3/cm^2/sec$)
Controlled fabrics	
Kenaf	59.44
Ramie	63.89
Blended fabrics	
Kenaf: Ramie	59.44
75:25	61.67
50:50	63.33
25:75	
SED±	1.11
CD (0.05)	2.31

The results were mean of five observations.

Thermal conductivity for controlled and blended fabrics

The analytical data pertaining to thermal conductivity of controlled and blended fabric were tested and blended fabric were tested and recorded in table 4.

It is apparent from the table 4 that among controlled fabrics, the highest thermal conductivity was found in ramie fabric (0.214 CLO) and minimum was recorded in kenaf fabric (0.110 CLO). The highest value of thermal conductivity for controlled fabric was responsible for its better heat transfer.

In case of blended fabric the maximum value of thermal conductivity were noticed in kenaf/ramie 75:25 (0.147 CLO) followed by kenaf/ramie 50:50 (0.116 CLO) whereas, minimum thermal conductivity recorded in kenaf/ramie 25:75(0.052 CLO).

From the statistical analysis it has been found that controlled have significant difference. Moreover, the interaction effects also have significant difference which is seen between the blended fabrics.

Table 4: Thermal conductivity for controlled and blended fabrics

Fabric	Air permeability ($cm^3/ cm^2/sec$))
Controlled fabrics	
Kenaf	0.110
Ramie	0.214
Blended fabrics	
Kenaf: Ramie	
75:25	0.147

50:50	0.116
25:75	0.052
SED±	0.122
CD (0.05)	0.23

The results were mean of five observations

Conclusion

The primary need of people to dress has changed as time passed because different high-tech fibers, yarns, fabrics and finishing applications has changed. So nowadays comfort properties in an important phenomenon to be observed while selecting clothing. The clothing comfort is divided into some groups and this paper presents the detailed explaination of clothing comfort. The study will be useful for the manufacturers in terms of selection of blend percentages in regards to its comfort properties.

References

1. Darin V. Energy work and leisure, London Heinemann educational, Booksley, 1982.
2. Booth JE. Principle of Textile Testing. Third Edn, Newnes Butterword London, 1968, 353-354.
3. Miller B, Tyomkin I. Spontaneous transplanar uptake of liquid by fabrics. Textile Res. J. 1984;56(10):706-712.
4. Shinkle H. Textile testing, physical, Chemical and micro- scopical. D.B. Taraporevala sons and co. Pvt. Ltd., New Delhi, 1970, 132-142.
5. Hatch KL. Textile science, west publishing company, Minneapolis/ Saint Paul, 1999, 292.

Chapter - 5
A Short Review on Bio-Marker of Hepatocellular Carcinoma

Authors

Kinjal P. Patel
Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Dipti Gohil
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Sweta Besh
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Dilsar Gohil
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Cyril Sajan
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Rajesh A. Maheshwari
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Chapter - 5

A Short Review on Bio-Marker of Hepatocellular Carcinoma

Kinjal P. Patel, Dipti Gohil, Sweta Besh, Dilsar Gohil, Cyril Sajan and Rajesh A. Maheshwari

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant cancers and has a high mortality rate. In order to reduce the risk of failure of new medicines, predicting which drugs will prove toxic to the liver is an important aspect of the drug development process. To provide stratified care for patients with liver disease, we urgently need non-invasive tools that can effectively phenotype patients based on their degree of liver injury, natural history, and clinical outcomes. It is unthinkable that the choice of intervention in an individual patient still remains, in many circumstances, an empirical exercise involving "trial and error". Biomarker research and its dissemination should aim to overcome these barriers to individualising care. The most common traditional biomarkers of drug-induced liver injury, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have several limitations. So, there is need for other biomarker with its success application. In this review, biomarkers such as Heat shock protein, Squamous cell carcinoma antigen, Hepatocyte growth factor, Insulin-like growth factor-II, transforming growth factor-β1, lncRTNAs, Osteoponti was studied.

Keywords: Hepatocellular carcinoma, biomarker, liver diseases, liver tumor, diagnosis

1. Introduction

A biomarker refers to a measurable biological trait used to objectively assess normal or abnormal biological processes or reactions to therapeutic treatments. Examples encompass gene expression patterns, levels of specific proteins in bodily fluids, or alterations in brain electrical activity. These biomarkers are categorized based on their utility, such as diagnostic, prognostic, pharmacological, and surrogate biomarkers. The entire range of

valid biomarkers can be grouped into four types: detective, diagnostic, prognostic, and predictive biomarkers. Detective biomarkers pinpoint specific biomolecules associated with a particular disease, like identifying prostate-specific antigen as linked to prostate cancer. Diagnostic biomarkers identify individuals with a specific disease, such as detecting rheumatoid factors in the blood as a diagnostic marker for rheumatoid arthritis. Prognostic biomarkers indicate the likely disease progression with or without treatment, while predictive biomarkers focus on identifying individuals at risk in the early stages who may benefit from therapeutic intervention. Classified biomarkers based on their applications, including disease burden, diagnostic, prognostic, investigative, and therapeutic efficacy biomarkers [1-6]. As for hepatocellular carcinoma (HCC), it is among the most prevalent. Hepatocellular carcinoma (HCC) stands as one of the prevalent malignant cancers, with a notable elevation in mortality rates. The incidence and mortality of this disease show a consistent rise, particularly in Asia and Africa. While surgical resection remains the most efficacious treatment for HCC, its effectiveness is hindered by a high recurrence rate, early distant metastasis, frequent resistance to chemotherapy and radiation therapies, and the absence of symptoms in the initial stages, all contributing to a bleak prognosis. Consequently, the identification of effective biomarkers holds significant importance in facilitating early detection and enhancing the prognosis of HCC [7-12].

2. Biomarkers in the detection of HCC

2.1 Heat shock protein

Serum heat shock proteins (HSPs) emerge as promising tumor markers for assessing hepatocellular carcinoma (HCC). These proteins are induced in response to various stressors, including those associated with carcinogenesis. Notably, HSP70 has been recognized as a potentially sensitive marker for distinguishing early HCC from precancerous lesions. In individuals with HBV infection, the expression levels of GRP78, GRP94, or HSP90 have shown significant correlations with vascular invasion and intrahepatic metastasis. HSP27 has been identified in the sera of 90% of HCC patients and two HBV patients, but it was absent in normal sera. The optimal diagnostic threshold for HSP27 in HCC was determined to be 456.5 pg/mL, providing a sensitivity of 70% and specificity of 73%, with an AUC of 0.749 [13-14].

2.2 Squamous cell carcinoma antigen

Squamous cell carcinoma antigen (SCCA), belonging to the serpin (serine protease inhibitor) family, is normally active in a layer of the

squamous epithelium, and its heightened expression has been linked to tumorigenesis. Reports indicate its overexpression not only in hepatocellular carcinoma (HCC) tissue but also in the sera of HCC patients. Further exploration of serum SCCA levels as a diagnostic tool for HCC, employing a similar method, revealed sensitivities ranging from 18% to 84% and specificities ranging from 27% to 73%. While serum SCCA-IgM might emerge as a more promising biomarker for HCC diagnosis, utilizing an ELISA technique, SCCA-IgM demonstrated sensitivities ranging from 52% to 89% and specificities from 49% to 100% [15-17].

2.3 Hepatocyte growth factor

Hepatocyte growth factor (HGF) is a polypeptide growth factor with diverse biological activities, produced by various human organs. In a prospective study involving 99 patients with chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), serum HGF levels were notably higher in HCC patients compared to those with cirrhosis or chronic hepatitis without malignancy. HCC was consistently present in patients with a serum HGF concentration exceeding 0.6 ng/mL, regardless of their alpha-fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP) levels. Additionally, the detection of HGF holds significance for early diagnosis, monitoring treatment efficacy, and predicting the prognosis of HCC. HGF has been employed as a prognostic marker in HCC, particularly for anticipating early tumor recurrence and metastasis. However, it's important to note that elevated serum HGF levels are not exclusive to liver cancer; they can also occur in non-malignant conditions such as esophageal squamous cell carcinoma, lymphoma, coronary syndrome, aortic dissection, pulmonary embolism, cerebral infarction, and sepsis. Therefore, further research is essential to confirm the association between elevated HGF levels and inflammatory changes or malignancy [18, 19].

2.4 Insulin-like growth factor-II

Insulin-like growth factor-II (IGF-II) is a mitogenic polypeptide known for its ability to stimulate cell proliferation as well as the growth and differentiation of tissues and organs. Notably, circulating free IGF-II levels were found to be markedly elevated in hepatocellular carcinoma (HCC) compared to levels in chronic liver disease. The abnormal expression of IGF-II is observed during the development of HCC (47). While clinical studies have indicated that the detection of IGF-II can be beneficial in diagnosing and predicting the prognosis of HCC, there is limited availability of diagnostic data with clinical specimens in the existing literature [20-22].

2.5 Transforming growth factor-β1

Transforming growth factor-β1 (TGF-β1) is a cytokine with diverse biological functions, playing a crucial role in the regulation of normal and transformed cell growth and differentiation, angiogenesis, extracellular matrix formation, immunosuppression, and carcinogenesis. Studies have reported significantly higher levels of TGF-β1 and TGF-β1 mRNA in the serum of hepatocellular carcinoma (HCC) patients compared to individuals with non-malignant chronic liver diseases and a healthy control group [23]. Using a cutoff level of 1.2 μg/L for HCC diagnosis, the sensitivity was 89%, and the specificity was 94% (43). Additionally, some reports suggest that TGF-β1 has a sensitivity of 78% and a specificity of 29% for HCC diagnosis with a threshold of 64.3 ng/mL. However, it's important to note that TGF-β1 is up-regulated in various conditions such as extrahepatic tumors, wounds, angiogenesis, and fibrosis tissues, indicating a lack of disease specificity for TGF-β1 [23-24].

2.6 Glypican 3

Glypican 3 (GPC3), a cell-surface heparan proteoglycan, is not expressed in healthy adult livers. In hepatocellular carcinoma (HCC), its serum levels are significantly higher than those in other benign liver diseases. Presently, the sensitivity of GPC3 for HCC diagnosis varies from 36% to 65%, with specificity ranging from 65% to 100%. Additionally, GPC3 has shown greater sensitivity than alpha-fetoprotein (AFP) in detecting smaller HCC. GPC3 holds promise for the early diagnosis of HCC and distinguishing between malignant and benign liver tumors. However, conflicting reports suggest that GPC3 may not be superior to AFP and might not be useful for HCC diagnosis.

In specific study, the levels and positive rates of GPC3 for HCC were significantly higher than those for other diseases, indicating its clinical significance in HCC diagnosis. Unfortunately, its diagnostic sensitivity and specificity were reported at 42% and 96%, respectively, showing no clear superiority to AFP. Nevertheless, for small HCC cases with negative AFP, GPC3 demonstrated a diagnostic sensitivity and specificity of 52% and 98%, supporting its value in diagnosing small HCC with negative AFP [25-27].

2.7 Osteopontin

Osteopontin (OPN) is a glycophosphoprotein that binds to integrins and is expressed in various cell types, especially in transformed malignant epithelial cells. It plays a role in multiple cellular functions, including the regulation of survival, migration, invasion, and metastasis of tumor cells. In

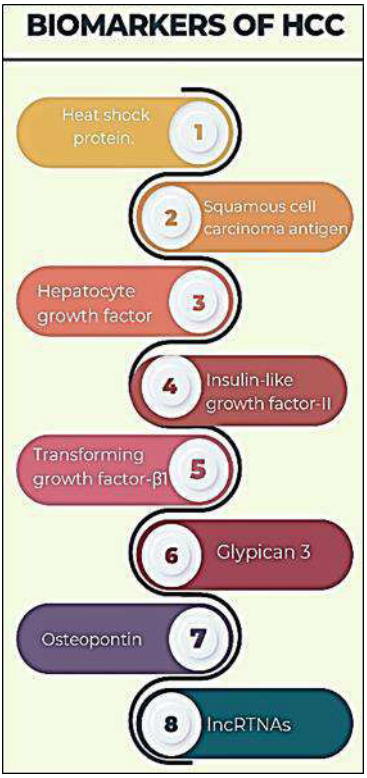
cancer, OPN overexpression is well-documented. Plasma levels of OPN were significantly higher in hepatocellular carcinoma (HCC) patients compared to those with chronic liver diseases. Its specificity and sensitivity for HCC diagnosis were reported at 92% and 26%, respectively, and its expression level was independent of alpha-fetoprotein (AFP) concentration in serum. The correlation between OPN and AFP levels was not found to be significant. Likewise, an increased plasma level of OPN has been proposed as a promising biomarker for the early stages of liver disease [27-33].

2.8 lncRTNAs

Long non-coding RNAs (lncRTNAs) are a new focus in cancer research. Although lncRNAs have no protein coding capacity, they are important in epigenetics as well as in regulating gene expression, playing an important role in various cancers. In the current study, we investigated the roles of lncRNA-D16366 in hepatocellular carcinoma (HCC) and expected to find a new biomarker for early detection and prognosis of the disease. ncRNA-D16366 was decreased in HCC, and might be an independent diagnostic and prognostic indicator in the disease. Its expression was influenced by tumor size, HbsAg, portal vein tumor thrombus, Child-Pugh score, therapies, and neoplasm metastasis. It had high diagnostic value, with an AUC of 0.752, accompanied by a sensitivity of 65.5% and a specificity of 84.6%. In addition, it was related to the prognosis of HCC. The study focused on MCM4, a protein associated with DNA replication and cell proliferation, as a potential biomarker for hepatocellular carcinoma (HCC) prognosis. The findings indicated a correlation between high expression of MCM4 and a worse prognosis, establishing MCM4 as an independent high-risk prognostic indicator for HCC patients. MCM4 is part of the minichromosome maintenance family (MCM), which plays a role in DNA replication initiation and elongation in eukaryotic cells. Previous research has highlighted the essential roles of MCM genes in various tumors, with studies demonstrating the significance of MCM4 overexpression in human laryngeal squamous cell carcinoma (LSCC). In the current study, sequential data extraction from TCGA and GEO databases validated MCM4 as a key gene. Real-time PCR analysis of 60 pairs of HCC tissues and adjacent tissues further confirmed the elevated expression of MCM4 in the tumor group. Additionally, results from HPA IHC data and western blot detection of HCC patients' tissues supported the high expression of MCM4 protein in liver cancer. In conclusion, the study proposed MCM4 as a potential biomarker for HCC prognosis, emphasizing its association with adverse outcomes. The research integrated data from large databases, real-time PCR, and protein expression analysis to provide a comprehensive understanding of MCM4's role in HCC.

Conclusion

Hepatocellular carcinoma (HCC) is a complex disease with diverse pathogenic mechanisms arising from various risk factors, making it challenging to characterize using a single biomarker. The exploration and optimization of combined tests involving multiple tumor biomarkers may hold greater value for the early diagnosis, staging, and prognosis prediction of HCC. As genomics and proteomics continue to advance, the discovery of new biomarkers tailored to diagnose different stages of HCC is expected. In the near future, the identification of novel non-invasive biomarkers for early diagnosis and personalized treatment of HCC stands out as one of the most promising areas in biomarker research.



Pictorial abstract

References

1. Wehling M. Biomarkers. In: Principles of Translational Science in Medicine. Academic Press, 2021, 135-165.

2. Lim PP, Bondarev DJ, Edwards AM, Hoyen CM, Macias CG. The evolving value of older biomarkers in the clinical diagnosis of pediatric sepsis. Pediatr Res. 2023;93(4):789-96.

3. Ball JR, Micheel CM, eds. Evaluation of biomarkers and surrogate endpoints in chronic disease, 2010.

4. Der Sarkissian S, Hessam S, Kirby JS, Lowes MA, Mintoff D, Naik HB *et al*. Identification of biomarkers and critical evaluation of biomarker validation in hidradenitis suppurativa: a systematic review. JAMA Dermatol. 2022;158(3):300-13.

5. Breiteneder H, Peng YQ, Agache I, Diamant Z, Eiwegger T, Fokkens WJ *et al*. Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma. Allergy. 2020;75(12):3039-68.

6. Morling JR, Guha IN. Biomarkers of liver fibrosis. Clin Liver Dis. 2016;7(6):139.

7. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2018;68(1):7-30.

8. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2019;69(1):7-34.

9. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A, *et al*. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.

10. Choi WT, Kakar S. Immunohistochemistry in the diagnosis of hepatocellular carcinoma. Gastroenterol Clin. 2017;46(2):311-25.

11. Hartke J, Johnson M, Ghabril M. The diagnosis and treatment of hepatocellular carcinoma. Semin Diagn Pathol. 2017;34(2):153-159.

12. Zhang S, Yue M, Shu R, Cheng H, Hu P. Recent advances in the management of hepatocellular carcinoma. J BUON. 2016;21(2):307-11.

13. Wang C, Zhang Y, Guo K, Wang N, Jin H, Liu Y, *et al*. Heat shock proteins in hepatocellular carcinoma: Molecular mechanism and therapeutic potential. Int J Cancer. 2016;138(8):1824-34.

14. Gruden G, Carucci P, Lolli V, Cosso L, Dellavalle E, Rolle E, *et al*. Serum heat shock protein levels in patients with hepatocellular carcinoma. Cell Stress Chaperones. 2013;18:235-41.

15. Soyemi OM, Otegbayo JA, Ola SO, Akere A, Soyemi T. Comparative diagnostic efficacy of serum squamous cell carcinoma antigen in hepatocellular carcinoma. BMC Res Notes. 2012;5:1-6.

16. Pozzan C, Cardin R, Piciocchi M, Cazzagon N, Maddalo G, Vanin V, *et al*. Diagnostic and prognostic role of SCCA-IgM serum levels in hepatocellular carcinoma (HCC). J Gastroenterol Hepatol. 2014;29(8):1637-44.

17. Mossad NA, Mahmoud EH, Osman EA, Mahmoud SH, Shousha HI. Evaluation of squamous cell carcinoma antigen-immunoglobulin M complex (SCCA-IGM) and alpha-L-fucosidase (AFU) as novel diagnostic biomarkers for hepatocellular carcinoma. Tumor Biol. 2014;35:11559-64.

18. Yu J, Chen GG, Lai PB. Targeting hepatocyte growth factor/c-mesenchymal-epithelial transition factor axis in hepatocellular carcinoma: Rationale and therapeutic strategies. Med Res Rev. 2021;41(1):507-24.

19. Faivre S, Rimassa L, Finn RS. Molecular therapies for HCC: Looking outside the box. J Hepatol. 2020;72(2):342-52.

20. Xu GS, Li ZW, Huang ZP, Brunicardi FC, Jia F, Song C, *et al*. MiR-497-5p inhibits cell proliferation and metastasis in hepatocellular carcinoma by targeting insulin-like growth factor 1. Mol Genet Genomic Med., 2019, 7(10).

21. Zhang Z, Lei B, Chai W, Liu R, Li T. Increased expression of insulin-like growth factor-1 receptor predicts poor prognosis in patients with hepatocellular carcinoma. Medicine, 2019, 98(44).

22. Huang Z, Su G, Bi X, Zhang L, Xu Z, Wang G. Over-expression of long non-coding RNA insulin-like growth factor 2-antisense suppressed hepatocellular carcinoma cell proliferation and metastasis by regulating the microRNA-520h/cyclin-dependent kinase inhibitor 1A signalling pathway. Bioengineered. 2021;12(1):6952-66.

23. Devan AR, Pavithran K, Nair B, Murali M, Nath LR. Deciphering the role of transforming growth factor-beta 1 as a diagnostic-prognostic-therapeutic candidate against hepatocellular carcinoma. World J Gastroenterol. 2022;28(36):5250.

24. Radwan AA, Hefney NE, Kholef EF, Elebidi A, Mahmoud H. Transforming Growth Factor B as a Marker of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C Virus Infection. Rep Biochem Mol. Biol. 2023;11(4):702.

25. Guo M, Zhang H, Zheng J, Liu Y. Glypican-3: a new target for diagnosis and treatment of hepatocellular carcinoma. J Cancer. 2020;11(8):2008.

26. Shih TC, Wang L, Wang HC, Wan YJ. Glypican-3: a molecular marker for the detection and treatment of hepatocellular carcinoma. Liver Res. 2020;4(4):168-72.

27. Liu S, Wang M, Zheng C, Zhong Q, Shi Y, Han X. Diagnostic value of serum glypican-3 alone and in combination with AFP as an aid in the diagnosis of liver cancer. Clin Biochem. 2020;79:54-60.

28. Wan HG, Xu H, Gu YM, Wang H, Xu W, Zu MH, *et al*. Comparison osteopontin vs. AFP for the diagnosis of HCC: a meta-analysis. Clin Res Hepatol Gastroenterol. 2014;38(6):706-14.

29. Lee HJ, Yeon JE, Suh SJ, Lee SJ, Yoon EL, Kang K, *et al*. Clinical utility of plasma glypican-3 and osteopontin as biomarkers of hepatocellular carcinoma. Gut Liver. 2014;8(2):177.

30. Zhang Y, Gao J, Bao Y, Liu Y, Tong Y, Jin S, *et al*. Diagnostic accuracy and prognostic significance of osteopontin in liver cirrhosis and hepatocellular carcinoma: a Meta-analysis. Biomarkers. 2022;27(1):13-21.

31. Ahmed E, Ehab A, Khaled ME, Elkholy RM. Role of Osteopontin as a Potential Marker of Hepatocellular Carcinoma. Med J Cairo Univ. 2020 June;88:1203-11.

32. Nardo AD, Grün NG, Zeyda M, Dumanic M, Oberhuber G, Rivelles E, *et al*. Impact of osteopontin on the development of non-alcoholic liver disease and related hepatocellular carcinoma. Liver Int. 2020;40(7):1620-33.

33. Kang YS, Jeong EJ, Seok HJ, Kim SK, Hwang JS, Choi ML, *et al*. Cks1 regulates human hepatocellular carcinoma cell progression through osteopontin expression. Biochem Biophys Res Commun. 2019;508(1):275-81.

34. Deng X, Bi Q, Chen S, Chen X, Li S, Zhong Z, *et al*. Identification of a five-autophagy-related-lncRNA signature as a novel prognostic biomarker for hepatocellular carcinoma. Front Mol. Bio Sci. 2021;7:611-626.

35. Han TS, Hur K, Cho HS, Ban HS. Epigenetic associations between lncRNA/circRNA and miRNA in hepatocellular carcinoma. Cancers. 2020;12(9):2622.

36. Yao J, Hua X, Shi J, Hu X, Lui K, He K *et al*. LncRNA THEMIS2-211, a tumor-originated circulating exosomal biomarker, promotes the growth and metastasis of hepatocellular carcinoma by functioning as a competing endogenous RNA. FASEB J. 2022;36(4):e22-238.
37. Mallela VR, Rajtmajerová M, Trailin A, Liška V, Hemminki K, Ambrozkiewicz F. miRNA and lncRNA as potential tissue biomarkers in hepatocellular carcinoma. Non-coding RNA Res, 2023.

Chapter - 6
Enhancing the Genetic Gain of Vegetables through Speed Breeding Technique

Authors

Siddhanath Shendekar
Ph.D. Scholar, Department of Agricultural Botany (Genetics and Plant Breeding), Mahatma Phule Krishi Vidyapeeth, Rahuri, Maharashtra, India

Nitin Patil
Ph.D. Scholar, Department of Horticulture (Vegetable Science), Mahatma Phule Krishi Vidyapeeth, Rahuri, Maharashtra, India

Varsha Singh
Ph.D. Scholar, Department of Botany (Plant Molecular Biology), Dayanand Angelo-Vedic College, Chatrapati Shahu Ji Maharaj University, Kanpur, Uttar Pradesh, India

Megha Meshram
Ph.D. Scholar, Department of Agricultural Botany (Seed Science and Technology), Mahatma Phule Krishi Vidyapeeth, Rahuri, Maharashtra, India

Shubhangi Deokar
Ph.D. Scholar, Department of Horticulture (Vegetable Science), Mahatma Phule Krishi Vidyapeeth, Rahuri, Maharashtra, India

Chapter - 6

Enhancing the Genetic Gain of Vegetables through Speed Breeding Technique

Siddhanath Shendekar, Nitin Patil, Varsha Singh, Megha Meshram and Shubhangi Deokar

Abstract

A conventional breeding method takes 10-15 years to release variety due to long generation time of crops. Speed breeding is key solution to such issues of long generation time, and accelerates the variety development process by manipulating photoperiod, temperature and humidity. Additionally, it also uses immature seed germination, and embryo rescue technique to further reduce the generation time. Vegetable improvement is need of an hour to overcome the problems of nutrient deficiency, worldwide. Speed breeding technique reduces generation time in vegetables and produce 5-6 generations per year, which ultimately increase the genetic gain. To further increase in genetic gain, speed breeding technique must be combined with other techniques such as high throughput phenotyping, marker assisted selection, haplotype breeding, genomic selection and gene editing. Thus, speed breeding is key technique to abridge the generation time and faster release of variety. This chapter discus mainly about, how to increase genetic gain in vegetables through speed breeding technique.

Keywords: Vegetables, speed breeding and genetic gain.

Introduction

Climate change and increasing world population, are two major issues now a day's. After green revolution, almost all countries achieved sufficiency in cereal and pulses. But when we see growth rate of population, this current production of cereals and pulses are not sufficient to feed them. Commercializing of vegetable production is more important now days, because feeding a billions of population with only cereal crops is not possible. Although cereals contribute large part of diet but it can't provide all the essential nutrients. In addition to this, we are able to give the economic stability to the farmers by vegetable production as, they give six to ten time

more yield than cereal crops in a year. One of the important concept in plant breeding is genetic gain. It can be defined as the amount of increase in performance of particular crop, that is achieved annually through artificial selection. Simply "genetic gain" is defined as the improvement in average genetic value in a population or the improvement in average phenotypic value due to selection within a population over cycles of breeding (Hazel and Lush, 1942). Changing climate conditions are affecting the production of the vegetable crops worldwide which leads to reduced total yield of the vegetable crops. To prevent the effect of climate change we have to develop the climate smart varieties that can stand with adverse climatic conditions. By using different breeding methods, we can develop new varieties with such traits.

Vegetable breeding is largely depending on conventional breeding methods, up to date. Genetic gains for most of the crop in relation to yield potential and its stability, host plant resistance to pathogens and pests affecting crops, adaptation to stressful environments, use of available resource with high efficiency and different quality traits need to be increased through different breeding methods. In view to meet the global challenges like climate change, a growing world population and the need for resource efficient farming systems, plant breeding innovation will definitely need to play a role. New plant varieties that can better stand pests and diseases with fewer inputs, plants that have stable yield despite a changing climate and plants with increased productivity, by maximizing resource use efficiency in regard of water, land and nutrients can contribute to meet these goals (Pereira 2016).

The current pace of vegetable breeding is not up to the mark to feed growing population. Traditional breeding methods take several years to bred new variety for specific traits. After crossing of parents, it needs ample time to achieve homozygosity. In addition to this it needs time for preliminary yield trials and multilocation trials. This all steps takes almost take 10-15 years. Techniques such as shuttle breeding, double haploid system, embryo rescue technique are also plays a crucial role to reduce the time require to release a variety. But these techniques have several limitations. As we know genetic gain is well explained by breeder's favorite equation. In this equation, length of generation time kept in denominator. If length of generation time is more, defiantly genetic gain will be less and vice versa.

$$\Delta G = (\sigma a)\ (i)\ (r)/L$$

Here, ΔG means genetic gain, 'σ_a' means additive genetic variance, 'i' means selection intensity and 'r' means selection accuracy and 'L' means length of generation time. Different techniques are available to increase the

additive variance. In addition to this, marker assisted selection plays important role to increase selection accuracy. Speed breeding is a technique which increase genetic gain by manipulating photoperiod, temperature and humidity. It is possible to take five to six generations per year by using speed breeding technique. It is possible to increase genetic gain in vegetable by speed breeding technique. In addition to this speed breeding technique can be integrated with other breeding techniques such as gene editing, genomic selection, marker assisted selection to further increase genetic gain in vegetable crops. In this chapter, we elaborated speed breeding concept, how to increase genetic gain in vegetables by speed breeding, technological aspects of speed breeding, integration of speed breeding with other techniques, then challenges and limitations of speed breeding in vegetables.

Evolution of traditional breeding methods

Plant genetic resources provide the raw material to bred new varieties of crops (Doebley *et al.* 2006). These, in turn, provide the basis for more productive and resilient varieties that are better able to cope with stresses such as pest and disease resistance, water logging and drought condition. Approach to the modern breeding methods over the traditional one has many advantages. Reduction in time to incorporate the specific trait into the variety, precisely is one of them.

Traditional breeding methods take many years to release new crop variety that has all of the desired traits. In comparison, the utilization of genetic engineering to improve crops can be a faster and more precise approach. Unlike traditional breeding, genetic engineering makes it possible to select the specific traits desired and insert the genes that responsible for specific traits into the plant (Ulukan 2009). In plant breeding methods, domestication was earlier, then plant introduction started. After that selection method came into force, such as pure line, mass selection to utilize available variability in crop. When variability was finished, hybridization based methods such as, pedigree, bulk and backcross breeding were evolved.

Limitation of conventional breeding methods

When it comes to the conventional breeding strategy, there are certain significant issues and limitations that plant breeder must deal with. Cultivars develop slowly in traditional breeding methods than when utilizing contemporary breeding techniques or genetic engineering. With traditional breeding techniques, it takes a long period and a lot of work to develop a new cultivar. The methods used now to create new cultivars are mostly phenotype dependent. The outcomes of traditional breeding techniques are frequently

uncertain. All the conventional breeding methods are depending on conventional plant phenotyping, which many be misled due to environmental effects.

Emergence of speed breeding as a solution

The future demand for agricultural products will be influenced by grain varieties with their capacity to adapt to environmental changes. It is essential to develop new varieties that suit our requirements by plant breeding. As a consequence, plant breeders are increasingly focusing their efforts on creating genetic resistance to diseases as well as tolerance for abiotic stresses such as drought, heat, and cold. However, traditional plant breeding is restricted in its ability to meet these requirements due to the annual breeding cycle and other biological and genetic constraints. The creation of new, better cultivars of the majority of agricultural plants often takes many years. It is very uncommon for 4-6 generations of inbreeding to be required after the crossing of selected parent lines in order to generate genetically stable lines for agronomic features and yield evaluation. This is particularly time intensive for field crops, which usually have just one or two generations each year (Kaushik *et al*. 2021).

Speed breeding is a technique of rapid generation development because it enables significant reductions in crop harvest times, quicker agricultural research, and increased food supply to meet the needs of an ever-growing population (Sarkar and Aminul 2020). Speed breeding in controlled environment growth chambers may be used to accelerate plant development for a number of scientific purposes, including phenotyping mature plant traits, mutant research, and plant transformation. A glasshouse environment enhanced with LED lighting allows rapid generation cycling through single seed descent (SSD), with plant density scaled up for large-scale crop development efforts. The speed breeding technique is gaining popularity since it shortens the breeding cycle and accelerates agricultural research by allowing for rapid generation development.

It is possible to produce up to six generations per year of spring wheat (*Triticum aestivum*), durum wheat (*Triticum dur*um), barley (*Hordeum vulgare*), chickpea (*Cicer arietinum*), and pea (*Pisum sativum*) using speed breeding, and four generations per year of canola (*Brassica napus*) using speed breeding.

Fundamentals of speed breeding

Speed breeding started with NASA'S effort to grow wheat plants in space. Scientist's from University of Queensland adopted this concept on earth and developed several protocols of speed breeding in different crops. Later, these

concepts were adopted by many researchers in world. Speed breeding reduces the crop's generation time by utilizing appropriate day length, light intensity, light quality, humidity, and temperature to encourage biomass accumulation, stimulate flowering, and hasten seed production. It comprises germinating immature seeds, employing an extended photoperiod to hasten plant growth, and hastening generation time. In order to increase flowering in long-day plants, it uses a glasshouse, greenhouse, with increased lighting regimes (Watson *et al*., 2018). Generally, for long day plants we require more photoperiod than normal day length. So, in case of speed breeding condition we require extended photoperiod up to 22 hours, so that plants will flowers early. In case of short day plants it requires minimum photoperiod to flower. Speed breeding mainly depends on some key factors such as extended photoperiod, temperature and humidity control. When we compare the varietal development in speed breeding with other conventional breeding methods, speed breeding takes very less time because it attempts homozygosity very early.

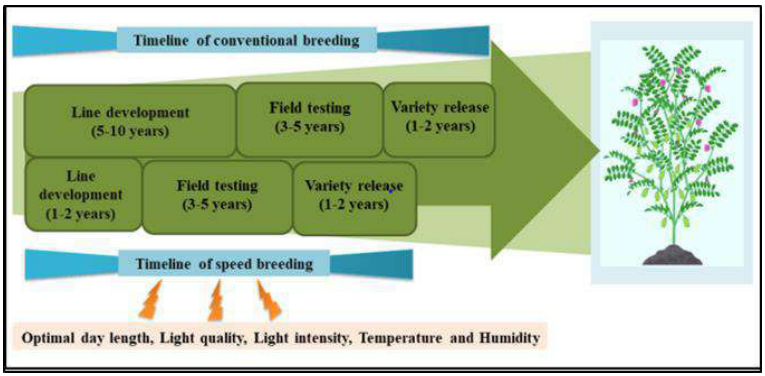


Fig 1: Comparison of speed breeding technique with conventional breeding (Shendekar *et al*., 2023)

In above figure we can see, speed breeding mainly focus on line development period, later all the processes are same in both the methods. In this way speed breeding reduces generation time by manipulating the photoperiod, temperature and humidity.

Vegetables as a target crops

Importance of vegetables

The food we consume contains the substances which nourishes our body are called as nutrients. Carbohydrates, proteins, fats, minerals and vitamins are major five nutrients which our body requires in daily diet. Vegetables are the rich source of these nutrients specially vitamins and minerals.

Table 1: Vegetables as a source of nutrients

Sr. No.	Major Nutrients	Source
1.	Proteins	Drumstick leaves, Colocasia leaves, peas and Beans
2.	Carbohydrates	Tapioca, Sweet potato, Potato, Elephants foot
3.	Vitamins	
	Vitamin A	Carrot, Leafy vegetables, Sweet potato, Turnip green and Pumpkin
	Vitamin B	Cabbage, Lettuce, Kale, Potatoes, Tomato and Peppers
	Vitamin C	Cabbage, Knol-khol, Cauliflower, Turnip, Tomato, Pepper and Fenugreek leaves
	Vitamin D	Vegetable greens
	Vitamin E	Lettuce, Vegetable greens like Cabbage
	Vitamin K	Green leafy vegetables
4.	Minerals	
	Calcium	Carrot, Beans, Cabbage Lettuce, Onion, Peas, Spinach, Fenugreek and Amaranths
	Phosphorus	Potato, Tomato, Carrot, Cucumber, Spinach and Lettuce
	Iron	Bitter gourd, Cabbage, Lettuce, Spinach, Beans, Tomato and Onion
	Iodine	Okra, Onion and Asparagus

Balanced diet

Important role played by the vegetable crops in the balanced diet by providing not only the energy but also the nutrients like minerals and vitamins required for out body. Indian council of medical research (ICMR) has recommended a balanced diet pattern for an average man's daily needs.

Daily requirement of an average man

According to the recommendation of ICMR, an average man with omnivorous food habit should consume 125 g of green leafy vegetables, 100 g of roots and tubers and 75 g of other vegetables. The recommendation for an average woman is more of less same with the except that roots and tubers should be consumed by them @ 75 g per day.

Vegetables as protective food

There are number of vegetable crops which contain antioxidants, bioflavonoids and other compounds which help in prevention of various kinds of diseases.

Antioxidants

These are the substances which neutralize free radicals that are formed during metabolism of foods or by smoking or exposure to pollutants. Free

radicals neutralized by vitamins, minerals and amino acids which are present in fairly higher amounts in some of the vegetables. For example, most leafy vegetables, carrot, sweet potatoes, pumpkin and turnip green are rich in beta carotene. Peas and beans are rich in essential amino acid.

Bioflavonoids

Bioflavonoids increase the efficiency of vitamin C and protect the body from free radicals. One such bioflavonoid is found in onion and garlic is quercetin, which has been indicated to give protection against cancer and heart diseases.

Challenges in vegetable breeding

The Indian vegetable sector is expanding more quickly. The following are limits of vegetable cultivation in India, despite the fact that many areas of vegetable development and production techniques have been created.

Perishable nature of vegetables

Fresh vegetables are like living organisms and as such undergo normal life processes even after harvest. They respire, loss of water occurs through transpiration and undergo chemical changes if not sold immediately after harvest. Deterioration of vegetables is also influenced considerably by temperature, atmospheric humidity and other factors. The losses in leafy vegetables and fruit vegetables are much more than in root and tuber vegetable crops. Thus, a considerable quantity of vegetables produced in our country is wasted every year.

Ignorance on nutritive value of vegetables

A majority of community is quite unaware about the nutritive value of different vegetable crops. Hence, in spite of available facilities for cultivation they are not giving much attention to vegetable gardening. In our country most of the population residing in villages are not educated who do not realize the importance of vegetable crop which are an important source of vitamins and minerals.

Non availability of sufficient quantity of quality seed in time

There should be proper arrangement for supplying good vegetable seeds for both early and late crops. The vegetable seed industry is largely in the hands of private agencies and few of them have adequate facilities for scientific production. As a result, the seeds available in the market are often of doubtful origin and usually give indifferent performance. National Seed Corporation, New Delhi started supply of improved and hybrid seeds of many

vegetables directly and through its branches to cultivators and vegetable growers.

Insect pest attack

Due to the tenderness of vegetables, the insect pest, disease and weed attack is more in vegetable crops than cereals/ fruit crops/forest trees.

Adverse climatic conditions

Current scenario of the changing climate leads to rapid reduction in the vegetable production worldwide such as drought, water flooding, high and low temperature affect the growth and development of the vegetable crop. So there need of such breeding programme which will give the climate resilient varieties to the farmers.

Speed breeding vegetable crops

Plant breeders are increasingly focusing their efforts on creating genetic resistance to diseases as well as tolerance for abiotic stresses such as drought, heat, and cold. However, traditional plant breeding is restricted in its ability to meet these requirements due to the annual breeding cycle and other biological and genetic constraints. The creation of new, better cultivars of the majority of agricultural crops often takes many years. It is very uncommon for 4–6 generations of inbreeding to be required after the crossing of selected parent lines in order to generate genetically stable lines for agronomic features and yield evaluation.

Speed breeding can speed up transgenic pipelines as well as backcrossing and trait pyramiding. Speed breeding takes place in an enclosed space with artificially produced LED light (such as halogen lamps) that has a PAR of 400-700 nm, a photoperiod of 22 hours, and 2 hours of darkness per day. The temperature is kept at room temperature, and the relative humidity should be between 60 and 70 percent. Speed breeding can decrease crop generations because it shortens the time it takes for a crop to reach maturity. This is especially true for vegetable crops like tomatoes, potatoes, and amaranths, which can reach maturity in eight generations as opposed to two in the field due to early flowering and fruiting under continuous light (Kaushik *et al*., 2021).

Advantages of speed breeding in vegetables

Increased genetic gain with speed breeding

Through re-domestication, plant variety registration, phenotypically and genotypically assisted trait introgression, and speed breeding, the genetic gain

is hastened. While traditional breeding normally takes a long time, it can accelerate the number of generations per year using premature seed germination and photoperiod responsiveness (Samantara *et al*., 2022). They were able to execute genome-wide testing for different qualities like grain production, grain wetness, and hauteur of plants attributable to the speed-breeding process, which produced several generations of maize in a year. They demonstrated that speed breeding can expedite breeding and improve the accuracy of selection for genomes (Croser *et al*. 2016).

Shortened breeding cycles and reduced costs

The subsequent steps are necessary for any crop enhancement programme:

a) Choosing ideally suited parents to combine their complementary qualities.

b) Crossings including the chosen parents and the subsequent generation of offspring.

c) In accordance with desired features, the most promising offspring are chosen and genetically improved.

d) Choosing the best offspring for testing in various intended.

e) Registering a the variety, producing seeds and giving it to farmers (Shimelis & Laing, 2012).

Enhanced adaptability and resistance in vegetable crops

As a result of the photoperiod being lengthened, plants that benefit from longer daylight hours, such as pepper, tomato, and amaranth, have shorter generation intervals. Scientist reveal that the CAB-13 gene can be added to tomatoes to increase their tolerance to continuous light, enabling them to adapt to longer photoperiods (Velez-Ramirez *et al*., 2014; Chiurugwi *et al*., 2019). Consequently, speed breeding can help to facilitate the breeding programme for many vegetable crops. Wheat, rice, corn, rye, oats, barley, sorghum, and millets are examples of plants in the poaceae family that are produced primarily for their starchy fruits. In order to create new kinds with appealing features including disease resistance, drought tolerance, and greater yields, speed breeding has been adopted. Through speed breeding, "YNU31-2-4," a salt-tolerant rice variety, was created. The gene was inserted with the aid of an SNP marker. Crops such as oats, different Brassica species, chickpeas, peas, grass peas, quinoa, and *Brachypodium distachyon* develop as quickly as possible thanks to the speed breeding technique (Hickey *et al*., 2017; Ghosh *et al*., 2018; Jähne *et al*., 2020; Rana *et al*., 2019).

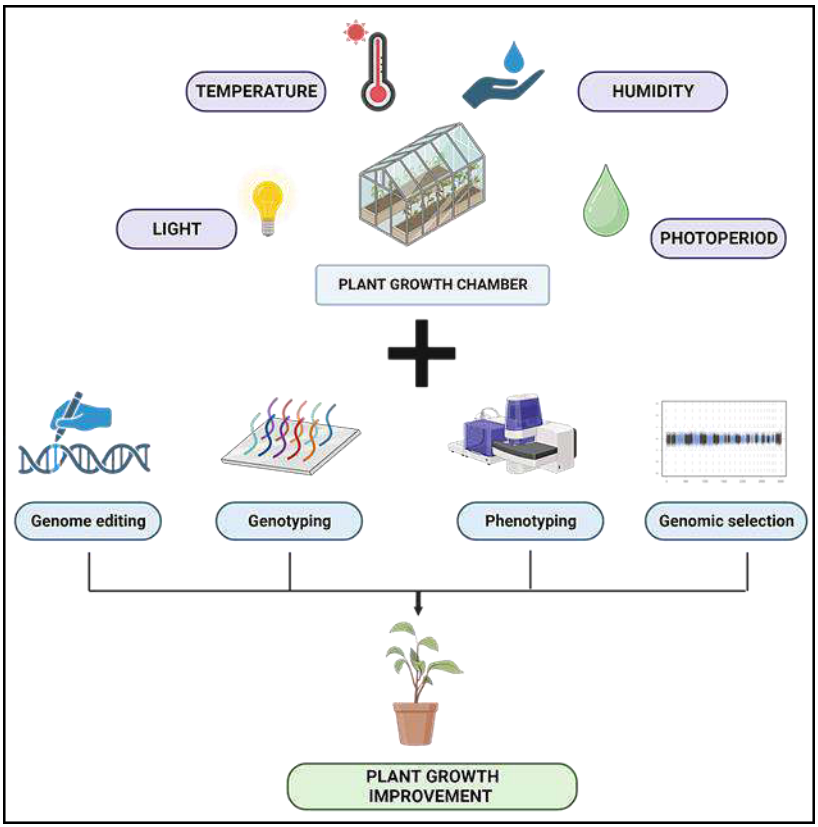


Fig 2: The implementation of speed breeding and its integration with other breeding techniques expedites the process of plant improvement.

Speed breeding technique

In speed breeding, few factors are need to be controlled that is, temperature, photoperiod and humidity. Along with this it further reduces generation time by harvesting immature seed.

Photoperiod regime

As we know sun is ultimate source of energy for plans. Based on photoperiod requirements plants are divided into three groups such as short day, long day and day neutral. Long day plants flowers well when we give extra photoperiod than normal. In case of short day plant, this process is reverse. A day neutral plant does not bother about photoperiod. In speed breeding condition, for long day plants extra photoperiods were provided artificially by using LED lights within 400-700 nm.

Temperature and humidity

Optimum temperature and humidity are key aspects to achieve proper germination and plant stand. In speed breeding condition, temperature can be setup around 25 ℃ and humidity around 60-70% to achieve better crop stand.

Immature seed germination

In speed breeding condition, seeds are harvested before maturity and germinated in normal condition or by use of particular growth regulator to further reduce the time requires for complete maturity. In this way generation time can be reduce in maximum extent.

Case studies

Success stories in vegetables using speed breeding

In today's scenario, speed breeding, is an innovation that quickens the breeding cycle of plants in an effort to boost production and strengthen crop endurance. For various crops, several speed breeding techniques, such as speed breeding I, II, and III, have proved effective. Its ability to produce 2 to 8 generations every year has been demonstrated in tests on a variety of cereal, legume, oilseed, fruit trees, and veggie crops. The quickest technological enhancement has been seen in cereal crops such as *Avena sativa, Hordeum vulgare, Triticum aestivum, Oryza sativa* and *Sorghum bicolor*. *Triticum aestivum* had the most revolutions each year, eight, of any of them. According to the speed breeding method, several varieties of legumes, as well as oilseed crops, trees containing fruits and vegetables have shortened crop life-spans. As a result, flowering occurs considerably earlier than typical in fruit trees and vegetable crops, and this eventually aids plant breeding programs. Its superiority to conventional breeding techniques is a result of this.

Speed breeding combined with other biotechnological techniques

The modification of genomes, selection of genomic material, high-throughput capabilities phenotyping, and genotyping are some examples of contemporary plant breeding methods that can be combined with speed breeding. A number of significant developments in the field of biotechnology have occurred during the past ten years, including the emergence of third-generation genome editing (GE) tools, the sequencing of genomes, advances in plant-based synthetic biology, and bioengineering (Altpeter *et al*., 2016; Wang *et al*., 2019; Zhang *et al.,* 2019a). By carefully altering the genomes of both plants and animals, genome editing technologies have revolutionized the field of biological science. A total of three generations can be broadly distinguished in genome editing: First-generation tools include mega

nucleases and zinc finger nucleases, second-generation tools include effector nucleases that resemble transcription activators, and third-generation tools include the clustered regularly interspaced short palindromic repeat nuclease mechanism (Puchta *et al*., 1993; Wright *et al*., 2005; Christian *et al*., 2010; Butler *et al*., 2016; Tang *et al.,* 2017; Yin *et al*., 2017; Anzalone *et al*., 2019; Manghwar *et al*., 2019; Lin *et al*., 2020). Through the use of genetic modification (GM) technological devices, plants have been created that yield more, have more nutritional value, and are more resistant to pesticides, insects, and illnesses. Recently, a number of GE tools have been invented created, especially the highly effective and adaptable clustered regularly interspaced short palindromic repeats (CRISPR) with nucleases technique. Transgenic organisms or CRISPR are mostly introduced into plants using particular transmission mechanisms during the primary stages of the GE technique. The drawbacks of GE technologies include lengthy and challenging processes, the possibility for tissue injury, DNA assimilation into the genome of the host organism, and poor effectiveness in transformation. Nanotechnology has emerged as a ground-breaking and contemporary solution to these problems.

Table 2: Integrating speed breeding with other biotechnological techniques

GE based tool	Generation	Uses	References
Meganuclease (MegaN)	First-generation tools	Expensive and time-consuming, because it calls for enzymes that are unique to the desired sequence.	Townsend *et al*., 2009
Zinc finger nucleases (ZFNs)	First-generation tools	Location-specific nucleases that only cleave DNA at predetermined locations.	Sander *et al*., 2011
Transcription activator-like effector nucleases (TALENs)	Second-generation tools	Nucleases with a specified site, exclusively cleaving DNA at those places.	Ramirez *et al*., 2008
CRISPR)/CRISPR-associated protein 9 Cas9) nuclease system	Third-generation tools	For applications such as enhancing important crops	Boch *et al*., 2009

The development of novel crop varieties can be considerably accelerated by the use of speed breeding strategies and programmes for gene editing like CRISPR-Cas9. Farmers can quickly generate a number of generations of the aforementioned modified plants via speed breeding when GE introduces desired features, such as insect resistance or higher nutritional value (Haroon *et al*., 2020). Speed breeding as well as selective genomics are used to increase the hereditary advantage since they shorten the breeding cycle and result in higher-quality plant varieties in a shorter amount of time (Samantara *et al*.,

2022). The cultivation of crops in the arena of genetic engineering is getting more and more dependent on genotyping, the procedure of determining an organism's genetic make-up. Breeders can use it to find desired genetic indicators and choose plants for rapid breeding. This enables crop improvement to be done in a more focused manner.

Contributions to food security and sustainable agriculture

The idea of speed breeding originated when scientists discovered that plants could grow under artificial light roughly 150 years ago (Sharma *et al*., 2018). Finally, research into how light affects various plant types was conducted. The modern era of breeding for crops and the exploration of the prospect of cultivating food in space to suit the demands of astronauts on the international space station were ushered in by NASA's establishment of a cooperative research programme with Utah State University for the quick development of *Triticum aestivum* on the space station in the 1980s and they also achieve success by developing first dwarf variety of *Triticum aestivum* known as "USU-Apogee" via speed breeding (Bugbee & Koerner, 1997).

Speed breeding is considerably more efficient than conventional breeding, which could lead to a reduction in the requirement for space as well as additional commodities. As a result, breeders that operate on a smaller scale or with fewer resources would find it easier to get started. via allowing for a greater number of plant offspring to cycle through each year than in traditional breeding processes, it can speed up the introduction and selection of genetic variety (Temesgen, 2022). As a result of the increased breeding management it provides, it is able to more precisely choose particular genetic features when compared to the traditional approach.

Challenges and Limitations

All things in the modern era are moving faster quickly, allowing for more work to be completed in the shortest possible period of time, including interactions and responses. This shows that in the future modernization and advancements will also be referred to as progression. So, why not plants in a time when all things pass on to subsequent generations at a faster speed? The issue that arose currently proceeded to the identification of speed breeding as the most effective breeding technique. There are a number of difficulties and restrictions with speed breeding that must be taken into account, such as the fact that countries that are developing lack qualified and engaged breeders of plants and plant breeding workers, which is a significant obstacle that can impede government organizations from executing speed breeding (Shimelis *et al.*, 2019). This type of breeding requires specialized, but scarce, technology

for the earliest generational decision-making regarding characteristics (Ribaut *et al*., 2010). Investments in breeding technologies must take costs and rewards into account from an economic standpoint, including benefits that are both reversible and irreversible (Lenaerts *et al*., 2019).

Therefore, we may state that speed breeding refers to a series of techniques that entail altering the environmental conditions in which crop genotypes are produced in order to hasten flowering and seed set so that the next reproductive generation can emerge as soon as feasible (Wanga *et al*., 2021). Additionally, it gives progressive advantages over traditional techniques for early cultivar production. The breeding programme is expedited by combining it with other contemporary technology. However, because it is a new technology, it has significant disadvantages, including a high initial cost, a lack of appropriate resources, and the need for qualified employees.

Future prospects

Today's agriculture is greatly affected by climate change. Due to climate change new races of pest and diseases are coming out. To withstand in adverse climatic conditions we need smart varieties of crop, which gives better yield in adverse climate. It needs faster breeding approach because, by conventional breeding, it is difficult because of long generation time. Speed breeding is key solution for these issues. This speed breeding technique must be combined with other breeding approaches such as genomic selection, marker assisted selection and gene editing. In short day crops protocols need to be standardized.

Conclusion

Speed breeding is important breeding method to reduce time period for releasing a variety, ultimately to tackle the problem of climate change and global food security. Vegetables are the key components of our daily diet, because it provides almost all sorts of nutrients. Development of climate smart varieties is one of the important aspects in vegetable breeding, but long generation time restricts this. Thus, speed breeding is ray of hope to strengthen the research in vegetable breeding. By integrating speed breeding with other techniques such as gene editing, marker assisted selection, haplotype breeding, genomic selection it is possible to increase vegetable production in great extent.

References

1. Ahmar S, Mahmood T, Fiaz S, Mora-Poblete F, Shafique MS, Chattha MS, *et al*. Advantage of nanotechnology-based genome editing system and its application in crop improvement. Frontiers in Plant Science. 2021;12:663-849.
2. Ahmar S, Saeed S, Khan MHU, Khan SU, Mora-Poblete F, Kamran M, *et al*. A revolution toward gene-editing technology and its application to crop improvement. Int. J Mol. Sci. 2020a;21:1-28. Doi: 10.3390/ijms21165665
3. Altpeter F, Springer NM, Bartley LE, Blechl AE, Brutnell TP, Citovsky V, *et al*. Advancing crop transformation in the era of genome editing. Plant Cell. 2016;28:1510-1520. Doi: 10.1105/tpc.16.00196
4. Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, *et al*. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature. 2019;576:149-157.
5. Boch J, Scholze H, Schornack S, Landgraf A, Hahn S, Kay S, *et al*. Breaking the code of DNA binding specificity of TAL-type III effectors. Science. 2009;326:1509-1512.
6. Bugbee B, Koerner G. Yield Comparisons and Unique Characteristics of the Dwarf Wheat Cultivar 'USU-Apogee'. Advances in Space Research. 1997;20(10):1891-1894.
7. Butler NM, Baltes NJ, Voytas DF, Douches DS. Gemini virus mediated genome editing in potato (*Solanum tuberosum* L.) using sequence specific nucleases. Front. Plant Sci. 2016;7:10-45. Doi: 10.3389/fpls.2016.01045
8. Chandrasekaran R, Rajiv P, Abd-Elsalam KA. Carbon Nanotubes: Plant Gene Delivery and Genome Editing. Amsterdam: Elsevier Inc, 2020.
9. Chiurugwi T, Kemp SJ, Powell W, Hickey LT. Speed Breeding Orphan Crops. Theoretical and Applied Genetics. 2019;132(3):607616.
10. Christian M, Cermak T, Doyle EL, Schmidt C, Zhang F, Hummel A, *et al*. Targeting DNA double-strand breaks with TAL effector nucleases. Genetics. 2010;186:757-761. Doi: 10.1534/genetics.110.120717
11. Croser J, Pazos-Navarro M, Bennett RM, Tschirren S, Edwards K, Erskine W, *et al*. Time to Flowering of Temperate Pulses *In Vivo* and Generation Turnover *in vivo-in vitro* of Narrow-Leaf Lupin Accelerated by Low Red to Far-Red Ratio and High Intensity in The Far-Red Region. Plant Cell Tissue and Organ Culture. 2016;127(3):591-599.

12. Doebley JF, Gaut BS, Smith BD. The molecular genetics of crop domestication. Cell. 2006;7:1309-1321.
13. Ghosh M, Ghosh I, Godderis L, Hoet P, Mukherjee A. Genotoxicity of engineered nanoparticles in higher plants. Mutat. Res. Genet. Toxicol. Environ. Mutagene. 2019;842:132-145. Doi: 10.1016/j.mrgentox.2019.01.002
14. Giraldo JP, Wu H, Newkirk GM, Kruss S. Nanobiotechnology approaches for engineering smart plant sensors. Nat. Nanotechnol. 2019;14:541-553. Doi: 10.1038/s41565-019-0470-6
15. Gudi S, Kumar P, Singh S, Tanin MJ, Sharma A. Strategies for accelerating genetic gains in crop plants: Special focus on speed breeding. Physiology and Molecular Biology of Plants. 2022;28(10):1921-1938.
16. Haroon M, Zafar MM, Ma F, Afzal R, Batool M, FI UB, *et al*. Conventional Breeding, Molecular Breeding and Speed Breeding; Brave Approaches to Revamp the Production of Cereal Crops. Preprints. 2020;I:28-33.
17. Hazel LN, Lush JL. The efficiency of three methods of selection. Journal of Heredity, 1942, 393-399.
18. Hickey LT, Germán SE, Pereyra SA, Diaz JE, Ziems LA, Fowler RA, *et al*. Speed breeding for multiple disease resistance in barley. Euphytica. 2017;213:64. Doi: 10.1007/s10681-016-1803-2
19. Hong WJ, Kim YJ, Kim EJ, Kumar Nalini, Chandran A, Moon S, *et al*. CAFRI-Rice: CRISPR applicable functional redundancy inspector to accelerate functional genomics in rice. Plant J. 2020;104:532-545. Doi: 10.1111/tpj. 14926
20. Jähne F, Hahn V, Würschum T, Leiser WL. Speed breeding short-day crops by LED-controlled light schemes. Theoret. Appl. Genet. 2020;133:2335-2342. doi: 10.1007/s00122-020-03601-4.
21. Johora F. Speed Breeding: A Ray of Hope for Food Security (Doctoral dissertation, Bangabandhu Sheikh Mujibur Rahman Agricultural University), 1706.
22. Jorasch P. The global need for plant breeding innovation. Transgenic Research. 2019;28(2):81-86.
23. Kaushik Prashant, Suniti Rawat, Rahul Kumar. Speed breeding: an advance breeding approach to enhance crop generation; 2021; 1(12). (e-ISSN: 2582-8223).

24. Lenaerts B, Collard BCY, Demont M. Review: Improving Global Food Security through Accelerated Plant Breeding. Plant Science. 2019;287:110-207.

25. Lenaerts B, Collard BCY, Demont M. Review: Improving Global Food Security through Accelerated Plant Breeding. Plant Science. 2019;287:110-207.

26. Lin Q, Zong Y, Xue C, Wang S, Jin S, Zhu Z, *et al*. Prime genome editing in rice and wheat. Nat. Biotechnol. 2020;38:582-585. doi: 10.1038/s41587-020-0455-x

27. Manghwar H, Lindsey K, Zhang X, Jin S. CRISPR/Cas system: recent advances and future prospects for genome editing. Trends Plant Sci. 2019;24:1102-1125. Doi: 10.1016/j.tplants.2019.09.006

28. Meena RK, Koli DK, Koli GK, Meena RK, Annu. Speed Breeding: A Powerful Tool to Accelerate Crop Research. Biotica Research Today. 2022;4(5):382-384.

29. Pereira A. Plant abiotic stress challenges from the changing environment. Front Plant Sci. 2016;7:11-23. https://doi. org/10.3389/fpls2016.0112.

30. Puchta H, Dujon B, Hohn B. Homologous recombination in plant cells is enhanced by in vivo induction of double strand breaks into DNA by a site-specific endonuclease. Nucleic Acids Res. 1993;21:5034-5040. Doi: 10.1093/nar/ 21.22.5034

31. Ramirez CL, Foley JE, Wright DA, Müller-Lerch F, Rahman SH, Cornu TI, *et al*. Unexpected failure rates for modular assembly of engineered zinc fingers. Nat. Methods. 2008;5:374-375.

32. Rana MM, Takamatsu T, Baslam M, Kaneko K, Itoh K, Harada N, *et al*. Salt Tolerance Improvement in Rice through Efficient SNP Marker-Assisted Selection Coupled with Speed-Breeding. International Journal of Molecular Sciences. 2019;20(10):25-85.

33. Ribaut J, De Vicente MC, Delannay X. Molecular Breeding in Developing Countries: Challenges and Perspectives. Current Opinion in Plant Biology. 2010;13(2):213-218.

34. Samantara K, Bohra A, Mohapatra SR, Prihatini R, Asibe F, Singh L, *et al*. Breeding More Crops in Less Time: A Perspective on Speed Breeding. Biology. 2022;11(2):275.

35. Samantara K, Bohra A, Mohapatra SR, Prihatini R, Asibe F, Singh L, *et al*. Breeding More Crops in Less Time: A Perspective on Speed Breeding. Biology. 2022;11(2):275.

36. Sander JD, Dahlborg EJ, Goodwin MJ, Cade L, Zhang F, Cifuentes D, *et al*. Selection-free zinc-finger-nuclease engineering by contextdependent assembly (CoDA), 2011.

37. Sarkar S, Aminul Islam AKM. Speed Breeding: An Effective Breeding Technique for Rapid Generation Advance in CropEC Agriculture, 2020, 09-11.

38. Sharma S, Kumar A, Dhakte P, Raturi G, Vishwakarma G, Barbadikar KM, *et al*. Speed Breeding Opportunities and Challenges for Crop Improvement. Journal of Plant Growth Regulation. 2022;42(1):46-59.

39. Shendekar S, Kute N, Madhu B, Gadpayale D, Meshram M, Basavaraj PS, *et al*. Unlocking Crop Potential: Speed Breeding and its Synergies with Modern Breeding Techniques.

40. Shimelis H, Laing M. Timelines in Conventional Crop Improvement: Pre Breeding and Breeding Procedures. Australian Journal of Crop Science. 2012;6(11):1542-1549.

41. Shimelis H, Gwata E, Laing M. Crop Improvement for Agricultural Transformation in Southern Africa. Routledge EBooks, 2019, 97-103.

42. Tang X, Lowder LG, Zhang T, Malzahn AA, Zheng X, Voytas DF, *et al*. A CRISPR-Cpf1 system for efficient genome editing and transcriptional repression in plants. Nat. Plants. 2017;3:17018. Doi: 10.1038/nplants.2017.18

43. Temesgen B. Speed Breeding to Accelerate Crop Improvement. International Journal of Agricultural Science and Food Technology. 2022;8(2):178-186.

44. Townsend JA, Wright DA, Winfrey RJ, Fu F, Maeder ML, Joung JK, *et al*. High-frequency modification of plant genes using engineered zinc-finger nucleases. Nature. 2009;459:442-445.

45. Ulukan H. The evolution of cultivated plant species: classical plant breeding versus genetic engineering. Plant Systematics and Evolution. 2009;280:133-142.

46. Velez-Ramirez AI, Van Ieperen W, Vreugdenhil D, Van Poppel PMJ A, Heuvelink E, *et al*. A Single Locus Confers Tolerance to Continuous Light and Allows Substantial Yield Increase in Tomato. Nature Communications, 2014, 5(1).

47. Wang JW, Grandio EG, Newkirk GM, Demirer GS, Butrus S, Giraldo JP, *et al*. Nanoparticle-mediated genetic engineering of plants. Mol. Plant. 2019;12:1037–1040. doi: 10.1016/j.molp.2019.06.010

48. Wanga MA, Shimelis H, Mashilo J, Laing M. Opportunities and Challenges of Speed Breeding: A Review. Plant Breeding. 2021;140(2):185-194.

49. Watson A, Ghosh S, Williams MJ, Cuddy WS, Simmonds J, Rey MD, *et al*. Speed breeding is a powerful tool to accelerate crop research and breeding. Nature plants. 2018;4:23-29.

50. Wright DA, Townsend JA, Winfrey RJ, Irwin PA, Rajagopal J, Lonosky PM, *et al*. High-frequency homologous recombination in plants mediated by zinc-finger nucleases. Plant J. 2005;44:693-705. Doi: 10.1111/j.1365-313X.2005. 02551.x

51. Wu H, Nißler R, Morris V, Herrmann N, Hu P, Jeon S, *et al*. Monitoring plant health with near-infrared fluorescent H_2O_2 nano sensors. Nano Lett. 2020;20:2432-2442. doi: 10.1021/acs.nanolett.9b05159

52. Yin K, Gao C, Qiu JL. Progress and prospects in plant genome editing. Nat. Plants. 2017;3:1-6.

53. Zhang H, Demirer GS, Zhang H, Ye T, Goh NS, Aditham AJ, *et al*. DNA nanostructures coordinate gene silencing in mature plants. Proc. Natl. Acad. Sci. U.S.A. 2019a;116:7543-7548. Doi: 10.1073/pnas.18182 90116

54. Zhao X, Meng Z, Wang Y, Chen W, Sun C, Cui B, *et al*. Pollen magnetofection for genetic modification with magnetic nanoparticles as gene carriers. Nat. Plants. 2017;3:956-964. Doi: 10.1038/s41477-017-0063-z

Chapter - 7

The Impact of National Education Policy: A Comprehensive Analysis

Author

Dr. Shilpa N. Khare
Assistant Professor,
XXXXXXXXXXXXXXXXXXX

Chapter - 7

The Impact of National Education Policy: A Comprehensive Analysis

Dr. Shilpa N. Khare

Abstract

The National Education Policy (NEP) in India, implemented in 2020, has significantly impacted the country's education landscape. The policy's emphasis on inclusive education aims to bridge socio-economic gaps by providing equitable access to quality learning. It introduces a holistic approach, promoting skill development, digital literacy and a flexible curriculum, preparing students for a rapidly changing job market.

The NEP's focus on technology integration and online learning addresses the need for modern educational tools, albeit with challenges related to the digital divide. It aspires to transform higher education by fostering international collaborations, enhancing research and promoting a multidisciplinary approach.

However, challenges such as implementation hurdles, financial constraints and the need for teacher training persist. The policy's success hinges on addressing these challenges, ensuring inclusivity, and fostering adaptability to emerging educational needs. The NEP, with its ambitious goals, has the potential to reshape India's education system, making it more responsive to the demands of the 21st century and fostering socio-economic development.

Keywords: National education policy, integration emerging trends pedagogy

Introduction

Education stands as the cornerstone of societal progress, a beacon guiding nations towards enlightenment, innovation, and prosperity. In this era of rapid global evolution, the importance of a robust and responsive education system cannot be overstated. National Education Policies (NEPs) emerge as catalysts for change, shaping the destiny of nations by redefining educational paradigms. This essay embarks on a comprehensive exploration of the

profound impact that NEPs have on educational landscapes, socio-economic development, and the overarching trajectory of a nation. At its core, a National Education Policy encapsulates a nation's vision for its education sector. It is not merely a bureaucratic document but a visionary roadmap that delineates strategies, objectives, and methodologies for the holistic development of the populace. Beyond the confines of classrooms, NEPs are intricate blueprints designed to sculpt the intellectual prowess of future generations, address socio-economic disparities and propel nations onto the global stage of competitiveness.

a) **Objectives of NEP:** The National Education policy encompasses the following objectives.

1. Integration of holistic learning

The NEP seeks to move beyond rote memorization and encourage holistic learning. It emphasizes the integration of arts, sports, and vocational education into the mainstream curriculum to nurture well-rounded individuals capable of thriving in diverse professional landscapes.

Flexible and multidisciplinary education: An objective of the NEP is to introduce flexibility and multi-disciplinarity in education. This shift allows students to explore a range of subjects before specializing, fostering a broader understanding of various disciplines and encouraging a more informed choice of career paths.

2. Inclusivity: Ensuring equal educational opportunities

Inclusivity stands as a pivotal objective of the NEP, aiming to make quality education accessible to all, irrespective of socio-economic backgrounds, gender, or geographical location. The policy envisions a system where every child, regardless of their circumstances, has the opportunity to unlock their full potential through education.

Affirmative action and scholarships: NEP introduces affirmative action measures to address historical disadvantages, ensuring marginalized groups have equal access to educational resources. Additionally, the policy emphasizes the provision of scholarships to economically disadvantaged students, reducing barriers to entry and promoting inclusivity.

Special education initiatives: Recognizing the diverse learning needs of students, the NEP advocates for the integration of special education initiatives. This includes creating an inclusive environment for differently-abled students and tailoring educational approaches to accommodate various learning styles.

3. Skill development: Aligning education with employability

In response to the rapidly evolving job market, the NEP places a strong emphasis on skill development as a core objective. The policy envisions an educational ecosystem that not only imparts theoretical knowledge but also equips students with practical skills necessary for the contemporary workforce.

Entrepreneurship and vocational training: NEP encourages the integration of entrepreneurship and vocational training into the education system. By fostering an entrepreneurial mindset and providing practical skills training, the policy aims to create a workforce capable of contributing to economic development and innovation.

Industry-academia collaboration: To ensure the relevance of education to the demands of the job market, the NEP promotes increased collaboration between educational institutions and industries. This collaborative approach helps align curricula with industry needs and provides students with exposure to real-world challenges.

4. Digital transformation: Embracing technological advancements

In the era of rapid technological advancement, the NEP recognizes the transformative potential of digital tools in education. The policy sets objectives to leverage technology for the enhancement of teaching methodologies, accessibility, and overall educational outcomes.

Digital infrastructure: NEP focuses on building digital infrastructure to facilitate e-learning and ensure connectivity in remote areas. This includes equipping schools with necessary technology, providing access to digital resources, and fostering a culture of digital literacy.

E-learning platforms and resources: To supplement traditional teaching methods, the NEP encourages the development and utilization of e-learning platforms and digital resources. This objective aims to provide students with a diverse range of learning materials and opportunities for self-paced learning.

5. Research and innovation: Fostering a culture of inquiry

The NEP recognizes the pivotal role of research and innovation in driving societal progress. The policy sets objectives to foster a culture of inquiry, creativity, and scientific temper among students and educators.

Research-based learning: NEP encourages a shift towards research-based learning, where students are actively involved in projects, experiments,

and independent research. This approach aims to cultivate a spirit of curiosity and critical thinking from an early age.

Establishment of research institutes: The policy envisages the establishment of research institutes and centres of excellence across disciplines. This objective seeks to create hubs of innovation, where cutting-edge research contributes to advancements in science, technology, and various fields of knowledge.

b) The dynamic role of stakeholders

Education is a collective endeavour that extends far beyond the confines of classrooms and textbooks. The successful implementation and impact of a National Education Policy (NEP) depend heavily on the active participation and collaboration of diverse stakeholders. This point highlights the dynamic roles played by policymakers, educators, parents, students, and the community in shaping and executing the objectives of a National Education Policy, emphasizing the shared responsibility that underpins the transformative potential of education.

1. Policymakers: Architects of the educational landscape

Visionary leadership: At the forefront of the NEP are policymakers who conceive and articulate the vision for the nation's education. Their role is akin to that of architects, designing a blueprint that shapes the educational landscape for years to come. Policymakers set the overarching objectives, allocate resources, and formulate guidelines that govern the implementation of the NEP.

Strategic decision-making: Policymakers are responsible for strategic decision-making, ensuring that the NEP aligns with the broader goals of national development. This involves assessing the needs of the evolving job market, addressing socio-economic disparities, and incorporating feedback from various stakeholders to create a comprehensive and forward-looking policy.

2. Educators: Facilitators of transformation

Curriculum implementation: Educators, including teachers and school administrators, are pivotal in translating the policy into actionable steps. They play a crucial role in implementing changes in curricula, adapting teaching methodologies, and aligning classroom practices with the objectives outlined in the NEP.

Professional development: Educators are not just recipients of policy directives; they are active participants in their interpretation and execution. Continuous professional development becomes essential as educators navigate the evolving educational landscape, incorporating new teaching techniques, technology integration, and staying abreast of the latest pedagogical advancements.

Innovative teaching practices: The success of the NEP depends on educators fostering an environment of innovation and critical thinking. Embracing new and creative teaching practices not only enhances the learning experience but also equips students with the skills required in the 21st-century workforce.

3. Parents: Partners in educational journey

Active engagement: Parents play a crucial role as partners in the educational journey of their children. Their active engagement is vital for the successful implementation of the NEP. This involvement extends beyond merely supporting academic endeavours to actively participating in school activities, parent-teacher associations and discussions about educational policies.

Home learning environment: Creating a conducive learning environment at home is another aspect of parental responsibility. NEPs often emphasize the importance of parental involvement in fostering a love for learning, encouraging curiosity, and providing additional support for academic growth.

Advocacy for educational policies: Parents serve as advocates for educational policies within the community and in interactions with policymakers. Their insights and feedback provide a valuable perspective that policymakers can incorporate for refining and adapting the NEP over time.

4. Students: Active participants in their learning journey

Ownership of learning: Students are not passive recipients but active participants in their learning journey. The NEP encourages students to take ownership of their education, fostering a sense of responsibility and self-directed learning.

Feedback and input: Students' perspectives are valuable in shaping educational policies. The NEP should provide mechanisms for students to provide feedback on their learning experiences, ensuring that policies resonate with their needs, aspirations and challenges.

Emphasis on holistic development: Beyond academic achievements, the NEP often emphasizes holistic development. Students are encouraged to participate in extracurricular activities, sports and community service, fostering a well-rounded approach to education.

5. Community: Creating a supportive ecosystem

Community involvement: The broader community, including local leaders, businesses, and civic organizations, plays a crucial role in creating a supportive educational ecosystem. Community involvement can take the form of mentorship programs, internship opportunities, and support for educational initiatives.

Resource mobilization: Communities can contribute to resource mobilization for schools, helping bridge gaps in infrastructure, technology, and other essential resources. This collaborative approach ensures that schools are adequately equipped to implement the objectives of the NEP.

c) Shapes curriculum and pedagogy

The National Education Policy (NEP) serves as a guiding force in reshaping the educational landscape, influencing not only what students learn but also how they learn it. A critical aspect of this transformation lies in the reformulation of curriculum and pedagogical approaches. This point highlights the multifaceted ways in which the NEP navigates the realms of curriculum design and pedagogy, aiming to foster a dynamic, inclusive, and future-ready learning environment.

1. Flexible curriculum design: Unleashing creativity and critical thinking

Shift from rote learning: One of the pivotal objectives of the NEP is to move away from the traditional approach of rote learning towards a more holistic and flexible curriculum. This paradigm shift aims to foster creativity and critical thinking among students, nurturing skills that are vital for success in the 21st century world.

Multidisciplinary approach: NEP advocates for a multidisciplinary approach to education, breaking down the silos between subjects. By integrating diverse disciplines into a cohesive curriculum, students gain a broader understanding of interconnected knowledge, promoting a more holistic worldview.

Early exposure to varied subjects: The policy encourages early exposure to a variety of subjects, allowing students to explore and discover their interests before specializing. This not only empowers students with a

more informed choice of academic paths but also ensures a well-rounded educational experience.

2. Emphasis on skill development: Beyond academic knowledge

Incorporating 21st century skills: The NEP recognizes the evolving demands of the job market and the need for students to possess a diverse skill set. Therefore, the policy emphasizes the integration of 21st-century skills such as critical thinking, communication, collaboration, and problem-solving into the curriculum.

Entrepreneurial and vocational skills: In alignment with the emphasis on skill development, NEP promotes the integration of entrepreneurial and vocational skills into the curriculum. This prepares students not just for employment but for creating job opportunities and contributing to economic growth.

Technology and digital literacy: Acknowledging the digital age, the policy underscores the importance of technology and digital literacy. The curriculum is designed to equip students with the skills needed to navigate a technology-driven world, enhancing their adaptability and competitiveness.

3. Inclusive education: Addressing diverse learning needs

Catering to diverse learning styles: NEP advocates for inclusive education that addresses the diverse learning needs of students. This includes recognizing and accommodating different learning styles, ensuring that the curriculum is accessible to all, regardless of cognitive or physical differences.

Specialized training for educators: To support inclusive education, NEP calls for specialized training for educators in catering to diverse learning needs. This ensures that teachers are equipped with the knowledge and skills to create an inclusive and supportive learning environment.

Incorporating local and indigenous knowledge: Inclusivity in curriculum design extends to the incorporation of local and indigenous knowledge. NEP emphasizes the importance of acknowledging diverse cultural perspectives, enriching the educational experience for students and fostering a sense of cultural identity.

4. Active pedagogy: Fostering engaged learning

Experiential learning: The NEP promotes active pedagogy, emphasizing experiential learning methods. This involves learning by doing, engaging students in practical activities, experiments, and real-world projects. Such approaches enhance understanding and retention of concepts.

Critical inquiry and questioning: Pedagogical approaches are reshaped to encourage critical inquiry and questioning. NEP envisions classrooms where students actively participate in discussions, analyze information critically, and develop a curiosity-driven approach to learning.

Teacher as a facilitator: The role of teachers transforms from mere disseminators of information to facilitators of learning. NEP encourages educators to guide students, foster independent thinking, and create an environment where curiosity and creativity thrive.

5. Continuous evaluation and assessment: Moving beyond exams

Comprehensive assessment system: NEP envisions a shift from the traditional exam-centric assessment system to a more comprehensive one. Continuous and comprehensive evaluation methods are introduced to assess various aspects of a student's development, including skills, attitudes, and values.

Assessment reforms for holistic development: The policy emphasizes assessment reforms that align with the goal of holistic development. This includes assessing not only academic achievements but also co-curricular activities, life skills and values, providing a more comprehensive view of a student's capabilities.

Reducing exam-related stress: NEP aims to reduce the stress associated with exams by introducing flexible board examinations and promoting a more learner-centric assessment system. This fosters a positive learning environment that encourages exploration and experimentation.

6. Integration of technology: Digital transformation in education

Digital learning platforms: NEP acknowledges the transformative role of technology in education and advocates for the integration of digital learning platforms. This includes leveraging online resources, interactive educational tools, and digital libraries to enhance the learning experience.

Blended learning models: The policy supports the implementation of blended learning models, combining traditional classroom teaching with online resources. This hybrid approach ensures flexibility, personalized learning experiences, and the utilization of technology to cater to diverse learning styles.

Teacher training in technology integration: Recognizing the importance of teachers as key facilitators in the integration of technology, NEP emphasizes the need for teacher training programs. Educators are

equipped with the skills to effectively use technology in teaching, creating a seamless blend of traditional and digital learning. Cultural Sensitivity and Inclusivity: The community also contributes to fostering a culturally sensitive and inclusive environment. NEPs often seek to incorporate diverse perspectives and address cultural nuances to ensure that education is relevant and accessible to all.

d) Inclusive design and accessibility

In an era that values diversity and inclusivity, the National Education Policy (NEP) stands as a key instrument in shaping educational systems that are accessible to all. Inclusive design, coupled with a commitment to accessibility, is essential to ensuring that education becomes a truly transformative force, leaving no one behind. Some key points are-

1. Understanding inclusive design in the NEP

Defining inclusive design: Inclusive design, as reflected in the NEP, goes beyond a mere checkbox approach to accessibility. It is a philosophy that aims to create learning environments and educational materials that can be accessed, understood, and utilized by individuals with diverse backgrounds, abilities, and learning styles.

Catering to diverse learning styles: The NEP recognizes that learners have different styles of learning. Inclusive design accommodates these differences by providing a variety of teaching methods and materials, ensuring that every student can engage with the content in a way that suits their individual needs.

Addressing socio-economic disparities: Inclusivity in the NEP extends to addressing socio-economic disparities. The policy includes provisions for scholarships, financial aid, and other support mechanisms to ensure that education is not a privilege confined to a few but is accessible to all, irrespective of their economic background.

2. Accessibility features in educational infrastructure

Physical accessibility: The NEP acknowledges the importance of physical accessibility in educational infrastructure. It emphasizes the need for schools and institutions to be designed in a way that is accessible to individuals with physical disabilities, ensuring ramps, elevators, and other facilities are in place.

Technological accessibility: In an increasingly digital age, technological accessibility is paramount. The NEP promotes the use of technology in

education but also recognizes the importance of ensuring that digital resources and platforms are accessible to all. This includes considerations for individuals with visual or hearing impairments, ensuring that content is available in multiple formats and that technology is a tool for inclusivity rather than a barrier.

Multilingual accessibility: Recognizing the linguistic diversity within a nation, the NEP emphasizes the importance of multilingualism. Inclusive design ensures that educational materials are available in multiple languages, allowing students from various linguistic backgrounds to engage with the curriculum effectively.

3. Inclusive education practices

Special education initiatives: The NEP places a strong emphasis on special education initiatives, recognizing that some students may require additional support. Inclusive design incorporates strategies for making learning materials accessible to students with diverse learning needs, ensuring that no one is excluded based on their abilities.

Teacher training for inclusive practices: Inclusive education is not just about infrastructure and materials; it also involves equipping educators with the skills to foster an inclusive classroom environment. The NEP recognizes this by emphasizing teacher training programs that focus on inclusive practices, enabling educators to cater to diverse learning styles and abilities.

Adaptations for diverse learning styles: Inclusive design encourages the creation of adaptable learning materials. This means that educational content can be easily customized to meet the needs of different learners. Whether through visual aids, auditory resources, or tactile materials, inclusive design ensures that the curriculum is flexible and responsive to diverse learning styles.

4. Inclusivity beyond the classroom

Community engagement: Inclusive education is not limited to what happens within the classroom walls. The NEP promotes community engagement as a crucial component of inclusivity. This involves creating awareness and understanding within communities about the diverse learning needs of students, fostering an environment that supports inclusive education.

Parental involvement: Parents are integral stakeholders in the education of their children. Inclusive design includes strategies for actively involving parents in the learning process, providing them with resources and guidance to support their children's education effectively.

Collaboration with NGOs and support organizations: The NEP recognizes the importance of collaboration with non-governmental organizations (NGOs) and support organizations that specialize in inclusive education. These collaborations ensure that the expertise and resources of such organizations are leveraged to create a more inclusive educational system.

5. Digital inclusivity

Accessible online learning platforms: With the increasing use of online learning platforms, the NEP underscores the importance of ensuring digital inclusivity. This involves making online resources accessible to individuals with disabilities, providing alternative formats, and incorporating features such as closed captions for video content.

Internet connectivity and digital divide: The NEP addresses the digital divide by acknowledging the importance of internet connectivity. Inclusive design takes into account the disparities in access to technology, striving to bridge the gap and ensure that all students, regardless of their socio-economic background, have equal access to online learning resources.

E-learning for diverse learning styles: Inclusive design in the digital realm extends to creating e-learning materials that cater to diverse learning styles. This includes interactive content, multimedia resources, and adaptive learning platforms that can be personalized to meet the needs of individual learners.

6. Assessing and measuring inclusivity

Comprehensive assessment methods: Inclusive education is reflected in the assessment methods outlined in the NEP. The policy advocates for comprehensive assessment approaches that go beyond traditional exams, taking into account a student's overall development, including skills, values, and attitudes.

Feedback mechanisms: Inclusivity in education involves creating feedback mechanisms that allow students to express their experiences and challenges. The NEP encourages the establishment of channels through which students can provide feedback on the inclusivity of the educational environment, ensuring that their voices are heard.

Regular audits and evaluations: To measure the effectiveness of inclusive design, the NEP suggests regular audits and evaluations of educational institutions. These assessments consider factors such as infrastructure accessibility, teacher preparedness for inclusive practices, and the overall inclusivity of the learning environment.

e) Socio-economic impact

The National Education Policy (NEP) in India, introduced in 2020, has had far-reaching socio-economic implications. The policy, designed to revamp the education system, aims to address the evolving needs of a dynamic society. Its impact can be assessed through various lenses, including access to education, skill development, economic empowerment, and social inclusivity.

1. One of the primary socio-economic impacts of the NEP is the emphasis on inclusive education. The policy strives to provide equitable access to quality education across different socio-economic strata. By promoting early childhood care and education, the NEP seeks to reduce disparities in learning outcomes. This inclusive approach not only addresses educational inequalities but also contributes to social cohesion and economic mobility.
2. The NEP's focus on holistic development and skill enhancement is another key aspect. By integrating vocational education into mainstream curriculum from an early age, the policy aims to equip students with practical skills essential for the workforce. This shift towards a more skill-oriented education system is expected to enhance employability, thereby positively impacting the country's economic productivity. Furthermore, the NEP promotes a flexible and multidisciplinary approach to education. The introduction of a liberal arts model enables students to explore diverse subjects, fostering critical thinking and creativity. This approach not only produces well-rounded individuals but also meets the demands of a rapidly changing job market, where interdisciplinary skills are increasingly valued. The socio-economic benefit lies in creating a workforce that can adapt to evolving industries and contribute to innovation and economic growth.
3. The policy's endorsement of technology in education is another transformative element. The integration of digital tools and online learning platforms facilitates wider access to educational resources, bridging geographical gaps. This digital push not only enhances the learning experience but also aligns education with the demands of the digital economy. However, challenges related to digital infrastructure and accessibility need to be addressed to ensure that the benefits of technology are widespread. In terms of higher education, the NEP aims to make India a global education hub. The policy encourages collaborations with international institutions, facilitating knowledge exchange and attracting foreign students. This internationalization of

education can have significant economic implications by bringing in foreign exchange, fostering innovation through global partnerships, and enhancing the overall quality of higher education in the country.

The NEP also addresses issues related to teacher training and professional development. By emphasizing continuous learning for educators and promoting a merit-based approach, the policy seeks to improve the quality of teaching. This, in turn, contributes to better learning outcomes for students, setting the stage for a more skilled and knowledgeable workforce.

f) Challenges & critiques

While the National Education Policy (NEP) in India has been lauded for its ambitious goals and transformative vision, it has also faced several challenges and critiques. Understanding these concerns is crucial for refining the implementation process and ensuring that the policy's objectives are met effectively.

1. Implementation challenges

One of the primary critiques revolves around the feasibility and effective implementation of the NEP. The policy introduces a range of reforms, from foundational to higher education, requiring significant resources, infrastructure and a coordinated effort. The sheer scale and complexity of executing these changes pose challenges, especially in a diverse and populous country like India.

2. Financial constraints

The successful execution of the NEP requires substantial financial investment. Critics argue that the proposed budget allocations may not be sufficient to meet the demands of the ambitious reforms outlined in the policy. Adequate funding is crucial for infrastructure development, teacher training, technology integration, and other key components of the NEP.

3. Digital divide

The emphasis on technology and online learning, while promising, highlights the existing digital divide. Disparities in access to digital devices and the internet can widen educational inequalities, leaving students from economically disadvantaged backgrounds at a disadvantage. Addressing this digital divide is essential for ensuring the inclusivity of the NEP.

4. Standardization vs. diversity

Critics argue that the NEP's push for a standardized approach to education may undermine the cultural and linguistic diversity of the country. The three-

language formula, while intended to promote multilingualism, has faced resistance in regions where there are concerns about the imposition of a particular language, potentially leading to a loss of local languages and cultures.

5. Assessment and examination system

The NEP proposes a shift from a rote-based examination system to one that assesses critical thinking and conceptual understanding. However, transitioning from a deeply ingrained examination culture poses challenges. Critics worry about the need for comprehensive teacher training, changes in curriculum design, and the acceptance of new evaluation methods.

6. Inclusive education

While the NEP emphasizes inclusive education, there are concerns about its effectiveness in addressing the needs of marginalized and differently-abled students. Specialized infrastructure, trained educators, and tailored curricula are essential for ensuring that the education system caters to the diverse needs of all students.

7. Political and social resistance

Implementing reforms in education often faces resistance from various stakeholders, including political entities, teacher unions, and communities with entrenched educational practices. Negotiating these political and social challenges is critical for the successful implementation of the NEP.

8. Monitoring and evaluation

A robust monitoring and evaluation mechanism is crucial for assessing the impact of the NEP and making necessary adjustments. Ensuring accountability and transparency in the implementation process is essential for addressing challenges and refining policies over time.

g) Future progress & recommendations

The future progress of the National Education Policy (NEP) in India relies on effective implementation, continual assessment, and adaptive strategies. Here are recommendations for the sustained success and evolution of the NEP:

1. **Increased budget allocation:** Ensure adequate financial resources for the successful implementation of the NEP. Increased budget allocations should cover infrastructure development, teacher training, technology integration, and initiatives targeting marginalized communities.

2. **Digital infrastructure development:** Address the digital divide by investing in digital infrastructure and ensuring widespread access to technology. This includes providing devices and internet connectivity to students in rural and economically disadvantaged areas.
3. **Teacher training and professional development:** Prioritize comprehensive and ongoing teacher training programs to equip educators with the skills needed for the evolving education landscape. Continuous professional development should focus on pedagogical innovations, technology integration and student-centric teaching methods.
4. **Inclusive education strategies:** Implement targeted strategies to ensure that the benefits of the NEP reach all segments of society, including marginalized and differently-abled students. This involves developing inclusive curricula, providing necessary support services, and creating a conducive learning environment for diverse needs.
5. **Community engagement:** Foster community engagement and collaboration in the education process. Encourage active involvement of parents, local communities, and other stakeholders in decision-making processes, school management, and educational initiatives to create a sense of ownership and responsibility.
6. **Regional language promotion:** Emphasize the preservation and promotion of regional languages to maintain cultural diversity. The three-language formula should be implemented with sensitivity to linguistic and cultural considerations, avoiding any imposition of a particular language.
7. **Flexible assessment systems**: Gradually transition towards a more flexible and holistic assessment system. This should include a shift from rote memorization to evaluating critical thinking, creativity, and problem-solving skills. Implement pilot projects and gather feedback to refine assessment methods.
8. **International collaborations:** Strengthen international collaborations in higher education to enhance the global competitiveness of Indian institutions. Facilitate partnerships with renowned universities, encourage faculty exchanges, and promote research collaborations to foster a culture of innovation and excellence.

9. **Autonomy and accountability:** Balance institutional autonomy with accountability. Ensure that educational institutions have the freedom to innovate while maintaining accountability for quality education. A transparent and fair regulatory framework should facilitate this balance.
10. **Research and innovation:** Promote a culture of research and innovation within educational institutions. Encourage interdisciplinary research, provide incentives for innovation, and create avenues for the application of research outcomes to address real-world challenges.
11. **Monitoring and evaluation:** Establish a robust monitoring and evaluation mechanism to assess the impact of the NEP at regular intervals. Use data-driven insights to identify areas of success, challenges, and areas needing improvement. Make policy adjustments based on these evaluations.
12. **Public awareness campaigns:** Conduct public awareness campaigns to inform stakeholders about the goals and benefits of the NEP. This includes disseminating information about policy changes, their implications, and ways in which individuals and communities can contribute to the success of the reforms.
13. **Adaptability to changing needs:** Design the NEP as a dynamic and adaptable framework that can respond to changing educational, economic, and societal needs. Periodic reviews and updates should be conducted to ensure that the policy remains relevant and effective in a rapidly evolving environment.

h) Conclusion

By addressing these recommendations, the National Education Policy can progress towards its goals, contributing to the development of a robust, inclusive, and globally competitive education system in India. It requires collaborative efforts from policymakers, educators, communities, and other stakeholders to create a transformative impact on the nation's educational landscape.

References

1. An Empirical Study on NEP. [National Education Policy] with Special Reference to the Future of Indian Education System and Its effects on the Stakeholders, Pawan Kalyani, 2020.

Chapter - 8
An Overview of Systematic Review and Meta-Analysis

Author

Suresh Velumani
Professor, Sumandeep Nursing College, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India

Chapter - 8

An Overview of Systematic Review and Meta-Analysis

Suresh Velumani

Abstract

Within the domain of academic research, the fundamental aim of a systematic review and meta-analysis is to provide a comprehensive and unbiased synthesis of relevant studies in a single document. This is accomplished by a thorough and detailed assessment. The systematic review methodology distinguishes itself from typical narrative reviews by virtue of its systematic and organised approach to exploring the literature, in contrast to the largely descriptive nature of the latter. Systematic reviews, as indicated by their name, need a thorough plan and rigorous search tactics to minimise bias. The goal is to systematically locate, evaluate, and synthesise all relevant research articles on a certain topic. Frequently, systematic reviews include the crucial component of meta-analysis, which use statistical techniques to combine data from several research into a unified and measurable structure. Systematic reviews are often found in academic discourse, and specific organisations and databases have been created with the stated purpose of promoting and disseminating these studies. The Cochrane Collaboration is a notable example that is widely acknowledged and accepted in the domain of healthcare.

Keywords: Systematic reviews, synthesis, quantitative, meta-analysis & cochrane

Introduction

The demands of nurse researchers and other healthcare professionals who are enthusiastic about doing systematic reviews and meta-analyses have been especially taken into consideration while developing this article. The information that follows is devoted to helping these people navigate the several crucial phases that make up this demanding procedure. These procedures involve the crucial work of establishing inclusion and exclusion criteria for research projects, as well as the skill of developing a clear and concise review question. We also explore the complexities involved in carrying out a thorough search for pertinent research evidence, the methodical

extraction of relevant data, the critical process of identifying and assessing the potential for bias in clinical trials, and, lastly, the implementation of meta-analyses to combine and get significant insights from a body of literature. This article functions as a thorough resource, providing essential guidance and information to anyone wishing to do systematic reviews and meta-analyses in the healthcare industry.

The history of systematic review

The history of systematic reviews began in the 1970s and 1980s when people started using the terms 'systematic reviews' and 'meta-analyses' in health-related fields. At first, there was confusion about what these terms meant. In 1995, Chalmers and Altman suggested that 'meta-analysis' should only be used to describe the process of combining statistics.

As more and more people got interested in systematic reviews, international groups were formed with experts from different fields to promote and improve systematic reviews. This collaboration helped the methods for conducting systematic reviews to get better and change over time.

Definition

Systematic reviews aim to provide a comprehensive, unbiased synthesis of many relevant studies in a single document using rigorous and transparent methods.

(Aromataris & Pearson, 2014)

The goals of a systematic review can include

- Finding evidence from around the world.
- Checking and improving current practices.
- Identifying areas where more research is needed.
- Solving conflicts in research results.
- Making clear statements to help make decisions.

Comparing literature review and systematic review

Literature review	Systematic review
• The selection of studies can be based on personal judgment. • Typically, no clearly defined methodology is followed. • There's a higher chance of bias or systematic errors.	• Guided by a predefined protocol. • Follows a structured research approach. • Measures are taken to minimize bias. • Conducts thorough and methodical

• The search scope is usually limited. • Findings may not be easily replicated, and the process lacks transparency.	searches for information. • Employs transparent and replicable methods.

Characteristics of a high-quality systematic review

- Well-defined objectives and research questions.
- Clear inclusion and exclusion criteria, set in advance as part of the protocol.
- A comprehensive search strategy to find all relevant studies, whether they are published or not.
- Critical assessment of the studies that are included.
- Analysis of the data extracted from these studies.
- Presentation and synthesis of the findings derived from the research.
- Transparent reporting of the methodology and methods used to carry out the review.

Detailed steps for conducting any systematic review and meta-analysis

1. Formulate the review question

The initial step in conducting a systematic review involves formulating a research question. Without a well-defined research question, the process of identifying suitable resources and relevant literature evidence becomes arduous and time-consuming. To create a robust clinical question, it's imperative that the question is closely aligned with the problem at hand. Furthermore, the question must be structured to facilitate a focused search for a precise answer. To accomplish this, the question should be articulated across all four components of its anatomy.

- The Patient or Problem being addressed.
- The Intervention or Exposure being utilized.
- The Comparison Intervention or Exposure.
- The Clinical outcome of interest.

For example, in the clinical scenario we are considering, the following questions should be posed: "Is animal-assisted therapy more effective than music therapy in managing aggressive behaviour in elderly individuals with dementia?". In this case, P (Patient) refers to Elderly Patients with Dementia, I (Intervention) to Animal-assisted therapy, C (Comparison) to Music Therapy, and O (Outcome) to Aggressive behaviour.

When formulating questions using the PICO framework, it is essential to determine the type of question you are addressing, whether it's related to Diagnosis, Etiology, Diagnosis, Prognosis, or Prevention. The table provided below illustrates how Problem, Intervention, Comparison, and Outcome will vary based on the type of review question you are addressing.

A well formulated question will helps to determine your Inclusive and Exclusive criteria, creation of search strategy, collecting data and presentation of your results.

PICO worksheet

Define your question using PICO: Population, Intervention, Comparison, and Outcome.

Population
Who are the relevant patients? Think about age, sex, geographic location, or specific characteristics that would be important to your question. Describe the most important characteristics of the patient. (e.g., age, disease/condition, gender).
Intervention
What is the management strategy, diagnostic test, or exposure that you are interested in? Describe the main intervention. (e.g., drug or other treatment, diagnostic/screening test)
Comparison
Is there a control or alternative management strategy you would like to compare to the intervention or indicator? Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard).
Outcome
What are the patient-relevant consequences of the intervention? Describe what you're trying to accomplish, measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis).
Time (optional)
What is the time it takes to demonstrate an outcome OR the period in which patients are observed? Describe the time period of the study (e.g. 6-months following childbirth).

PICO(T) templates/examples

Therapy

In ___ [P] ___, do/does ___ [I] ___ result in ___ [O] ____ when compared

with ___ [C] ___ over ___ [T] ___?

Example

In nursing home residents with osteoporosis, do hip protectors result in fewer injuries from slips, trips, and falls when compared with standard osteoporosis drug therapy over the course of their stay?

Etiology

Are ___ [P] ___ with ___ [I] ___ over ___ [T] ___ more likely to ___ [O] ____ when compared with ___ [C] ___?

Example

Are female non-smokers with daily exposure to second-hand smoke over a period of ten years or greater more likely to develop breast cancer when compared with female non-smokers without daily exposure to second-hand smoke?

Diagnosis

Is/are ___ [I] ___ performed on ___ [P] ___ more effective than ___ [C] ___ over ___ [T] ___ in ___ [O] ___?

Example

Are self-reporting interviews and parent reports performed on children aged 5-10 more effective than parent reports alone over a four-week consultation process in diagnosing depression?

Prevention

In ___ [P] __, do/does ___ [I] ___ result in ___ [O] ____ when compared with ___ [C] ___ over __ [T] ___?

Example

In emergency room visitors, do hand sanitizing stations result in fewer in-hospital infections when compared with no hand sanitizing stations over a year-long pilot period?

Prognosis

Do/does ___ [I] ___ performed on ___ [P] ___ lead to ___ [O] ___ over ___ [T] ____compared with ___ [C] ___?

Example

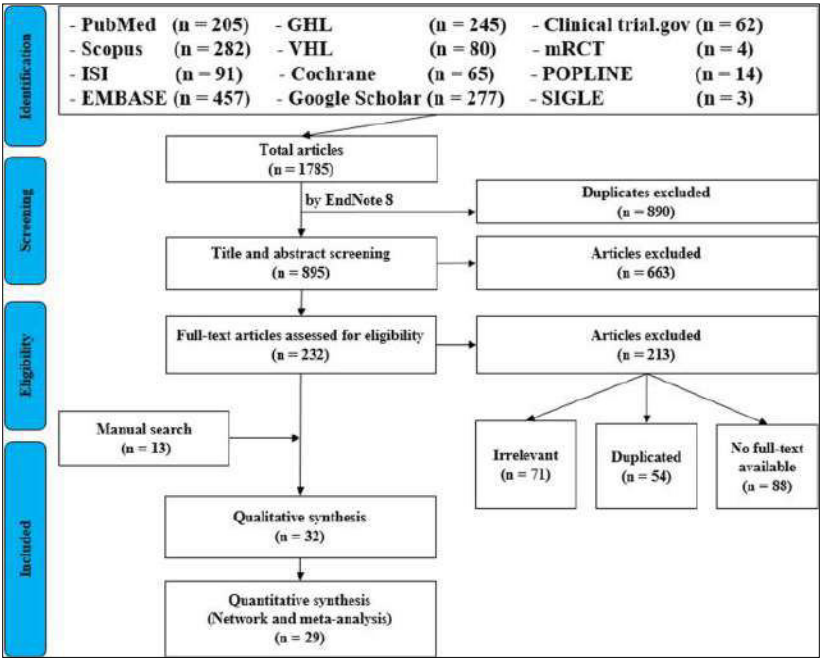
Do regular text message reminders performed on patients recently diagnosed with diabetes lead to a lower occurrence of forgotten insulin

doses over the first six months of treatment compared with no reminders?

2. Define inclusion and exclusion criteria

Once your research question is established, the next crucial step is to define your inclusion and exclusion criteria. These criteria serve as the set of characteristics that determine whether a study qualifies to be included or disqualified from your review. This differentiation between systematic and traditional narrative reviews lies in the pre-specification of these criteria, which dictate which studies are included or excluded from the review. During the search phase of your review, you'll encounter a large number of abstracts. To identify potential studies for systematic review, each abstract undergoes careful scrutiny based on its relevance and acceptability.

In a systematic review, the fundamental question is, "Is this study relevant and suitable for inclusion in the review?" Every systematic reviewer formulates their own set of inclusion and exclusion criteria, tailored to the unique purpose of their review. However, these criteria generally fall into one or more categories, encompassing aspects such as the study population, nature of the intervention, outcomes examined, time duration, cultural and language considerations, research design, and publication date. Each study is evaluated against these predetermined inclusion and exclusion criteria to determine whether it qualifies for inclusion in the review.



3. Develop search strategies and locate studies

A proper use of database and search filters allow you to narrow your results hence, researcher can retrieve the articles that are most appropriate and relevant to the research question. Filter options are vary by database that include Article publication dates, language, age, sex, species and subject. The significant in developing an ideal search strategy is to balance the sensitivity that is retrieving a high proportion of relevant studies and receiving lower proportion of irreverent studies.

First, we search in different databases and save all the results in one place. Then, we organize these results in an Excel sheet. According to the AMSTAR guidelines, it's recommended to search in at least two databases for systematic reviews/meta-analyses, but searching in more databases can give us better and more accurate results. The choice of which databases to use depends on the specific research questions. For clinical trials, you'd mainly rely on databases like Cochrane, mRCTs, or the International Clinical Trials Registry Platform (ICTRP).

In our case, we suggest using 12 databases, including PubMed, Scopus, Web of Science, EMBASE, and others. These databases cover a wide range of articles in tropical medicine and related fields. Some databases have specific search requirements, so we may need to adjust our search terms for each one. For example, in Google Scholar, we'd use specific search terms like "ebola virus" and "vaccine vaccination vaccinated immunization" and set it to search for these terms in the article titles.

After gathering all the records, we put them in a program called Endnote to remove any duplicates. Then, we export the remaining references to an Excel sheet. We make sure to remove references that have the same title and author published in the same year or the same journal. The exported Excel file includes essential information like the authors' names, publication year, journal, DOI, URL link, and an abstract for screening. This helps us manage and review the collected information effectively.

4. Select studies

Once after retrieving the comprehensive list of abstract, reviewer must filter the studies on the basis of inclusion criteria. The process of review is usually done by at least two reviewers to establish inter-rater reliability. The researcher team must agree on inclusion and exclusion criteria for the articles you are interested to review.

Selection of studies takes place under following guidelines.

- Screen each potentially useful study by reading title of the study and apply your inclusion and exclusion criteria.
- Decide whether to include the study in the review.
- Record the decision and reason for inclusion/ exclusion of the study screening.

5. Data extraction and quality assessment

Once after identifying the studies to be included in systematic review, Next step is to extract and analyze the data presented on that studies. In case of small number of studies were included, were reviewer probably don't need to go for coding the data for computer analysis instead summarize the information from the data extracted from selected studies. If a reviewer conducts an analytical review meta-analysis to compare the data from several studies, reviewer has to computerize the data. Data extraction by at least two reviewers is always important again for establishing inter-rater reliability and to avoid errors.

Elements of data extraction

- Consider the review question and objective.
- Consider inclusion and exclusion criteria.
- **Consider the Study Characteristics:** Such as Full citation, objectives, intervention, Location, Duration, Design and methodology, outcome measures and results.

In this step, we collect data from the full-text articles we've included and put it in an organized Excel sheet. Before using it, we test this sheet with some random studies. It's a good idea to gather both adjusted and non-adjusted data because it helps us consider potential factors that might affect the analysis later. This data collection should be done by 2-3 different reviewers. The Excel sheet is usually divided into categories like study and patient details, outcomes, and a quality assessment tool. If there are graphs in the articles, we use software tools to extract the data from them. There are equations available to help with data extraction and estimating standard deviation (SD).

For assessing the quality of the studies, there are various tools available depending on the study design. We recommend having 2-3 reviewers independently assess the study quality and add this information to the data extraction form to reduce bias. To ensure accuracy, we suggest a data checking step where each article is compared with the information in the extraction

sheet using evidence photos. This helps detect any mistakes or discrepancies in the data. Assigning different reviewers, if possible, for this task can be even more reliable.

There are many tools available in recent years to assess the quality of each RCT included in systematic reviews Quality assessment elements

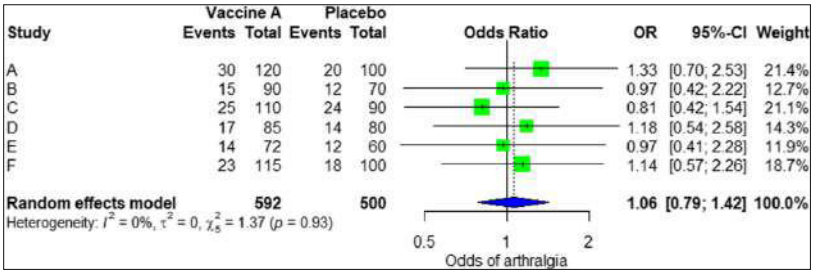
- Clinical question clearly stated?
- Search methods used to identify relevant studies clearly described?
- Was a comprehensive literature search performed?
- Are the inclusion/exclusion criteria used to screen primary studies clearly described?
- Was there duplicate study selection and data extraction?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?
- Were the methods used to combine the findings of studies appropriate?
- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Was publication bias assessed?
- Was the conflict of interest stated?
- Are the stated conclusions supported by the data presented? Rate the overall quality of the SR as "Good", "Fair" or "Poor" using questions.

There are other more comprehensive recommended guidelines and standards available such as the Consolidated Standards of Reporting Trials (CONSORT Statement), as well as articles providing recommendations for improving quality in RCTs and meta-analyses for psychological interventions.

6. Analysis and interpret the results

There are numerous statistical programme available to calculate the effects sizes for meta-analysis, such as review manager endorsed by Cochrane collaboration. Effect sizes of meta-analysis are stated along with 95% confidence interval, and presented in both quantitative and graphical form (e.g. Forest plots). Forest plots visually depict every trial as a horizontal diamond shape with the middle representing the study effect size and end point represent the zero mark. Often the left side of the graph represents the side

favoring to the treatment and right side represent favor to the control condition. Bottom of the graph is summarize effect size or diamond represent all of the individual studies pooled together. Preferably, we would like to see entire diamond falling below zero indicate that intervention is favored over the control. The last step in writing processes summarizing the findings, and providing recommendations for clinical work. (e.g., Interventions are effective, for whom and under what condition) and research (e.g., Intervention required further research).



Random effect model forest plot for comparison of vaccine A versus placebo

To explain basic meta-analysis, we use made-up data for studying the safety and effectiveness of an Ebola vaccine. In our example, we're looking at a specific vaccine, let's call it "A". We only analyzed this vaccine because there weren't enough studies for the other vaccines, which we'll discuss in a narrative review. In our analysis, we assumed that the studies were quite different from each other, so we chose a random effect model. We looked at the safety of vaccine A and saw that there were some adverse events after the injection. Let's say we included six studies that met our criteria. We conducted a meta-analysis for each of the adverse events, such as "arthralgia", using the R meta package. The results are shown. For arthralgia, the odds ratio (OR) is 1.06 with a confidence interval from 0.79 to 1.42, and a p-value of 0.71. This means there's no significant link between the injection of vaccine A and arthralgia because the OR is close to one, and the p-value is not less than 0.05. We can also visualize the results in a forest plot, where we see the results of six studies (A to F). The green boxes represent each study's effect size, and the bigger the box, the more weight the study has (larger sample size). The blue diamond in the middle represents the combined result of all six studies. In this case, the blue diamond crosses the line at OR = 1, indicating no significant association. We can confirm this because the 95% confidence interval includes one, and the p-value is greater than 0.05. As for heterogeneity (how different the studies are from each other), we found I2 = 0%, which is rare in real studies. It means these studies were quite similar.

Conclusion

Article caters all the researchers and health care professionals to carry out systematic review and meta-analysis effectively and thus helps to implement Evidence based practice appropriately.

References

1. Purssell E, McCrae N. A Brief History of the Systematic Review: How to Perform a Systematic Literature Review, 2020. ISBN 978-3-030-49671-5.
2. UC Library Guides. Systematic Reviews in Health: Getting Started: The Research Question [Internet]. Canberra.libguides.com, 2019 [cited 18 July 2019]. Available from: https://canberra.libguides.com/systematic/question
3. Oxman AD, Sackett DL, Guyatt GH. For the Evidence-Based Medicine Working Group. Users' guides to the medical literature: I. how to get started. JAMA. 1993;270:2093-5.
4. Subject Guides. Systematic Reviews for Health: 1. Formulate the Research Question [Internet]. Utas.libguides.com, 2019 [cited 18 July 2019]. Available from: http://utas.libguides.com/SystematicReviews/FormulateQuestion
5. Fineout-Overholt E, Johnston L. Teaching EBP: asking searchable, answerable clinical questions. Worldviews On Evidence-Based Nursing. 2005;2:157-160.
6. [Internet]. Pdfs.semanticscholar.org. 2019 [cited 18 July 2019]. Available from: https://pdfs.semanticscholar.org/a6b4/d6d01bd19a67e794db4b70207a45d47d82f3.pdf
7. Research Guides. Systematic Reviews: Step 2: Define Inclusion/Exclusion Criteria [Internet]. Learn.library.ryerson.ca, 2019 [cited 18 July 2019]. Available from: https://learn.library.ryerson.ca/systematic_reviews/step2
8. Lib Guides. Systematic Reviews: Define Inclusion/Exclusion Criteria [Internet]. Guides.lib.usf.edu, 2019 [cited 18 July 2019]. Available from: https://guides.lib.usf.edu/c.php?g=848629&p=6073758
9. Research Guides. Systematic Reviews: Creating a Search Strategy [Internet]. Guides.lib.umich.edu, 2019 [cited 18 July 2019]. Available from: https://guides.lib.umich.edu/c.php?g=283340&p=2126706

10. Uman L. Systematic Reviews and Meta-Analyses [Internet]. PubMed Central (PMC), 2019 [cited 18 July 2019]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3024725/

11. Tawfik GM, Dila KAS, Mohamed MYF *et al*. A step by step guide for conducting a systematic review and meta-analysis with simulation data. Trop Med Health 47, 46 (2019). https://doi.org/10.1186/s41182-019-0165-6

12. Research Guides: Systematic reviews: Study selection and appraisal [Internet]. Guides.himmelfarb.gwu.edu. 2019 [cited 18 July 2019]. Available from: https://guides.himmelfarb.gwu.edu/c.php?g=27797&p=170445

13. Research & Subject Guides. Systematic Reviews: Data Extraction [Internet]. Guides.library.stonybrook.edu, 2019 [cited 18 July 2019]. Available from: https://guides.library.stonybrook.edu/c.php?g=226681&p=3624445

14. LibGuides. Systematic Reviews, a Guide: Data Extraction [Internet]. Researchguides.ebling.library.wisc.edu, 2019 [cited 18 July 2019]. Available from: https://researchguides.ebling.library.wisc.edu/systematic-reviews/author/data

15. Research Guides. Systematic Reviews & Meta-analyses: Data Extraction [Internet]. Guides.lib.vt.edu. 2019 [cited 18 July 2019]. Available from: https://guides.lib.vt.edu/SystematicReviews/DataExtraction

16. John W, Williams J, Gierisch J, McDuffie J, Strauss J, Nagi A, *et al*. study quality assessment-systematic reviews [Internet]. Ncbi.nlm.nih.gov, 2019 [cited 18 July 2019]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK82786/

Chapter - 9
Statistical Analysis of Various Empirical Studies for Research

Author

Dr. Shilpa N. Khare
Assistant Professor, Maharshi Dayanand College, Parel,
Mumbai, Maharashtra, India

Chapter - 9

Statistical Analysis of Various Empirical Studies for Research

Dr. Shilpa N. Khare

Abstract

This study is a exploration of the statistical analyses employed in diverse empirical studies across various research domains. The synthesis of these studies reveals a rich tapestry of statistical methodologies used to interpret and derive meaningful insights from empirical data. Within this compilation, a wide array of statistical tools is observed, spanning traditional parametric tests to sophisticated multivariate analyses. The review showcases the versatility and adaptability of statistical techniques to different research contexts, emphasizing their pivotal role in elucidating patterns, relationships, and trends within empirical data. Notably, the abstract highlights prevalent themes in statistical methodologies, such as the increasing use of machine learning algorithms and Bayesian approaches, signifying the evolving landscape of research methodologies. It also underscores the significance of rigorous statistical practices, emphasizing the need for transparency and robustness in data analysis. Furthermore, the abstract delves into challenges encountered in statistical analyses across these empirical studies, including issues related to sample size determination, confounding variables, and the interpretation of complex statistical outputs. This nuanced exploration aims to enhance the methodological awareness of researchers, fostering a deeper understanding of the intricacies involved in statistical analyses.

Keywords: Statistical analysis, significant, challenges, methodology

1. Introduction

In the realm of scientific research, empirical studies play a pivotal role in advancing our understanding of the world around us. These studies are grounded in real-world observations and measurements, providing a foundation for evidence-based decision-making. However, the sheer volume and diversity of empirical studies necessitate rigorous statistical analysis to draw meaningful conclusions and make informed interpretations. This

introduction explores the importance of statistical analysis in the context of various empirical studies, highlighting its role in ensuring the reliability and validity of research findings. Empirical studies, by definition, rely on direct observation or experience rather than theoretical or abstract considerations. Researchers gather data through experiments, surveys, or observations to answer specific research questions and test hypotheses. The results of these studies contribute to the body of knowledge in various fields, ranging from psychology and sociology to medicine and environmental science.

Statistical analysis serves as the backbone of empirical research, allowing researchers to extract meaningful patterns and insights from complex datasets. The primary goals of statistical analysis in empirical studies include describing the data, making inferences about populations based on sample data, and testing hypotheses. These statistical techniques provide a quantitative framework for researchers to quantify relationships, identify trends, and assess the generalizability of their findings. One key aspect of statistical analysis in empirical studies is the exploration of central tendency and variability within the data. Descriptive statistics, such as mean, median, and mode, help summarize the main features of a dataset, providing a concise overview of its characteristics. Understanding the central tendency allows researchers to identify typical values, while measures of variability, such as standard deviation, highlight the spread of data points. These statistical summaries offer a foundation for further analysis and interpretation.

In addition to descriptive statistics, inferential statistics play a crucial role in empirical research. Inferential statistics enable researchers to draw conclusions about populations based on a sample of data. Hypothesis testing, a common inferential statistical technique, involves comparing observed data with expected values to determine whether any observed differences are statistically significant. This process helps researchers assess whether their findings are likely to be generalizable to the broader population.

Empirical studies across various disciplines often involve experimental designs, where researchers manipulate independent variables to observe their effects on dependent variables. Statistical analysis of experimental data includes techniques such as analysis of variance (ANOVA) and regression analysis. ANOVA allows researchers to compare means across multiple groups, while regression analysis explores relationships between variables, helping identify predictors and outcomes. Moreover, the burgeoning field of meta-analysis has gained prominence in aggregating findings from multiple empirical studies. Meta-analysis employs statistical techniques to synthesize results from different studies, providing a comprehensive overview of the

existing body of evidence. This approach enhances the generalizability and reliability of research findings by pooling data from diverse sources.

As technology advances, the complexity of empirical studies has increased, leading to the integration of advanced statistical methods and machine learning techniques. Big data analytics, for instance, enables researchers to analyze massive datasets to uncover hidden patterns and relationships. Machine learning algorithms, such as neural networks and decision trees, contribute to predictive modelling and classification in diverse research domains.

2. Study design

The study design for the statistical analysis of various empirical studies plays a crucial role in ensuring the reliability and validity of research findings. A well-crafted study design provides a roadmap for collecting, analyzing and interpreting data, guiding researchers in their quest to address specific research questions and test hypotheses across diverse disciplines. Following are some crucial areas reflecting design

1) Research objectives and hypotheses formulation

At the outset, researchers need to clearly define the objectives of their study and formulate hypotheses that guide the investigation. These objectives serve as the foundation for subsequent decisions related to study design, sample selection, and data collection. Hypotheses, grounded in existing literature and theoretical frameworks, articulate the expected relationships between variables under investigation.

2) Study type and design

The choice of study type and design depends on the research objectives and the nature of the phenomena being studied. Empirical studies can take various forms, including observational studies, experiments, surveys, and case-control studies. The selection of the appropriate design hinges on the researcher's ability to control variables, manipulate conditions, and draw causal inferences.

a) **Observational studies:** These studies involve the observation of subjects in their natural environment without manipulation of variables. Cross-sectional, case-control, and cohort studies fall under this category, providing valuable insights into associations and potential risk factors.

b) **Experimental studies:** Experimental designs involve the manipulation of independent variables to observe their effects on

dependent variables. Randomized controlled trials (RCTs) are the gold standard in experimental research, allowing researchers to establish cause-and-effect relationships.

3) Sampling strategy

The process of selecting participants, or the sample, is critical to the external validity and generalizability of study findings. Random sampling methods, such as simple random sampling or stratified random sampling, enhance the representativeness of the sample. Alternatively, non-random sampling methods may be employed based on practical considerations and research goals.

4) Data collection methods

Researchers must carefully choose data collection methods aligned with the study design. Surveys, interviews, observations, and experiments are common approaches. The selection of measurement tools and instruments should be based on their validity and reliability to ensure the accuracy and consistency of data.

5) Variables and measurements

Identification and operationalization of variables are pivotal steps in the study design. Independent and dependent variables should be clearly defined, and measurement scales (nominal, ordinal, interval, ratio) chosen based on the nature of the data. Careful consideration of potential confounding variables is crucial to control for extraneous influences on the relationships under investigation.

6) Statistical analysis plan

The statistical analysis plan outlines the methods that will be employed to analyze the collected data. Descriptive statistics, such as means, medians, and standard deviations, provide an initial overview, while inferential statistics, including t-tests, analysis of variance (ANOVA), regression analysis, and chi-square tests, help test hypotheses and draw inferences about the population.

7) Ethical considerations

Ethical considerations should be integrated into the study design to ensure the protection of participants and the integrity of the research process. Informed consent, confidentiality, and adherence to ethical guidelines are paramount.

8) Power and sample size calculation

Power analysis helps researchers determine the sample size needed to detect a significant effect if it exists. Adequate sample size enhances the

study's ability to detect true relationships and increases the reliability of results.

9) Data management and quality assurance

Rigorous data management practices, including data cleaning, validation, and documentation, contribute to the overall quality of the study. Regular checks for data accuracy and consistency are essential to minimize errors and biases.

3. Types of empirical studies and corresponding statistical methods

Empirical studies span a wide range of disciplines and research questions, each demanding unique approaches to data collection and analysis. Various types of empirical studies necessitate corresponding statistical methods to draw meaningful inferences. Here, we explore some common types of empirical studies and the statistical methods associated with each.

1) Observational studies

Observational studies involve the collection and analysis of data without intervening or manipulating variables. Key types include:

a) **Cross-sectional studies:** These studies examine a snapshot of a population at a specific point in time. Descriptive statistics such as proportions and prevalence rates are common and inferential statistics like chi-square tests may be used to identify associations.

b) **Cohort studies:** Cohort studies follow a group over time to investigate the development of certain outcomes. Survival analysis (Kaplan-Meier curves) and Cox proportional hazards models are common statistical tools.

2) Experimental studies

Experimental studies involve manipulating independent variables to observe their effects on dependent variables. Common types include:

a) **Randomized Controlled Trials (RCTs):** RCTs involve random assignment of participants to experimental and control groups. Statistical methods include t-tests for continuous outcomes and chi-square tests for categorical outcomes. Analysis of covariance (ANCOVA) and regression analysis are used to control for covariates.

b) **Field experiments:** These experiments take place in a real-world setting. Statistical methods align with those of traditional RCTs, with an emphasis on controlling for external factors.

3) Quasi-experimental studies

Quasi-experimental studies lack random assignment but still involve manipulation of independent variables. Statistical methods are adapted to address issues of confounding. Before-and-After Studies: Paired t-tests or non-parametric tests are employed to compare outcomes before and after an intervention. Regression analysis can control for confounding variables.

Interrupted Time Series: Time series analysis, such as autoregressive integrated moving average (ARIMA) models, is used to analyze data collected at multiple time points.

4) Survey research

Surveys collect data through questionnaires or interviews to understand attitudes, behaviours, and characteristics of a population. We consider here as follows:

1. **Descriptive surveys:** Descriptive statistics like means and percentages summarize survey responses. Confidence intervals provide estimates of precision.
2. **Comparative surveys:** T-tests, chi-square tests, and analysis of variance (ANOVA) compare groups based on survey responses.

5) Case-control studies

Case-control studies compare individuals with a particular condition (cases) to those without it (controls), investigating potential risk factors.

Odds ratios: Logistic regression is commonly used to calculate odds ratios, quantifying the association between exposure variables and the outcome.

6) Longitudinal studies

Longitudinal studies follow individuals or groups over an extended period, capturing changes over time.

Growth curve models: These models analyze repeated measures and account for individual variability in growth trajectories. Latent Growth Curve Models: These models incorporate latent variables to explore patterns of change over time.

7) Meta-analysis

Meta-analysis involves combining results from multiple studies to derive overall conclusions.

Effect size calculation: Standardized mean differences or odds ratios are often calculated as effect sizes.

Forest plots: These graphical representations show individual study results and the overall combined effect.

8) Big data analytics

With the advent of big data, statistical methods adapted to handle large datasets have become crucial.

Machine learning algorithms: Regression analysis, decision trees, clustering, and neural networks are employed for prediction and classification.

Text mining and natural language processing: These methods analyze unstructured data, such as text from social media or online forums.

9) Qualitative research

While qualitative research often involves non-statistical analysis, it plays a vital role in understanding complex phenomena. We consider here

Thematic analysis: This method identifies themes and patterns within qualitative data.

Content analysis: This approach categorizes and quantifies textual data for interpretation**.**

Challenges in statistical analysis

Statistical analysis is a powerful tool for extracting meaningful insights from data, but it comes with its own set of challenges. Researchers and analysts face various hurdles that can impact the accuracy, reliability, and validity of their findings. Here, we explore some of the key challenges in statistical analysis:

1) Data quality and integrity

One of the fundamental challenges in statistical analysis is ensuring the quality and integrity of the data. Inaccurate, incomplete, or biased data can significantly compromise the validity of statistical results. Issues such as missing data, measurement errors, and outliers can distort the analysis, leading to incorrect conclusions.

2) Sampling bias

Obtaining a representative sample is crucial for the generalizability of study findings. However, sampling bias can occur if the sample is not truly random or if certain groups are systematically excluded. This bias can lead to

results that are not reflective of the broader population, limiting the external validity of the study.

3) Confounding variables

Identifying and controlling for confounding variables is a persistent challenge in statistical analysis. Confounding variables are extraneous factors that may affect the relationship between the independent and dependent variables. Failure to account for these variables can lead to spurious associations and inaccurate conclusions.

4) Overfitting and underfitting

In predictive modelling, such as regression analysis, there is a risk of overfitting or underfitting the model to the data. Overfitting occurs when a model is too complex and captures noise in the data as if it were a genuine pattern, leading to poor generalization to new data. On the other hand, underfitting occurs when the model is too simple to capture the underlying patterns, resulting in poor predictive performance.

5) Multicollinearity

Multicollinearity arises when two or more independent variables in a regression model are highly correlated. This can make it challenging to isolate the individual effect of each variable on the dependent variable. Multicollinearity may lead to inflated standard errors and imprecise estimates.

6) Small sample size

Statistical analyses, especially inferential statistics, require an adequate sample size to draw meaningful conclusions. Small sample sizes can result in low statistical power, making it difficult to detect true effects. Moreover, small samples may be more susceptible to random variation, leading to less stable estimates.

7) Publication bias

There is a tendency for studies with statistically significant results to be published more frequently than those with non-significant results. This publication bias can skew the overall body of evidence, leading to an overestimation of effect sizes and potentially misleading conclusions.

8) Misinterpretation of statistical significance

The concept of statistical significance is widely used but can be misunderstood. A result being statistically significant does not necessarily imply practical significance or real-world importance. Researchers and

readers should carefully consider the effect size and the context of the study to avoid misinterpretation.

9) Assumption violations

Many statistical methods, such as regression analysis and analysis of variance, rely on certain assumptions about the data distribution. Violations of these assumptions, such as non-normality or homoscedasticity, can affect the accuracy of results. Applying statistical tests without checking assumptions can lead to unreliable findings.

10) Complexity of advanced methods

With the advent of machine learning and advanced statistical methods, researchers face the challenge of selecting and interpreting complex models. These methods often require a deep understanding of algorithms and may be prone to over-optimization, making it crucial for researchers to strike a balance between model complexity and interpretability.

11) Ethical considerations

Ethical challenges in statistical analysis include issues related to data privacy, consent, and responsible use of statistical models. Ensuring that data is handled ethically and that results are communicated transparently is essential to maintain the trust of participants and the broader community.

4. Significance of statistical analysis

Statistical analysis holds immense significance across various disciplines, playing a pivotal role in advancing knowledge, informing decision-making, and fostering evidence-based practices. Whether in scientific research, business, healthcare, social sciences, or public policy, statistical analysis provides a systematic and quantitative framework for interpreting data. Here are some key aspects highlighting the significance of statistical analysis:

1) Data summarization and descriptive statistics

Statistical analysis allows researchers and analysts to summarize and describe large datasets effectively. Descriptive statistics, such as mean, median, mode, and measures of variability, provide concise and meaningful insights into the central tendencies and dispersion of data. This summarization facilitates a clear and interpretable presentation of complex information.

2) Inference and generalization

Statistical analysis enables researchers to make inferences about populations based on samples. Through hypothesis testing and confidence

intervals, researchers can draw conclusions about the significance of observed effects, helping to generalize findings from a subset to a larger population. This process enhances the external validity of research studies.

3) Decision-making in business and industry

In the business world, statistical analysis is instrumental in decision-making processes. From market research and product development to quality control and risk assessment, businesses rely on statistical methods to analyze data and make informed decisions. Techniques such as regression analysis and predictive modeling contribute to strategic planning and resource allocation.

4) Scientific research and hypothesis testing

In scientific research, statistical analysis is a cornerstone for testing hypotheses and evaluating the significance of experimental results. Through methods like analysis of variance (ANOVA) and t-tests, researchers assess whether observed differences are likely due to true effects or random chance. This rigorous testing is essential for validating scientific theories and contributing to the cumulative knowledge of a particular field.

5) Public health and epidemiology

Statistical analysis is crucial in public health for tracking and analyzing disease patterns, assessing risk factors, and evaluating the effectiveness of interventions. Epidemiological studies employ statistical methods to understand the distribution and determinants of health-related events, informing public health policies and interventions.

6) Quality improvement and process control

Industries use statistical analysis for quality improvement and process control. Statistical process control (SPC) techniques monitor and control manufacturing processes, ensuring consistency and minimizing defects. Control charts and Six Sigma methodologies are common statistical tools in this context.

7) Social sciences and survey research

Social sciences rely heavily on statistical analysis to examine patterns of human behaviour, attitudes, and societal trends. Survey research, for instance, employs statistical techniques to analyze responses and draw conclusions about populations. Statistical methods help social scientists uncover patterns, test hypotheses, and make evidence-based recommendations.

8) Environmental studies and data interpretation

Environmental studies involve the collection and analysis of data related to ecosystems, climate, and pollution. Statistical analysis aids in interpreting environmental data, assessing the impact of human activities, and identifying trends. Techniques like spatial analysis and regression modelling contribute to understanding complex environmental systems.

9) Financial analysis and risk management

Financial analysts use statistical methods to analyze stock market trends, assess investment risks, and make predictions about future market behaviour. Risk management in finance relies on statistical models to quantify and mitigate potential risks associated with investment portfolios.

10) Education and educational research

Statistical analysis is prevalent in educational research, where it is used to assess the effectiveness of teaching methods, evaluate interventions, and measure student performance. Educational policymakers rely on statistical data to inform decisions about curriculum design and resource allocation.

11) Policy evaluation and evidence-based policymaking

In the realm of public policy, statistical analysis is essential for evaluating the impact of policies and interventions. Policymakers rely on evidence-based approaches to inform decisions, and statistical methods provide the tools to analyze data and assess the effectiveness of **various policy measures.**

5. Future directions

The future of statistical analysis in empirical studies holds exciting prospects, driven by advancements in technology, the increasing complexity of datasets, and the integration of interdisciplinary approaches. As researchers continue to push the boundaries of knowledge, several key trends and future directions emerge in the realm of statistical analysis. Some key areas are-

1) Big data analytics

The era of big data has ushered in a new paradigm for statistical analysis. As datasets grow in size and complexity, traditional statistical methods face challenges in scalability and efficiency. Future directions involve the development of advanced algorithms and computational tools capable of handling massive datasets. Machine learning techniques, such as deep learning, are likely to play a significant role in uncovering intricate patterns and relationships within big data.

2) Machine learning integration

The integration of machine learning into statistical analysis is a prominent future direction. Machine learning algorithms, including neural networks, random forests, and support vector machines, offer powerful tools for predictive modelling, classification, and pattern recognition. Researchers will increasingly leverage these techniques to extract insights from diverse empirical studies, especially in fields like healthcare, finance, and social sciences.

3) Explainable AI (XAI)

As machine learning models become more complex, there is a growing emphasis on developing explainable AI (XAI). Future statistical analysis will focus on creating interpretable models that provide transparent insights into decision-making processes. This is particularly crucial in fields like healthcare, where model interpretability is vital for gaining trust among practitioners and ensuring ethical use of algorithms.

4) Bayesian methods and probabilistic programming

Bayesian statistical methods are gaining traction for their ability to incorporate prior knowledge and update beliefs as new data becomes available. Probabilistic programming languages, such as Stan and Pyro, allow researchers to express complex statistical models more flexibly. Future directions involve the widespread adoption of Bayesian methods and the refinement of probabilistic programming languages for a broader range of applications.

5) Reproducibility and open science

Ensuring the reproducibility of statistical analyses is an emerging concern in research. Future directions involve promoting transparency and openness in statistical practices. Initiatives like open-source software, pre-registration of studies, and the sharing of datasets and code contribute to reproducible research. Improving accessibility to statistical tools and resources will empower researchers to validate and replicate findings.

6) Multimodal and multivariate analysis

The integration of data from diverse sources, such as images, text, and sensor data, presents new challenges and opportunities. Future statistical analysis will focus on developing techniques for multimodal and multivariate analysis. This includes methods for integrating information from different data types, uncovering hidden relationships, and extracting meaningful insights from complex, heterogeneous datasets.

7) Ethical considerations in statistical analysis

The ethical implications of statistical analysis are gaining prominence. Future directions involve addressing issues related to bias, fairness, and transparency in algorithmic decision-making. Researchers will increasingly prioritize ethical considerations in study design, data collection, and the interpretation of results to ensure responsible and equitable use of statistical methods.

8) Quantum computing in statistical analysis

The advent of quantum computing holds promise for revolutionizing statistical analysis. Quantum algorithms have the potential to solve complex optimization and simulation problems more efficiently than classical computers. As quantum computing technologies mature, researchers may explore their application in statistical modelling and optimization tasks.

9) Dynamic and adaptive study designs

Traditional study designs often follow a fixed protocol, but future directions involve the adoption of dynamic and adaptive designs. These designs allow researchers to modify aspects of the study in response to interim analyses, improving efficiency and increasing the likelihood of detecting true effects. Adaptive clinical trials, for example, can optimize sample sizes and treatment allocations based on accumulating data.

10) Interdisciplinary collaboration

The future of statistical analysis lies in increased collaboration across disciplines. Researchers will engage in interdisciplinary partnerships, combining statistical expertise with domain-specific knowledge. This collaborative approach ensures that statistical methods are tailored to the unique challenges of different fields, leading to more meaningful and impactful analyses.

6. Conclusion

In conclusion, the journey through the landscape of statistical analysis for various empirical studies unveils the indispensable role this discipline plays in shaping our understanding of the world. From medical research to social sciences, education, business, and beyond, statistical analysis stands as the compass guiding researchers through the intricate terrain of data. As we reflect on the significance, challenges, and future directions, several key takeaways emerge as follows

Firstly, the significance of statistical analysis cannot be overstated. It serves as the bridge between raw data and meaningful insights, providing

researchers with the tools to uncover patterns, test hypotheses, and draw robust conclusions. In the realm of scientific research, statistical analysis is the cornerstone for validating theories, making evidence-based decisions, and contributing to the cumulative knowledge of various fields.

Secondly, the challenges inherent in statistical analysis underscore the need for methodological rigor, critical thinking, and ongoing advancements. Issues such as data quality, sampling bias, and confounding variables necessitate careful consideration and meticulous application of statistical methods. Ethical considerations, transparency, and the responsible use of statistical models further underscore the importance of a principled approach to analysis.

Looking ahead, the future of statistical analysis promises exciting developments. The integration of machine learning, big data analytics, and Bayesian methods opens new frontiers for exploration. The emphasis on explainable AI, ethical considerations, and interdisciplinary collaboration reflects a commitment to ensuring that statistical analysis not only advances knowledge but does so responsibly, ethically, and with a focus on transparency. As we navigate this future terrain, it becomes evident that statistical analysis is not just a set of techniques but a dynamic and evolving discipline. The advent of quantum computing, the exploration of dynamic study designs, and the increasing emphasis on reproducibility signal a field in constant flux. Researchers must not only adapt to these changes but actively contribute to shaping the future of statistical analysis through innovation, collaboration, and a commitment to ethical practices.

In the grand tapestry of empirical studies, statistical analysis weaves together the threads of observation, experimentation, and interpretation. It transforms data into knowledge, uncertainty into confidence, and complexity into clarity. The diverse case studies explored exemplify how statistical methods are applied across various domains, each study presenting its unique challenges and opportunities. In the hands of researchers and analysts, statistical analysis is a powerful tool, a compass that not only guides exploration but also charts the course for informed decision-making. It is a discipline that thrives on curiosity, rigor, and the relentless pursuit of truth. As we conclude this exploration, we recognize that statistical analysis is not merely a means to an end but an integral part of the scientific journey, propelling us forward into a future where the answers to our most pressing questions are waiting to be uncovered through the lens of statistical insight.

References

1. Zulfiqar Ali, Bala Bhaskar S. Basic statistical tools in research and data analysis.
2. Yasha Pushak, Holger Hoos H. Advanced statistical analysis of empirical performance scaling.

Chapter - 10
Consequences of Post Covid Effects

Authors

Korapati Rama Rao
Assistant Professor, Sultan-ul-Uloom College of Pharmacy, Mount Pleasant, Banjara Hills, Hyderabad, Telangana, India

Dr. Baba Shankar Rao Garige
Associate Professor, School of Pharmacy, Anurag University, Venkatapur, Ghatkesar, Medchal, Hyderabad, Telangana, India

Vaishnavi Munnangi
Associate Professor, Princeton College of Pharmacy, Chowdariguda, Narapally, Ghatkesar, Medchal, Telangana, India

Neela Swapna
Associate Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy, Chowdariguda, Ghatkesar, Medchal, Telangana, India

Dr. Narender Boggula
Associate Professor, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India

Chapter - 10

Consequences of Post Covid Effects

Korapati Rama Rao, Dr. Baba Shankar Rao Garige, Vaishnavi Munnangi, Neela Swapna and Dr. Narender Boggula

Abstract

The COVID-19 pandemic has led to unanticipated pressures on all aspects of human life. Multiple approaches to eliciting protective immunity must be rapidly evaluated. Numerous efforts have been made to develop an effective vaccine for this novel corona virus, resulting in a race for vaccine development. To combat COVID-19, all nations must focus their efforts on widespread vaccination with an effective and safe vaccine. Globally, concerns about potential long-term adverse effects of vaccines have led to some apprehension about vaccine use. A vaccine's adverse effect has an integral role in the public's confidence and vaccine uptake. This article reviews the current primary literature regarding adverse effects associated with different COVID-19 vaccines in use worldwide. The success of mass COVID-19 vaccination campaigns rests on widespread uptake. However, although vaccinations provide good protection, they do not offer full immunity and while they likely reduce transmission of the virus to others, the extent of this remains uncertain. This produces a dilemma for communicators who wish to be transparent about benefits and harms and encourage continued caution in vaccinated individuals but not undermine confidence in an important public health measure. Following the COVID-19 virus epidemic, extensive, coordinated international research has led to the rapid development of effective vaccines. Although vaccines are now considered the best way to achieve collective safety and control mortality, due to the critical situation, these vaccines have been issued the emergency use licenses and some of their potential subsequence side effects have been overlooked. At the same time, there are many reports of side effects after getting a COVID-19 vaccine. While the number of studies investigating the post-COVID-19 condition is increasing, there is no agreement on how this new disease should be defined and diagnosed in clinical practice and what relevant outcomes to measure. The common complications are cerebrovascular disorders including cerebral venous sinus thrombosis, transient ischemic attack, intracerebral hemorrhage, ischemic

stroke, and demyelinating disorders including transverse myelitis, first manifestation and neuromyelitis optica. These effects are often acute and transient, but they can be severe and even fatal in a few cases. Finally, discovering whether these disorders are accidental or whether the vaccine is the main cause of them requires future studies, ongoing efforts to gather evidence, and long-term monitoring.

Keywords: COVID-19, adverse effects, vaccine, SARS Covid-2, bell's palsy, guillain-barre syndrome

Introduction

The hope and hype that the media and public at large are placing on having as soon as possible a vaccine that protects against COVID-19 is the result of the great triumphs that vaccines have had and are having in the control of infectious diseases. However, there is a long series of infectious diseases in which vaccines are only partially effective and we have a series of sensational vaccine defeats. Indeed, each disease is an immunological problem in itself: even today, with all the data at one's disposal, it is difficult to predict what kind of vaccine can be truly effective. This difficulty is even greater for COVID-19, a new disease in which ongoing studies in laboratories worldwide are adding new data at a tremendous pace. SARS-CoV2, the coronavirus responsible for COVID-19 is an RNA virus, and these viruses generally have a high mutation rate. Genetic instability has long been considered to represent a challenge to develop effective vaccines against RNA viruses [1, 2].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a newly identified member of the human coronaviruses family that was discovered during the outbreak of the highly transmissible respiratory disease in Wuhan, China in 2019. SARS-CoV-2 causes the Coronavirus disease 19 (COVID-19) and is now continuing to spread worldwide causing a global pandemic [2-4].

Advantages of covid vaccine

COVID-19 vaccines have played a crucial role in combating the global pandemic caused by the SARS-CoV-2 virus. The advantages of COVID-19 vaccines are numerous and have contributed to the reduction of infections, hospitalizations, and deaths. Here are some key advantages of COVID-19 vaccines:

- **Prevention of severe illness:** COVID-19 vaccines have been shown to significantly reduce the risk of severe illness, hospitalization, and death among individuals who contract the virus. This has helped alleviate the burden on healthcare systems and saved countless lives.
- **Reduction in transmission:** Vaccinated individuals are less likely to transmit the virus to others. This is crucial in slowing down the spread of the virus and achieving herd immunity, which ultimately contributes to ending the pandemic.
- **Variants mitigation:** While some COVID-19 variants may partially evade immunity, vaccines have shown effectiveness in reducing the severity of illness caused by these variants. They continue to be an important tool in managing the evolution of the virus.
- **Shortening the pandemic:** Widespread vaccination efforts have helped to bring down infection rates and contribute to the gradual control of the pandemic. As more people get vaccinated, the overall impact of the virus diminishes.
- **Protecting vulnerable populations:** COVID-19 disproportionately affects certain populations, such as the elderly and individuals with underlying health conditions. Vaccination helps protect these vulnerable groups and reduces their risk of severe illness.
- **Safe and effective:** Extensive clinical trials and monitoring have shown that authorized COVID-19 vaccines are safe and effective at preventing illness. The benefits of vaccination far outweigh the potential risks.
- **Return to normalcy:** Vaccination campaigns have enabled societies to ease restrictions, resume economic activities, and restore a sense of normalcy, which is vital for both individuals and communities.
- **Global control:** Vaccination efforts are key to controlling the virus on a global scale. By helping to reduce transmission everywhere, vaccines contribute to the prevention of new variants and future outbreaks.
- **Research and scientific advancement:** The rapid development of COVID-19 vaccines has led to advancements in vaccine technology and research methodologies, which could have implications for future vaccine development.
- **Public health and community protection:** Widespread vaccination protects not only the individual but also the community as a whole.

It helps create a "shield" of immunity, reducing the overall prevalence of the virus.

- **Cost-effectiveness:** Vaccination is generally more cost-effective than treating severe cases of COVID-19. By preventing illness, vaccines also alleviate the economic burden associated with healthcare costs and lost productivity.
- **Rapid deployment:** The emergency response to the pandemic has demonstrated the ability to rapidly develop and distribute vaccines in unprecedented timeframes, setting a precedent for addressing future health crises.

It's important to note that while COVID-19 vaccines offer significant advantages, achieving widespread vaccination coverage remains a challenge due to factors such as vaccine hesitancy, access issues, and global distribution disparities. Public health efforts continue to focus on addressing these challenges to maximize the benefits of COVID-19 vaccination [5-8].

The coronavirus disease 2019 (COVID-19) pandemic has necessitated rapid responses from healthcare systems and research networks globally. Although a large amount of comprehensive data on acute symptoms and clinical management has been collected and analysed, there are currently no established clinical definition or Core Outcome Sets (COS) [8, 9].

Post-COVID condition health consequences

Recent editorials and National Institutes of Health (NIH) and WHO sponsored conferences have drawn attention to an increasing number of people experiencing health consequences following the acute phase of SARS-CoV-2 infection and are calling for research into the risk factors, clinical features, diagnosis, management and outcomes. Increasing funding opportunities have subsequently followed. It is important to note that most data regarding post-COVID-19 condition have been generated prior to the condition definition announcement. Thus, earlier studies may not fit the proposed definition criteria. Post-COVID-19 condition extends beyond the cardio-respiratory system to affect most other bodily systems both anatomically and physiologically. Although causes of post-COVID-19 condition are unclear, persistent immune activation may be involved. Risk factors for different syndromes of post-acute SARS-CoV-2 sequela have not been characterised, but it has been hypothesised that several post COVID-19 condition phenotypes may exist, although pathophysiology, management, and outcomes are currently unknown [10-12].

Long-term health consequences of COVID-19 remain unknown, but reports suggest that prolonged symptom duration and limitations in functioning are common among hospitalised as well as non-hospitalised adults and children. The spectrum of long-lasting symptoms is wide and varies from mild discomfort to severe adverse effects on physical, cognitive, and psychosocial health, with important wider implications on functioning, including employment and school attendance [2, 13].

The most common reaction, local injection site reaction, occurred primarily after the Covaxin vaccination (50.8%) more than the Covishield (34.93%) at a median of 1 day (inter quartile range - IQR 0-1) after the second dose and lasted for a median of 3 days (IQR 1-3). Delayed local arm reactions occurred primarily after the Covishield vaccination (1.4%) more than the Covaxin (0.7%) at a median of 4 days (IQR 1-7) after the first vaccine and lasted for a median of 1.5 days (IQR 1-3). Urticaria occurred primarily after the Covishield vaccination at a median of 1 day after the first dose and earlier, that is < 1-3) after the second vaccine and lasted for a median of 3 days (IQR 1-10). Other cutaneous findings, which were less commonly seen with both vaccines, included are 18 reports of swelling at other sites, 3 pityriasis rosea-like reactions, 3 morbilliform rash, 1 petechiae, 1 pernio-like rash, and 1 urticarial vasculitis (Figure 1) and hair fall in 94 patients (9.1%). The data for post-vaccination systemic reactions from various studies showed fever, fatigue, myalgia and headache to be most common, which match our study - fever (49%), no reaction (37.4%), bodyache (31%), headache (23.2%), arthralgia (12%), myalgia (9.1%), chills (9%) being more common than sore throat (6%) and diarrhoea (1.6%) [14-17].

Exact aetiology of immediate local reactions due to both vaccines is unclear. Excipients like polyethylene glycol have been attributed to cause immediate hypersensitivity reactions and urticaria. Delayed large local reactions were the most common, followed by local injection site reactions, urticarial eruptions, and morbilliform eruptions [18].

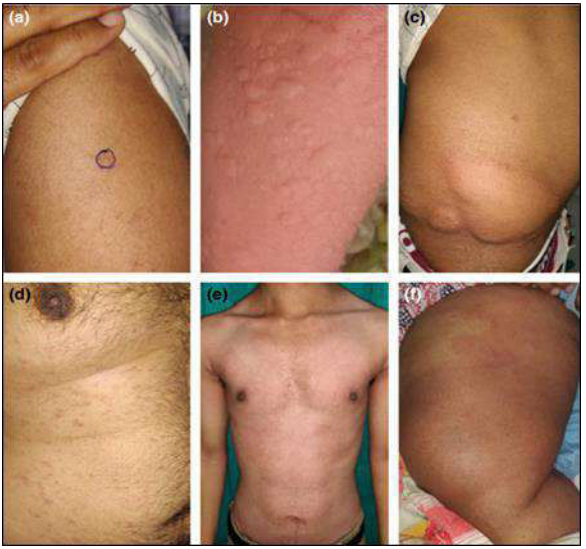


Fig 1: Cutaneous adverse reactions after administration of Covishield and Covaxin COVID-19 vaccines: (a) Local injection site reaction over left upper arm, (b) Delayed injection site reaction over left forearm, (c) Urticarial wheals over right flank region, (d) Pityriasis rosea, (e) Morbilliform rash, (f) Urticarial vasculitis lesions over upper right thigh

Rapid vaccine-induced population immunity is a key global strategy to control COVID-19. Vaccination programmes must maximise early impact, particularly with accelerated spread of new variants. Most vaccine platforms use a two-dose prime-boost approach to generate an immune response against the virus S1 spike protein, the titres of which correlate with functional virus neutralisation and increase with boosting. To enable larger numbers of people to receive the first dose, delayed administration of the second dose has been advocated and implemented by some. The impact of previous SARS-CoV-2 infection on the need for boosting is not known [19-21].

Type of vaccine associated with adverse reactions

This study included reports indicating the type of vaccine used was linked to adverse reactions among participants. Types of vaccines included in this study are Pfizer-BioNTech, Oxford-AstraZeneca, Sinopharm, and Moderna. According to the studies, the type of vaccine given was connected to adverse reactions among participants. Side effects are 2.9 times more prevalent in first-time Sinopharm vaccination recipients. However, Pfizer-BioNTech vaccination recipients were 1.4 times more likely to suffer an adverse reaction following the second dosage. According to Sinopharm vaccine recipients,

people with connected comorbidities had a statistically significant higher percentage of adverse effects than others. According to Pfizer-BioNTech vaccine recipients, individuals having a history of past infection with COVID-19 reported a statistically significant higher percentage of adverse effects than the others.

Dyspnea, death, pyrexia, tiredness, and headache were the most prevalent serious reports of Pfizer-BioNTech. Another study found that the majority of Pfizer-BioNTech users have mild-to-moderate negative effects. Side effects of the Oxford-AstraZeneca (ChAdOx1 nCoV-19) vaccinations include fatigue, headache, tenderness, local discomfort, myalgia, fever, asthenia, induration, and allergic skin. Local effects were observed less frequently after the second dosage of both vaccines than after the first dose, as was the case with Pfizer-BioNTech.

Moderna, another mRNA vaccine, had similar adverse effects as Oxford-AstraZeneca (ChAdOx1 nCoV-19), including headache, asthenia, and myalgia. However, no participant experienced serious local or systemic reactions after receiving both mRNA vaccines, chadOx1-ncov-19 (astraZeneca) and Moderna. Another study revealed that persons who received Moderna vaccinations (who had heart disease and COVID-19) had serious outcomes, such as fatalities. The majority of BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna] mRNA vaccination patients experienced cardiovascular-adverse responses within 7 days of receiving both the first and second doses [22-25].

Impact of the adverse reactions

We looked at the severity of the reactions or the impact of adverse reactions on daily life as vaccination side effects can impair one's capacity to conduct daily tasks. The majority of the reactions were mild to moderate in nature and did not affecting daily tasks, appearing within 1–2 days following vaccination and dissipating within a few days. On the first day following vaccination, the impact of mRNA vaccination, BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna], on everyday life activities was most often reported among vaccine recipients. 60% of Pfizer vaccination participants experienced moderate side effects and 75% felt the vaccine had little influence on their regular lives. Another study described the effect of vaccines on work and daily life for participants who had received ChAdOx1 and BNT162b2 COVID-19, with the majority of adverse effects occurring within 24 h of vaccination, with varying duration of symptoms, and approximately half indicating that they were impacted for more than 24 h. Women were more

likely than males to experience moderate-to-severe side effects that interfered with their daily activities. However, the majority of individuals, regardless of gender, reported that the COVID-19 vaccine had no effect on their everyday activities and that any adverse effects were minor [26, 27].

Discussion

Several adverse reactions to COVID-19 vaccines have been identified in this review. Local and systemic side effects are among the most common adverse reactions to all COVID-19 vaccines, as previously stated in the studies included. Local side effects include joint or muscle pain tenderness, itching, induration and paresthesia in the injection site. Meanwhile fever, chills, fatigue, headache, nausea, myalgia, pyrexia, and dyspnea are among the systemic side effects. Local and systemic adverse events occurred within 7 days of receiving COVID-19 vaccines, with fever, fatigue, and headache being the most common systemic adverse reactions. This finding is consistent with other study that confirmed the incidence rate of frequent adverse effects among healthcare workers was 32.1% for fever, 69.1% for muscle ache, and 48.7% for headache. While injection-site pain was the most common local adverse effect.

Other adverse reactions previously mentioned were allergic, such as skin burning, rashes, and red welts on the lips and face also cardiovascular adverse reactions. Severe allergic reactions following COVID-19 vaccination are extremely rare, but have garnered attention due to potentially fatal outcomes and a high level of uncertainty. Other research indicates that cardiovascular side effects such as tachycardia, flushing, hypertension, hypotension, and peripheral coldness have also been reported. Other studies found that people who received the Pfizer/BioNTech vaccine had a higher rate of cardiovascular adverse events than people who received other types of vaccines. However, all reported adverse events were mostly mild, and did not following by hospital admission.

Vaccine type and dose were also linked to different patterns of interference with work and daily life. There were fewer adverse reactions reported after the second dose of ChAdOx1 vaccination than after the first dose, and the effects on daily life and work were minor. Another form of COVID-19 vaccine linked to mild or moderate severity adverse effects reported following Moderna vaccination, with no influence or interference in work-life activities. Another study discovered that 79.7% of health workers who were immunized with the BNT162b2 mRNA vaccine were able to return to work [28-31].

Previous study backs up our findings that COVID-19 vaccination adverse responses are modest and have no effect on the recipient's everyday life. This finding is also supported by another study which described the efficacy of vaccines ranged from 60% to 90% which are always efficient against asymptomatic (SARS-CoV-2) infection, symptomatic COVID-19, COVID-19 hospitalization, severe or critical hospitalization, and death. 42 Deaths following COVID-19 vaccination, as reported in one study, have no connection to the vaccine, but rather to heart disease or COVID-19. The issue of excess death from COVID-19 immunization is a scientifically challenging matter that is influenced by the type of vaccines used, the age and health condition of the vaccinated population. It can be interpreted that host immunity and the type of vaccine are known to influence COVID-19 vaccine adverse responses.

Inconsistencies in adverse reactions may also be caused by symptoms connected with culture or languages. The majority of studies were conducted in developed countries where citizens have a greater understanding and awareness of vaccine adverse reactions therefore the adverse event reporting rate might be higher. Whereas the public may be perplexed by the disparities in results, which are dependent on the research design and subject studies. Therefore, as recommendation, it is critical to disseminate clear information to the public, about vaccine side effects, potential adverse reactions, and safety level of the vaccines provided. Multi-strategies at individual, organization and population level need to be employed to reduce vaccine hesitancy [32-36].

There are various limitations to this study. First, this analysis only gathered evidence from observational studies, which are prone to biases such as confounding, information, and selection bias. Observational studies, on the other hand, aid in finding adverse events or negative effects that demand a longer time of follow-up. Second, due to the limitations of the keywords and database, the findings may not have captured all of the evidence in the literature; however, this study did aid in mapping the available evidence in observational studies [6, 37].

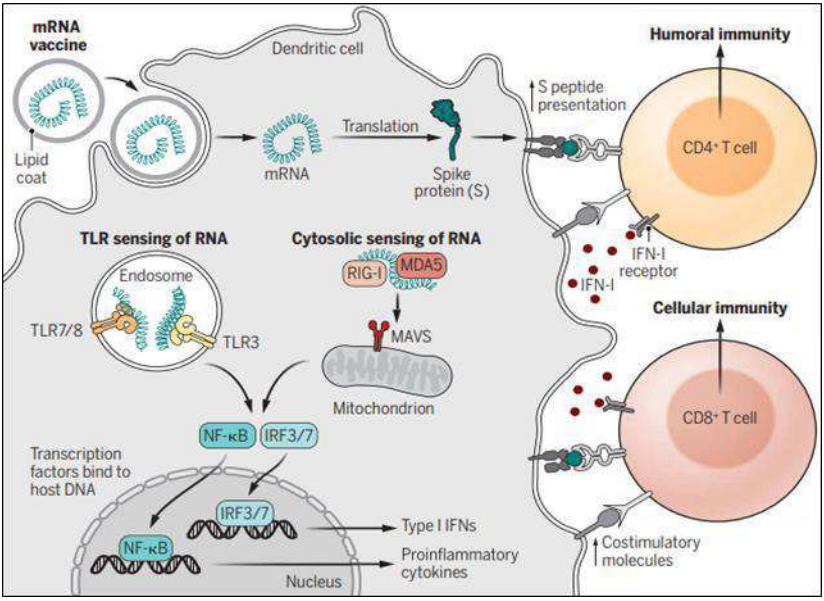


Fig 2: mRNA vaccine activation of DC and induction of IFN-I. After uptake, mRNA is translated into spike protein and presented as cell-surface MHC-bound peptides to CD4+ and CD8+ T cells. Cytosolic sensing of RNA by RIG-I and MDA5 plus TLR binding within endosomes leads to activation of IFN regulatory factor 3/7 (IRF3/7) and nuclear factor κB (NF-κB), which bind to DNA inducing gene transcription, and production of IFN-I and proinflammatory cytokines, respectively. MAVS, mitochondrial antiviral-signalling protein. Through up-regulation of DC costimulatory molecules, production of stimulatory cytokines, and a direct action on T cells, IFN-I guides and promotes the adaptive immune response of T and B cells.

Neurological complications following COVID-19 vaccination

According to reports published in the VAERS (Vaccine Adverse Event Reporting System) database, COVID-19 vaccines have several local and systemic neurological complications that occur in different people, from mild to severe, depending on age, sex, history of the disease, and pre-existing immunity. Complications usually appear within one day to 1 month after injection and are usually acute, transient, and self-limiting, but in severe cases lead to hospitalization and intensive care. On the other hand, women have the highest incidence of neurological complications because they induce a stronger immune response against foreign antigens, which can lead to the targeting of self-antigens and lead to autoimmune disorders. Adverse reactions after the second dose of the vaccine are reported more than in the first dose [37, 38].

Mild neurological effects of the COVID-19 vaccine include weakness, numbness, headache, dizziness, imbalance, fatigue, muscle spasms, joint pain, and restless leg syndrome are more common, while tremors, tinnitus, and herpes zoster are less common. On the other hand, severe neurological complications included Bell's palsy, Guillain-Barre syndrome (GBS), stroke, seizures, anaphylaxis, and demyelinating syndromes such as transverse myelitis and acute encephalomyelitis. Among these, the most dangerous neurological complication caused by COVID-19 vaccines, especially adenovirus based, is cerebral venous sinus thrombosis in women of childbearing age [39].

According to the WHO, in the case of side effects of inactivated virus-based vaccines, especially Sinopharm, the most common local and systemic adverse reactions are injection site reactions, fatigue, fever, headache, and allergic dermatitis, which are self-limiting, and the person does not need to be hospitalized. It is noteworthy that rare and scattered reports have been published on the side effects of Sinopharm and other inactivated virus-based vaccines (Table 1). Vaccine reactivity has been linked to a temporary increase in inflammatory cytokines that act on blood vessels, muscles, and other tissues. In other words, we will observe the fu-like syndrome for several consecutive days after vaccination. According to a recent report on the Sputnik vaccine, side effects are included headache, joint pain, fever, and fu-like symptoms. According to published information on the side effects of other adenovirus vaccines, it is essential to properly evaluate the efficacy of the Sputnik vaccine and publish relevant data to decide on its side effects. COVID-19 vaccination can sometimes have severe side effects on nervous system, including the brain, spinal cord, cranial nerves, and peripheral nerves, and has been shown to have adverse vascular, metabolic, inflammatory, and functional effects on the brain [40-45].

Acute neurological disorders

These disorders include, transverse myelitis, acute diffuse encephalomyelitis (ADEM), Bell's palsy, GBS, encephalopathy and seizures. Each type of vaccine can play a different role in increasing the risk of manifestation of these disorders (Tables 2, 3). The COVID-19 vaccine-related convulsions can be attributed to the synthesis and release of spike proteins, which cause severe inflammation and hyperthermia. Hyperthermia, in turn, increases glial cell activity and increases blood-brain barrier permeability. Following these events, as expected, peripheral blood cells and albumin enter the brain and disrupt the osmotic balance. In connection with brain disorders, the possible mechanism is the entry of inflammatory mediators secreted by

peripheral blood cells into the brain and the destruction of myelin and axonal degeneration. The presence of SARS-CoV-2 spike domain S1 antibodies in CSF (Cerebrospinal Fluid Analysis) may explain neurological complications after vaccination, such as encephalopathy and seizures [46-49].

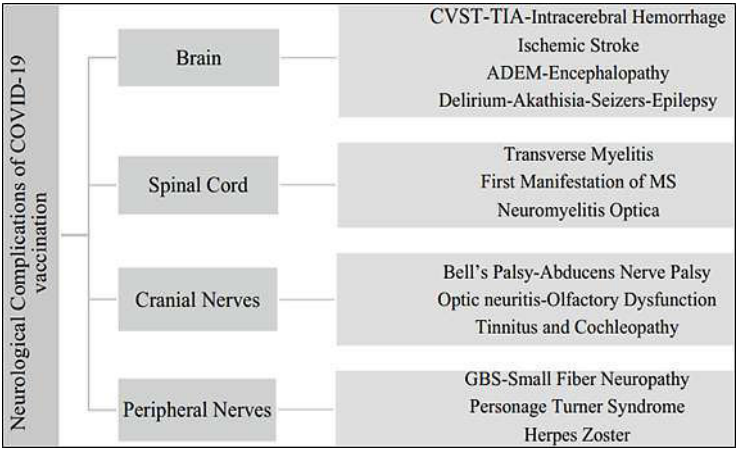


Fig 3: Classification of neurological complications observed after COVID-19 vaccination

Table 1: Reported neurological complications for inactivated virus-based vaccines

Vaccine name	Complications
Inactivated virus Sinovac	Headache
	Transverse myelitis
	Bell's palsy
	Acute disseminated encephalomyelitis
	Neuromyelitis optica
Sinopharm	Multiple sclerosis relapse
	Neuromyelitis optica
Covaxin	Bell's palsy

COVID-19 vaccination also affects the cranial and peripheral nerves and causes side effects such as Bell's palsy (facial nerve palsy-7 cranial nerve), abducens nerve palsy (lateral rectus ocular muscle nerve palsy-6 cranial nerve), impaired vision, olfactory, hearing, Guillain-Barre syndrome (GBS), small fiber neuropathy, Parsonage-Turner syndrome, and also herpes zoster. In this case, too, the known mechanism is the induction of autoimmunity by molecular mimicry. Bell's palsy and small fiber neuropathy are more commonly observed in mRNA-based vaccines. GBS is also a peripheral nerves and nerve roots injury that presents with severe motor weakness and

paralysis of the legs or four limbs and is more common in the elderly after vaccination with adenovirus-based vaccines. Tere have been many reports of the Pfizer vaccine being associated with olfactory, visual, auditory, and sometimes abducens nerve palsy. Olfactory dysfunction ranges from a lack of sense of smell to an olfactory hallucination (phantosmia) that results from a bilateral disturbance or enhancement of the olfactory pathway and the olfactory bulb. Hearing disorders can vary from hearing loss to tinnitus and dizziness. Also, there is ample evidence that the Pfizer and AstraZeneca vaccines are associated with optic nerve inflammation and vision disorders and are more common in middle-aged people [8, 50-53].

Table 2: Reported neurological complications for mRNA-based vaccines

Vaccine name	Complications
mRNA-based vaccine Pfizer	Headache
	Transverse myelitis
	Bell's palsy
	Acute disseminated encephalomyelitis
	Neuromyelitis optica
	First manifestation of multiple sclerosis
	Small fiber neuropathy
	Encephalopathy
	Transient ischemic attack
	Ischemic stroke
	Intracerebral hemorrhage
	Delirium
	Akathisia
	Herpes zoster
	Seizers
	Parsonage–Turner syndrome
	abducens nerve palsy
	Tinnitus and cochleopathy
	Olfactory dysfunction and phantosmia
Moderna	Transverse myelitis
	First manifestation of multiple sclerosis
	Bell's palsy
	Encephalopathy
	Small fiber neuropathy
	Herpes zoster
	Epilepsy

	Intracerebral hemorrhage

Table 3: Reported neurological complications for adenovirus-based vaccines

Vaccine name	Complications
Adenovirus-based vaccine AstraZeneca	Headache
	Transverse myelitis
	Bell's palsy
	Acute disseminated encephalomyelitis
	Cerebral venous sinus thrombosis
	Intracerebral hemorrhage
	Ischemic stroke
	Encephalopathy
	Parsonage–Turner syndrome
	Herpes zoster
	Tinnitus and cochleopathy
	Seizers
Johnson & Johnson	Cerebral venous sinus thrombosis
	Transverse myelitis
	Transient ischemic attack
Sputnik	Headache
	Multiple sclerosis

Herpes zoster is a disease that occurs as a result of the reactivation of the varicella-zoster virus (VZV) after receiving the COVID-19 vaccine. The process that causes the disorder is probably explained by the fact that the varicella-zoster virus CD8+killer cells, after vaccination, are temporarily unable to control VZV due to the extensive change of simple CD8+cells to the COVID-19 virus CD8+killer cells. Therefore, vaccination is like a shock to the recurrence of VZV and subsequent herpes zoster. mRNA-based vaccines can increase the risk of herpes zoster. There was a recent report of Ramsey Hunt Syndrome (RHS after the Pfizer vaccination. RHS leads to facial nerve palsy, vestibulocochlear neuropathy, and glossopharyngeal nerve neuropathy, so it causes numbness of the face, tongue, and hearing loss. In addition, skin blisters have been observed in the ear area, leading us to hypothesize that reactivation of VZV could be a cause for RHS as well as Bell's palsy [54-56].

Specific adverse events

Thrombosis

Recently, several reports of thrombocytopenia with thrombosis, most notably cerebral venous sinus thrombosis or cerebral venous thrombosis

(CVT) within 28 days of vaccination, have been associated with Ad26.COV2.S (Janssen) and AZD1222 (AstraZeneca), both of which use the adenovirus-vector platform. Reports of thrombosis could have implications for vaccine uptake all over the world. Consequently, many nations have altered their vaccination guidelines. AZD1222 was made available only to adults older than 40 years in the UK, older than 55 years in Canada, and older than 60 years in Germany. As a result of 6 reports of CVT, the FDA and CDC recommended a pause in the administration of Ad26.COV2.S vaccine in the US on April 13, 2021 [57-59].

Guillain-Barre syndrome (GBS)

In developed countries, Guillain-Barre syndrome (GBS) is one of the leading causes of acute flaccid paralysis, characterized by autonomic dysfunction, sensory abnormalities, and varying degrees of weakness. Although the specific pathophysiology is not known, this disorder is believed to result from an autoimmune response. mRNA from the approved mRNA vaccines gains access into the human cell and directs it to synthesize a copy of the spike protein found on the virus's surface and produce antibodies against it. These antibodies become primed to inactivate the virus before it can cause the disease. Sometimes, however, a patient's immune response can trigger the synthesis of antibodies against myelin, causing GBS [60, 61].

Acute transverse myelitis

Acute transverse myelitis is an uncommon neurologic condition affecting people aged 35 to 40 years at an incidence of 1.34 to 4.6 cases/million adults per year. Of the reported adverse events after immunization recorded in the VAERS, 341 were neurologic events, 122 of which were cases of transverse myelitis. Interleukin (IL)-17 and IL-6 appear to be involved in the pathogenesis of transverse myelitis. In myelitis, cerebrospinal fluid analysis findings show increased IL-6 levels. By regulating cytokines, IL-17 stimulates astrocytes to produce IL-6, which forms nitric oxide metabolites and causes CNS damage [62, 63].

Myocarditis and Pericarditis

Myocarditis is an inflammation of the myocardial tissue without signs of ischemia and has various causes and diverse patterns. In a study involving 7 patients with myocarditis between February 1 and April 30, 2021, 4 were diagnosed within 5 days after receiving COVID-19 vaccination. These 4 patients, who had received the second dose of an mRNA vaccine, reported chest pain and had increased biomarker levels suggestive of myocardial tissue injury. Cardiac magnetic resonance imaging results showed characteristics of myocarditis [64].

Cutaneous reactions

In a study from December 2020 to February 2021, 414 cutaneous symptoms were noted after administration of an mRNA vaccine. Injection-site reactions, with delayed local reactions and urticarial and morbilliform eruptions, were the most commonly observed findings. Among recipients with first-dose reactions, 43% also had recurrences after their second dose. Other reactions less commonly reported were pernio/chilblain, pityriasis rosea-like reactions, zoster, cosmetic filler reactions, and herpes simplex exacerbations. Some dermatologic symptoms, like pernio/chilblain, imitated COVID-19 symptoms. None of the patients reported serious adverse effects after receiving either of the doses. As a result, researchers concluded that COVID-19 vaccination generally causes only mild and self-limiting reactions, and people should not be discouraged from the vaccination because of them [65].

Glomerular disease

Since mass-vaccination campaigns began in January 2021, the incidence of vaccine-associated glomerular disease has increased. Symptoms of recurrent glomerular diseases or new glomerular diseases have appeared, especially after administration of the mRNA vaccines. The pathogenesis behind vaccine-associated glomerular disorders is not clearly understood. However, an immunogenic response to vaccines has been noted as a possible cause. Minimal change disease, anti-glomerular basement membrane disease, membranous glomerular disease, and immunoglobulin A nephropathy are some of the glomerular lesions observed after vaccination. Some case reports have described patients with gross hematuria after vaccination who were later found to have immunoglobulin A nephropathy. The majority of vaccine-related cases were typically seen within 1 to 3 weeks after vaccination. Management of the glomerular disease must be on a case-by-case basis depending on the severity and remission status, because the benefits of vaccination outweigh the rare risk of glomerular disease [9, 66].

Conclusion

COVID-19 is a global health concern that has spread worldwide and has dramatically changed global sociopolitical, economic, and cultural aspects of humanity. COVID-19 vaccines became more and more critical due to the limited prevention and treatment options available. To end the pandemic crisis, the development of affordable, effective, safe and transportable vaccines has become necessary.

Due to the short development time and the novelty of the technologies adopted, these vaccines will be deployed with several unresolved issues that

only the passage of time will permit to clarify. Technical problems connected with the production of billions of doses and ethical ones connected with the availably of these vaccines also in the poorest countries, are imminent challenges facing us. It is our tenet that in the long run more than one vaccine will be needed to ensure equitable global access, protection of diverse subjects and immunity against viral variants.

Vaccinations positively impact all aspects of life including an individual's economic stability and health. Vaccination enhances both physical and mental well-being; in terms of the COVID-19 vaccine, it helps to reduce the rate of transmission and the risk of severe disease and death. Thus, in-person schooling, job, and more active socialisation and travel opportunities decrease psycho-social issues, especially among the vulnerable groups. Several clinical, psychological, and sociological studies have illustrated that there is a significant relationship between individual attitudes towards COVID-19 vaccine and the successful fulfilment of the vaccination strategy.

The medical treatments used during the illness can be costly and can have a negative social and financial effect on both an individual patient and society, especially in the countries with low-income economies, poor national health services, and high number of COVID-19 cases. Adopting a broad societal perspective as a vaccination programme strategy is crucial for not only enhancing individual and societal economic well-being, but also for positive intergenerational effects (e.g., preventing death among (grand)parents, social inclusion and better lifelong opportunities.

This study confirmed prior findings that the COVID-19 immunization caused mostly mild or non-severe side effects. This review discovered some adverse reactions to COVID-19 vaccinations with most prevalent adverse reactions to all COVID-19 vaccinations are local and systemic side effects. Other previously cited side events included allergic responses and cardiovascular problems. The type of vaccine and dose were linked to the various adverse reaction patterns. Individual daily activities are not severely influenced or interfered with. Deaths following COVID-19 vaccination have nothing to do with the vaccine, but rather with heart disease or COVID-19. It is critical to give the public with accurate information on vaccine side effects, probable adverse reactions, and the safety level of the vaccines provided. To reduce vaccine hesitancy, multiple measures must be implemented at the individual, organizational, and population levels. Future research could look into the impact of the vaccine on patients of various ages and medical conditions.

References

1. Public Health England COVID-19 vaccination programme, 2020.
2. Department of Health and Social Care Priority groups for coronavirus (COVID-19) vaccination: advice from the JCVI, 2020.
3. Polack FP, Thomas SJ, Kitchin N. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603-2615.
4. Voysey M, Clemens SAC, Madhi SA. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.
5. Ramasamy MN, Minassian AM, Ewer KJ. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2021;396(10267):1979-1993.
6. Varsavsky T, Graham MS, Canas LS. Detecting COVID-19 infection hotspots in England using large-scale self-reported data from a mobile application: a prospective, observational study. Lancet Public Health. 2021;6:e21-e29.
7. Wise J. COVID-19: people who have had infection might only need one dose of mRNA vaccine. BMJ. 2021; 372:n308.
8. Manisty C, Otter AD, Treibel TA. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. Lancet. 2021;397(10279):1057-1058.
9. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R *et al*. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-416.
10. Sadoff J, Gray G, Vandebosch An, Cardenas V, Shukarev G, Grinsztejn B *et al*. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-2201.
11. Mansanguan S, Charunwatthana P, Piyaphanee W, Dechkhajorn W, Poolcharoen A, Mansanguan C *et al*. Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents. Trop. Med. Infect. Dis. 2022;7(8):196.
12. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al*. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-1032.

13. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med. 2007;356(24):2457-2471.

14. Greenland S. Invited Commentary: Dealing with the Inevitable Deficiencies of Bias Analysis-and All Analyses. Am J Epidemiol. 2021;190(8):1617-1621.

15. Sun J, He WT, Wang L *et al*. COVID-19: epidemiology, evolution, and cross-disciplinary perspectives. Trends Mol Med. 2020; 26(5):483-495.

16. Baden LR, El Sahly HM, Essink B, *et al*. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403-416.

17. Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-2615.

18. Medeiros KS, Costa APF, Sarmento ACA *et al*. Side effects of COVID-19 vaccines: a systematic review and meta-analysis protocol of randomised trials. BMJ Open. 2022;12:e050-278.

19. Wang J, Kaperak C, Sato T, Sakuraba A. COVID-19 reinfection: a rapid systematic review of case reports and case series. J Invest Med. 2021;69(6):1253-1255.

20. Shen M, Xiao Y, Zhuang G, Li Y, Zhang L. Mass testing-An underexplored strategy for COVID-19 control. Innovation. 2021;2(2):100114.

21. Warren GW, Lofstedt R. COVID-19 vaccine rollout risk communication strategies in Europe: a rapid response. J Risk Res. 2021;24(3-4):369-379.

22. Liu Y, Ye Q. Safety and Efficacy of the Common Vaccines against COVID-19. Vaccines. 2022;10(4):513.

23. Liu JY, Chen TJ, Hou MC. Does COVID-19 vaccination cause excess deaths? J Chin Med Assoc. 2021;84(9):811-812.

24. Jeong S, Hong S, Oh T *et al*. Analysis of older adults visiting the emergency department with fever as a suspected Covid-19 vaccine-related adverse reaction: a retrospective multicenter study. J Infect Chemother. 2022;28(8):1159-1164.

25. Paltiel AD, Schwartz JL, Zheng A, Walensky RP. Clinical outcomes of a COVID-19 vaccine: implementation over efficacy. Health Aff. 2021;40(1):42-52.

26. Al Khames Aga QA, Alkhaffaf WH, Hatem TH. Safety of COVID-19 vaccines. J Med Virol. 2021;93(12):6588-6594.

27. Menni C, Klaser K, May A, *et al*. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis. 2021;21(7):939-949.

28. Sadoff J, Gray G, Vandebosch A, *et al*. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-2201.

29. Beatty AL, Peyser ND, Butcher XE *et al*. Analysis of COVID-19 vaccine type and adverse effects following vaccination. JAMA Netw Open. 2021;4(12):e214-0364.

30. Spencer JP, Trondsen Pawlowski RH, Thomas S. Vaccine adverse events: separating myth from reality. Am Fam Physician. 2017;95(12):786-794.

31. Abu-Halaweh S, Alqassieh R, Suleiman A *et al*. Qualitative assessment of early adverse effects of Pfizer-biontech and sinopharm covid-19 vaccines by telephone interviews. Vaccines. 2021;9(9):950.

32. Rabail R, Ahmed W, Ilyas M *et al*. The side effects and adverse clinical cases reported after COVID-19 Immunization. Vaccines. 2022;10(4):1-25.

33. Kimmel SR. Vaccine adverse events: separating myth from reality. Am Fam Physician. 2002;66(11):2113-20.

34. Shinde V, Bhikha S, Hoosain Z *et al*. 2019nCoV-501 Study Group. Efficacy of NVX-CoV2373 covid-19 vaccine against the B.1.351 variant. N Engl J Med. 2021;384(20):1899-1909.

35. Cohen J. Vaccine designers take first shots at COVID-19. Science. 2020;368(6486):14.

36. Knoll MD, Wonodi C. Oxford-AstraZeneca COVID-19 vaccine efficacy. Lancet. 2021;397(10269):72-74.

37. Tran VN, Nguyen HA, Le TTA, Truong TT, Nguyen PT, Nguyen TTH *et al*. Factors influencing adverse events following immunization with AZD1222 in Vietnamese adults during first half of 2021. Vaccine. 2021;39(44):6485-6491.

38. Park MJ, Choi YJ, Sangchun Choi S. Emergency Department Utilization by In-hospital Healthcare Workers after COVID-19 Vaccination. J Korean Med Sci. 2021;36(27):e196.

39. Doroftei B, Ciobica A, Ilie O-D, Maftei R, Mini-Review IC. Discussing the reliability and efficiency of COVID-19 vaccines. Diagnostics (Basel). 2021;11(4):579.

40. Adorni F, Prinelli F, Bianchi F, Giacomelli A, Pagani G, Bernacchia D *et al*. Self-reported symptoms of SARS-CoV-2 infection in a nonhospitalized population in Italy: cross-sectional study of the EPICOVID19 web-based survey. JMIR Public Heal Surv. 2020;6(3):e21-866.

41. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij Rammerstorfer S *et al*. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396(10249):467-478.

42. Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH, *et al*. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020;396(10249):479-488.

43. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN *et al*. An mRNA vaccine against SARS-CoV-2-preliminary report. New Engl J Med. 2020;383(20):1920-1931.

44. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, *et al*. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. New Engl J Med. 2020;383(24):2320-2332.

45. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatulin AI, Shcheblyakov DV, Dzharullaeva AS, *et al*. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet. 2020;396(10255):887-897.

46. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al*. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-593.

47. Finsterer J. Neurological side effects of SARS-CoV-2 vaccinations. Acta Neurol Scand. 2022;145(1):5-9.

48. Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, *et al*. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. JAMA. 2020;324(10):951-960.

49. Ghiasi N, Valizadeh R, Arabsorkhi M, Hoseyni TS, Esfandiari K, Sadighpour T, *et al*. Efficacy and side effects of Sputnik V, Sinopharm and AstraZeneca vaccines to stop COVID-19; a review and discussion. Immunopathologia Persa. 2021;7(2):31.

50. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, *et al*. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21(1):39-51.

51. Cao L, Ren L. Acute disseminated encephalomyelitis after severe acute respiratory syndrome coronavirus 2 vaccination: a case report. Acta Neurol Belg. 2021;122(3):793-795.

52. Khan E, Shrestha AK, Colantonio MA, Liberio RN, Sriwastava S. Acute transverse myelitis following SARS-CoV-2 vaccination: a case report and review of literature. J Neurol. 2021;269(3):1121-1132.

53. Athyros VG, Doumas M. A possible case of hypertensive crisis with intracranial haemorrhage after an mRNA anti-COVID-19 vaccine. Angiology. 2022;73(1):87.

54. Finsterer J, Redzic Z. Symptomatic peduncular, cavernous bleeding following SARS-CoV-2 vaccination induced immune thrombocytopenia. Brain Hemorrhages. 2021;2(4):169-171.

55. Ieppala Sripriya, A Vishal Reddy, Nellutla Shalini, Narender Boggula. Novel Coronavirus Disease (Covid-19): A Literature Based Review. Research and Advances in Pharmacy and Life Sciences. 2020;2(2):9-20.

56. Reyes-Capo DP, Stevens SM, Cavuoto KM. Acute abducens nerve palsy following COVID-19 vaccination. J Am Assoc Pediatr Ophthalmol Strabismus. 2021;25(5):302-303.

57. Sairam Pasam, Vasudha Bakshi, Narender Boggula. Therapeutic Management for Covid-19: A Pandemic Disease-An Evidence Based Design. International Journal of Pharmaceutical Science & Innovation. 2022;2(2):35-50.

58. Montgomery J, Ryan M, Engler R, *et al*. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol. 2021;6(10):1202-1206.

59. McMahon DE, Amerson E, Rosenbach M, *et al*. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. J Am Acad Dermatol. 2021;85(1):46-55.

60. Bomback AS, Kudose S, D'Agati VD. De novo and relapsing glomerular diseases after COVID-19 vaccination: what do we know so far? Am J Kidney Dis. 2021;78(4):477-480.

61. Gutierrez S, Dotto B, Petiti JP, *et al*. Minimal change disease following influenza vaccination and acute renal failure: just a coincidence? Nefrologia. 2012;32(3):414-415.

62. Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A, *et al*. Myocarditis and pericarditis after vaccination for COVID-19. JAMA. 2021;326(12):1210-1212.

63. Kim HW, Jenista ER, Wendell DC *et al*. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol. 2021;6(10):1196-1201.

64. Sun J, He WT, Wang L, *et al*. COVID-19: epidemiology, evolution and cross-disciplinary perspectives. Trends Mol Med. 2020;26(5):483-495.

65. Provenzani A, Polidori P. Covid-19 and drug therapy, what we learned. Int. J Clin. Pharm. 2020;42(3):833-836.

66. Roya Hosseini, Nayere Askari. A review of neurological side effects of COVID-19 vaccination. European Journal of Medical Research. 2023;28:102.

Chapter - 11
Gaseous Biofuels for Sustainable Energy

Authors

P. Vijayakumary
Department of Renewable Energy Engineering, AEC&RI, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India

R. Divyabharathi
Department of Renewable Energy Engineering, AEC&RI, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India

Chapter - 11

Gaseous Biofuels for Sustainable Energy

P. Vijayakumary and R. Divyabharathi

Abstract

Biomass provides 32% of all the primary energy use in the country at present. The current availability of biomass in India is estimated at about 750 million metric tonnes per year and, out of which 230 million tons are surplus (MNRE). The potential of lignocellulosic biomass has shown to provide the alternative energy resources or platform to fossil fuel energy. An advantage of biomass over conventional fuel relies on its extensive availability in nature and the renewable nature. Biomass not only support in economic development but also creates an eco-friendly environment in sustainable way producing of biofuels. Wide range of biofuels can be produced from biomass through the thermochemical or biochemical methods. This chapter focuses on generation of gaseous biofuels like biogas, producer gas and biohydrogen from biomass. These biofuels could find their application for thermal, mechanical and electrical energy generation. Anaerobic digestion is the opted technology for biogas generation from wet biomass. Gasification technology can be utilized for energy conversion of low moisture herbaceous and woody biomass to producer gas. Hydrogen can be synthesized from producer gas by employing suitable technologies.

Keywords: Gasification, producer gas, biogas, biohydrogen, renewable

Introduction

Biomass can be categorized broadly as woody, non-woody biomass and animal wastes. Woody biomass comprises of forests, agro-industrial plantations, bush trees, urban trees and farm trees. Wood, bark, branches and leaves constitute the above ground woody biomass. Woody biomass is generally a high valued commodity and has diverse use such as timber, raw material for pulp and paper, pencil and matchstick industries and cooking fuel. Non-woody biomass comprises of crop residues like straw, leaves and plant stems, processing residues like saw dust, bagasse, nutshells and husks, and domestic wastes such as food, rubbish, and organic fraction of municipal

solid wastes. Animal wastes constitute the wastes from the animal husbandry. Biomass utilization can reduce deforestation and help to provide a secure, competitive energy source.

Biomass characteristics

The ease and efficiency with which biomaterials can be converted to energy are largely determined by their physicochemical properties. There is no standardized method for the characterization of biomaterial with respect to its potential for conversion to energy for fuels. In the case of thermo-chemical conversion processes, proximate analysis, ultimate analysis and heating value are important parameters. In the case of biochemical conversion processes, moisture content, the amount and chemical form of the carbohydrate constituents of the biomaterials are important parameters.

Anaerobic digestion

Anaerobic digestion is a type of biochemical conversion involving the microbial digestion of biomass in the absence of air. An anaerobe is a microscopic organism that can live and grow without external oxygen or air. It extracts oxygen by decomposing the biomass at low temperatures up to 65 °C, in presence of moisture (80%). It produces biogas which is a mixture of methane 55-65% and CO_2 35-45% and some impurities such as hydrogen sulphide in traces. The gas can be burned directly or upgraded to superior fuel gas (methane) by removing the CO_2 and impurities.

The residue of the anaerobic digestion may consist of protein-rich sludge and liquid effluents. These can be used as animal feed or for soil treatment after certain processing. In general, one kg of dry organic material will produce 0.036 m^3 of methane (at standard temperature and pressure) or 36 m^3 biogas/1000 kg biomass. The sizes of anaerobic digestion plants vary from 2 m^3 to 2000 m^3.

Science of biogas production

It is a three-stage process in which three groups of bacteria are involved.

a) Hydrolytic and acidogenic bacteria.

b) Acetogenic bacteria.

c) Methanogenic bacteria.

Hydrolysis

Starch and Glycogen are hydrolysed to disaccharides by the action of amylases. Subsequently the disaccharides are cleaved to monosaccharides by a glycosidase. Cellulose is hydrolysed to cellobiose and subsequently to

glucose by cellulase and cellobiase which include both exo and endo glucanases. Lipases and esterase's hydrolyse fats and lipids. Proteases catalyse the cleavage of peptide bonds of proteins.

Acidogenesis and acetogenesis

a) Degradation of monosaccharides

A typical metabolic pathway for the degradation of monosaccharides is the Embden-Mayerhof-Pamas (EMP) pathway or Glycolysis. The end product of Glycolysis in Yeast is ethanol and in bacteria is acetic acid.

b) Degradation of fatty acids

It is generally agreed that the anaerobic degradation of long chain fatty acids and acetic acid can then either be liberated or the acetate can be transferred to other functional compounds.

c) Decomposition of amino acids

In nature and in anaerobic biological processes, proteolytic species of *Clostridium* are largely responsible for the anaerobic decomposition of amino acids. From a molecule of glutamic acid a molecule of pyruvic acid and a molecule of acetic acid are formed.

In these two steps, both anaerobic and facultative anaerobic bacteria are involved. The genera, associated with the hydrolysis and acid production, are *Clostridium, Aerobacter, Bacillus, Escherichia, Micrococcus, Paracholobacterium, Proteus, Pseudomonas, Sarcina* and *Streptomyces.*

Methanogenisis

The low molecular weight acids produced in the acid production stage are further degraded to methane and carbon dioxide by the highly specialised group of bacteria referred to as methane producing bacteria or methanogens.

$$CH_3COOH \longrightarrow CH_4 + CO_2$$

$$CO_2 + 4H_2 \longrightarrow CH_4 + H_2O$$

About two third of methane is derived from acetate conversion and the one third as a result of CO_2 reduction.

Types of biogas plants

Floating gas holder digester (KVIC): The floating gas holder digester which is used in India is known as Khadi Village Industries Commission (KVIC) plant. This type was developed in India and is usually made of masonry. It runs on a continuous basis and uses mainly cattle dung as input

material. The gasholder is usually made of steel, although new materials such as ferro cement and bamboo-cement have already been introduced. The original version of this floating gasholder digester was a vertical cylinder provided with partition wall except for the small sizes of 2 and 3 m^3 of gas per day. The main characteristic of this type is the need for steel sheets and welding skill.

Fixed dome digester: In fixed dome digester, the gas holder and the digester are combined. This digester, which was developed and is widely used in China, runs on a continuous batch basis. Accordingly, it could digest plant waste as well as human and animal wastes. It is usually built below ground level; hence it is easier to insulate in a cold climate. The digester can be built from several materials, e.g. bricks, concrete, lime concrete and lime clay. This facilitates the introduction and use of local materials and manpower. The variable pressure inside the digester was found to cause no problems in China in the use of the gas.

Modified fixed dome digesters: In the Chinese fixed dome digester, a manhole is provided on the top of the plant. By modifying this design, two designs of Janata and Deenbandhu fixed dome digesters have been developed. In the Janata fixed dome digester, the bottom is flat concrete, the digester is cylindrical wall and the dome is a segment of sphere with the brick masonry. In the Deenbandhu fixed dome biogas digester, the lower part of concrete is segment of sphere and the upper part of brick masonry is hemisphere.

Factors affecting biogas production

1. pH or Hydrogen ion concentration: Microorganisms will be very active and biodigestion will be very efficient in the pH range of 6.5 to 7.5
2. Temperature: Methane bacteria work best at a temperature between 35- 38 °C. The fall in gas production starts at 20°C and stops at a temperature of 10 °C. The optimum mesophilic temperature lies at about 35 °C, while the optimum thermophilic temperature is around 55 °C.
3. Total solid content of the feed material: Total solid content of 8 – 10% helps in biodigesting the material at a faster rate. Raw cow dung contains 80-82% of moisture and the balance 18-20% is termed as total soilds. Cow ding is mixed usually in the proportion of 1:1 in order to bring the TS to 8-10%
4. Loading rate: Amount of raw material fed to the digester per day

per unit volume. Most municipal sewage treatment plants operate at aloading rate of 0.5-1.6 kg of volatile solids per m^3 per day.

5. Seeding: Digested sludge rich in methane formers is added as seeding to increase the number of methane formers
6. Uniform feeding
7. Diameter to depth ratio of digester: Gas production per unit volume of didigester capacity was maximum when the diameter to depth ratio was 0.66 to 1.00
8. Carbon to Nitrogen ratio: The optimum C/N ratio that best suits for maximum microbiological activity is 30:1 because during the process of biomethanation anaerobes use carbon 25 to 30 times more than that of nitrogen
9. Nutrients: The major nutrients required by the bacteria in the digester are C, H_2, O_2, N_2, P and S. To maintain proper balance of N_2 and P, chopped leguminous plants and night soil should be added
10. Mixing or stirring: mixing improves biomethanation
11. Retention time: Period of retention of material for biogas generation, inside the digester. This period will depend on type of feedstocks and the temperature. Normal value of retention period is between 30 and 45 days and in some cases 60 days
12. Types of feedstock: When feedstock is woody or contains lignin, then biodigestion becomes difficult
13. Toxicity due end product: The digested slurry, if allowed to remain in the digester beyond a certain time, becomes toxic to the microorganism and might cause fall in the fermentation rate
14. Pressure: Biogas production will be better at low pressure
15. Acid accumulation inside the digester: Neem cake is added to convert intermediate products like acetic, propionic and butyric acids to methane to avoid acid accumulation

Gasification

Gasification is the thermo-chemical transformation of biomass into a combustible gaseous product in a controlled amount of oxidant supply. The reactions are carried out at elevated temperatures of 500-1300 °C and atmospheric or elevated pressures up to 33 bar. As the biomass flows through the gasifier, it gets dried, pyrolysed, oxidized and reduced. Carbon and hydrogen of biomass reacts with oxygen and yield carbon dioxide and

steam respectively and are then reduced to carbon monoxide and hydrogen in the reduction zone of the gasifier. The product gas is termed as producer gas, clean, odourless and colourless and has a calorific value of 950 -1200 kcal/m^3.

Chemistry of gasification

In conventional producer gas theory, the reactions take place in four zones of a deep fuel bed, namely the oxidation, reduction and pyrolysis and drying zones. In the pyrolysis zone, biomass is converted to char, tar and oils and gas. In the oxidation zone, oxygen in the air-steam blast reacts with the carbon. In the reduction zone, CO_2 from the oxidation zone reacts with carbon to produce CO, one of the major components of producer gas.

$C + O_2 \rightarrow CO_2 + 393800$ kJ/kg mol (Combustion reaction)

$C + H_2O \rightarrow CO + H_2 - 131400$ kJ/kg mol (Water gas reaction)

$CO + H_2O \rightarrow CO_2 + H_2 + 41200$ kJ/kg mol (Water shift reaction)

$C + CO_2 \rightarrow 2CO - 172600$ kJ/kg mol (Boudouard reaction)

$C + 2H_2 \rightarrow CH_4 + 75000$ kJ/kg mol (Methane reaction)

Gasifiers

Gasifier is an equipment which can gasify a variety of biomass such as wood waste, agricultural waste etc. It is essentially a chemical reactor where the biomass gets dried, heated, pyrolysed, partially oxidized and reduced as it flows through it. The commonly used gasifiers for biomass gasification are as below.

Up draft gasifiers: In up draft gasifiers, air enters below the combustion zone and the producer gas leaves near the top of the gasifier. The gas produced has practically no ash but contains tar and water vapour because of passing of gas through the unburnt fuel. These gasifiers are suitable for tar free fuels like charcoal, especially in stationary engines.

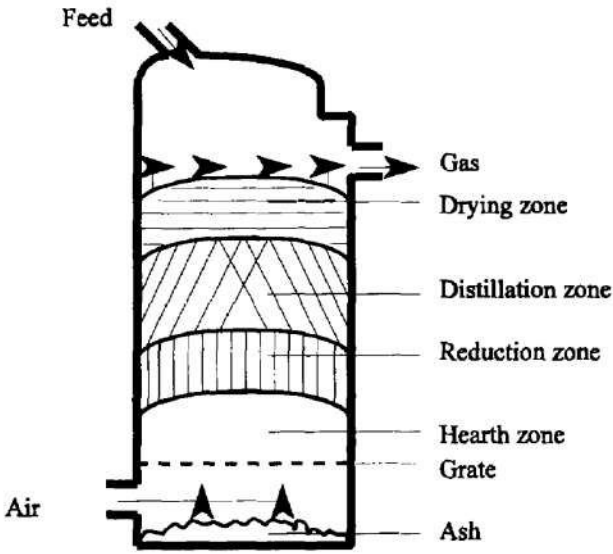


Fig 1: Up draft gasifier

Down draft gasifiers: In down draft gasifiers, air enters at the combustion zone and the gas produced leaves near the bottom of the gasifier. The gas produced has less tar and more ash. These gasifiers are suitable for fuels like wood and agricultural wastes. They may be used for power generation upto 150 kW.

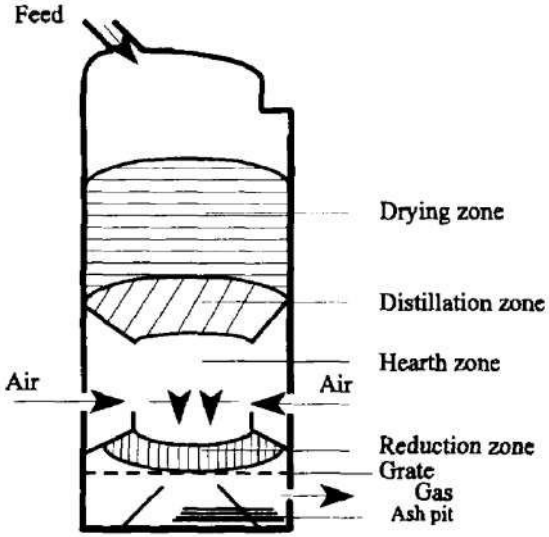


Fig 2: Down draft gasifier

Cross draft gasifiers: In cross draft gasifiers, the gas produced passes upwards in the annular space around the gasifier that is filled with charcoal. The charcoal acts as an insulator and a dust filter. They are usually suitable for power generation upto 50 kW.

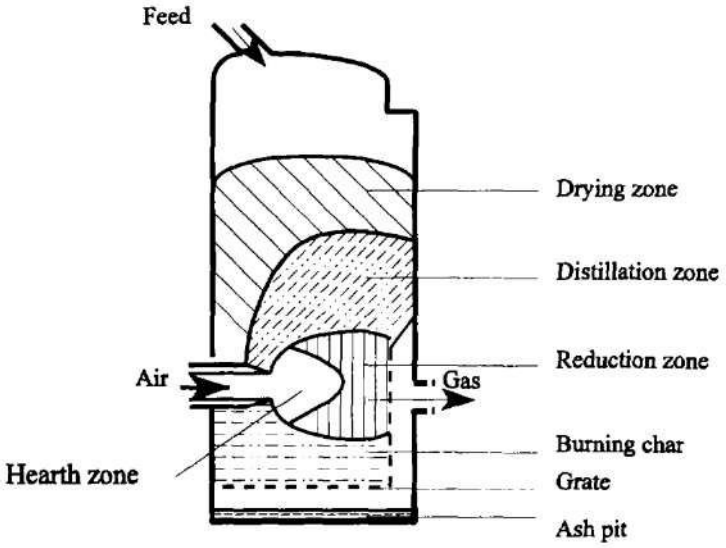


Fig 3: Cross draft gasifier

Fluidized bed gasifiers: Fluidized bed generally contains either inert material (sand) or reactive material (limestone or catalyst). These aid heat transfer and provide catalytic or gas clearing action. The bed material is kept in fluid state by the rising column of the gas. Normally the operating temperature of the bed is maintained within the range of 750-950 °C, so that the ash zones do not get heated to its initial deformation temperature and this prevents clinkering or slagging.

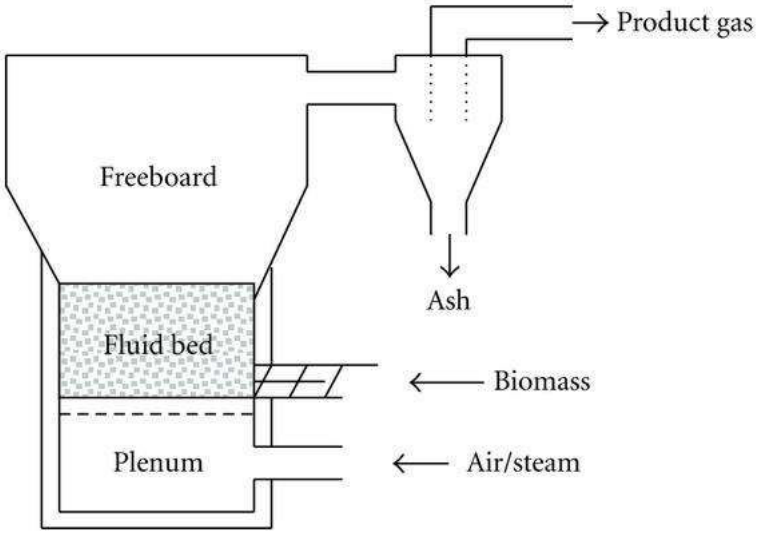


Fig 4: Fluidized bed gasifier

Recent gasification technologies

Plasma gasification: An important evolution in gasification technology, plasma gasification which uses plasma torches, provides very high temperature which aids in thermal degradation of any organic matter into its constituent elements and inorganic portion as vitrified slag. The main advantage of plasma gasification over conventional gasification was increased rate of reaction due to high temperature ionized gas and is a successful technology for thermal conversion of municipal solid waste to useful gases.

Hydrothermal gasification: In this technology, biomass is treated with hot compressed water above 350 °C and 20 MPa pressure to get a combustible gas. As the reactivity of water is high at these conditions, this method enables quick and complete gasification of biomass. In hydrothermal gasification, almost complete gasification is possible when reaction condition is properly adjusted. This technology is suitable for wet biomass, which could not be subjected to thermochemical gasification.

Applications of producer gas

Producer gas can be used for combustion and production of liquid fuel. After careful cleaning and conditioning, can be used to run internal combustion engines for power generation. Producer gas requires less modification of existing engines. It may also be used as a transport fuel.

Hydrogen synthesis

Hydrogen production through thermochemical methods can be achieved using biomass as the feedstock. Most prominent technologies for hydrogen production from biomass involve reforming, gasification, and pyrolysis. These processes provide synthesis gas, mainly consisting of hydrogen and carbon monoxide. This synthesis gas can be subjected to downstream processes to produce pure hydrogen.

Hydrogen production though gasification process involves two steps. In the first step, biomass is converted into producer gas or synthesis gas, a hydrogen-rich fuel gas using oxygen or steam as gasifying agent. In the second step, pure hydrogen is generated from synthesis gas using a gas separation unit.

Another promising technology for biohydrogen production is dark fermentation, a process which involves microorganisms to produce hydrogen from biomass. Dark fermentation is carried out without oxygen and light, with facultative anaerobes and strict anaerobes acting on the substrate to produce hydrogen. The factors influencing the efficiency of dark fermentation are biomass pretreatment, the sugar concentration in the substrate, the microorganisms participating in the reaction, and pH.

Conclusion

Gaseous biofuels are considered to be the most promising renewable alternatives needed in achieving the goals of reducing overall dependence on fossil fuels as well as lowering CO_2 emissions. After careful cleaning and conditioning of biogas and producer gas, they can be used to run internal combustion engines for power generation and could be used as a transport fuel. Hydrogen is used for fueling fuel cells. It can also be used as transport fuel and synthesis of many chemicals.

References

1. Hubert Stassen E. Small-Scale Biomass Gasifiers for Heat and Power A Global Review, world bank technical paper number 296, Energy Series, 1995.
2. Kamaraj S, Angeeswaran R, Divyabharathi R. Text book on Thermochemical Conversion Technologies. A.E Publications, Coimbatore, 2014.
3. Kirubakaran V, Sivaramakrishnan V, Nalini R, Sekar T, Premalatha M, Subramanian P *et al*. A review on gasification of biomass. Renewable Sustainable Energy Rev. 2009;13:179-186.

4. Pugalendhi S, Shalini R, Gitanjali J, Subramanian P. Introduction to renewable sources of energy. TNAU, Coimbatore, 2019.
5. Rai GD. Non-conventional Energy Sources. Khanna Publishers, New Delhi, India, 2002.
6. Rao S, Parulekar BB. Energy Technology-Nonconventional, Renewable and Conventional. Khanna publishers, New Delhi, India, 2002.
7. Sergio C. Capareda. Introduction to Biomass energy conversions, CRC Press, Taylor & Francis Group.
8. Turn S, Kinoshita C, Zhang Z, Ishimura D, Zhou J. An experimental investigation of hydrogen production from biomass gasification. Int. J Hydrogen Energy. 1998;23:641-648.
9. https://mnre.gov.in/bio-energy/current-status.

Indexing and Abstracting in Following Databases

1. Bowker: A ProQuest Affiliate

2. Crossref

ISBN 9788196830922

₹ 739 US$ 16

Published by
Bright Sky Publications,
Office No.3, 1st Floor, Pocket - H34, Sec - 3,
Rohini, New Delhi-110085, India
Phone: +91-9911215212, +91-9999744933
Email: brightskypublications@gmail.com

Peer Reviewed & Refereed

ADVANCED STUDIES IN MULTIDISCIPLINARY RESEARCH

CHIEF EDITOR
DR. SUPRITA JHA

Bright Sky Publications
New Delhi

VOLUME
7

Third year B.Pharmacy Semester-VI

TEXT BOOK OF HERBAL DRUG TECHNOLOGY

(Strictly as per new PCI Regulations, New Delhi)

Dr. RAJ KUMAR MOLMOORI
KAVETI VAMSHI SHARATHNATH
Dr. NARENDER BOGGULA
KRISHNA BHEEMANAPALLY

TEXT BOOK OF HERBAL DRUG TECHNOLOGY

(Strictly as per new PCI Regulations, New Delhi)

Third year B.Pharmacy Semester-VI

Dr. RAJ KUMAR MOLMOORI
Principal
Government Polytechnic College, Madhira,
Khammam, Telangana, India – 521 401.

KAVETI VAMSHI SHARATHNATH
Associate Professor
Nalla Narasimha Reddy Education Society's Group of Institutions,
School of Pharmacy, Chowdariguda, Ghatkesar, Telangana, India – 500 088.

Dr. NARENDER BOGGULA
Associate Professor
CMR College of Pharmacy, Kandlakoya,
Medchal, Hyderabad, Telangana, India – 501 401.

KRISHNA BHEEMANAPALLY
Associate Professor
Nalla Narasimha Reddy Education Society's Group of Institutions,
School of Pharmacy, Chowdariguda, Ghatkesar, Telangana, India – 500 088.

2024 Edition

Rs.

ISBN No.

Published by

Taurus Publishers

3-2-330, Chappal Bazar, Kachiguda, Hyderabad-500 027

Ph : 9000002723

Preface

People with open minded will always try to seek for the new things and information from many sources.

It gives immense pleasure to place before a large community of pharmacy students, my humble work on "**Text Book of Herbal Drug Technology"** for B.Pharmacy students. My aim in writing this book is to present the fundamental principles of **Text Book of Herbal Drug Technology** for the pharmacy students on modern lines. Keeping in view the requirement of the students and the teachers, this book has been written to cover all the topics with the desired limits of the prescribed syllabus. I hope the book will be useful and meets the requirements of students and academicians. Most of the information in this book has represented in a very simple manner. The aim of this book is to make the subject easy and understandable to the students and the faculty.

We sincerely hope that the content of this book will help the students of B.Pharmacy. This book covers five units as per the regulated syllabus of B.Pharmacy third year semester VI prescribed by PCI, New Delhi.

The structure of this book is simple, self-explanatory and easy for the readers to grasp the subject. We hope this book will not only help the students in their learning for the examinations but also for the future.

We will be enormously happy and obligated if you send suggestions and corrections for upgrading the book.

Authors

Acknowledgement

No one who achieves success does without acknowledging the help of others. First and foremost, we would like to thank almighty God for giving us the opportunity, knowledge, ability and strength to undertake this work and to preserve and complete it satisfactorily.

To write a book of this magnitude, it needs lot of patience, skills and expertise over the subject, which I have gained because of opportunity given to me by my teachers and friends. Writing a book is harder than we thought and more rewarding than we could have ever imagined.

We owe a deep debt to gratitude to our Parents and Family members for their whole hearted support, love and trust.

Preparing this book was a collective adventure and I am most grateful to all authors for their cooperation and for the time and the effort they spent to write their respective contributions. I appreciate also their patience, especially as the editing process took much more time than initially expected.

Last but not least, we would also express a special thanks to publishers for their encouragement and publishing the book.

"The beautiful thing about learning is that no one can take it away from you."

Authors

SYLLABUS

HERBAL DRUG TECHNOLOGY (Theory)

Scope: This subject gives the student the knowledge of basic understanding of herbal drug industry, the quality of raw material, guidelines for quality of herbal drugs, herbal cosmetics, natural sweeteners, nutraceutical etc. The subject also emphasizes on Good Manufacturing Practices (GMP), patenting and regulatory issues of herbal drugs.

Objectives: Upon completion of this course the student should be able to:

1. Understand raw material as source of herbal drugs from cultivation to herbal drug product.
2. Know the WHO and ICH guidelines for evaluation of herbal drugs.
3. Know the herbal cosmetics, natural sweeteners, nutraceuticals.
4. Appreciate patenting of herbal drugs, GMP.

Course content:

UNIT-I

Herbs as raw materials

Definition of herb, herbal medicine, herbal medicinal product, herbal drug preparation.

Source of Herbs, selection, identification and authentication of herbal materials.

Processing of herbal raw material.

Biodynamic agriculture

Good agricultural practices in cultivation of medicinal plants including organic farming. Pest and pest management in medicinal plants: Biopesticides/ Bioinsecticides.

Indian systems of medicine

a) Basic principles involved in Ayurveda, Siddha, Unani and Homeopathy.

b) Preparation and standardization of Ayurvedic formulations viz Aristas and Asawas, Ghutika, Churna, Lehya and Bhasma.

UNIT-II

Nutraceuticals

General aspects, Market, growth, scope and types of products available in the market.

Health benefits and role of nutraceuticals in ailments like diabetes, CVS diseases, cancer, irritable bowel syndrome and various gastro intestinal diseases.

Study of following herbs as health food

Alfalfa, Chicory, Ginger, Fenugreek, Garlic, Honey, Amla, Ginseng, Ashwagandha, Spirulina.

Herbal-drug and herb-food interactions

General introduction to interaction and classification.

Study of following drugs and their possible side effects and interactions: Hypericum, Kava-kava, *Ginkgo biloba*, Ginseng, Garlic, Pepper & Ephedra.

UNIT-III

Herbal cosmetics

Sources and description of raw materials of herbal origin used via, fixed oils, waxes, gums, colours, perfumes, protective agents, bleaching agents, antioxidants in products such as skin care, hair care and oral hygiene products.

Herbal excipients

Herbal Excipients – Significance of substances of natural origin as excipients - colorants, sweeteners, binders, diluents, viscosity builders, disintegrants, flavours & perfumes.

Herbal formulations

Conventional herbal formulations like syrups, mixtures and tablets and novel dosage forms like phytosomes.

UNIT-IV

Evaluation of drugs

WHO & ICH guidelines for the assessment of herbal drugs stability testing of herbal drugs.

Patenting and regulatory requirements of natural products

a) Definition of the terms: Patent, IPR, Farmers right, Breeder's right, Bioprospecting and Biopiracy.

b) Patenting aspects of Traditional Knowledge and Natural Products. Case study of Curcuma & Neem.

Regulatory issues

Regulations in India (ASU DTAB, ASU DCC), Regulation of manufacture of ASU drugs - Schedule Z of Drugs & Cosmetics Act for ASU drugs.

UNIT-V

General introduction to herbal industry

Herbal drugs industry: Present scope and future prospects.

A brief account of plant-based industries and institutions involved in work on medicinal and aromatic plants in India.

Schedule T – Good Manufacturing Practice of Indian systems of medicine

Components of GMP (Schedule – T) and its objectives.

Infrastructural requirements, working space, storage area, machinery and equipments, standard operating procedures, health and hygiene, documentation and records.

INDEX

UNIT – I

HERBS AS RAW MATERIALS

Introduction

Medicinal and aromatic plans constitute a major part of the flora, which provides raw materials for use in the pharmaceuticals, cosmetics and drug industries. In one of the studies by WHO, it isestimated ha 80 percent of the population of developing countries relies on traditional plant-based medicines for their health requirements. India and China are the two major producing countries having 40 percent of the global biodiversity and availability of rare species. These are well known as the home of medicinal and aromatic crops that constitute a segment of the flora and provide raw materials to the pharmaceutical, cosmetics, fragrance, flavour etc. industries. From the trade data available, it is clear that the global market for medicinal plants has always been large and has been on increase in the recent past. The trade of medicinal plants from Indiais estimated Rs.550 crores.

Herb

Herb is defined as any plant with leaves, seeds, or flowers used for flavouring, food, medicine or perfume (or) herbs are crude plant material which may be entire, fragmented or powdered. Herbs include the entire aerial parts, leaves, flowers, fruits, roots, seeds, bark (stem/root) 0f trees, tubers, rhizomes or other plant parts.

An herb, also spelled as "herb," is a type of plant that is valued for its culinary, medicinal, aromatic, or ornamental properties. Herbs are typically grown for their leaves, stems, flowers, or seeds, which are used in various ways to enhance the flavour of food, provide therapeutic benefits, add fragrance, or beautify spaces.

Culinary herbs are commonly used to season and flavour dishes in cooking, adding unique tastes and aromas to recipes. Examples of culinary herbs include basil, thyme, rosemary, oregano, parsley, and mint. Medicinal herbs have been used for centuries in traditional medicine practices to treat various health issues. Some herbs are believed to possess healing properties, and their extracts or preparations are used to alleviate symptoms or promote well-being.

Aromatic herbs are known for their pleasant fragrances and are often used in perfumes, cosmetics, and aromatherapy. Lavender, chamomile, and eucalyptus are examples of aromatic herbs. Ornamental herbs are grown for their visual appeal in gardens or landscapes. These herbs often have attractive flowers, foliage, or growth habits that add beauty to outdoor spaces. Herbs can be cultivated in gardens, pots, or even indoors, depending on the specific needs of each plant. They are used fresh, dried, or in various processed forms like oils, teas, and extracts.

Herbal medicine

Practice of using herbs and herbal preparations to maintain health and to prevent, alleviate or cure disease or a plant or plant part or an extract or mixture of these used in herbal medicine.

Herbal medicine, also known as herbalism or botanical medicine, refers to the practice of using plants and plant-derived substances for their medicinal properties to promote health, prevent illness, or treat various medical conditions. This approach to healing is one of the oldest forms of medicine, dating back thousands of years and spanning numerous cultures and traditions around the world.

Herbal medicine involves the use of various parts of plants, including leaves, stems, flowers, roots, and seeds, to create preparations such as teas, tinctures, extracts, poultices, and capsules. These preparations can be consumed orally, applied topically, or inhaled, depending on the intended therapeutic effect.

Herbal medicinal products

These are medicinal products where the active ingredient consists mainly of herbal substances.

Herbal medicinal products, often referred to as herbal remedies or herbal supplements, are products made from plants or plant extracts that are used for their therapeutic or medicinal properties. These products have been used for centuries in various cultures around the world as a form of traditional medicine. Herbal medicinal products can come in various forms, including teas, tinctures, capsules, tablets, creams, and more.

The active ingredients in herbal medicinal products are derived from different parts of plants, such as leaves, flowers, roots, stems and bark. These active compounds are believed to have specific beneficial effects on health and well-being. Some examples of commonly used herbal medicinal products include echinacea for immune support, *Ginkgo biloba* for cognitive enhancement, and St. John's wort for mood regulation.

It's important to note that while many people use herbal medicinal products for their potential health benefits, the scientific evidence supporting their effectiveness can vary widely. Some herbal remedies have been extensively studied and are supported by clinical research, while others might lack rigorous

scientific validation. Additionally, just like any other form of medicine, herbal products can also have potential side effects, interactions with other medications, and varying degrees of safety.

Regulations regarding the production, marketing, and sale of herbal medicinal products can vary by country. In some places, these products are regulated as dietary supplements, while in others, they may be subject to stricter regulations similar to pharmaceutical drugs. It's advisable for individuals considering the use of herbal medicinal products to consult with a healthcare professional before starting any new treatment regimen, especially if they have pre-existing medical conditions or are taking other medications.

Herbal drug preparations

They are prepared from herbal materials by different process, which is extraction with various solvents, purification, concentration and other processes. It includes such as powders, extracts and juices.

Herbal drug preparations are formulations made from plant materials or extracts that are used for medicinal purposes. These preparations can take various forms and are often derived from different parts of plants, including leaves, flowers, roots, stems, and bark. Herbal drug preparations have been used for centuries as a part of traditional medicine and continue to be utilized in modern healthcare systems as well.

Finished herbal products

Finished herbal products consist of one or more herbal preparations made from one or more herbs i.e., from different herbal preparations made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”. It includes various herbal formulations like tablets, syrups, capsules, semisolid dosage forms, etc. They may contain excipients in addition to active ingredients.

Source of herbs

Herbs or medicinal plants can be obtained from two sources viz:

a) Wild source & b) Cultivated source.

Wild source

The plants are obtained from the wild source such as forests, plains, river banks, etc, where they are found in their wild form. Collection from wild sources is suitable for plants which are abundant in nature and are easily available. Obtaining herbs from a wild source is easy, economical, less time consuming, and has a decreased cost of labour, however it also offers various disadvantages such as the quality of the plants cannot be predicted due to various environmental changes.

The plants will not be uniform in their growth and yielding characteristics. Modern scientific techniques cannot be applied to increase the yield as well as quality. If the plants are obtained continuously from wild sources for prolonged periods it may lead to depletion of raw materials from the wild.

Cultivated source

In recent times, medicinal plants have been systematically cultivated by applying modern scientific techniques. Obtaining herbs from cultivated sources offer various advantages which are as follows;

- ✓ Quality and purity are ensured.
- ✓ Better yield and more profit.
- ✓ Ensures regular supply of raw material.
- ✓ Application of modern scientific techniques is possible.

Steps involved in the selection, identification, and processing of herbal raw materials

Herbs are subjected to various stages starting from their selection, identification, cultivation, collection, storage and processing until the final product is formed.

Selection, identification and authentication of herbal drugs

Where applicable, the species or botanical variety selected for cultivation should be the same as that specified in the national pharmacopoeia or recommended by other authoritative national documents of the end-user's country. In the absence of such national documents, the selection of species or botanical varieties specified in the pharmacopoeia or other authoritative documents of other countries should be considered. In the case of newly introduced medicinal plants, the species or botanical variety selected for cultivation should be identified and documented as the source material used or described in traditional medicine of the original country.

Steps involved in processing of herbal drugs

The detailed steps involved in the processing of herbal drugs are discussed below:

1. Selection of herbs
2. Identification & authentication
3. Cultivation of herbs
4. Collection of herbs
5. Processing of herbal raw material

Identification tests should be specific for the herbal material and are usually a combination of three or more of the following:

- Macroscopic characters,
- Microscopic characters,
- Chromatographic procedures,
- Chemical reactions.

Authentication is especially useful in cases of drugs that are frequently substituted or adulterated with other varieties which are morphologically and chemically indistinguishable. Several herbal drugs in the market still cannot be

identified or authenticated based on their morphological or histological characteristics. Use of wrong drugs may be ineffective or it may worsen the condition.

Processing of herbal materials

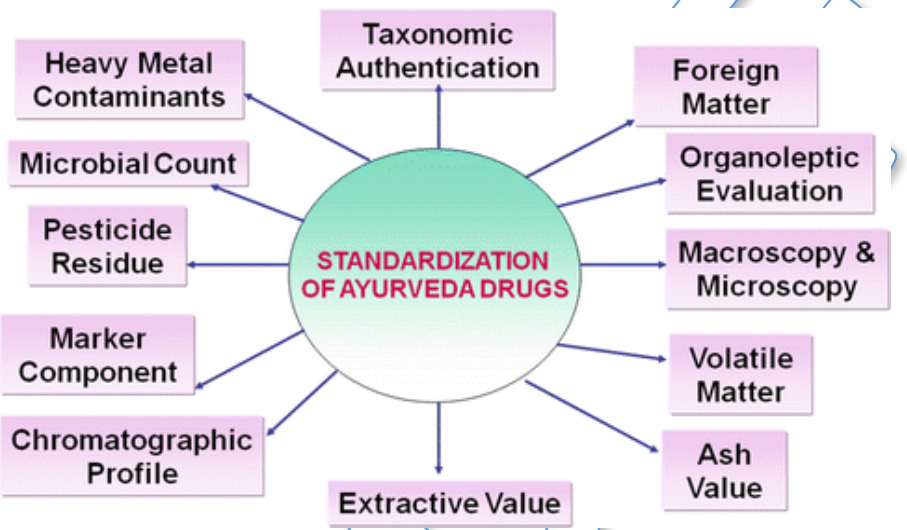
Depending on the intended use, herbal materials could be regarded as starting materials and herbal preparations could be regarded as intermediates in the process of producing finished herbal products, or as herbal dosage forms for therapeutic applications. In the latter case, simple herbal dosage forms may be prepared either from herbal materials (such as unprocessed seeds or plant exudates) or herbal preparations (such as ground powders and dried extracts) ready for administration to patients. These herbal dosage forms, produced under Good Manufacturing Practices (GMP) conditions, include decoctions, tea bags, granules, syrups, ointments or creams, inhalations, patches, capsules, tablets and pills, among others.

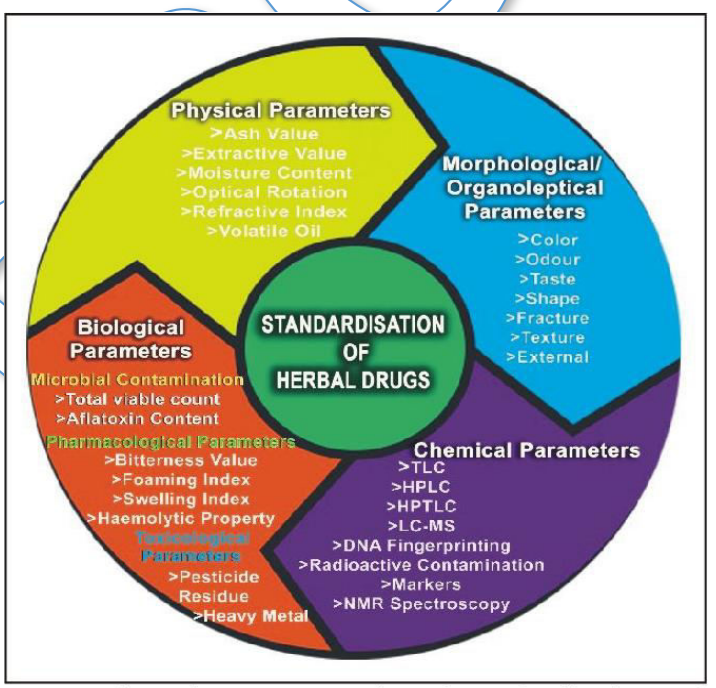
- Collection of drugs
- Time of collection
- Harvesting
- Primary processing
- Drying
- Specific processing
- Garbling
- Packing
- Storage

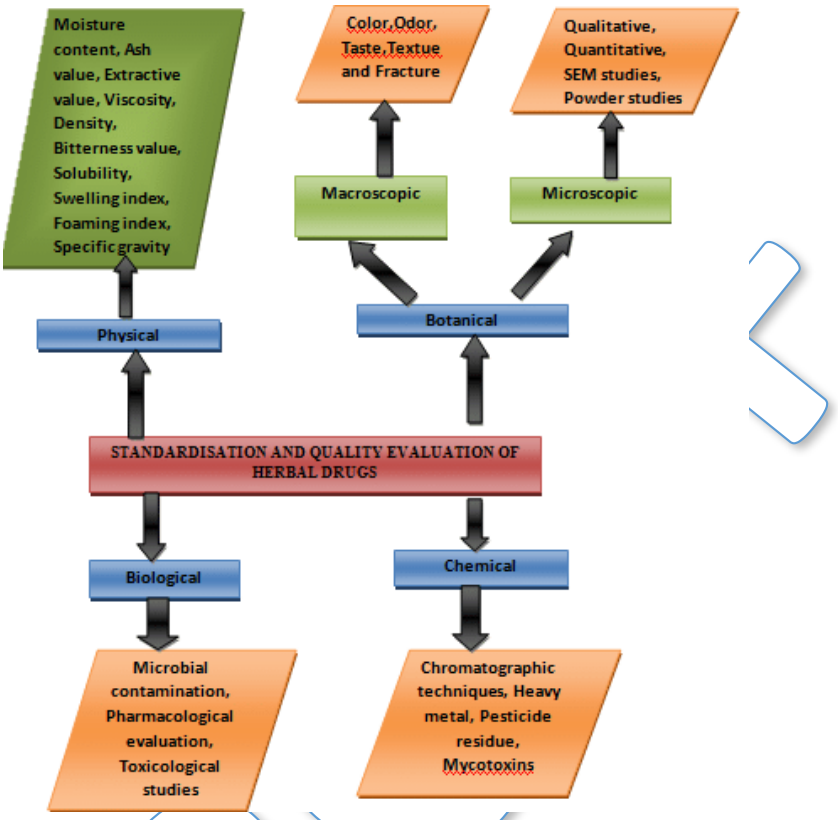
Safety management of toxic herbs

Among the herbal medicines (and their source medicinal plants) being used in traditional medicine contexts in different parts of the world, some are known to contain toxic substances that may lead to severe side-effects or even death. In general, these toxic herbal materials and their preparations or dosage

forms have narrow therapeutic windows between elective dose and lethal dose. Examples of such toxic/effective therapeutic agents are cardio-active herbal preparations such as powdered digitalis and digitalis capsules which at the proper dosages, are excellent therapeutic cardiotonic agents, but are lethal when an overdose is taken.







Biodynamic agriculture

Biodynamic agriculture was developed during the 1920s by Rudolf Steiner. Steiner argued that spirituality lays the foundation for the renewal of agriculture. In particular, he encouraged farmers to develop a personal relationship with plants, animals, soil, and even with manure in order to think more holistically about agriculture. Since then, biodynamic agriculture has been experimented with and implemented by farmers around the world.

Biodynamics has much in common with other organic approaches – it emphasizes the use of manures and composts and excludes the use of synthetic (artificial) fertilizers on soil and plants. Methods unique to the biodynamic approach include its treatment of animals, crops, and soil as a single system, an emphasis from its beginnings on local production and distribution systems, its use of traditional and development of new local breeds and varieties.

Biodynamic agriculture uses various herbal and mineral additives for compost additives and field sprays. WHO has developed a series of technical guidelines relating to the quality control of herbal medicines of which these WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants based.

In contrast, crop rotation and an assortment of animal life are an important part of sustainable agriculture. The practice of rotating crops from field to field and raising varied animal species, along with cover crops and green manures, encourages healthy soil, reduces parasites and controls weeds and pest.

Biodynamic farming treats animals, crops and soil as a single system and facilitates the use of traditional systems and development of new local breeds and varieties. It uses various herbal and mineral additives in the manufacture of composts and field sprays. Biodynamic farming also emphasizes on the use of astronomical sowing and moon planting calendar. Bio dynamic farming promotes composting, green manuring crop rotations, inter cropping, mixed cropping, etc, as well as employing predators, parasites, which are natural enemies of pests.

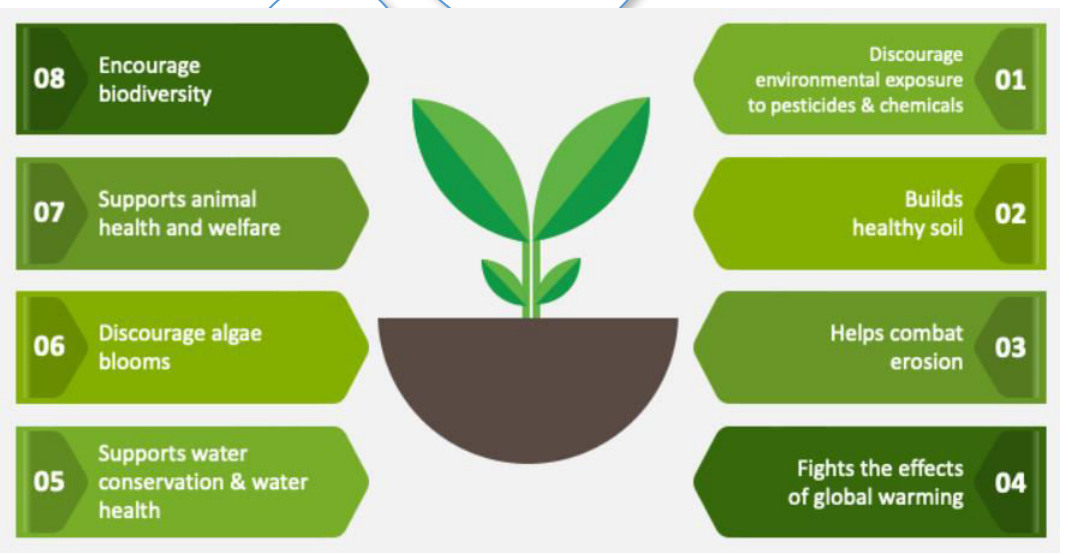
It's important to note that biodynamic practices can vary among farmers and regions. Some farmers might adopt all aspects of biodynamics, while others might incorporate certain principles based on their specific circumstances and beliefs. Biodynamic agriculture is recognized by various certification organizations, and products labeled as "biodynamic" have met the criteria of these organizations.

Good agricultural practices (GAP) in cultivation of medicinal plants

It describes general principles including quality control measures and provides technical details forcultivation of medicinal plants. The guidelines described for GAP are intended to streamline the cultivation of medicinal plants as per the well-regulated methods and follow a systematic way in the cultivation process as it is important for the production of good quality plant material.

The various stages of processing which are included in good agricultural practice (GAP) are described as follows;

- ✓ Seeds and propagation material
- ✓ Cultivation
- ✓ Soil and fertilization
- ✓ Irrigation
- ✓ Crop maintenance
- ✓ Harvesting
- ✓ Primary processing
- ✓ Packaging
- ✓ Storage and transport
- ✓ Staff requirements
- ✓ Documentation
- ✓ Quality assurance



Benefits of organic farming

Organic farming

An integrated farming system that strives for sustainability, the enhancement of soil fertility and biological diversity whilst, with rare exceptions, prohibiting synthetic pesticides, antibiotics, synthetic fertilizers, genetically modified organisms, and growthhormones. Organic agriculture is a production system that sustains the health of soils, ecosystems and people. It relies on ecological processes, biodiversity and cycles adapted to local conditions, rather than the use of inputs with adverse effects. Organic agriculture combines tradition, innovation and science to benefit the shared environment and promote fair relationships and a good quality of life for all involved. Organic farming is primarily of two types, namely: Pure organic farming and integrated organic farming.

Pure organic farming involves avoiding all artificial chemicals. Every fertilizer and pesticide that is used are derived from completely natural sources such as blood meal or bone meal.

Integrated organic farming involves integrating techniques aimed at achieving ecological requirements and economic demands such as integrated pest management and nutrients management.

Nutrients management in organic farming: Organic farming follows a healthy wayof farming for both crops as well as consumers. In this method, composted organic manure is used for nutrition of crops and thus, improves the organic content and fertility of the soil. Apart from manures, bacterial and fungal biofertilizers are also used for enhancing the soil nutrients.

Organic farming is an agricultural approach that prioritizes the use of natural and sustainable practices to cultivate crops and raise live stock. It aims to create a harmonious balance between farming practices and the environment, while also promoting the health and well-being of consumers, farmers, and the broader ecosystem. Organic farming emphasizes the avoidance of synthetic chemicals, genetically modified organisms (GMOs), and excessive use of non-

renewable resources. Instead, it relies on traditional and innovative techniques that work in harmony with natural processes.

Key principles and practices of organic farming include:

- Soil Health: Organic farming focuses on maintaining and enhancing soil health through practices such as composting, cover cropping, and crop rotation. Healthy soil promotes nutrient availability, water retention, and microbial diversity, which in turn improves plant health and yields.
- Avoidance of Synthetic Inputs: Organic farming prohibits the use of synthetic pesticides, herbicides, and fertilizers. Instead, it relies on natural alternatives, such as beneficial insects, companion planting, and organic-approved pest management methods.
- Biodiversity: Organic farms often prioritize biodiversity by planting a variety of crops and utilizing diverse habitats to create a balanced ecosystem. This helps control pests naturally and improves overall resilience to environmental challenges.
- Animal Welfare: Organic livestock farming places a strong emphasis on the well-being of animals. It mandates access to outdoor spaces, proper nutrition, and humane treatment of animals.
- Genetic Modification: Organic farming avoids the use of genetically modified organisms (GMOs) in both plant and animal production. This is to maintain the integrity of natural genetic diversity and prevent potential environmental and health risks associated with GMOs.
- Water Conservation: Organic farming practices aim to reduce water consumption through techniques like mulching, efficient irrigation systems, and water management strategies that minimize runoff and water pollution.
- Non-Chemical Weed Control: Instead of relying on synthetic herbicides, organic farming employs methods like hand weeding, mulching, and cover cropping to manage weeds and maintain healthy crop growth.

- ❖ Certification and Standards: Many countries have established organic certification programs that set standards for organic farming practices. Farms must adhere to these standards to be officially recognized as organic producers and to label their products as organic.

Benefits of organic farming include:

- o Environmental Benefits: Organic farming reduces the use of synthetic chemicals, leading to healthier soil and water systems. It also promotes biodiversity and helps mitigate climate change by sequestering carbon in the soil.
- o Health Benefits: Organic foods are often perceived as healthier because they contain fewer pesticide residues and may have higher levels of certain nutrients.
- o Community and Local Economy: Organic farming often supports local communities by creating jobs and promoting sustainable agriculture practices.
- o Long-Term Sustainability: By preserving soil health and biodiversity, organic farming helps ensure the long-term productivity of agricultural land.

However, it's important to note that organic farming also has challenges, such as potentially lower yields compared to conventional methods and higher labour requirements for certain practices. Additionally, achieving widespread adoption of organic farming practices can require a transition period and investment in education and resources. In recent years, organic farming has gained popularity as consumers become more interested in sustainable and healthy food choices. It's a dynamic field that continues to evolve with advancements in research and technology.

Applications of organic farming:

Organic farming has a wide range of applications across various aspects of agriculture, food production, and environmental conservation. Here are some key applications of organic farming:

1. Crop Production:

- Fruits and Vegetables: Organic farming methods are commonly used to cultivate a diverse range of fruits and vegetables, including tomatoes, lettuce, strawberries, and peppers.
- Grains: Organic practices can be applied to crops like rice, wheat, oats, and barley.
- Herbs and Spices: Many herbs and spices, such as basil, oregano, and turmeric, are cultivated using organic methods.

2. Livestock Production:

- Poultry: Organic farming principles can be applied to raising organic chickens, turkeys, and other poultry, ensuring access to outdoor spaces, organic feed, and humane treatment.
- Cattle: Organic beef and dairy production emphasize pasture grazing, organic feed, and ethical treatment of animals.
- Pigs: Organic pig farming focuses on providing outdoor access, natural bedding, and organic feed.

3. Specialty Products:

- Organic Dairy: Organic dairy farming avoids the use of synthetic hormones and antibiotics, and the animals are fed organic feed.
- Organic Eggs: Organic egg production involves providing hens with outdoor access, organic feed, and humane living conditions.
- Organic Honey: Organic beekeeping practices focus on maintaining healthy bee colonies without the use of synthetic chemicals.

4. Agroforestry:

- Organic farming principles can be integrated into agroforestry systems, where trees are combined with crops and livestock to create sustainable and biodiverse landscapes.

5. Urban and Small-Scale Farming:

- Organic farming techniques can be adapted to urban and small-scale agriculture, such as rooftop gardens, community gardens, and vertical farming systems.

6. Medicinal and Aromatic Plants:

- Many medicinal and aromatic plants, such as lavender, chamomile, and echinacea, are grown using organic practices to ensure the purity of their therapeutic properties.

7. Seed Production:

- Organic farming plays a role in producing organic seeds that are free from genetic modification and synthetic treatments.

8. Organic Fibers:

- Organic farming methods are applied to produce organic cotton, wool, and other natural fibers for textiles.

9. Restoration Agriculture:

- Organic practices can be employed in ecological restoration efforts, such as re-establishing native plant communities and regenerating degraded land.

10. Global Agriculture:

- Organic farming is practiced around the world, from small family farms to large-scale operations, contributing to sustainable food production in various climates and regions.

11. Research and Innovation:

- Organic farming serves as a platform for research and innovation in sustainable agriculture, leading to the development of new techniques, practices, and technologies.

12. Education and Advocacy:

- Organic farming serves as an educational tool to raise awareness about the importance of sustainable and environmentally friendly agricultural practices.

13. Tourism and Eco-Friendly Practices:

- Organic farms often attract visitors interested in learning about sustainable farming practices, contributing to agritourism and promoting eco-friendly lifestyles.

These applications demonstrate the versatility and adaptability of organic farming methods across different types of agricultural production, catering to the growing demand for environmentally conscious and healthy food choices.

Advantages of organic farming:

Organic farming offers a range of advantages that contribute to sustainable agriculture, environmental protection, and healthier food production. Some of the key advantages of organic farming include:

1. Environmental Benefits:

- Reduced Chemical Use: Organic farming avoids synthetic pesticides, herbicides, and fertilizers, which helps minimize soil and water pollution and preserves the health of ecosystems.
- Soil Health: Organic practices, such as composting and cover cropping, enhance soil structure, nutrient content, and microbial diversity, leading to healthier and more fertile soils.
- Biodiversity: Organic farms often have higher levels of biodiversity due to crop diversity, habitat preservation, and reduced chemical inputs, which can contribute to more resilient ecosystems.

2. Improved Food Quality:

- Reduced Chemical Residues: Organic foods generally have lower levels of pesticide residues compared to conventionally produced foods, which can lead to healthier food options for consumers.
- Nutrient Content: Some studies suggest that organic crops may contain higher levels of certain nutrients due to the emphasis on soil health and nutrient availability.

3. Healthier for Consumers:

- Reduced Exposure to Harmful Chemicals: Organic foods are produced without synthetic pesticides, herbicides, and GMOs, potentially reducing consumers' exposure to potentially harmful chemicals.
- Antibiotic and Hormone-Free: Organic animal products come from animals that are raised without the routine use of antibiotics and synthetic growth hormones, addressing concerns about antibiotic resistance and hormone exposure.

4. Support for Animal Welfare:

- Humane Animal Treatment: Organic livestock farming emphasizes animal welfare by providing animals with access to outdoor spaces, appropriate diets, and living conditions that promote their well-being.

5. Long-Term Soil Fertility:

- Sustainable Nutrient Management: Organic farming relies on natural nutrient cycling, cover cropping, and composting, which helps maintain soil fertility over the long term without depleting resources.

6. Climate Change Mitigation:

- Carbon Sequestration: Organic farming practices can increase carbon sequestration in the soil, helping to mitigate climate change by capturing atmospheric carbon dioxide.

7. Support for Local Communities:

- Local Economy: Organic farms often support local economies by creating jobs, promoting small-scale farming, and contributing to local food systems.
- Community Engagement: Organic farms can foster connections between consumers and producers through farmers' markets, community-supported agriculture (CSA) programs, and farm visits.

8. Resilience to Climate Variability:

- Diverse Crop Rotation: Organic farms often use crop rotation and diversification, which can enhance resilience to pests, diseases, and extreme weather events.

9. Preservation of Genetic Diversity:

- Non-GMO: Organic farming prohibits the use of genetically modified organisms (GMOs), helping to preserve natural genetic diversity and reduce potential environmental risks associated with GMOs.

10. Reduction in Antibiotic Resistance:

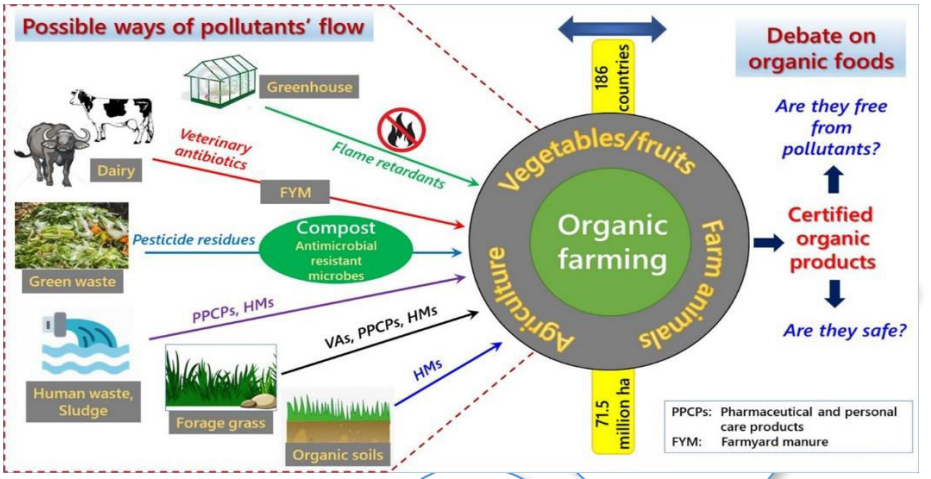
- Organic livestock production's limited use of antibiotics helps mitigate the development of antibiotic-resistant bacteria, which is a growing concern in conventional agriculture.

11. Educational and Cultural Value:

- Organic farming practices often have educational and cultural value, promoting traditional and sustainable farming knowledge and practices.

It's important to note that while organic farming offers numerous advantages, it also has some challenges, such as potentially lower yields compared to conventional methods and higher labour requirements. Additionally, the

effectiveness of organic farming practices can vary depending on factors such as location, climate, and farm management techniques.



Pest and pest management in medicinal plants

Crop rotation, mixed cropping, organic control, hand weeding are the other techniques used in organic farming to maintain soil fertility and for pest- weed control. These systems of pest and weed management and soil protection make organic farming the best method. Sometimes, natural or other organically approved insecticides like neem pesticides are also used.

Pest is an undesired animal or plant which causes loss of cultivated plants. The different types of pests infecting medicinal plants are as follows-

Types of pests:

1. Weeds
2. Insects
3. Fungi/ viruses
4. Non-insect pests

Methods of pest control

Different techniques are followed to achieve pest control effectively. These methods are discussed as follows:

I. Agricultural method

II. Biological method

III. Mechanical method

IV. Chemical method

Disease management

Diseases can be a major concern for organic farmers as it might reduce crop yields. So, supplying important macro and micronutrients and adopting crop rotationis crucial to prevent various plant diseases. Even the soil is enriched with useful microbes, fungi, and bacteria to prevent harmful organisms in check. Organic fruits and vegetables are not theonly examples of successful organic products. Recently, dairy products which are organic are noticeable. Livestock is another example of organic farming. Here, they follow a strict means of farming like animals feed on organic food only. Hormones or other genetic engineering practicesfor high yield are not allowed on animals.

Biopesticides/bioinsecticides for pest management

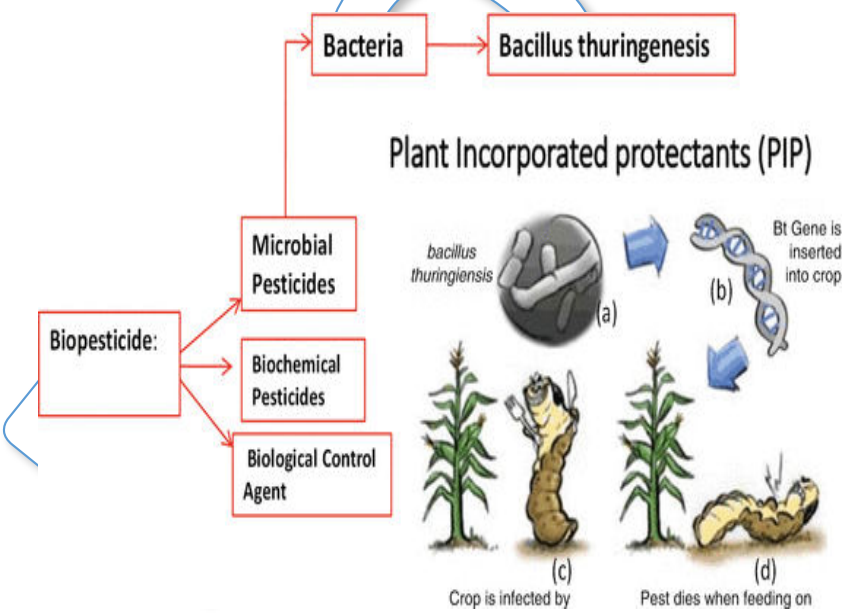
These are pesticides obtained from natural sources like microorganisms, plants, animals, insects and certain minerals. They offer enormous advantages over chemical pesticides which are as follows.

Bio-pesticides: The term bio-pesticides define compounds that are used to manage agricultural pests by means of specific biological effects rather than as broader chemical pesticides. It refers to products containing bio-control agents - i.e., natural organisms or substances derived from natural materials (such as animals, plants, bacteria, or certain minerals), including their genes or metabolites, for controlling pests. According to the FAO definition, bio-pesticides include those bio-control agents that are passive agents, in contrast to bio-control agents that actively seek out the pest, such as parasitoids, predators, and many species of entomo-pathogenic nematodes. The latter bio-control agents used to manage potato pests.

Thus bio-pesticides cover a wide spectrum of potential products that can be classified as follows:

Microbial pesticides: Pesticides that contain microorganisms, like bacteria, fungi or virus, which attack specific pest species, or entomo-pathogenic nematodes as active ingredients. Although most of these agents attack insect species (called entomo-pathogens; products referred to as bio-insecticides), there are also microorganisms (i.e., fungi) that control weeds (bio-herbicides).

Plant-Incorporated Protectants (PIPs): These include pesticidal substances that are produced in genetically modified plants/organisms (i.e., through the genetic material that has been incorporated into the plant). Both the protein and itsgenetic material are regulated by Environmental protection agency, the plant itself is not regulated. The production of transgenic plants that express insecticidal endo-toxins derived from the soil bacterium.



Biochemical pesticides: pesticides based on naturally occurring substances that control pests bynon-toxic mechanisms, in contrast to chemical pesticides that contain synthetic molecules that directly kill the pest. Biochemical pesticides fall into different biologically functional classes, including

pheromones and other semi-chemicals, plant extracts, and natural insect growth regulators. These are naturally occurring chemical substances which are obtained from insects and animals which have the ability to control the pests by non-toxic mechanisms. These include substances like insect sex pheromones.

Examples:

1. *Bacillus thuringiensis*, a bacterium capable of causing disease of Lepidoptera, Coleoptera and Diptera, is a well-known insecticide example. The toxin from *B. thuringiensis* (Bt toxin) has been incorporated directly into plants through the use of genetic engineering. The use of Bt Toxin is particularly controversial. Its manufacturers claim it has little effect on other organisms, and is more environmentally friendly than synthetic pesticides.
2. Entomo-pathogenic fungi (e.g., *Beauveria bassiana, Isaria fumosorosea, Lecanicillium,* and *Metarhizium* spp.), plant disease control agents: include Trichoderma spp. and *Ampelomyces quisqualis* (a hyper-parasite of grape powdery mildew).
3. *Bacillus subtilis* is also used to control plant pathogens and beneficial nematodes attacking insect (e.g., *Steinernema feltiae*) or slug (e.g., *Phasmarhabditis hermaphrodita*) pest's entomopathogenic viruses (e.g., *Cydia pomonella granulovirus*) weeds and rodents have also been controlled with microbial agents. Various naturally occurring materials, including fungal and plant extracts, have been described as biopesticides.
4. Insect pheromones and other semi-chemicals.
5. Biopesticides may include natural plant-derived products, which include alkaloids, terpenoids, phenolics and other secondary chemicals. Certain vegetable oils such as canola oil are known to have pesticidal properties.

Advantages of bio pesticides over chemical pesticides

They offer several advantages over chemical pesticides, which are synthetic compounds manufactured for pest control. Here are some of the advantages of biopesticides over chemical pesticides:

- They are non-toxic to plants, animals as well as humans.
- They are biodegradable and do not leave any toxic residues.
- They are less expensive and can be grown along with the cultivated medicinal plants.
- They are eco-friendly and do not affect soil fertility.
- They are safe to handle and use.
- Target specificity
- Reduces resistance development
- Shorter pre-harvest intervals
- Compatibility with beneficial organisms
- Minimal impact on non-target plants
- Integrated Pest Management (IPM)
- Sustainability and public perception

It's important to note that while biopesticides offer numerous advantages, they may also have limitations, such as variability in effectiveness due to environmental conditions, slower action compared to some chemical pesticides, and the need for proper storage and handling to maintain their viability. As with any pest management strategy, the selection of biopesticides or chemical pesticides should be based on the specific pest situation, crop type, and local conditions.

Indian systems of medicine

The Indian System of Medicine is of great antiquity. It is the culmination of Indian thought of medicine which represents a way of healthy living valued with a long and unique cultural history, as also amalgamating the best of

influences that came in from contact with other civilizations be it Greece (resulting in Unani Medicine) or Germany (Homeopathy) or our scriptures/sages which gave us the science of Ayurveda, Siddha as also Yoga & Naturopathy. Like the multifaceted culture in our country, traditional medicines have evolved over centuries blessed with a plethora of traditional medicines and practices.

A separate Department of Indian Systems of Medicine and Homoeopathy (ISM & H) was set up in 1995 to ensure the optimal development and propagation of AYUSH systems of health care. The Department of ISM & H was re-named as the department of AYUSH (an acronym for - Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homoeopathy) in November 2003. With an increase in lifestyle related disorders there is a worldwide resurgence of interest in holistic systems of health care, particularly with respect to the prevention and management of chronic, non-communicable and systemic diseases. It is increasingly understood that no single health care system can provide satisfactory answers to all the health needs of modern society.

Basic principles involved in Ayurveda, Siddha, Unani and Homeopathy

Ayurvedic system of medicine:

Ayurveda is one of the oldest systems of medicine originated from India. The word Ayurveda is made up of two parts Ayu + Veda. Ayu means life and Veda means Knowledge. Thus, Ayurveda means “science of life”. It deals both physical and mental health and also covers art of living. In Ayurveda health is defined as a well- balanced metabolism and happy state of being. It deals with all aspect of human life which are emanating from body, mind, external factors and natural intrinsic factors. In this system diseases are cured by using drugs, diets, exercise and surgery. Body (Sharira), mind (manas) and Soul (Atma) are the triploid of life in which equal attention should be given for the achievement of sound health.

Ayurveda classifies the body into three basic biological elements which are known as Vata, Pita, Kapha. These elements originate from five basic elements

airs (Vayu), energy (Tej), space (Akash), Water (Jal) and Soil (Dharti). The biochemical combination of space and air form Vata. Pitta is composed of energy and water and Kapha is derived from the combination of water and soils.

Siddha system of medicine:

Siddha system of medicine is practiced in some parts of South India especially in the state of Tamil Nadu. It has close affinity to Ayurveda yet it maintains a distinctive identity of its own. This system has come to be closely identified with Tamil civilization. The term 'Siddha' has come from 'Siddhi'- which means achievement. Siddhars were the men who achieved supreme knowledge in the field of medicine, yoga or tapa (meditation).

It is a well-known fact that before the advent of the Aryans in India a well-developed civilization flourished in South India especially on the banks of rivers Cauvery, Vaigai, Tamira Arani etc. The system of medicine in vogue in this civilization seems to be the precursor of the present-day Siddha system of medicine. During the passage of time, it interacted with the other streams of medicines complementing and enriching them and in turn getting enriched. The Materia medica of Siddha system of medicine depends to large extent on drugs of metal and mineral origin in contrast to Ayurveda of earlier period, which was mainly dependent upon drugs of vegetable origin.

According to the tradition eighteen Siddhars were supposed to have contributed to the development of Siddha medicine, yoga and philosophy. However, literature generated by them is not available in entirety. In accordance with the well-known self-effacing nature of ancient Indian Acharyas (preceptors) authorship of many literary works of great merit remains to be determined. There was also a tradition of ascribing the authorship of one's work to his teacher, patron even to a great scholar of the time. This has made it extremely difficult to clearly identify the real author of many classics.

Unani system of medicine:

Unani medicine is a system of alternative medicine that originated in ancient Greece but is now practiced primarily in India. Involving the use of herbal remedies, dietary practices, and alternative therapies, Unani medicine addresses the prevention and treatment of disease. According to practitioners of Unani medicine, achieving a balance of the bodily fluids known as "the four humors" (blood, phlegm, yellow bile, and black bile) is essential to health. Another key principle of Unani medicine is that disease results from an imbalance in air, earth, water, and fire, four elements thought to comprise all that exists in nature, including the human body. In addition, Unani medicine is partly based on the principle that environmental conditions, including the quality of water and air,) can significantly impact health. In Unani medicine, conditions are often treated with herbal formulas containing a variety of natural substances. For example, a formula known as Khamira Abresham Hakim Arshad Wala contains such botanicals as saffron, cardamom, Indian bay leaf, and citron. Considered a tonic, Khamira Abresham Hakim Arshad Wala is said to enhance heart health and aid in the treatment of cardiovascular problems like high blood pressure and angina. Commonly prescribed treatments in Unani medicine also include dietary changes, leech therapy, and surgery.

Unani medicine is largely based on principles proposed by such physicians as Hippocrates and Galen. In addition, a number of Arab and Persian scholars (including the Arab philosopher and physicist Avicenna) have contributed to the development of Unani medicine. The word "Unani" means "Greek" in Arabic. Unani medicine was introduced in India around the tenth century.

Homeopathy system of medicine:

Homeopathy is an alternative medical practice in which extremely dilute amounts of certain natural substances are used to treat various ailments. Homeopathy is also known as homeopathic medicine and was developed in Germany more than 200 years ago. Homeopathic treatments are highly individualized, and there is no uniform prescribing standard for homeopathic

practitioners. There are hundreds of different homeopathic remedies, which can be prescribed in a variety of different dilutions for thousands of symptoms.

The holistic nature of homeopathy means each person is treated as a unique individual. Their body, mind, spirit and emotions are all considered in the management and prevention of disease. Taking all these factors into account a homeopath will select the most appropriate medicine. Homeopathic medicine based on the individual's specific symptoms and personal level of health to stimulate their own healing ability. Homeopathic medicines are safe to use as they rarely cause side-effects. This means when used appropriately under the guidance of a qualified homeopath they can be taken by people of all ages, including babies, children and pregnant or breastfeeding women. Every science has certain fundamental principles which guide the whole system.

Preparation and standardization of Ayurvedic formulation

Aristas

Arista, an Ayurvedic preparation, is effectively used to treat many diseases. It is obtained by soaking the crude drugs, either in powdered form or as decoction, in jaggery solution. While doing so, it undergoes fermentation to produce alcohol, which helps to extract the phytoceuticals from the crude drugs. Though the requirement for herbal medicines is increasing, the major drawbacks encountered by the herbal drug companies include lack of proper documentation, validation and determination of biomarkers besides the non-existence of rigid quality control profiles for herbs and their formulations.

This creates an urgent need for standardization of herbal drugs, which enhances the quality, safety and efficacy of their use for various ailments. The present investigation deals with standardization of Saraswatarista which is majorly used as stimulant, soporific, emmenagogue, nervine tonic, and cardio tonic, stomachic, carminative and diuretic. It is also used in the treatment of central

nervous system disorders and dermatological problems. The main objective of the study includes formulation of Saraswatarista, subjected to phytochemical, physicochemical, microbiological, toxicological and pharmacological evaluations using modern analytical tools.

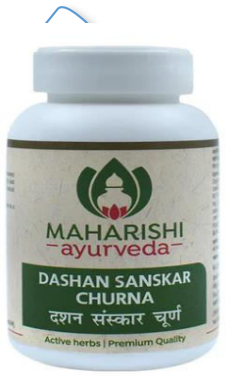
Preparation

Asava Arishta is special Ayurvedic medicine made by soaking herbs (the drugs), either in the form of dry powder or decoction–liquid (Kashaya/kwatha), in a solution of jaggery or sugar. It is kept such for a specified period of time so that it undergoes a process called Sandhana kriya (fermentation) this fermentation generates alcohol which facilitates the extraction of the active principles contained in the herbs or drugs. The alcohol is self-generated and acts as a preservative. The alcoholic content is limited to a maximum of 11% as per the standardization. To prepare Arishta, the mentioned herbs or drugs are coarsely powdered (Yavakuta churna) and then decoction (Kashaya/ kwatha) is prepared from them.

The prepared decoction (Kashaya) is then strained and kept in a safe place in the fermentation vessel, pot, or barrel. jaggery (gud), sugar or honey, according to the formula, is separately dissolved, boiled, filtered and added in the fermentation vessel where decoction is kept. Mentioned Prakshepa Dravyas are made into fine powder and added to that vessel. In the end, an herb called Dhataki Pushpa, (if included in the formula) is added. The mouth of the vessel is completely covered with an earthen lid. The edges of the lid are sealed with clay-smeared cloth in seven consecutive layers. The container is then kept in a heap of paddy. Use of paddy is to ensure a constant temperature during the period of fermentation and also it accelerates the fermentation process. After the specified period, the earthen lid is removed carefully, and the contents of the vessel are examined to ascertain the process of fermentation (Sandhana karma) has been completed or not. The content or fluid is then decanted and

strained and kept as it is for two to three days. It is again strained to mix sediments properly and packed in a glass or pet bottles.

Standardization



Asavas and Aristas are alcoholic preparations, prepared either by soaking the powdered drugs or the decoction of a drug, in a solution of jaggery along with a fermenter for a specified period of time, during which it undergoes fermentation to produce alcohol. These self-generated alcohols facilitate the extraction of active principles present in the drug and also serve as a preservative.

Ghutika

Medicine made into circular shape mass dosage form, is called as Gutika. This can be compared with pills in modern pharmaceutics. Vati is made in the shape of flat circular mass and it is similar to tablet. If the Gutika or Vati medicine is modified into long oval solid shape form, then it is called as Varti. This is commonly used for local administration in anal canal, vaginal canal, penis, eye for different diseases. Medicine moulded into big circular mass form is known as Vataka. Aushadhi churna is mixed with Sarkara and moulded like Pinda (circular mass) then it is called as Pinda or Pindi. Modaka will be having circular shape and having big size, possessing weight around 20g, 50g.

Preparation

General method of preparation: The drugs of plant origin are dried and made into fine powders separately. The minerals are made into Bhasma or Sindura, unless otherwise mentioned. In case where Parada and Gandhaka are mentioned, Kajjali is made first and other drugs are added with it one by one according to the formula. These are put into a Khalva and ground to a soft paste with the prescribed fluids. When more than one liquid is mentioned for grinding, they are used in succession. When the mass is properly ground and is in a condition to be made into Pills, Sugandha dravyas are added and ground

again. The criteria to determine the final stage of the formulation before making pills is that, it should not stick to the fingers when rolled in between two fingers. Pills may be dried in the shade. In case where sugar or jaggery is mentioned, Paka of these should be made on mild fire and removed from the oven. The powders at these ingredients are added to that Paka and briskly mixed. When still warm, Vatakas should be rolled and dried in Shade. For the preparation of Vati Sarngadhara has mentioned the ratio of ingredients that Sita should be taken 4 times, Guda should be taken 2 times, Guggulu and Madhu should take equal quantity and other liquids taken 2 times more than that of Curna used for Vati.

Standardization

Standardization expression is used to describe all measures, which are taken during the manufacturing process and quality control leading to a reproducible quality. It also encompasses the entire field of study from birth of a plant to its clinical application. It also means adjusting the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity respectively by adding excipients or by mixing herbal drugs or herbal drug preparations.

Churna

Churna is defined as a fine powder of drug or drugs in Ayurvedic system of medicine. Drugs mentioned in patha, are cleaned properly, dried thoroughly, pulverized and then sieved. The Churna is free flowing and retains its potency for one year, if preserved in airtight containers. Triphala churna, Trikatu churna, Drakeshadi churna and Sudharsana churna are some of examples. Churna formulation is similar to powder formulations in Allopathic system of medicine. In recent days Churna is formulated into tablets in order to fix the dose easily. These forms of medicament are prescribed generally because of their particle size. Smaller the particle size greater is the absorption rate from G.I.T and hence the greater is bioavailability. It is prescribed by the Ayurvedic physician for treating conditions such as diabetes, indigestion, constipation etc.

Indigestion is a common ailment affecting the general population and in allopathy system antacids are commonly prescribed. Since the usage of such aluminium containing antacids cause deleterious effects like alzheimer's disease upon long term usage, we explored an alternative and safe remedy for indigestion. Hence, we prepared a Churna with natural ingredients commonly used by mankind for culinary purposes. Thus, the present study examined the favourable influence of four spices formulated into Churna said to have digestive property.

Standardization

In the few decades, there has been exponential growth in the field of herbal medicines. Most of the traditional system of medicine is effective but they lack standardization. So, there is a need to develop a standardization technique. Standardization of herbal formulation is essential in order to assess the quality, purity, safety and efficacy of the drug. Dabur Triphala Churna is used for immune system stimulation, improvement of digestion, relief of constipation, gastrointestinal tract cleansing, and relief of gas, treatment of diabetes and treatment of eye disease. The present research study deals with standardization of Dabur Triphala Churna [ex. *Emblica officinalis* (Garetn.) (Amla), *Terminalia bellirica* (Gaertn.) Roxb. (Baheda) and *Terminalia chebula* (Retz.) (Harada)]. The standardization of this formulation, the organoleptic characters, physical properties, the various physicochemical properties such as moisture content, ash values, extractive values were carried out. Heavy metal content studies were also carried out to ascertain the quality, purity and safety of this herbal formulation.

Lehya

Lehya are semisolid Malt/Jam like preparation of drugs, prepared by adding jaggery or sugar and boiled with the prescribed liquid till the correct

constituency is obtained. Then spices and Ghee are added and stirred well. After cooling honey is also added. This means preserving the water extract of medicines in Sugar media. Preparation Avaleha or Lehyam is one of the forms of Ayurvedic medicine which is semi-solid in consistency. It is prepared from mentioned drugs or herbs with the addition of Gur (jaggery), Sharkara (sugar or sugar candy) and boiled with prescribed Swarasa (drug juice) or Kwatha/Kashayam (decoction). Avaleha is also termed as Modaka, Guda, Khanda, Rasayana, Leha, Lehyam etc.

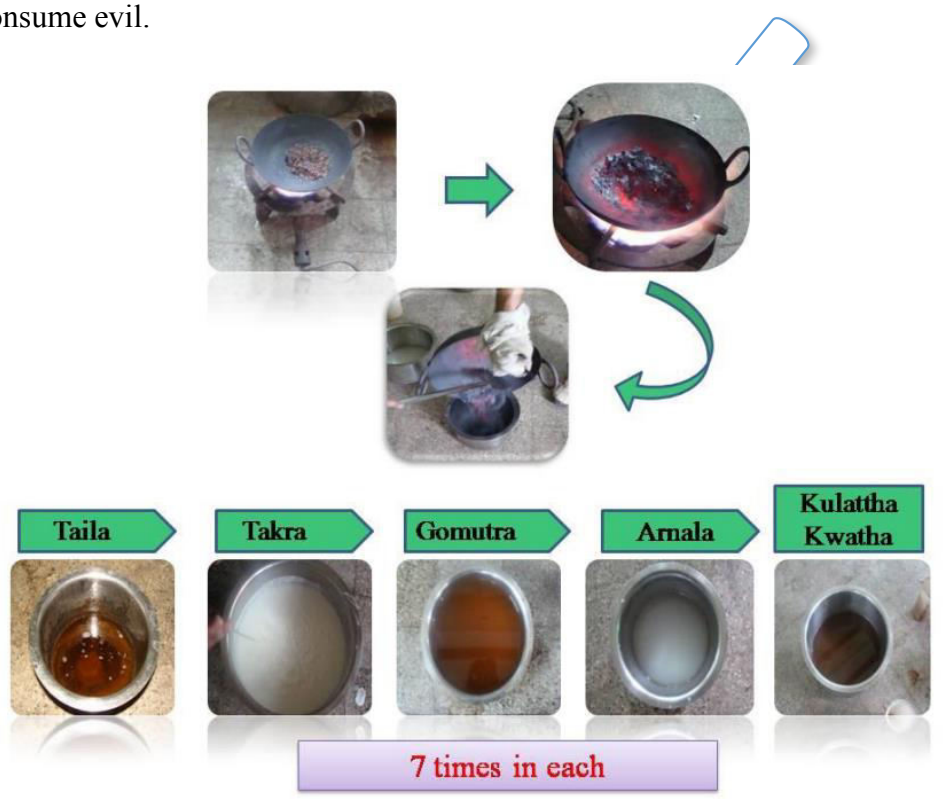
Standardization

Standardization is an important aspect for maintaining and assessing the quality and safety of the polyherbal formulation as these are combinations of more than one herb to attain the desire therapeutic effect. The polyherbal formulation has been standardized on the basis of organoleptic properties, physical characteristics, and physicochemical properties.

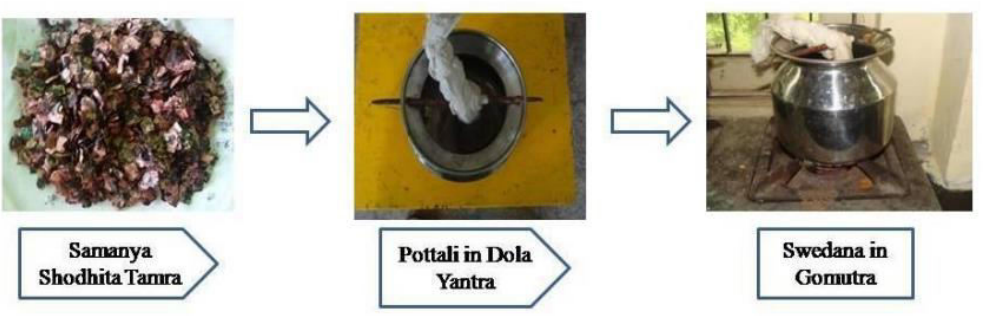
Bhasma

Bhasma is a calcined preparation in which the gem or metal is converted into ash. Gems or metals are purified to remove impurities and treated by triturating and macerating in herbal extracts. The dough so obtained is calcinated to obtain the ashes. Bhasma is a Sanskrit word that means “bone ash,” “cinder” or “disintegration.” It comes from the root bha, meaning “delusion,” “appearance” or “likeness,” and sma, meaning “ever” or “always.” In Hinduism and yoga, bhasma is sacred ash. In some traditions, it is thought to contain the energy of Shiva. In the traditional Indian medical system of Ayurveda, bhasma is a type of medicinal powder made through calcination of stones, gems, minerals or metals. There are a wide range of bhasmas used to treat many types of ailments. In the spiritual context, bhasma symbolizes burning the ego to ashes in order to unite with the higher Self or the divine. It represents liberation from the limitations of mortal life and freedom from the cycle of reincarnation. It is also a reminder of the temporary nature of the physical body, which will one day return to ashes. Also called vibhooti, bhasma

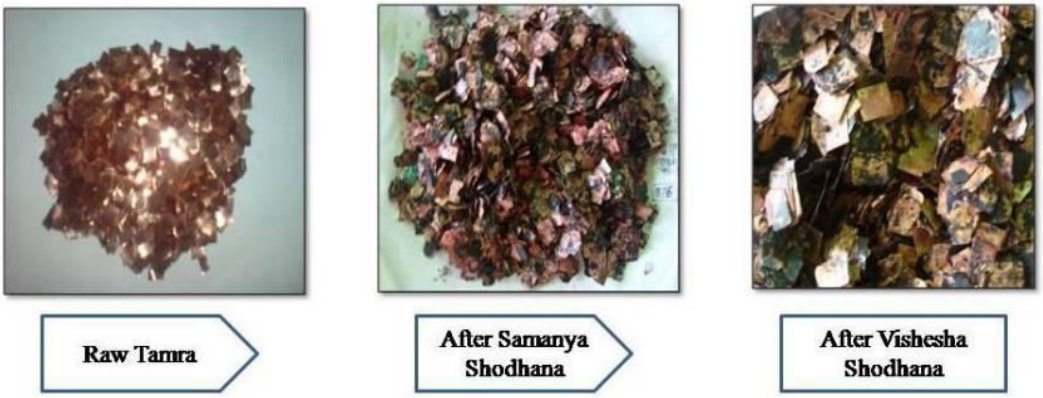
is the sacred ash from the fire of a yogi or saint or from the sacrificial fire known as yajna in which special wood, herbs, grains, ghee and other items are offered as part of a worship ritual. Bhasma is thought to destroy sin and consume evil.



Samanya Shodhana procedure of Tamra



Vishesha Shodhana procedure of Tamra



Appearance of raw, Samanya Shodhita and Vishesha Shodhita Tamra

Preparation

The preparation of Lauha bhasma (iron ash) was carried out following the procedure described in the Ayurvedic Formulary of India. The raw material Lauha curna (Iron powder) was procured from the market in Trichy, India. The preparation involves the following major steps–samanya shodhana (normal purification), vishesha shodhana (special purification), bhanupaka (exposure to sunlight), sthali paka (roasting in an iron pan) and putapaka (calcination).

The various physicochemical evaluation include colour, odour, pH, taste, fineness, loss on drying at 105 ^{0}C, total ash, acid insoluble ash, water soluble ash and particle size mesh test. Tests for heavy/toxic metals should be carried out for standard formulation and their permissible limits.

The following parameters are employed in the evaluation/standardization of Ayurvedic formulations:

- Test for colour
- Test for odour
- Test for foreign matter
- Test for powder microscopy particle size
- Test for loss of drying (105 ^{0}C)/moisture content

- Test for total ash (5% aq. extract)
- Test for water soluble extractive value
- Test for alcohol soluble extractive value
- Test for bulk density
- Assay for specific ingredients
- Test for TLC/HPTLC/HPLC
- Test for heavy metals/toxic metals
- Test for pesticide residues
- Test for microbial contamination
- Test for specific pathogens
- Test for shelf life
- Test for aflatoxins

UNIT-II

NUTRACEUTICALS

Introduction

Nutraceuticals are a group of products that are more than a food but less than a pharmaceutical. It is a substance which may be regarded as a food or part of a food which provides medical or health benefits, helps in prevention and treatment of a disease. These are foods which provides health benefits to reduce the risk of chronic diseases and basic nutrition. A nutraceutical may be a naturally nutrient- rich food such as spirulina, garlic, soy or a specific component of a food like omega-3 oil from salmon. They are also known as medical foods, nutritional supplements and dietary supplements. It ranges from isolated nutrients, dietary supplements, genetically engineered "designer" foods, herbal products, and processed products such as cereals and soups.

They have received considerable interest because of their presumed safety and potential nutritional and therapeutic effects. Foods and nutrients play a vital role in the normal functioning of the body. They help to maintain the health of the individual and to reduce the risk of various diseases. Worldwide acceptance of this fact formed a recognition link between "nutrition" and "health", and thus the concept of “nutraceuticals” evolve dietary active compounds in human nutrition is one of the most important areas of investigation. Examples of nutraceuticals are natural foods, antioxidants, dietary supplements, daisy products, citrus fruits, vitamins, minerals, milk and cereals. These products are generally consumed without medical prescription and supervision. They play vital role in human health and long life.

Nutraceuticals are products that combine elements of nutrition and pharmaceuticals. They are often considered to be a hybrid between food and medicine. The term "nutraceutical" is derived from "nutrition" and "pharmaceutical," highlighting the dual nature of these products. Nutraceuticals are consumed as part of a regular diet to provide health benefits beyond basic nutritional value. They are formulated to offer specific physiological or medicinal effects.

Nutraceuticals can take various forms, including dietary supplements, functional foods, beverages, and herbal products. They are typically designed to promote health, prevent disease, or address specific health conditions. Unlike pharmaceutical drugs, which are primarily used to treat or cure medical conditions, nutraceuticals are often used to support overall wellness and complement a healthy lifestyle.

Nutraceutical is “any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease”. A functional food is defined as “any modified food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains”. A nutraceutical therefore is not a functional food. It is a dietary supplement that encompasses nonnutritive food components such as

phytochemicals, vitamins and minerals, amino acids or botanical compounds such as bioflavonoids or phytochemicals. It is consumed simply for its health promotional or nutritional benefits rather than for its taste, flavour or aromatic attributes. One class of such substances are phytochemicals, which are physiologically active, naturally occurring compounds synthesized by plants that are not classified as nutrients but nonetheless impart a health benefit when consumed. Medicinal herbs, too, have long been valued for their health protecting compounds. Scientists are now working to create nutraceuticals that have higher and more consistent levels of bioactive compounds.

General aspects of nutraceuticals

Nutraceuticals are a broad category of products that bridge the gap between food and pharmaceuticals. They are typically dietary supplements or functional foods that provide health benefits beyond basic nutritional value. Here are some general aspects of nutraceuticals:

- Definition: The term "nutraceutical" is a portmanteau of "nutrition" and "pharmaceutical." It encompasses products that offer health benefits and may include vitamins, minerals, herbal extracts, amino acids, antioxidants, probiotics, and other bioactive compounds.
- Health Benefits: Nutraceuticals are designed to promote health and well-being by providing specific health benefits. These benefits can include enhancing immunity, improving digestive health, supporting cardiovascular health, reducing the risk of chronic diseases, and addressing specific health concerns.
- Natural and Bioactive Ingredients: Nutraceuticals often contain natural and bioactive compounds derived from food sources, such as fruits, vegetables, herbs, and other plants. These compounds can have therapeutic properties and are believed to contribute to the product's health benefits.
- Supplement Form: Nutraceuticals are commonly available in supplement

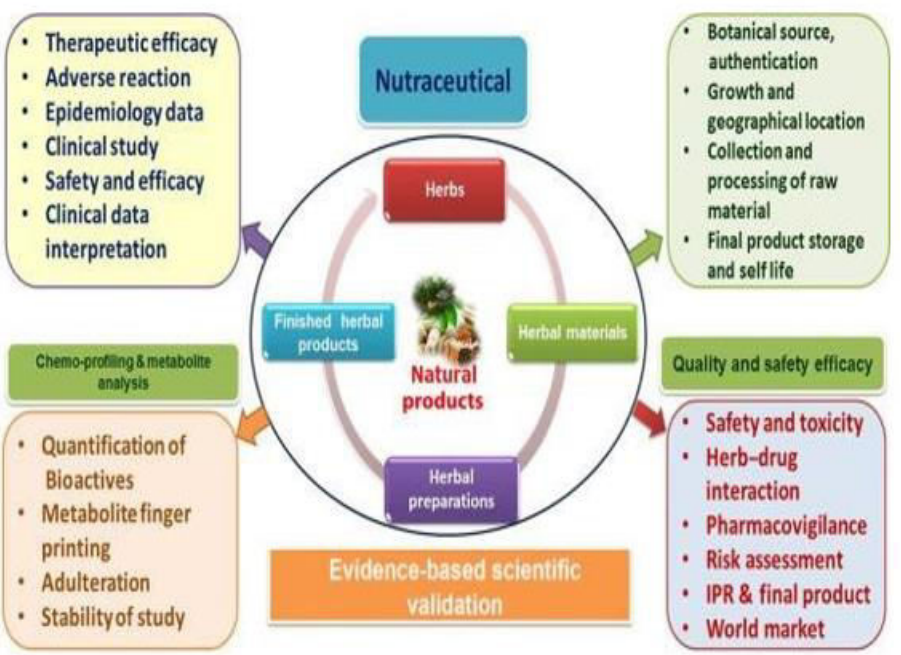
form, including capsules, tablets, powders, and liquids. This makes them convenient for individuals to incorporate into their daily routines.

- Functional Foods: Some nutraceuticals are incorporated into everyday foods and beverages, known as functional foods. Examples include fortified cereals, probiotic yogurt, and beverages containing added vitamins and antioxidants.
- Regulation: The regulation of nutraceuticals varies by country. In some regions, they are regulated as dietary supplements, while in others, they may be subject to more stringent regulations as pharmaceuticals or food additives. In many countries, nutraceuticals are subject to labeling and quality control requirements.
- Safety: While nutraceuticals are generally considered safe when used as directed, it's important to follow dosage instructions and consult with a healthcare professional, especially if you have underlying health conditions, are pregnant or nursing, or are taking other medications.
- Scientific Research: The efficacy of nutraceuticals is often supported by scientific research, including clinical trials and studies. Many researchers and companies in the industry invest in scientific research to establish the health benefits and safety of their products.
- Diverse Product Range: Nutraceuticals encompass a wide range of products, including vitamins, minerals, herbal supplements, probiotics, omega-3 fatty acids, coenzyme Q10, and more. Each product is designed to address specific health concerns or provide targeted benefits.
- Preventive and Therapeutic: Nutraceuticals can be used both preventively and therapeutically. Some individuals take them as a proactive measure to maintain good health, while others use them to manage or alleviate specific health conditions.
- Complementary to Conventional Medicine: Nutraceuticals are often used as complementary or adjunctive therapies alongside conventional medical

treatments. They may help support overall health and wellness but are not typically intended as standalone treatments for serious medical conditions.

- Consumer Awareness: Consumer interest in nutraceuticals has grown significantly in recent years, driven by a desire for natural and alternative healthcare options. This has led to a wide variety of products available in the market.
- Quality Control: Reputable nutraceutical companies prioritize quality control and may adhere to industry standards and third-party testing to ensure the purity and potency of their products.

Nutraceuticals can play a role in promoting health and addressing specific health concerns, but it's essential to approach them with a clear understanding of their intended use, dosage, and potential interactions with other medications or supplements. Consulting with a healthcare professional before adding nutraceuticals to your diet is advisable, especially if you have specific health goals or medical conditions.



Classification of nutraceuticals

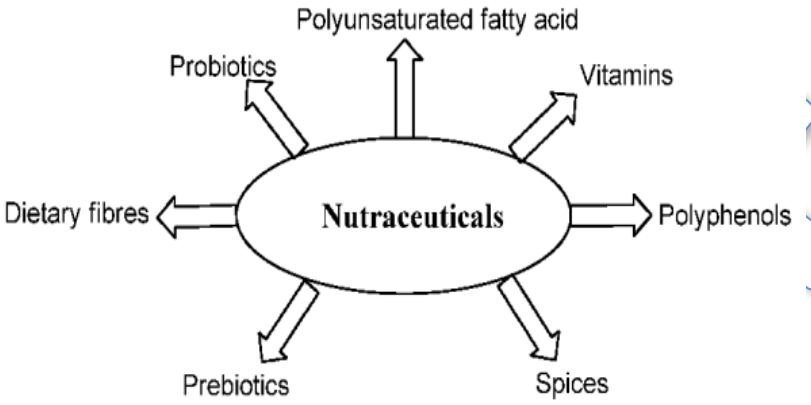
The food sources used as nutraceuticals are all natural and canbe categorized as;

- Dietary Fibers
- Probiotics
- Prebiotics
- Polyunsaturated fatty acids
- Anti-oxidants
- Polyphenols
- Spices

Class	Example
Inorganic mineral supplements	Minerals
Vitamin supplements	Vitamins
Digestive enzymes	Enzymes
Probiotics	*Lactobacillus acidophilus*
prebiotics	Digestive enzymes
Dietary fibers	Fibers
Cereals and grains	Fibers
Health drinks	Fruits juice
Anti-oxidants	Vitamin c
Phytochemicals	Carotenoids
Herbs as a functional food	Soya proteins

Examples of nutraceuticals

Scope and types of products available in the market



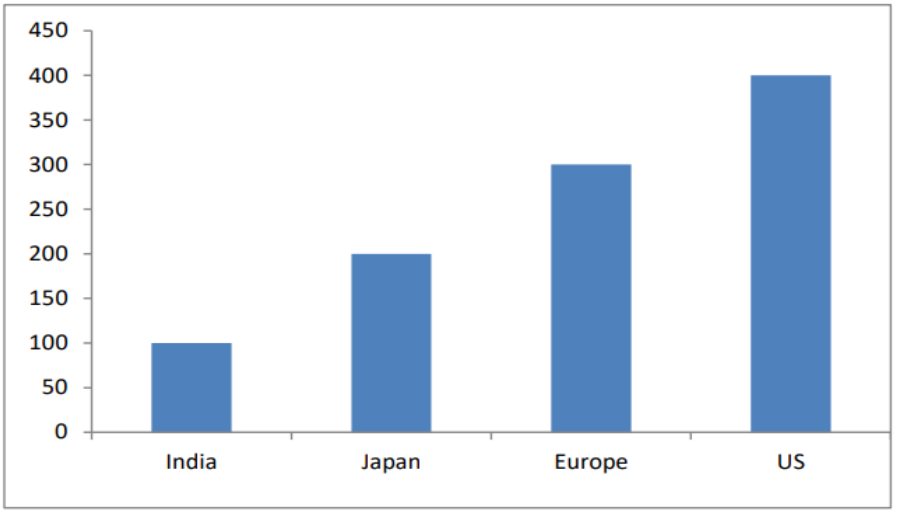
Nutraceutical from Nutrition and Pharmaceutical, in 1989 refers to foods having a medicinal effect on health of human beings. It consists of food supplements, herbal products, probiotics and prebiotics, medical foods meant for prevention and treatment of diseases. Major Nutraceuticals possess multiple therapeutic effects with lacking of unwanted effects. A Nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease. I try to redefine functional foods and Nutraceuticals. When food is being cooked or prepared using scientific intelligence with or without knowledge is called functional food. Thus, functional food provides the body with the required amount of vitamins, fats, proteins, carbohydrates, etc., needed for its healthy survival when functional food aids in the prevention, treatment of disease and disorder other than anemia, it is called a Nutraceutical.

Nutraceuticals are non-toxic food components which claimed to possess multiple therapeutic benefits. Some popular Nutraceuticals include glucosamine, ginseng, Echinacea, folic acid, cod liver oil, omega-3 fatty acid (MUFA, PUFA), calcium-enriched orange juice, green tea, plant phenols etc. Nutraceuticals can be organized in several ways depending upon its easier understanding and application, i.e., for academic instruction, clinical trial design, functional food development or dietary recommendations. Some of the

most common ways of classifying Nutraceuticals can be based on food sources, mechanism of action, chemical nature etc.

Market, growth

In India, functional foods are expected to see increased consumption over the next five years resulting in functional foods and beverages garnering greater product share in the market as opposed to dietary supplements. The total Indian nutraceuticals market in 2015 is expected to be roughly US $ 5 billion. In each product segment, manufacturers can expect a minor shift in consumption, driven by the demand for new and improved product as well their health claims. Interestingly, in the Indian market, the consumption of alternative herbal medicines and supplements (usually Ayurvedic and Homeopathic) is expected to have a detrimental effect on the nutraceutical market and is considered as a loss to the unorganized market by manufacturers. This segment promises huge potential to nutraceutical product manufacturers, through customization of their products to include natural and herbal ingredients. The success of the Chyawanprash supplements market being case in point.

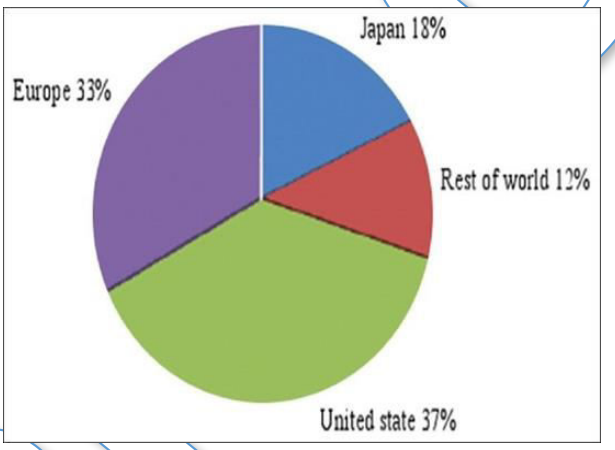


Nutraceutical market in different countries

Increased life expectancy, globally, has led to an increase in the incidence of lifestyle (age related) diseases such as diabetes, high blood pressure and

cholesterol, obesity etc. As a result, there has been a significant increase in the deaths due to lifestyle diseases worldwide. Consumers worldwide are looking to follow healthy lifestyles to obtain optimum nutrition to keep these diseases at bay, leading to an increase in nutraceutical consumption by health-conscious consumers.

Global demand of nutraceuticals: The nutraceutical industry lies under three main segments which include functional foods, dietary supplements, and herbal/natural products. Global nutraceutical market is estimated as USD 117 billion (INR 5148 billion). In 2007, nutraceuticals sale is projected to reach $74.7 billion at an AAGR (Average annual growth rate) of 9.9%. This assumes a world economic recovery in 2003 and an end to price competition.



According to a recent report, the total market for nutraceuticals in India is growing at 21 percent per annum. It is currently valued at INR 44bn (€621 m), but could be worth more than INR 95bn in four years. As a concept, "Nutraceuticals" is still in its stage of infancy in India. But it hasbeen growing much faster than global rates at CAGR (Compound annual growth rate) of 18% for the last 3 years driven by functional food and beverages categories. The most rapidly growing segments of the industry were dietary supplements (19.5 percent per year) and natural/herbal products (11.6 percent per year).

With the ever-changing lifestyle of humans, the antioxidant defense systems are often overloaded resulting in oxidative stress. Moreover, the levels of antioxidant defense mechanism decrease appreciably with age. These may result in the development of a great many diseases. Hence research over the past several decades have primarily focussed on different nutraceuticals. Anti-oxidant products may either function intrinsically to scavenge free radicals (e.g., vitamins, poly unsaturated fatty acids [PUFA]) or specifically stimulate the body's defense system. This review reflects the potential merits and demerits of nutraceuticals among healthy individuals. However, an individual's susceptibility to any particular disease predominantly depends upon genetic predisposition and lifestyle disorders like smoking, high alcohol consumption. So, the response of nutraceuticals canvary from person to person. Nutraceuticals have proven health benefits and their consumption (within their acceptable Recommended Dietary Intakes) will keep diseases at bay and allow humans to maintain an overall good health.

Health benefits

Today the exploration and exploitation of the disease fighting properties of a multitude of photochemical found in both food and non-food plants have created a renaissance in human health and nutrition research. At the same time, many opportunities for the development of novel dietary products have been created. With all new fields of study come new term knew as "Nutraceuticals". A term combining the words "nutrition" (a nourishing food or food component) and "pharmaceutical" (a medical drug), is a food or food product that provides health and medical benefits, including the prevention and treatment of disease. Such products may range from isolated nutrients, dietary supplements and specific diets to genetically engineered foods, herbal products and processed foods such as cereals, soups and beverages. Hippocrates, the father of Western medicine, said that people should "Let food be thy medicine".

The Indians, Egyptians, Chinese, and Sumerians are just a few civilizations that have provided evidence suggesting that food can be effectively used as medicine to treat and prevent disease this fact was supported by Ayurveda, the

five-thousand-year-old ancient Indian health science. In Japan during the 1980s the modern Nutraceutical market began to develop and now days the nutraceutical industry has grown alongside the expansion and exploration of modern Technologies Foods and nutrients play a vital role in normal functioning of the body. They are helpful in maintaining the health of the individual and in reducing the risk of various diseases. Nutraceuticals are medicinal foods that play a role in maintaining well-being, enhancing health, modulating immunity and thereby preventing as well as treating specific diseases. Thus, the field of Nutraceutical can be envisioned as one of the missing blocks in the health benefit of an individual.

It has been scientifically proved and supported that nutraceutical are efficacious to treat and prevent various disease conditions. About 2000 years ago, Hippocrates correctly emphasized "Let food be your medicine and medicine be your food". In the past five years, the world has witnessed the explosive growth of a multibillion-dollar industry known as Nutraceutical. The term "Nutraceutical" combines the word "nutrient" (a nourishing food or food component) with "pharmaceutical" (a medical drug). "Nutraceutical" is a term coined in 1979 by Stephen De Felice. It is defined "as a food or parts of food that provide medical or health benefits, including the prevention and treatment of disease." Nutraceuticals may range from isolated nutrients, dietary supplements, and diets to genetically engineered "designer" food, herbal products, and processed products such as cereals, soups, and beverages. A Nutraceutical is any nontoxic food extract supplement that has scientifically proven health benefits for both the treatment and prevention of disease.

Role of nutraceuticals in ailments like diabetes, CVS diseases, cancer, irritable bowel syndrome and various gastro intestinal diseases

Cardiovascular diseases

Worldwide, the burdens of chronic diseases like cardiovascular diseases, cancers, diabetes and obesity are rapidly increasing. In 2001, chronic diseases contributed approximately 59% of the 56.5 million total reported deaths in the

world and 46% of the global burden of disease. Cardiovascular diseases (CVD) are the name for the group of disorders of the heart and blood vessels and include hypertension (high blood pressure), coronary heart disease (heart attack), cerebrovascular disease (stroke), heart failure, peripheral vascular disease, etc. In 1999 CVD alone contributed to a third of global deaths and by 2010 it would be the leading cause of death in developing countries. Majority of the CVD are preventable and controllable. It was reported that low intake of fruits and vegetables is associated with a high mortality in cardiovascular disease. Many research studies have identified a protective role for a diet rich in fruits and vegetables against CVD. This apart, nutraceuticals in the form of antioxidants, dietary fibers, omega-3 polyunsaturated fatty acids (n-3 PUFAs), vitamins, and minerals are recommended together with physical exercise for prevention and treatment of CVD.

It has been demonstrated that the molecules like polyphenols present in grapes and in wine alter cellular metabolism and signalling, which is consistent with reducing arterial disease. Flavonoidsare widely distributed in onion, endives, cruciferous vegetables, black grapes, red wine, grapefruits, apples, cherries and berries. Flavonoids in plants available as flavones (containing the flavonoid apigenin found in chamomile); flavanones (hesperidins - citrus fruits; silybin-milk thistle flavanols (tea; quercetin, kaempferol and rutin grapefruit; rutin buckwheat; ginkgo flavonglycosides - ginkgo) play a major role in curing the cardiovascular diseases. Flavonoids block the angiotensin-converting enzyme (ACE) that raises blood pressure; by blocking the "suicide" enzyme cyclo-oxygenase that breaks down prostaglandins, they prevent platelet stickiness and hence platelet aggregation. Flavonoids also protect the vascular system and strengthen the tiny capillaries that carry oxygen and essential nutrients to all cells.

Diabetes

Diabetes mellitus is characterized by abnormally high levels of blood glucose, either due to insufficient insulin production, or due to its ineffectiveness. The most common forms of diabetes are type 1 diabetes (5%), an auto-immune

disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes occurs in pregnancy. Globally the total number of people with diabetes is projected to raise from 171 million in 2000 to 366 million in 2003. Docosahexaenoic acid modulates insulin resistance and is also vital for neurovisual development. This is especially important in women with gestational diabetes mellitus which foster the recommendation for essential fatty acids during pregnancy.

Lipoic acid is a universal anti-oxidant, now used in Germany for the treatment of diabetic neuropathy. It is possible that lipoic acid may be more effective as a long-term dietary supplement aimed at the prophylactic protection of diabetics from complications. Dietary fibers from psyllium have been used extensively both as pharmacological supplements, food ingredients, in processed food to aid weight reduction, for glucose control in diabetic patients and to reduce lipid levels in hyperlipidemia. Good magnesium status reduces diabetes risk and improves insulin sensitivity; chromium picolinate, calcium and vitamin D appear to promote insulin sensitivity and improve glycemic control in some diabetics; extracts of bitter melon and of cinnamon have the potentialto treat and possibly prevent diabetes. However, it has been suggested that nutraceuticals with meaningful doses of combinations may substantially prevent and presumably could be marketed legally.

Cancer

Flavonoids which block the enzymes that produce estrogen reduce of estrogen induced cancers. Phytoestrogens is recommended to prevent prostate/breast cancer. Soy foods are source of Iso-flavones, curcumin from curry and soya isoflavones possess cancer chemo preventive properties. Lycopene concentrates in the skin, testes, adrenal and prostate protects against cancer. Saponins contains anti-tumor and anti-mutagenic activities. Curcumin (diferuloylmethane) which is a polyphenol of turmeric possesses anti-carcinogenic, anti-oxidative and anti-inflammatory properties. Beet roots, cucumber fruits, spinach leaves, and turmeric rhizomes were reported to possess anti-tumor activity.

Irritable bowel syndrome

Inflammatory bowel diseases/syndrome (IBD/S), including Crohn's disease (CD) and ulcerative colitis (UC), are a group of idiopathic, chronic and relapsing inflammatory disorders of the gastrointestinal tract, whose incidence and prevalence has been increasing in the last decades. Nutraceuticals is a broad term used to describe any product derived from food sources claiming extra health benefits beyond the intrinsic nutritional value found in foods. The beneficial effects of nutraceutical compounds in human health have been emerging in the last decades. Although few clinical trials have been performed in IBD patients, nutraceuticals, such as herbal products or vitamins, are generally accepted as safer alternative/supplementation to conventional therapy. Various nutraceuticals are used to treat IBD are curcumin, aloe vera, the Bael, garlic, honey, probiotics, minerals.

Gastro intestinal disease

Eating habits and trends in food production and consumption have health, environmental and social impacts. Diet has implications on gut health. Gut complications, such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, and gluten therapy resistant celiac, result from overgrowth and imbalance of intestinal microbial flora, and are related to one's diet. Gut health determines an individual's overall health. The human gut has the following functions: (a) it breaks food down to nutrients, (b) it facilitates absorption of nutrients into the blood through intestinal walls, and (c) it prevents foreign and toxic molecules from entering the bloodstream. Gut malfunction, therefore, has a direct negative impact on human health. This review focuses on the role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutraceuticals are widely used (maximum) in treatment in GI disorders. Various nutraceuticals are used to treat GI disease are dietary fibers, curcumin, anti-oxidants, aloe vera, the Bael, garlic, honey, probiotics, minerals, carbohydrate diets, and omega-3-fatty acids.

Various nutraceuticals used against different diseases

S. No.	Disease	Examples
1	Alzheimer	Vitamin E & C, Alpha-lipoic acid
2	Cardiovascular	Flavonoids (onion, black grapes)
3	Parkinson	Vitamin E
4	Obesity	Chitosan, fenugreek, vitamin C
5	Diabetes	Calcium, vitamin, *Emblica officinalis*
6	Osteoarthritis	Glucosamine, chondroitin sulphate
7	Constipation	Buck wheat
8	Vision improving	Carrot, mangoes, spinach, kiwi, egg yolk
9	Anti-oxidant	Oats, fruits, carrots
10	Anti-inflammatory	Turmeric
11	Hypertension	Curry leaf, green tea
12	Hyperlipidemia	*Emblica officinalis*

Constipation

Constipation is a common gastrointestinal disorder that refers to inadequate bowl movement or hardness of passing intestinal contents. Difficulty in defecation is one of the commonly seen symptoms associated with hard and dry stool. Persistence of constipation can last for weeks or even longer, which may raise the necessity of medical intervention. Substances that either loosen stools or stimulate a bowel movement are called laxatives. For occasional constipation, laxatives are usually recommended for helping defecation. Lots of botanic products can promote this beneficial effect, and have been used even from ancient times. Senna is one of the mostly used therapies which comes from an important class of botanic laxatives, anthraquinone drugs. The class also has cascara, frangula, aloe, and rhubarb included, and is enriched in corresponding plants and herbs in forms of glucoside derivatives of anthracene,

i.e., the anthraquinones. Psyllium is a frequent bulk laxative for constipation. Psyllium was demonstrated to increase stool frequency and improve stool consistency.

Functional dyspepsia

Functional dyspepsia (FD) is one of the most prevalent chronic functional gastrointestinal disorders which includes three subtypes: postprandial distress syndrome (PDS), epigastric pain syndrome (EPS) and a subtype with both PDS and EPS features. *Pimpinella anisum* (Apiaceae), also known as aniseed, is one of the oldest species used in Egypt, Greece, Rome, and the Middle East. Its essential oil has been reported to have anti-spasmodic, secretolytic, secretomotor, and anti-bacterial effects. Extracts of *Pimpinella anisum* activated the NO-cGMP pathway and had a significant muscle relaxant effect. A double-blind, randomized clinical trial have confirmed the effects of *Pimpinella anisum* on relieving the symptoms of functional dyspepsia.

Acid reflux

Acid reflux, also known as gastroesophageal reflux disease (GERD), is the back flow of stomach acid into esophagus that causes the primary symptom as heartburn. It is one of most common digestive problems seen in daily life, and can be occasionally provoked by irritating foods like coffee or cold drinks. Alginic acid is a polysaccharide from brown seaweed. It has been used for many years in food, cosmetics, and pharmaceutical products as an approved ingredient by FDA, as emulsifier, thickener, and stabilizer. Aloe vera (A. vera) gel is an extract of *Aloe barbadensis*, which has wide applications for the treatment of GI disorders. A. vera gel has been reported to possess biological effects such as wound-healing, anti-microbial effects, anti-inflammatory, and anti-proliferation. All of these properties are important for the treatment of GERD. In a randomized, positive controlled trial, 4 weeks of A. vera syrup administration to subjects showed A. vera was safe, well tolerated and effective for reducing the symptoms of GERD.

Gastrointestinal neoplasia

Gastrointestinal neoplasia is a general name of the malignant disorders occur in gastrointestinal tract and its accessory organs. Among all types of cancer, gastrointestinal neoplasia is common in population all over the world and is highly associated with life-styles, which is believed can be actively prevented through appropriate lifestyle modification including dietary habits. Resveratrol is a polyphenol compound, similar to flavonoids like curcumin, which has been shown to target pro-inflammatory molecules and pathways.

Diverticular disease

Diverticular disease of the colon is one of the most common disorders with increasing prevalence in western countries. Diverticular disease is a medication status and characterized by the outpouching of the colonic mucosa and submucosa through the muscular layer. Diverticular disease has asymptomatic diverticulosis and symptomatic diverticulitis. Psyllium is a commonly used soluble dietary fiber from the husks of the psyllium (*Plantago ovata*) seed, associated with a potential role in the treatment and prevention of bowel diseases such as diverticulosis, irritable bowel syndrome and inflammatory bowel disease. Quercetin is a well-known polyphenol which is widely distributed in many fruits and plants like apples, onion, green tea, etc. Quercetin undergoes extensive phase II metabolism in the intestine and liver and presents as different forms of its metabolites. Moreover, quercetin is claimed to exert many biological functions against allergies, inflammation, microbes, ulcers, hepatotoxin, viruses and tumours.

Colon cancer

Colorectal cancer (CRC), also known as bowel cancer, colon cancer, or rectal cancer, is the third most common malignancy in the United States. Colorectal cancer usually begins with polyps, a nonspecific term to describe an unknown growth on epithelial wall of the colon. omega-3 is beneficial to human health, the secondary lipid oxidation products, especially in the presence of heme iron or pro-oxidants, are potential hazardous and so it is suggested to be used with

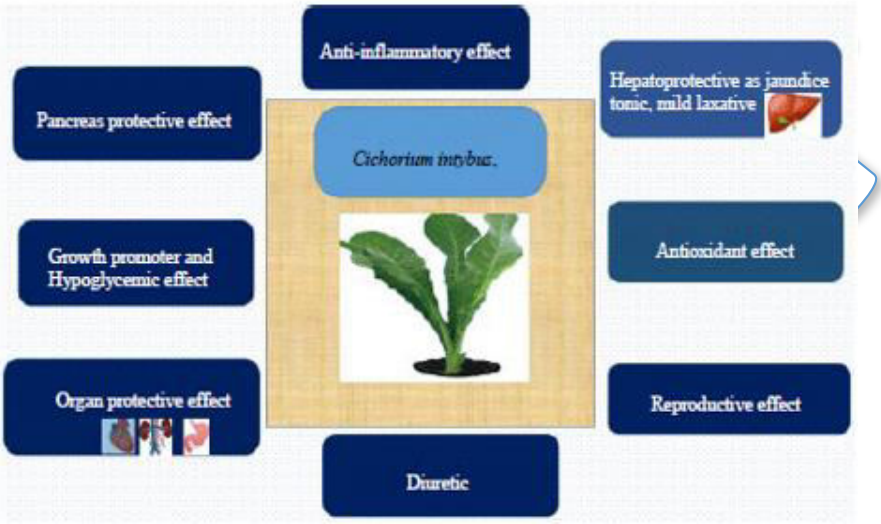
caution. Folic acid and folate are two forms of vitamin B, which are essential for DNA synthesis, repair, methylation and aberrations of which contribute to the development of colorectal cancer. Vitamin B is naturally present in in dark green leafy vegetables, beans, peas and nuts. Folate and folic acid are rich in fruits including oranges, lemons, bananas, melons and strawberries.

Herbs as health food

Alfalfa: Alfalfa is an herb. People use the leaves, sprouts, and seeds to make medicine. Alfalfa is used for kidney conditions, bladder and prostate conditions, and to increaseurine flow. It is also used for high cholesterol, asthma, osteoarthritis, rheumatoid arthritis, diabetes, upset stomach, and a bleeding disorder called thrombocytopenic purpura. People also take alfalfa as a source of vitamins A, C, E, and K_4; and minerals calcium, potassium,phosphorous, and iron. It is used in high cholesterol. Taking alfalfa seeds seems to lower total cholesterol and "bad" low-density lipoprotein (LDL) cholesterol in people with high cholesterol levels, kidney problems, bladder problems, prostate problems, asthma, arthritis and diabetes.

Chicory: Chicory (*Cichorium intybus*) is a perennial herbal plant of the dandelion family Asteraceae. In addition, chicory herb plays a key role as antioxidant, anti-inflammatory, sedative, immunological, productive and reproductive enhancer, cardiovascular, hypolipidemic, anti-cancer, anti-protozoal, gastroprotective, anti-diabetic, analgesic, anthelmintic, anti-

microbial, wound healing and bitter tonic without inducing therapeutic adverse effect. Also, chicory plant is a good and very important protective source for hepatocytes and other liver cells as well as it is used as prebiotic against some species of pathogenic bacteria for both *in vitro* and *in vivo*.



Ginger: It is the dried rhizomes of *Zingiber officinale*, belonging to family Zingiberaceae.It contains volatile oils, minerals, resins. Ginger oil contains zingiberene, bisabolene, curcumin. Resins contain phenolic ketones such as gingerols, shogaols, zingerone and other compounds. Ginger is commonly used for various types of "stomach problems," including motion sickness, morning sickness, colic, upset stomach, gas, diarrhea, irritable bowel syndrome (IBS), nausea, nausea caused by cancer treatment, nausea caused by HIV/AIDS treatment, nausea and vomiting after surgery, as well as loss of appetite. Other uses include pain relief from rheumatoid arthritis (RA), osteoarthritis, menstrual pain, and other conditions. However, there is not strong evidence to support the use of ginger for these conditions. Some people pour the fresh juice on their skin to treat burns. The oil made from ginger is sometimes applied to the skin to relieve pain. Ginger extract is also applied to the skin to prevent insect bites. In foods and beverages, ginger is used as a flavouring agent. In manufacturing, ginger is used as for fragrance in soaps and

cosmetics. One of the chemicals in ginger is also used as an ingredient in laxative, anti-gas, and antacid medications.

Fenugreek: Fenugreek (*Trigonella foenum-graecum*) is a legume and it has been used asa spice throughout the world to enhance the sensory quality of foods. It is known for its medicinal qualities like anti-diabetic, anti-carcinogenic, hypocholestermic, anti-oxidant, immunological activity etc. It contains alkaloids, flavonoids, coumarins, proteins, amino acids and steroidal saponins.

Garlic: It consists of dried bulbs of *Allium sativum*, belonging to the family Liliaceae. *Allium sativum* pulp contains vitamins especially B_1, vitamin C, vitamin A, flavonoids, ascorbic acid, phosphorous, potassium, sulphur, selenium, calcium, magnesium, germanium, sodium, iron, manganese and trace iodine. Garlic is being used from thousandsof years for its medicinal properties. Numerous researches have proved its beneficial role in cardiovascular condition. Indeed, garlic does indeed have cardioprotective

properties. Researches also proved its active role as anti-cancer, natural immunity booster, anti-oxidant, anti-biotic and anti-diabetic product. On other hand studies also report some side effects of garlic if it is used with blood-thinners, anti-HIV or hypoglycemic drugs.

Honey: It is a sugar like secretion deposited in honey comb by the bees *Apis mellifera*, *Apis dorsata* and other species of Apis belonging to family: Apidae. Honey is an aqueous solution containing 35% glucose, 45% fructose and 2% sucrose. It is used as demulcent, sweetening agent, nutrient, anti-septic and expectorant, pharmaceutical aid.

Amla: *Emblica officinalis* (i.e., *Phyllanthus emblica*/Indian gooseberry/Amla) has been used extensively as a nutraceutical in several diseases since it is known to boost immunity and offers numerous health benefits such as anti-oxidant, anti-inflammatory, and anti-aging effects. Phytochemically, it is composed of several bioactive compounds such as flavonoids (i.e., Quercetin,

Kaempferol), phenolic compounds (i.e., gallic acid, methyl gallate, ellagic acid, trigallayl glucose), tannins (i.e., Emblicanin A and B, phyllemblicin B, punigluconin, pedunclagin, chebulinic acid, corilagin, geraniin, ellagotannin), amino acids (i.e., glutamic acid, aspartic acid, alanine, lysine, proline, cystine), fatty acids (i.e., stearic acid, oleic acid, palmitic acid, myristic acid, linolenic acid, linoleic acid), alkaloids (i.e., phyllantine, phyllembein, phyllantidine), pectin, citric acid, ascorbic acid (Vitamin C), cellulose, gum, and albumin. It is used in the treatment of anaemia, diarrhoea, and jaundice etc.

Ginseng: It consists of roots of the plant *Panax ginseng* and other species of pabax belonging to the family Araliaceae. It contains saponins, glycosides, volatile oils, sterols, polysaccharides, minerals vitamin-B, biotin etc. Ginseng has beneficial antioxidant and anti-inflammatory properties. Ginseng could help improve brain functions like memory, behaviour and mood. Ginseng has been shown to benefit mental functions, feelings of calmness and mood in both healthy people and those with alzheimer's disease.

Ashwagandha: It consist of dried roots and stem bases of the plant *Withania somnifera* belonging to the family Solanaceae. The name "ashwagandha" is derived from two Sanskrit words: "ashwa" meaning "horse" and "gandha" meaning "smell," which roughly translates to "horse-like smell," or "horse essence," which could be a reference to the traditional belief that the root provides the strength, character, essence, or stamina of a stallion. Ashwagandha, has health benefits which are as follows such as it controls cholesterol levels, increases fertility in men, reduces anxiety, relieves stress, fights diabetes, controls hair fall, hinders, treat osteoporosis, rheumatic arthritis, treats cancer, increases blood production, prevents seizures, aids in muscle growth, stimulates the thyroid gland, reduces ocular diseases, anti-tumor, anti-inflammatory and antibacterial properties etc.

Spirulina: Spirulina is a biomass of cyanobacteria (blue-green algae) that can be consumed by humans and animals. The two species are *Arthrospira platensis* and *A. maxima*. As an ecologically sound, nutrient-rich dietary supplement, spirulina is being investigated to address food security and malnutrition, and as dietary support in long-term space flight or Mars missions. Its advantage for food security is that it needs less land and water than livestock to produce protein and energy. Dried spirulina contains 5% water, 24% carbohydrates, 8% fat, and about 60% (51–71%) protein. Provided in its typical supplement form as a dried powder, a 100g amount of spirulina supplies 290 kilocalories (1,200 kJ) and is a rich source (20% or more of the Daily

Value, DV) of numerous essential nutrients, particularly protein, B vitamins (thiamine, riboflavin and niacin, providing 207%, 306%, and 85% DV, respectively), and dietary minerals, such as iron (219% DV) and manganese (90% DV). The lipid content of spirulina is 8% byweight (table) providing the fatty acids, gamma-linolenic acid, alpha-linolenic acid, linoleic acid, stearidonic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid.

Summary

Functional foods and nutraceuticals are purported to be efficacious in the prevention and/or treatment of disease and the promotion of health due to the presence of specific concentrations of physiologically active components. The number of functional foods is potentially very large and encompasses natural foods, isolated components from these foods that are added to other foods or packaged as dietary supplements, and food components synthesized in the laboratory.

Although there is evidence to support the use of certain functional foods and nutraceuticals in companion animals, for a number of products beneficial effects are yet to be conclusively proven. Furthermore, it is important for the pet owner to realize that in the context of a balanced diet, no benefit may be gained from consumption of functional foods/nutraceuticals.

Herbal-drug and herb-food interactions

Introduction

According to the World Health Organisation, herbal medicines are defined as 'finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state oras plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines. Thus, herbal medicines contain a combination of pharmacologically active plant constituents that are claimed to work synergistically to produce an effect greater than the sum of the effects of the single constituents.

All medicines were derived from natural materials in the ancient time. Most of those early medicines are described under the broad heading "herbs," although that term may prove misleading. Even though people often think of herbs as plants or plant-derived materials, several commonly used items were obtained from animals and minerals. Further, although the term "herbs" suggests something that is beneficial and has little potential for harm, numerous toxic materials were used, such as foxglove, deadly nightshade, and jimson weed (Datura). Herbalists sometimes processed the herbs to change them from their original form. As the science developed the researchers attempted and succeeded to isolate some active constituents from herbs, so that the end products were not as nature presented them. For example, aconite was processed extensively in China to reduce its toxicity so that it could more readily be used, and borneol, the active constituent found in a few tropical plants, was isolated centuries ago in relatively pure form, a translucent crystal, for both internal and external use. The use of potent and toxic substances and the intentional alteration of natural substances are characteristics of production of modern drugs. Thus, some issues that arise today about interactions of herbs

and drugs may have already been encountered in earlier times when herbs were combined with each other.

The ancient Indian system of Ayurveda is practicing in India since 1500 BC; the main aim of this system is to preservation of normal health and curing the diseased one. Ayurveda has focused on patient safety and benefits. In fact, it is known that drug safety is a very basic and fundamental concept in medical practice. The current raised issue with respect to Alternative medicine and Ayurveda is increasing reports of Adverse Drug Reaction (ADR) related to herbal medicine. This may be due to increase in number of people taking herbal products either as a medicine or as a nutritional supplement. Such reports many a times neglect to identify the cause behind the event which can be pertaining to variety of issues which are already considered in Ayurveda but are neglected many a times either due to ignorance or negligence. There is misbelief that natural drugs are safe and devoid of toxicity.

There is a general belief by the public that herbal medicines are safe because they are natural. However, this is a hazardous oversimplification. Many different side effects to herbs have been reported and recently reviewed, including adverse events caused by herb-to-drug interactions. Since allherbal medicines are mixtures of more than one active ingredient, such combinations of many substances obviously increase the likelihood of interactions taking place. Hence, theoretically, the likelihood of herb-to-drug interactions is higher than drug-to-drug interactions, if only because synthetic drugs usually contain single chemical.

Even though herbal medicines are obtained from natural sources, their active ingredients are potent chemicals which can give rise to herb-drug or herb-food interactions. Herbal supplements and nutraceuticals are been purchased over the counter (OTC) and may be labelled as "All Natural" but that does not mean they are always safe.

Herbal supplements are not subject to review by the FDA and their use can often be risky when taken along with other drugs or foods. Following are the general guidelines which help minimizing herb-drug or herb-food interactions.

1. Avoid taking mucilage containing herbs like isapgol, flax with other drugs, as mucilage can inhibit the absorption of many drugs. Even mucilage containing drugs can alter the blood sugar levels which have to be considered in case of diabetic patients.
2. Spicy substances such as ginger, capsicum, etc. can enhance the absorption rate of some drugs, hence they need to be taken one hour after drug administration.
3. Heart tonic herbs such as hawthorn/digitalis/cactus, should be avoided when taking heart medications.
4. Caffeine containing herbs like green tea, kola nut, coffee and herbal stimulants like ephedra should be avoided when taking heart medications or mood-altering drugs or anti-depressants.
5. Avoid herbs or formulations containing liquorice when using diuretics like furosemide because liquorice can cause potassium depletion from the body.
6. While taking antidepressants like mono amino oxidase (MAO) inhibitors, avoid African aphrodisiac herbs containing yohimbine.
7. Green vegetables like broccoli, spinach, cabbage, etc. which have high vitamin-K content are reported to interact with anticoagulant drugs as vit-K has coagulation promoting effects.
8. Grape fruit juice interacts with calcium channel blockers (anti-hypertensives), lipid lowering drugs. psychiatric medications, oral contraceptives and anti-allergy medications. Grape juice modifies the metabolism pattern of these drugs in the liver.

Mechanisms of herb-to-drug interactions:

Herb-to-drug interactions are based on the same pharmacokinetic (changes of plasma drug concentration) and pharmacodynamic (drugs interacting at receptors on target organs).

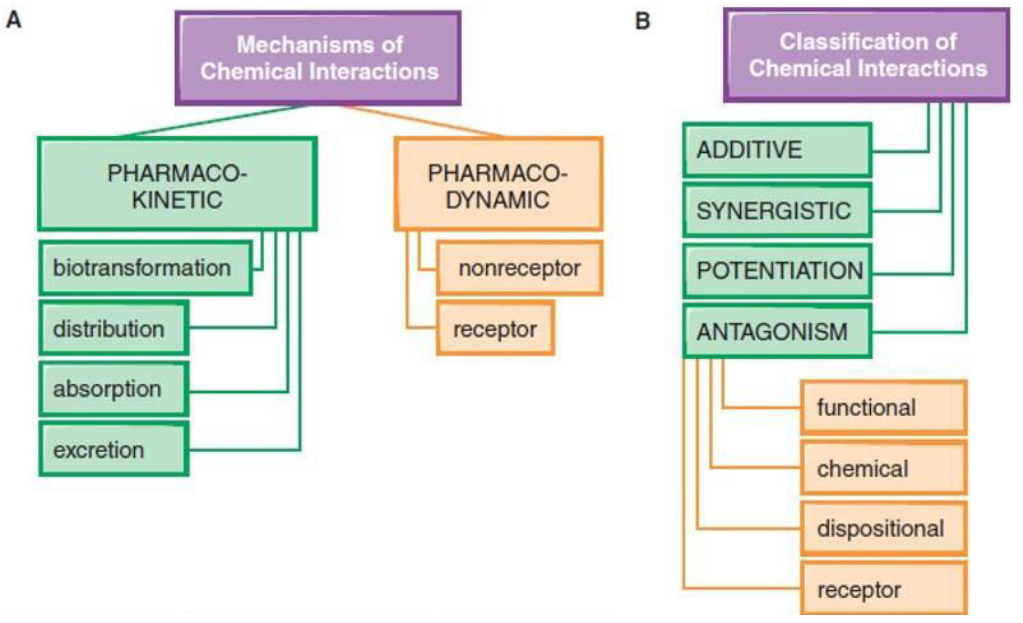
Principles as drug-to-drug interactions

A drug interaction is a change in the action or side effects of a drug caused by concomitant administration with a food, beverage, supplement, or another drug. There are many causes of drug interactions. For example, one drug may alter the pharmacokinetics of another. Alternatively, drug interactions may result from competition for a single receptor or signaling pathway. The risk of a drug-drug interaction increases with the number of drugs used. Over a third (36%) of the elderly in the U.S. regularly uses five or more medications or supplements, and 15% are at potential risk of a significant drug-drug interaction. When two drugs are used together, their effects can be additive (the result is what you expect when you add together the effect of each drug taken independently), synergistic (combining the drugs leads to a larger effect than expected), or antagonistic (combining the drugs leads to a smaller effect than expected). There is sometimes confusion on whether drugs are synergistic or additive, since the individual effects of each drug may vary from patient to patient. A synergistic interaction may be beneficial for patients, but may also increase the risk of overdose.

Pharmacokinetic interactions - that have been identified so far all point towards the fact that a number of herbs, most notably St. John's wort, can affect the blood concentration of different conventional medicines that are metabolized by cytochrome P450 (CYP, the most important phase-I drug-metabolizing enzyme system) and/or are transported by P-glycoprotein (a glycoprotein which influences drug absorption and elimination by limiting the cellular transport from the intestinal lumen into epithelial cells and by enhancing the excretionof drugs from hepatocytes and renal tubules into the adjacent luminal space). Polymorphisms in the genes for CYP enzymes and P-

glycoprotein may influence the interactions mediated through these pathways. Probe drugs used in pharmacokinetic trials include midazolam, alprazolam, nifedipine (CYP3A4), chlorzoxazone (CYP2E1), debrisoquine, dextromethorphan (CYP2D6), tolbutamide, diclofenac and flurbiprofen (CYP2C9), caffeine, tizanidine (CYP1A2) and omeprazole (CYP2C19). Fexofenadine, digoxin and talinolol have been extensively used in pharmacokinetic trials as P-glycoprotein substrates.

Pharmacodynamic interactions - have been less studied but may be additive (or synergetic), i.e., the herbal medicines potentiate the pharmacological/toxicological action of syntheticdrugs, or antagonistic, i.e., the herbal medicines reduce the efficacy of synthetic drugs. Warfarin interactions are a classic example of pharmacodynamic interactions. Theoretically,increased anticoagulant effects could be expected when warfarin is combined with coumarin- containing herbs (some plant coumarins exert anticoagulant effects) or with antiplatelet herbs. Conversely, vitamin K-containing herbs can antagonize the effect of warfarin (the action of warfarin is due to its ability to antagonize the cofactor function of vitamin K) entities.



Study of drugs and their side effects and interactions

Hypericum

St. John's Wort (*Hypericum perforatum*) extracts are widely used as a safe alternative to conventional anti-depressant drugs for mild to moderate forms of depressive disorders. The herb contains numerous compounds with documented biological activity, including the naphthodianthrone hypericin, a broad range of flavonoids, and the phloroglucinol hyperforin, which inhibits the re-uptake of several brain neurotransmitters, including 5-hydroxytryptamine (5-HT, serotonin). Pharmacodynamic interactions may occur when St. John's wort is given together with drugs that enhance 5-HT signaling in the brain (e.g., 5-HT re-uptake inhibitors, 5-HT ligands). St. John's wort has been shown to clinically interact with a number of conventional drugs mostly via these pharmacokinetic and/or pharmacodynamic mechanisms; such interactions take place with immunosuppressants (cyclosporine, tacrolimus, prednisone), hormones (oral pill, tibolone), cardiovascular drugs (the anti-coagulants warfarin and phenprocoumon, the cardiac inotropic drug digoxin, the anti-lipidemic drugs simvastatin, rosuvastatin and atorvastatin, the calcium blockers nifedipine and verapamil. More recent information suggests other chemicals like hyperforin may play a larger role. These chemicals act on messengers in the nervous system that regulate mood.

Kava-kava

Preparation from the rhizome and roots of *Piper methysticum* (Fam. Piperaceae) are used for the treatment of anxiety, and theavailable evidence suggests that kava extracts are superior to placebo for treating patients with anxiety disorders. Unfortunately, in the UK and various other European countries, the sale of kava is currently prohibited due to reports of potential hepatotoxicity. *In vitro*, kavalactones, the active ingredients of kava, have been shown to be potent inhibitors of several enzymes of the CYP450 system. However, clinical trials have shown that, at therapeutic doses, kava inhibits CYP2E1 but no other CYP isoforms, such as CYP3A4, CYP2D6 or CYP1A2. Some possible pharmacodynamic interactions, highlighted by single case reports have been postulated to occur when combining kava with benzodiazepines, anti-parkinson or anti-depressant drugs. Kava is applied to the skin for skin diseases including leprosy, to promote wound healing, and as a pain killer. It is also used as a mouthwash for toothaches. Kava is also consumed as a beverage in ceremonies to promote relaxation. Kava affects the brain and other parts of the central nervous system. The kava-lactones in kava are believed to be responsible for its effects.

Ginkgo biloba

Extracts from the leaves of the ginkgo tree (*Ginkgo biloba*, Fam. Ginkgoaceae) are used for the treatment of cognitive impairments, dementia, intermittent claudication and tinnitus. The effect of ginkgo on various CYP isoforms as well as on P-glycoprotein has been investigated in a number of clinical trials by using different probe drugs, such as alprazolam, midazolam, diazepam,

nifedipine (CYP3A4), caffeine (CYP1A2), chlorzoxazone (CYP2E1), debrisoquine (CYP2D6), tolbutamide, diclofenac, flurbiprofen (CYP2C), omeprazole, voriconazole (CYP2C19), fexofenadine, digoxin and talinolol (P-glycoprotein substrates). It is often mentioned that ginkgo can interact with anti-coagulant drugs. Clinical trials have also shown that ginkgo has no additive effect withaspirin on platelet aggregation, does not change the anti-platelet activity of clopidogrel and cilostazol. It may act as an anti-oxidant to slow down Alzheimer's disease and interfere with changes in the brain that might cause problems with thinking. Ginkgo seeds contain substances that might kill the bacteria and fungi that cause infections in the body. The seeds also contain a toxin that can cause serious side effects like seizures and loss of consciousness.

Ginseng

Panax quinquefolius (Fam. Araliaceae), commonly known as 'American ginseng', is an herbaceous perennial herb native to North America. A clinical study showed that American ginseng reduced the anticoagulant effect of warfarin in healthy volunteers. On the other hand, two clinical trials have recently shown that American ginseng did not affect the pharmacokinetics of the anti-retroviral drugs indinavir and zidovudine. *Panax ginseng* is also used for depression anxiety, general fatigue and chronic fatigue syndrome (CFS), multiple sclerosis for boosting the immune system, and for fighting particular infections in a lung disease called cystic fibrosis. These infections are caused by a bacterium named Pseudomonas. *Panax ginseng* is often referred to as a

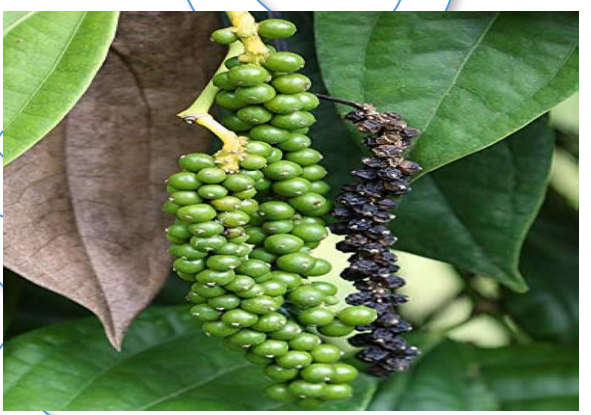
general well-being medication, because it affects many different systems of the body.

Garlic

Allium sativum L. (Fam. Alliaceae) is used in modern phytotherapy to treat hypercholesterolaemia and prevent arteriosclerosis although the clinical evidence is far from compelling. Garlic preparations include garlic powder standardized to contain 1.3% alliin and 0.6% allicin, garlic aged extract, which does not contain allicin but is high in water soluble phytochemicals, such as diallyl sulphides and garlic oil (i.e., essential oil obtained from the distillation of the cloves). Two garlic preparations, namely garlic oiland garlic powder, have been evaluated for their potential to affect CYP enzymes in clinical trials. The results suggest that, garlic oil may selectively inhibit CYP2E1, but not other CYP isoforms (such as CYP1A2, CYP3A4 or CYP2D6) and that garlic powder has no effect on CYP3A4. Recently, it has been shown that a 21-day garlic treatment (aged garlic extract) induces intestinal expression of P-glycoprotein without affecting intestinal or hepatic CYP34A in humans.

Pepper

The black pepper (*Piper nigrum* L) vine and its extracts have been used as a folk medicine in a variety of cultures and are the source of the most commonly used spice worldwide. The chemical piperine is a major bioactive component present in black pepper (and white pepper as well) that has numerous reported physiological and drug-like actions. The various evidences shows that black pepper may have health benefits, particularly in enhancing digestive tract function. There is suggestive evidence that black pepper piperinemay have nervous system benefits and may influence body energy usage in rats. Preliminary evidence in cell culture studies suggests that black pepper contains antioxidant constituents and possesses anti-inflammatory and anti-microbial properties. Black and white pepper might help fight germs (microbes) and cause the stomach to increase the flow of digestive juices. There is conflicting evidence about their role in cancer. Some evidence suggests pepper might protect against colon cancer, but other evidence suggests it might promote liver cancer.



Ephedra

Ephedra (*Ephedra gerardiana* Fam. Ephedraceae) is an herb. Usually, the branches and tops are used to make medicine, but the root or whole plant can also be used. Ephedra is banned in the U.S. due to safety concerns Ephedra is used for weight loss and obesity and to enhance athletic performance. It is also used for allergies and hay fever; nasal congestion; and respiratory tract

conditions such as bronchospasm, asthma, and bronchitis. It is also used for colds, flu, swine flu, fever, chills, headache, inability to sweat, joint and bone pain, and as a “water pill” to increase urine flow in people who retain fluids. Ephedra contains a chemical called ephedrine. Ephedrine stimulates the heart, lungs, and nervous system. There has been a lot of debate about the safety of ephedra and legal wrangling over its status.

UNIT – III

HERBAL COSMETICS

Introduction

The word cosmetic was obtained from Greek word "kosmtikos" means decorating skills, having the power. In ancient period it was used as colours for decoration to kill the animals and enemy by colouring his body to provoke fear in an enemy. Cosmetics belong to hunting, religion, fighting in prehistoric times 3000 BC. Later it is used as beautifying product and health care product. Cosmetics are developed to control various types of ailments and treatment to the skin like wrinkle, acne, aging, beautiful to control oily skin.

The concept of beauty and cosmetics dates back to ancient mankind and civilization. Generally herbal cosmetics are also referred to as natural cosmetics. Herbal cosmetics are formulated, using different cosmetic ingredients to form the base in which one or more herbal ingredients are used

to cure various skin ailments. Plants are highly used fordevelopment of new drug products for cosmeceuticals and pharmaceutical applications. Herbal cosmetics are the products in which herbs are used in crude or extract form. Herbal cosmetics, referred as Products, are formulated, using various permissible cosmetic ingredients to form the base in which one or more herbal ingredients are used to provide defined cosmetic benefits only, shall be called as "Herbal Cosmetics". Herbs do not produce instant cures. They offer a way to put the body in proper tune with nature.

A huge number of cosmetic and toiletry formulations have been designed and developed based upon Indian herbs recently. Other than traditionally documented applications, some modern trials have also been using the utility of Indian herbs in personal care products. The demand of herbal medicines is increasing rapidly due to their skin friendliness and lack of side effects. The best thing of the herbal cosmetics is that it is purely made by the herbs and shrubs and thus is side-effects free. The natural content in the herbs does not have any side effects on the human body; instead provide the body with nutrients and other useful minerals. The term cosmeceuticals were first used by Raymond Reed founding member of U.S. Society of Cosmetics Chemist in 1961. He actually used the word to brief the active and science-based cosmetics.

Benefits of herbal cosmetics

Herbal cosmetics offer several benefits that make them attractive to individuals seeking natural and skin-friendly beauty and skincare products. Here are some of the key benefits of using herbal cosmetics:

- *Natural Ingredients:* Herbal cosmetics are formulated using natural and plant-based ingredients, such as herbs, fruits, flowers, and essential oils. These ingredients are generally considered safe and gentle on the skin, reducing the risk of adverse reactions.
- *Free from Harmful Chemicals:* Herbal cosmetics are typically free from synthetic chemicals, including parabens, sulphates, phthalates, and

artificial fragrances. This reduces the likelihood of skin irritation, allergies, or other adverse effects associated with these chemicals.

- *Suitable for Sensitive Skin:* Many people with sensitive skin or allergies find herbal cosmetics to be a suitable alternative to conventional products. The absence of harsh chemicals and the use of natural ingredients can be less irritating to sensitive skin types.
- *Gentle Cleansing:* Herbal facial cleansers and soaps often provide gentle cleansing without stripping the skin of its natural oils. This helps maintain the skin's moisture balance and prevents it from becoming excessively dry.
- *Nourishment and Hydration:* Herbal moisturizers and lotions are designed to nourish and hydrate the skin. Ingredients like aloe vera, shea butter, and natural oils can provide long-lasting hydration and improve skin texture.
- *Anti-Aging Properties:* Many herbal cosmetics contain ingredients rich in antioxidants, vitamins, and minerals that may help combat the signs of aging. These ingredients can reduce the appearance of wrinkles, fine lines, and age spots.
- *Acne and Blemish Control:* Some herbal ingredients, such as tea tree oil, neem, and calendula, have natural antibacterial and anti-inflammatory properties. They can be effective in treating acne and blemishes without causing excessive dryness.
- *Hair Care:* Herbal shampoos, conditioners, and hair oils are designed to nourish and strengthen the hair. Natural ingredients like amla, hibiscus, and rosemary can promote hair health, reduce hair fall, and add shine.
- *Aromatherapy Benefits:* Herbal cosmetics often include essential oils, which not only add pleasant fragrances but may also offer aromatherapy benefits. Certain essential oils can promote relaxation, stress relief, and improved mood.
- *Environmental Consciousness:* Many herbal cosmetic brands prioritize sustainability and eco-friendliness. They may use organic farming practices, avoid animal testing, and use recyclable or biodegradable

packaging, aligning with environmentally conscious values.

- *Holistic Approach:* Herbal cosmetics often take a holistic approach to beauty and wellness. They aim to promote overall well-being, considering the connection between inner health and external appearance.
- *Customization:* Some herbal cosmetic brands offer customized products tailored to individual skin or hair types and concerns. This allows users to choose products that best suit their specific needs.
- *Cruelty-Free:* Many herbal cosmetic brands are committed to being cruelty-free, meaning they do not test their products on animals.

It's important to note that the effectiveness of herbal cosmetics can vary from person to person, depending on individual skin or hair types and specific concerns. To find the right herbal cosmetics for your needs, consider consulting with a dermatologist or skincare specialist and conducting patch tests to ensure compatibility with your skin.

Advantages of herbal cosmetics over synthetic

Herbal cosmetics are the modern trend in the field of beauty and fashion. These agents are gaining popularity as nowadays most women prefer natural products over chemicals for their personal care to enhance their beauty as these products supply the body with nutrients and enhance health and provide satisfaction as these are free from synthetic chemicals and have relatively less side-effects compared to the synthetic cosmetics.

Natural products: The name itself suggests that herbal cosmetics are natural and free from all the harmful synthetic chemicals which otherwise may prove to be toxic to the skin. Instead of traditional synthetic products different plant parts and plant extracts are used in these products, e.g., Aloe vera gel and coconut oil. They also consist of natural nutrients like vitamin E that keeps skin healthy, glowing and beautiful. For example, Aloe vera is an herbal plant species belonging to Liliaceae family and is naturally and easily available. There are a rising number of consumers concerned about ingredients such as

synthetic chemicals, mineral oils who demand more natural products with traceable and more natural ingredients, free from harmful chemicals and with an emphasis on the properties of botanicals.

Safe to use: Compared to other beauty products, natural cosmetics are safe to use. They are hypoallergenic and tested and proven by dermatologists to be safe to use anytime, anywhere. Since they are made of natural ingredients, people don't have to worry about getting skin rashes or experience skin itchiness. Example - BHA (Butylated Hydroxyanisole) and BHT (Butylated Hydroxytoluene) are closely related synthetic antioxidants and are used as preservatives in lipsticks and moisturizers. BHA and BHT can induce allergic reactions in the skin. The international Agency for Research on Cancer classifies BHA as a possible human carcinogen. Herbal cosmetics contain natural anti-oxidants like Vitamin C.

Compatible with all skin types: Natural cosmetics are suitable for all skin types. No matter if you are dark or fair, you will find natural cosmetics like foundation, eye shadow, and lipstick which are appropriate irrespective of your skin tone. Women with oily or sensitive skin can also use them and never have to worry about degrading their skin condition. Coal tar derived colours are used extensively in cosmetics; coal tar is recognized as a human carcinogen and the main concern with individual coal tar a colour (whether produced from coal tar or synthetically) is they can cause cancer. But natural colours that are obtained from herbs are safer.

Wide selection to choose from: Natural cosmetics may still be a new type in the beauty industry but they already offer a variety of beauty products for all make up crazy people out there to choose from. One will find a variety of foundation, eye shadow, lipstick, blush, mascara, concealer and many more which are all naturally formulated. Furthermore, one will find locally made natural cosmetics or those made by famous designers worldwide. There exist a large variety of herbal extracts, to name a few *Andrographis paniculata*

(Kalmegh), *Asparagus racemosus* (Shatawari), *Boswellia serrata* (Salai Guggal), Asphalt (Shilajit) etc.

Fits your budget: Natural cosmetics are not that expensive. In fact, some of these products are more affordable than synthetic ones. They are offered at discounted prices and are sold for a cheap price during sales. Just need to survey enough to look for great deals. An estimate of WHO demonstrates about 80% of world population depends on natural products for their health care, because of side effects inflicted and rising cost of modern medicine. World Health Organization currently recommends and encourages traditional herbal cures in natural health care programs as these drugs are easily available at low cost and are comparatively safe.

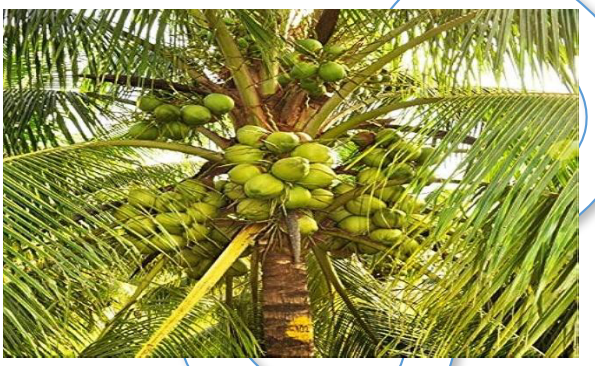
Not tested on animals: Some cosmetics are initially tested on animals to ensure that they are safe and effective to use for human. However, natural cosmetics need not be tested on animals. These natural formulations are tested by experts in laboratories using state of the art equipment with no animals involved.

No side effects: The synthetic beauty products can irritate your skin, and cause pimples. They might block your pores and make your skin dry or oily. With natural cosmetics, one need not worry about these. The natural ingredients used assure no side effects; one can apply them anytime, anywhere. For example, herbal cosmetics are free from parabens that are the most widely used preservative in cosmetics and can penetrate the skin. And are suspected of interfering with hormone function (endocrine disruption).

Regulatory status: The legal difference between a cosmetic and a drug is determined by a product intended use. Under present concept, the boundary at which a cosmetic product becomes drug is not well-defined and different laws and regulations apply to each type of product. The drugs and cosmetic Act 1940 define a drug and a cosmetic as; Drug- "All medicines for internal or external use of human beings or animals and all substances intended to be used for; or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in humans or animals".

Skin care products

Coconut oil: It is produced by crushing copra, the dried kernel, which contains about 60-65% of the oil. Coconut oil contains a high amount of glycerides of lower chain fatty acids. Coconut oilis derived from the fruit or seed of the coconut palm tree *Cocos nucifera*, family Arecaceae. The melting point of coconut oil is 24-25 ^{0}C (75-76 ^{0}F) and thus can be used easily in liquid or solid forms and is often used in cooking and baking. Coconut oil is excellent as a skin moisturizer and softener.

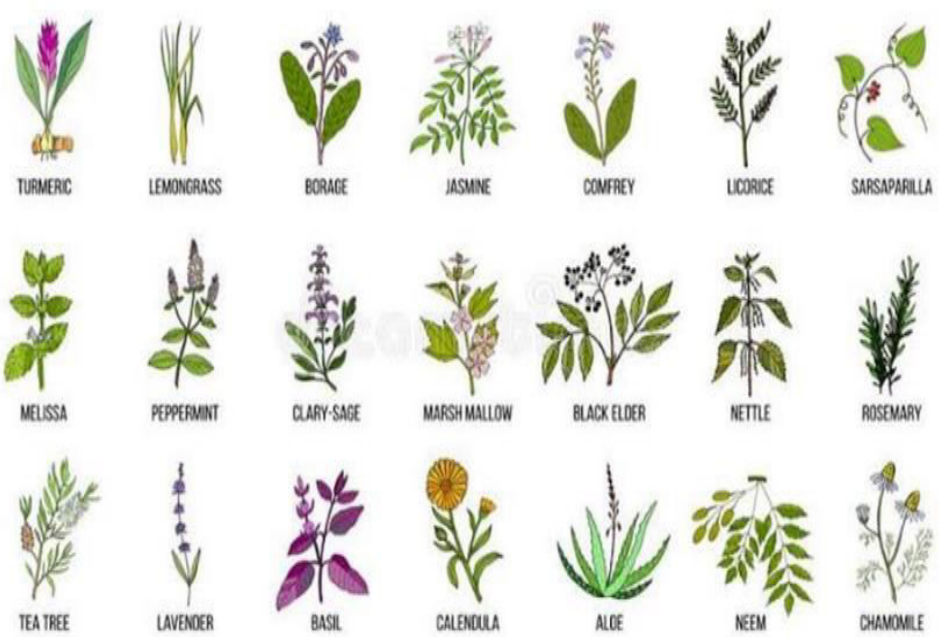


Sun flower oil: It is the non-volatile oil extracted from sunflower seeds obtained from *Helianthusannuus*, family Asteraceae. Sunflower oil contains lecithin, tocopherols, carotenoids and waxes.It has smoothing properties and is considered non-comedogenic. A simple yet cost-effective oil, well tried and tested for generations in a wide variety of emulsions formulated for face and body products.

Jojoba oil: It is a mixture of long chain, linear liquid wax esters extracted from the seeds of the desert shrub *Simmondsia chinensis*, family Simmondsiaceae. Jojoba oil is easily refined to remove any odour, colour it is oxidatively stable, and is often used in cosmetics as a moisturizerand as a carrier oil for exotic fragrances. Human sebum and jojoba oil are virtually identical. Sebum protects and moisturizes the skin and hair but is stripped away by chemicals, pollutants, sun and the aging process, resulting in dry skin and hair. Jojoba oil replenishes what skin and hair loss and restores them to their natural pH balance.

Olive oil: This oil is a fixed oil extracted from the fruits of *Olea europaea*, family Oleaceae. The major constituents are triolein, tripalmitin, trilinolein, tristearate, monosterate, triarachidin, squalene, β-sitosterol and tocopherol. It is used as skin and hair conditioner in cosmetics like lotions, shampoos etc. It is a potent fatty acid penetration enhancer.

Aloe vera: Aloe vera is an herbal plant species belonging to Liliaceae family that is found only in cultivation, having no naturally occurring populations, although closely related aloes do have presence in northern Africa. It is an ingredient in many cosmetics because it heals, moisturizes, and softens skin. Simply cut one of the Aloe vera leaves to extract the soothing gel. Aloe vera contains amino acids like leucine, isoleucine, saponin glycosides that provide cleansing action, vitamins A, C, E, B, choline, B_{12} and folic acid and provide anti-oxidant activity.



Best herbs for skin care

Herbal cosmetics are prepared using herbal ingredients to treat different ailments and to promote healthy life and for beautifying the skin without damaging the skin functions and structure. There are numerous herbs available naturally having different uses in cosmetic preparations for skincare. The herbal cosmetics have more advantages over the synthetic counterparts. Herbal cosmetics usage for skin has been increased in personal care system and more demand for natural cosmetics. Hence, herbal cosmetics are very safe and does not produce any toxic and adverse reactions compare to marketed cosmetics products.

Skin protection

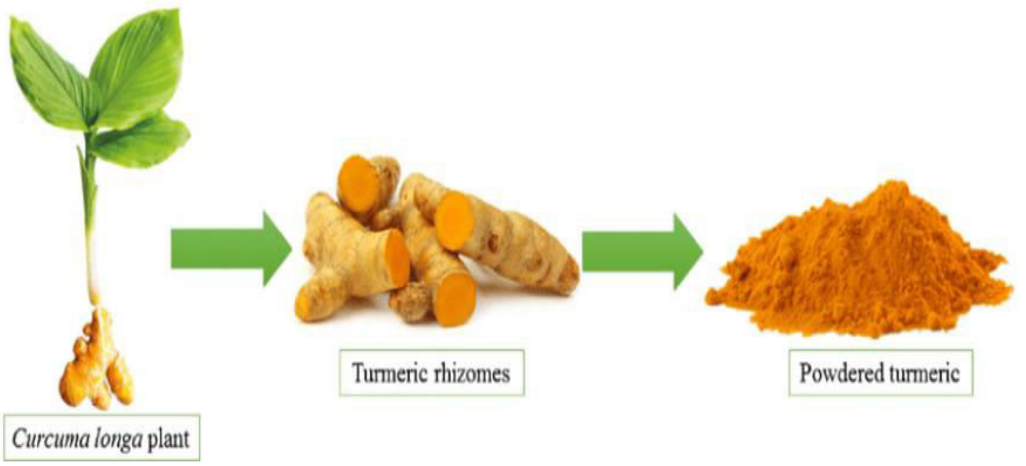
Green tea: Green tea is a Tea extracted from the leaves of *Camellia sinensis* belong to the family, Theaceae. It protects the skin from direct damage to the cell and moderate inflammation. The main active ingredient in green tea is catechin, it has antioxidant power which 20 times stronger than vitamin E. It was found that green tea extracts or an individual green tea polyphenol

(GTPP), especially epigallocatechin (EGC)-3-gallate (EGCG), inhibited two-stage chemical carcinogenesis. It is a premiere skin protectant. It protects against direct damage to the cell and moderates' inflammation.

Calendula: *Calendula officinalis* is reported to have a remarkable anti-oxidant activity, anti-inflammatory activity and wound healing activity. Essential oil of Calendula consists mainly of α-thujene, α-pinene, 1,8-cineole, dihydrotagetone and T-muurolol. Calendula in suspension or in tincture is used topically to treat acne, reducing inflammation, controlling bleeding and soothing irritated tissue. There is "limited evidence" that calendula cream or ointment is effective in treating radiation dermatitis.

Turmeric: It is a perennial plant and it is used in many celebrations of Hindus. Especially in Hindu wedding brides would rub with turmeric on their bodies for glowing look. New born babies also rubbed with turmeric on their forehead

for good luck. Traditionally women rub turmeric on their cheeks to produce a natural golden glow. It is a deep yellow-to-orange powder that comes reduce the number of Ultraviolet B (UVB)-induced sunburn cells in mice. It consists of demethoxycurcumin, bisdemethoxycurcumin, zingiberene, curcumol, curcumenol, eugenol, metatrihydrocurcumin, triethylcurcumin, curcumin, turmerin, turmerones. It is used as anti-septic, analgesic, anti-inflammatory, anti-oxidant, anti-malarial, insect repellent etc.



Anti-aging herbs

***Rhodiola rosea*:** It is commonly known as golden root, roseroot, Aaron's rod, arctic root, king's crown, lignum rhodium, orpin rose. It is a plant in the Crassulaceae family that habitats in cold regions of the world. Traditional folk medicine used *R. rosea* to increase physical endurance, work productivity, longevity, resistance to high altitude sickness, and to treat fatigue, depression, anemia, impotence, gastrointestinal ailments, infections, and nervous system disorders. *R. rosea* is rich in phenolic compounds, known to have strong anti-oxidant properties.

Carrot: It is obtained from the plant *Daucus carota* belonging to family Apiaceae. It is a valuable herb since ages as due to its richness in Vitamin A along with other essential vitamins. Carrot seed oil is used as anti-aging, revitalizing and rejuvenating agent. The carrot gets its characteristic and bright orange colour from β-carotene, and lesser amounts of α-carotene and γ-carotene. α and β-carotenes are partly metabolized into vitamin A in humans.

Gingko: In China and Japan, the leaves and nuts of the *Ginkgo biloba* (*G. biloba*) tree have been used for thousands of years to treat various medical conditions, including poor blood circulation; hypertension; poor memory, and depression, particularly among the elderly; male impotence. In addition, it is gaining a similar reputation as an anti-oxidant and anti-inflammatory agent. *Ginkgo biloba* belongs to family Ginkgoaceae, which grows to a huge size.

Neem: Neem or Margosa is a botanical relative of mahogany. It belongs to the family Meliaceae.The Latinized name of Neem *Azadirachta indica* is derived from the Persian. Azad=Free, dirakht=Tree, i-Hind=of Indian Origin. The common treatment for the dandruff is Neem as it produces anti-fungal, anti-bacterial, pain-relieving, and anti-compounds that would treat dandruff. It has blood purifier property and also enhance beauty.

Dandruff treatment

Henna: Henna comes from the plant *Lawsonia inermis* family Lythraceae, which contain a dye molecule called Lawsone, which when processed produces henna powder. Besides lawsoneother constituents present are gallic acid, glucose, mannitol, fats, resin (2%), mucilage and traces of an alkaloid. Leaves yield hennatannic acid and an olive oil green resin, soluble in ether and alcohol. Lawsone is isolated from the leaves of *L. inermis* has shown

significant anti-fungal anti-biotic effect. It is highly praised both for its high Vitamin C content and for the precious oil, which is extracted from its seeds and pulp and used as a treatment for hair and scalp problems. It is used in eye syndromes, hair loss, and children's ailments etc.

Shikakai: *Acacia concinna* Linn. (Leguminosae) is a medicinal plant that grows in tropical rainforests of southern Asia. The fruits of this plant are used for washing hair, for improving hair growth, as an expectorant, emetic, and purgative. It contains saponins, alkaloids, sugars, tannins, flavonoids and anthraquinone glycosides.

Neem: The herb, *Azadirachta indica*, family Meliaceae has been found to have the properties of a blood purifier, beauty enhancer. The common treatment for the dandruff. Neem as it produces anti-fungal, anti-bacterial, pain-relieving, and anti-compounds that would treat dandruff.

Hair care

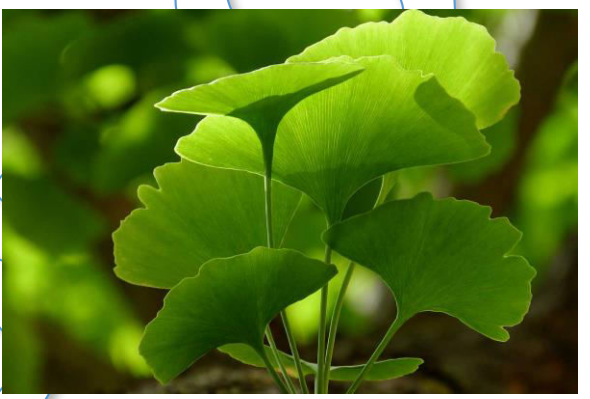
Amla: Amla is the name given to the fruit of a small leafy tree (*Emblica officinalis*), which grows throughout India and yields characteristics. It is an edible fruit. It is highly praised both for its high vitamin C content and for the precious oil, which is extracted from its seeds and pulp and used as a treatment for hair and scalp problems. It is used in eye syndromes, hair loss, and children's ailments etc. It contains tannins and minerals such as phosphorus, iron and calcium which provides nutrition to hair and also causes darkening of hair. It consists of calcium, phosphorus, iron, Vitamin B_1, riboflavin, niacin and vitamin C, used to stimulate thicker hair growth and prevents premature graying of hair.

Rose oil: There are mainly four species of roses for oil production. These are *Rosa damascena* Mill., *R. gallica* L., *R. moschata* Herrm. and *R. centifolia* L. Rose oil and rose water have many therapeutic effects. Rose oil helps soothe the mind and heals depression, grief, nervous stress andtension. It also helps to heal wound and skin health. It is used more commonly in perfumery. The key flavour compounds that contribute to the distinctive scent of rose oil are beta-damascenone, beta-damascone, beta-ionone, and oxide.

Eucalyptus oil: There are around 700 different species of Eucalyptus in the world, of which at least 500 produce a type of essential oil. It is produced by steam distillation from the leaves of Eucalyptus species (*E. cinerea F. Muell., E. baueriana F. Muell., E. smithii R. T. Baker, E. bridgesiana R. T. Baker, E. microtheca F. Muell., E. foecunda Schau., E. pulverulenta Sims, E. propinqua Deane and Maiden, E. erythrocorys F. Muell.*) etc. They are widely used in the preparation of liniments, inhalants, cough syrups, ointments, toothpaste and also as pharmaceutical flavours. The European Pharmacopoeia monograph for Eucalyptus oil sports a chromatographic profile: 1,8-cineole (eucalyptol; not less than70%), limonene (4- 12%), α-pinene (2-8%), α- phellandrene (less than 1.5%), β-pinene (less than 0.5%), camphor (less than 0.1%). Eucalyptus oil can help to get rid of dandruff, which in turn can help to promote healthy growth of hair.

Grape seeds: It promotes proliferation of hair follicle cells *in vitro* and that they possess remarkable hair cycle converting activity from the telogen phase to anagen phase *in vivo*.

***Ginkgo biloba*:** This leaf extract also promotes hair regrowth through combined effects on proliferation and apoptosis of the cells in the hair follicle, thus suggesting potential as a hair tonic.



Aloe: Aloe gel is used traditionally for hair loss and for improvement in hair growth following alopecia. Aloenin is the major constituent responsible for promoting hair growth without irritating the skin.

Almond oil: The almond oil is obtained from *Prunus dulcis*. It proves to be very nourishing, and softens and strengthens the hair. The almond oil also proves to be a very good cleansing agent.

Arachis oil: This is also a fixed oil obtained from the seeds of the *Arachis hypogea* belonging to the family Leguminoseae. The oil is pale yellow in colour, with a faint nutty odour. It is used in the preparation of hair oils and "Brilliantines".

Castor oil: This oil is obtained from the seeds of *Ricinus communis* belonging to the family, Euphorbiaceae. It is used as an emollient, in the preparation of lipstick, hair oils, creams and lotions.

Citronella oil: It is one of the essential oils obtained from the leaves and stems of different species of Cymbopogon family Cardiopteridaceae. The crisp, rich citrus or lemon like aroma of this oil drives away body odour and is used deodorants and body sprays, although in very small quantities, since it heavy doses it may give skin irritations. It can also be mixed with the bathing water to have a refreshing, body odour ending bath.


Olive oil: This oil is a fixed oil extracted from the fruits of *Olea europaea*, family oleaceae. The major constituents are triolein, tripalmitin, trilinolein, tristearate, monosterate, triarachidin, squalene, βsitosterol and tocopherol. It is used as skin and hair conditioner in cosmetics like lotions, shampoos etc. It is a potent fatty acid penetration enhancer.

Light liquid paraffin: It consists of a mixture of hydrocarbons in the form of an oily liquid which has no colour or odour. It is used in the manufacture of bath oils, hair oils, lotions and creams, due to its better spreadability.

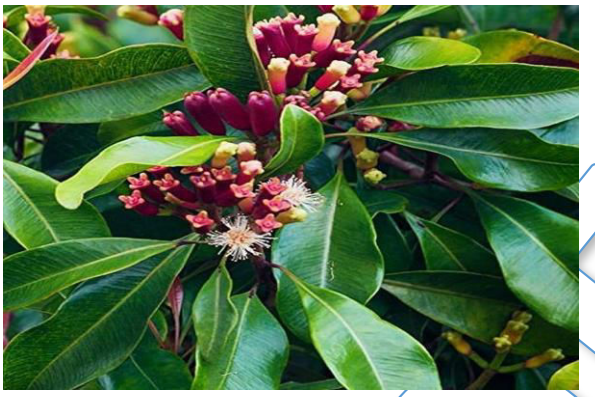
Oral care

Oral health/dental health is an inseparable part of general health. Oral health has an effect on general health as it causes considerable pain and suffering. It has an impact on a person's speech, selection of food, quality of life, and well-being. In view of the prevalence of oral diseases, their impact on individuals

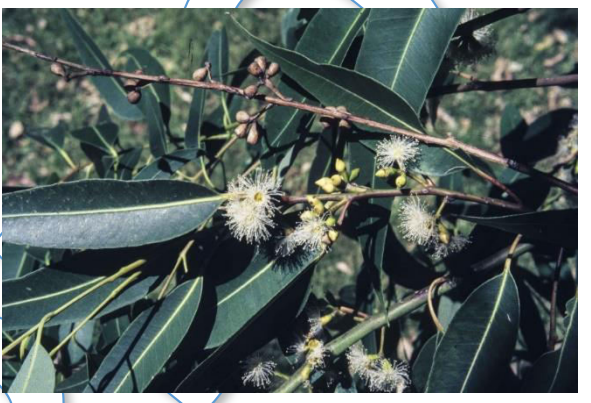
and society, and the expense of their treatment, oral diseases may be considered a major public health problem and they are listed among the most common of the chronic diseases that affect mankind. Oral diseases are the fourth most expensive diseases to treat in certain countries.

According to the World Health Organization (WHO) report, dental caries, though exhibiting a declining trend in many parts of the industrialized world, is still an important public health concern in many developing countries. The statistics suggest that dental caries affect 60-90% of school going children in developing countries. Loss of teethbecause of periodontitis often causes discomfort, and compromises the esthetics and function. Moreover, recent studies suggest an association between chronic low-grade infections such as periodontitis and systemic health problems (preterm low birth weight, cardiovascular diseases, diabetes mellitus, and chronic obstructive pulmonary disease). There is an immediate need for promoting preventive strategies that are socially acceptable, easily available, and at the sametime be cost-effective. This calls for the evolution of innovative strategies that are robust, efficient, and feasible.

Clove oil: Cloves are the aromatic flower buds of a tree in the Myrtaceae family, *Syzygium aromaticum*. In the past cloves were used as a remedy to ease the pain of toothache. Clove oil hasa local anaesthetic effect and temporarily numbs and relieves pain. It is used in the preparation ofsome tooth pastes and in clovacaine solution, a local anaesthetic used in oral ulceration and inflammation. Eugenol, which is extracted from essential oils including clove oil, is also mixed with zinc oxide to form temporary tooth restorations.



Eucalyptus saligna mouthwash gargle is used in Cameroon to treat mainly toothache, sorethroat and halitosis. It has been shown that the essential oil of the leaves of Eucalyptus globulus has anti-microbial activity against gram-negative bacteria (*E. coli*) as well as gram-positive bacteria (*S. aureus*) which are found in the oral cavity.



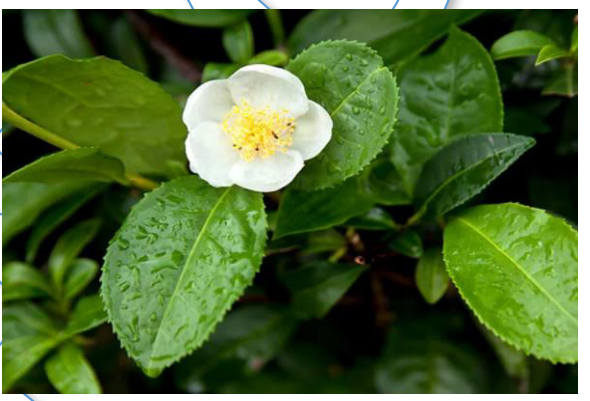
Moringa oleifera roots are also used to treat toothache in Cameroon by direct application on the tooth cavity. This plant has been found to be specific against *S. aureus, Vibrio cholerae*, and *Escherichia coli* and have no anti-fungal activity. Its anti-bacterial activity is responsible for its ability to calm toothache.

Allium sativum: It is one of the most extensively researched medicinal plants with a typical odour. Its anti-bacterial activity depends on allicin produced by enzymatic activity of allinase on allicin produced by enzymatic activity of allinase on allicin after crushing or cutting garlic clove. Garlic extract inhibits the growth of *Streptococcus mutans,* and therefore can be used as an effective remedy in the prevention of dental caries when used it is used as a constituent in toothpaste or mouthwash.

Tulsi (*Ocimum sanctum*): Tulsi consists of tannins (4.6%) and essential oil (up to 2%), eugenol (up to 62%), methyl eugenol (up to 86%), and α- and β-caryophyllene (up to 42%), methyl chavicol, linalool and 1,8-cineole. It has got anti-helminthic, analgesic, anti-pyretic, immune stimulatory, anti-ulcer, anti-microbial, anti-inflammatory property. Used in periodontitis.

Contraindicated in pregnant and lactating women, used with caution in children.

Green Tea (*Camellia sinensis*): Green tea contains polyphenol contents comprising catechin (C), epicatechin (EC), gallocatechin (GC), epigallocatechin (EGC) epicatechingallate (ECG), and epigalloc atechingallate. It is anti-inflammatory, anti-bacterial, anti-viral. Used in the treatment of periodontal disease.

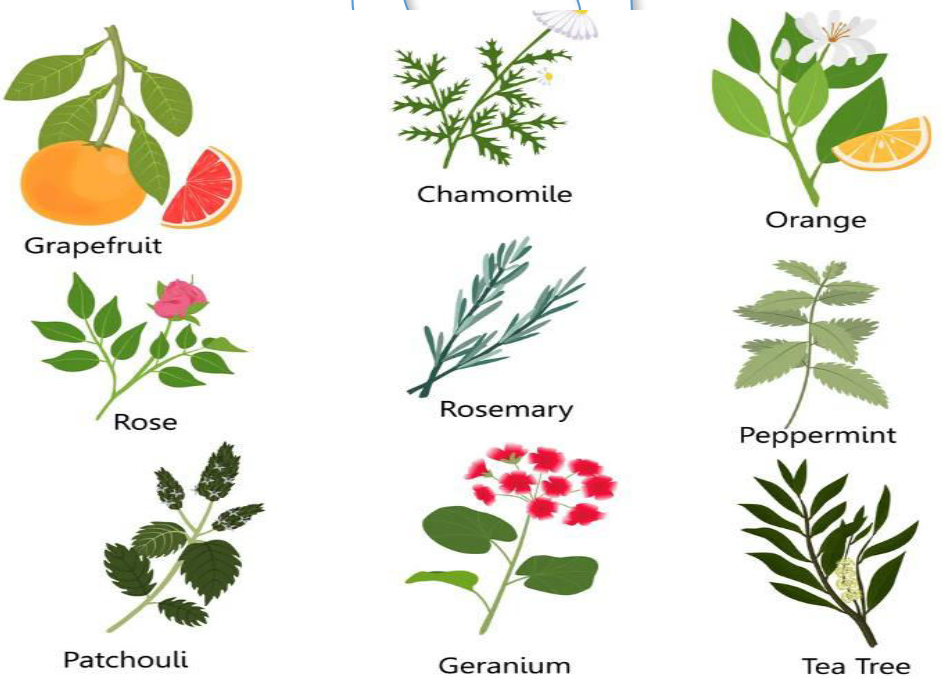


Marigold (*Calendula officinalis L*.) It is native to the Mediterranean areas. It is used for the treatment of skin disorders and pain, to facilitate healing after oral surgery and in oral cavity inflammations. It has also anti-edematous activity.

Grape seed extract: Grape seed extract contains pro-anthocyanidins (PA) which are potent anti-oxidants and are known to possess anti-inflammatory, anti-bacterial and immune-stimulating effects. It has been reported to strengthen collagen-based tissues by increasing collagen cross-links. In a study conducted to determine re-mineralizing effects of grape seed extract on artificial root caries, results showed that is a promising natural agent for non-invasive root caries therapy.

Papain: Papain is a proteolytic enzyme that comes from the latex of the leaves and fruits ofthe green adult papaya. It has an anti-inflammatory, bacteriostatic, bactericidal characteristic and is effective against gram positive and gram-negative organisms. Similar to human pepsin, papain acts as a chemical debridement ant-inflammatory agent, which does not damage healthy tissues and accelerates cicatrization process. Papain acts only in infected tissue as it lacks a plasmatic anti-protease called α-1-anti-trypsin.

Meswak: It is a derivative from Arak tree, is used by many people in different cultures as traditional toothbrush for oral hygiene. The meswak extract has also found its way into the dentifrices in the recent years as antiplaque and anti-gingivitis agents. Chewing sticks should be obtained from fresh stems of medicinal plants.

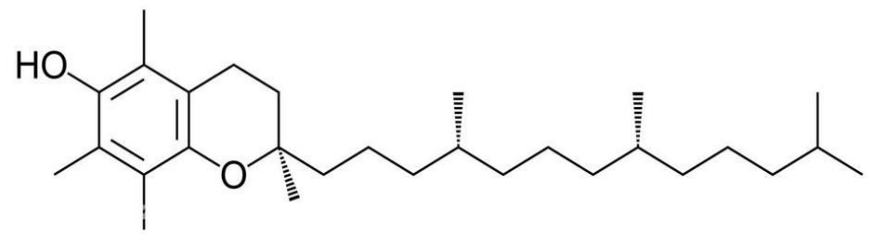


Essential oil plants

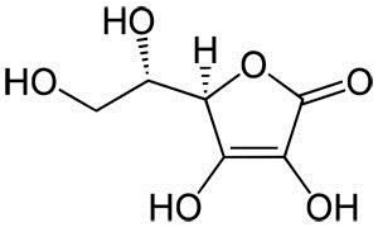
Healing herbs and medicinal plants flat icons

Anti-oxidants

Vitamin E: Sources of vitamin E is both plants and animals. It has free radical scavenging activity. It is mainly present is almonds, nuts, whole cereal grains, vegetable oils etc. The major lipophilic anti-oxidant in plasma membrane and tissues is α-tocopherol. The 30 naturally occurring molecules (4 tocopherols and 4 tocotrienols) all of which exhibit vitamin E activity.



Vitamin C: It prevents free radical damage by donating free radicals. It has immune boosting activity. It is mainly present in carrots, peaches, sweet potatoes, oranges, broccolis etc. It is necessary for hydroxylation of profile, precollege and lysine. It improves the changes caused by photo damage.



Tamarind: *Tamarindus indica* belongs to the family Fabaceae. The plant parts consist of amino acids, fatty acids and minerals. Tamarind is sweet acidic in taste due to the presence of tartaric acid. It is rich source of sugars, vitamin B and minerals. It exhibits high anti-oxidant capacity because of high phenolic content; thus, it is an important food source. Its anti-oxidant activity is used as anti-wrinkle in cosmetics. And also it has anti-ulcer activity.

In India more than 70% of the populations use herbal cosmetics for their health care. A present time herbal cosmetic has been marked up in personal care system and there is a great requirement for the herbal cosmetics in daily life. Healthy teeth, shiny hair and glowing skin are significant for the good looking of the human body. Herbal cosmetics are prepared, using cosmetic ingredients to form the base in which one and another herbal ingredient are used to treat different skin ailments and for the beautification. The chemical formulation of all these cosmetic products includes addition of various natural additives like waxes, oils natural colour, natural fragrances and parts of plants like leaves, etc.

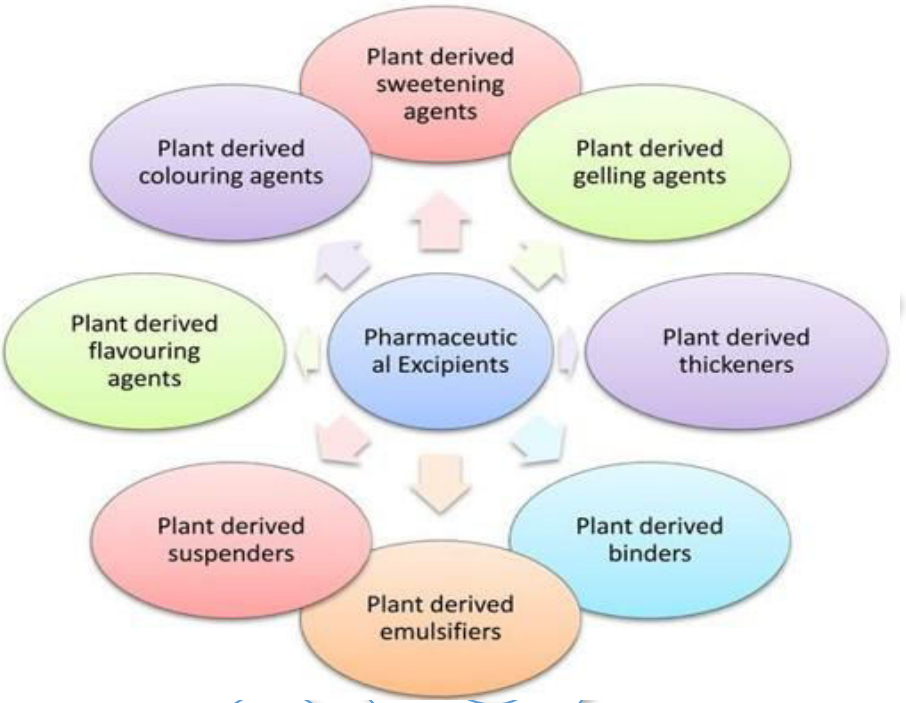
The cosmeceuticals are agents that lie elsewhere between pure cosmetics (lipstick and rouge) and pure drug (anti-biotics, corticosteroids) methods. Corrective formulation based natural beauty preparation, which has cosmetic value or safe additive properties in replacing synthetic ingredient. There is need to do more R and D in the field of herbal cosmetic to prove effectiveness and established herbal cosmetic in safety profile. It is needed to conduct adequate safety testing as per existing regulatory rule and present requirement. The ability to desire the right cosmetics for you depends on accurate ingredient knowledge, body Prakriti assessment, personal needs, customer perception about product, benchmark product. Quality control for ability and safety of herbal cosmetic products is of predominant importance. So quality control test must be carried out for herbal cosmetics. It is assumed to be safe for longer periods of time.

Herbal excipients

Excipients are defined as 'the substance used as a medium for giving a medicament. The specific application of natural polysaccharide polymers in pharmaceutical formulations include to aid in the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. Several pharmaceutical excipients of plant origin, like starch, agar, alginates, carrageen an, guar gum, xanthan gum, gelatine, pectin, acacia, tragacanth, and cellulose find applications in the pharmaceutical industry as binding agents, disintegrates, sustaining agents, protective's, colloids, thickening agents, gelling agents, bases in suppositories, stabilizers, and coating materials.

Herbal excipients are natural substances derived from plants that are used in pharmaceutical and nutraceutical formulations to aid in the manufacturing, stability, and delivery of active ingredients. Excipients are non-active components added to medications, supplements, and other products to provide various functions such as binding, disintegration, lubrication, and

solubilization. Herbal excipients are gaining interest due to their perceived natural and sustainable characteristics.



Advantages of herbal excipients

Biodegradable: Naturally occurring polymers produced by all living organisms. They show no adverse effects on the environment or human being.

Biocompatible and non-toxic: Chemically, nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence, they are non-toxic.

Economic: They are cheaper and their production cost is less than synthetic material.

Safe and devoid of side effects: They are from a natural source and hence, safe and without side effects.

Easy availability: In many countries, they are produced due to their application in manyindustries.

Classification of excipients

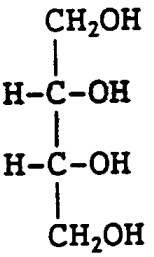
Excipients are commonly classified according to their application and function in the drugproducts:

- Herbal sweeteners
- Binders, diluents
- Disintegrants
- Colorants
- Viscosity builders
- Perfumery agents and flavouring agents

Herbal sweeteners:

Stevia: It is a very popular low-calorie sweetener. It's extracted from the leaves of a plant called *Stevia rebaudiana*. Several sweet compounds are found in stevia leaves. The main ones are stevioside and rebaudioside A. Both are hundreds of times sweeter than sugar, gram for gram. Therefore, stevia is very sweet but has virtually no calories. Additionally,a few human-based studies suggest stevia has health benefits. Stevia can lower highblood pressure in people with hypertension by 6–14%. However, it has no effect on blood pressure that is normal or only mildly elevated. Stevia has also been shown to lowerblood sugar levels in people with diabetes.

Erythritol: It is another low-calorie sweetener. It's a sugar alcohol found naturally in certain fruits. However, powdered erythritol available for purchase is most likely made via an industrial process. It contains 0.24 calories per g, or about 6% of the calories in an equal amount of sugar, with 70% of the sweetness. Erythritol doesn't spike blood sugar or insulin levels and has no effect on blood lipids like cholesterol ortriglycerides. It's absorbed into the body from the intestine but eventually excreted from the kidneys unchanged.



***Glycyrrhiza glabra*:** Liquorice roots, which are wrinkled and brown on the outside and yellow on the inside, contain glycyrrhizin, a compound that is 50 to 150 times as sweet ascane sugar.

Thaumatin: The thaumatins are a family of very sweet proteins present in the fruits of the tropical plant *Thaumatococcus daniellii* (Marantaceae) a bushy plant. Thaumatin elicits is a very sweet taste that is rated to be 2000 – 10000 times sweeter than sucrose, depending on purity and concentration. Thaumatin I and II are soluble in water and dil. alcohol. Thaumatin is effective at masking bitter notes often associated with pharmaceuticals or vitamins.

Natural binding agents: A binding agent (or binder) is a substance that holds or draws other materials together mechanically, chemically or as an adhesive, to form a cohesive whole.

Pectin: Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. In the food industry, folic acid incorporated microcapsules were prepared using alginate and combinations of alginate and pectin polymers so as to improve stability of folic acid. The blended alginate and pectin polymer matrix increased the folic acid encapsulation efficiency and reduced leakage from the capsules as compared to those made with alginate alone; they showed higher folic acid retention after freeze drying and storage.

Guar gum: Guar gum comes from the endosperm of the seed of the legume plant *Cyamopsistetragonolobus*. Refined guar splits are obtained when the fine layer of fibrous material, which forms the husk, is removed and separated from the endosperm halves by polishing. Strong acidscause hydrolysis and loss of viscosity, and alkalis in strong concentration also tend to reduceviscosity. It is insoluble in most hydrocarbon solvents.

Khaya gum: Khaya gum is a polysaccharide obtained from the incised trunk of the tree *Khaya grandifoliola* (family Meliaceae). The fact that the gum is naturally available, inexpensive and non-toxic has also fostered the interest in developing the gum for pharmaceutical use. Further work has also shown its potential as a directly compressible matrix system in the formulation of 61 controlled release tablet.

Different starches like rice, maize, corn wheat is also used a natural binding agent. They are added to the tablet formation to increase inter-particulate bonding strength in the tablets. The binder is added either in dry mix or mix in granulating liquid and form matrix with fillers and drug embedded in it.

Herbal diluents: Natural diluents include starches, hydrolyzed starches, and partially pregelatinized starches. Common diluents include anhydrous lactose, lactose monohydrate, and sugar alcohols such as sorbitol, xylitol and mannitol. Diluents provide better tablet properties such as improved cohesion or to promote flow.

Classification of diluents:

Diluents are classified on the basis of chemical nature and solubility. Organic materials Carbohydrates and modified carbohydrates are the major examples. i.e., lactose, starch and pre-gelatinized starch, sucrose, mannitol, sorbitol, powdered and microcrystalline cellulose.

Methyl-cellulose:

Methylcellulose is the organic material used as a diluent in the pharmaceutical formulation.It is the cellulose derivative. On the long-term use as a diluent in the pharmaceutical formulation it causes the various side effects. Mostly it causes the abdominal fullness,difficulty swallowing, nausea, rectal bleeding, stomach pain, and vomiting.

Dicalcium phosphate:

Dicalcium phosphate (DCP) is a combination of positively charged particles of calcium and negatively charged particles of hydrogen phosphate which is interchangeable with the phosphate in the body. Long term use of DCP results in upset in the balance of phosphates and other chemicals in the body. According to the material safety data sheet, the powdered form of DCP may irritate skin. Prolonged skin contact may lead to dry or chapped skin.

Binders: Excipients are also known as additives, which are used with active pharmaceutical ingredients to convert in to a pharmaceutical dosage form for

suitable administration. As name indicates, Binders are the excipient which is use to bind or hold all ingredients used in formulation of the dosage form. Binders are mixed in formulation to convey plasticity or to increase the bonding strength between the particles in formulation. The griping of ingredients in tablets and granules is very important which is enhanced by binders. They ensure that the formulations are manufactured according to required physical strength and quantity. Binders are used either in a solution or in a dry form depending on the ingredients in the formulation & the method of preparation of dosage form. Generally, binders are used in solid or semi-solid formulations. Examples of dosage form in which binders are used are as follow: Tablets, Pills, Pallets, Granules, and Pastes etc.

Viscosity builders: These are substances, which added to mixture, to increase its viscosity without substantially modifying its other properties, such as taste. They increase stability. It is desirable to increase the viscosity of dosage form to provide or to improve palatability orpourability.

Flavouring agents: Flavors are the mixed sensation of taste, touch, smell & sight. Nowadays, many artificial flavours are manufactured with the help of technology in flavouring industries. Many pharmaceutical industries use flavours in many formulations like: cough syrups, sedatives, anti-malarial and anti-biotic. Flavors are used as taste masking agents which hides the unpleasant taste or order of dosage form. A flavour enhances the likelihood of medicine and makes themmore compatible for patient's administration. Due to the use of flavours in dosage form children take medicines without any problem. Flavouring agents may be artificial or natural. Artificial flavouring agents are synthesized in laboratories while natural flavouring agents are extracted from plants. Sweetening agents also separated from plants and also manufactured synthetically. Examples of dosage form in which flavouring agents are used are as follow: tablets, pills, pallets, capsules, pastes, syrups, emulsions, suspensions, mouth washes etc. Examples of flavouring agents are black pepper, cardamom, fennel, ginger, peppermint, nutmeg and saffron.

Colouring agents: Colouring agents comes under the category of organoleptic agents. Colouring agents are widely used in pharmaceuticals, cosmetics and food industries. Colouring agentspromotes the appearance in pharmaceutical formulations. If any dosage form has unacceptable colour, the consumers avoid the dosage form for administration. Colouring agents give the attractiveness to the dosage form. Colouring agents are also used for differentiate of dosage form or for easy identification of dosage forms. Due to the use of colouring agents in dosage forms psychologically patients are attracted towards the dosage forms. Colouring agents are also used as dyes and widely used in cosmetics industries. All colouring agents used in pharmaceutical industries is approved or certified by FDA. Example of dosage forms in which colouring agents are used - tablets, pills, pallets, capsules, pastes, ointments, syrups, emulsions, suspensions etc.

Perfumery agents: An active ingredient is a compound which imparts the aroma to the perfume compositions or enhances the aroma of an existing perfume composition. Perfumery agents includes musk, sandalwood oil, rose oil, jasmine oil, benzoin, turpentine and lavender oil.

Herbal formulations

Herbal formulations mean a dosage form consisting of one or more herbs or processed herbs in specified quantities to provide specific nutritional, cosmetic benefits meant for use to diagnose, treat, mitigate diseases of human beings or animals, alter the structure or physiology of human beings or animals.

Herbal syrup

Syrup is a concentrated mixture of sugar in purified water. The oral use of liquid pharmaceutical has generally been justified on the basis of ease of administration to thoseindividuals who have difficulties in swallowing solid dosage forms. Ayurvedic herbal cough syrup comprising goodness of herbs such as tulsi, liquorice, ginger, vasaka which has been reported to provide effective relief in cough without causing adverse effects like those associated with the use of anti-histamines. Combination of these herbs with honey is

intended to provide additive benefit in relieving symptoms of acute non-productive cough.

Preparation of herbal syrup: An herbal syrup is prepared by combining a concentrateddecoction with either honey or sugar, and sometimes alcohol. The base of such a syrup is a strong herbal decoction. Mixing a decoction with honey or sugar helps to thicken and preserve the decoction. This increases the shelf life of the decoction and often creates a soothing application that benefits situations such as sore throat, cough, dry irritated tissues, and digestive issues. The added sweetener can also help to increase the palatability of some herbs. Many folks, including children, find syrups to be delicious. The basic proportions you want to use are 2 parts herbal decoction to 1 part honey or sugar. This is called a 2:1 ratio. This means that if you start with your herbs added to 4 cups of water and simmer down the liquid to 2 cups of decoction, then you will want to add 1 cup of honey or sugar to create and adequately preserve your syrup. Some herbalists like to use a 1:1 ratio of decoction to honey/sugar while others find a 1:1 ratio toresult in a syrup that is too sweet. The increased amount of honey/sugar relative to decoction in a1:1 ratio will be better preserved and hence last longer.

Herbal tablets

Tablets may be defined as the solid unit dosage form of medicament or medicaments with suitable excipients and prepared either by molding or by compression. It comprises a mixture of active substances and excipients usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders, glidantsand lubricants to ensure efficient tableting. Disintegrants to promote tablet break-up in thedigestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive or aid in visual identification of an unknown tablet. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

Tablet evaluation: Before a tablet is released out into the market it has to pass a few quality checks, which is mandatory. Evaluation of tablet includes the assessment of tablets physical, chemical and biological properties. To studies them the following test are formulated:

- Appearance
- Size and Shape
- Organoleptic properties
- Uniformity of thickness
- Hardness
- Friability
- Determination of pH
- Specific gravity
- Stability testing

Novel drug delivery system

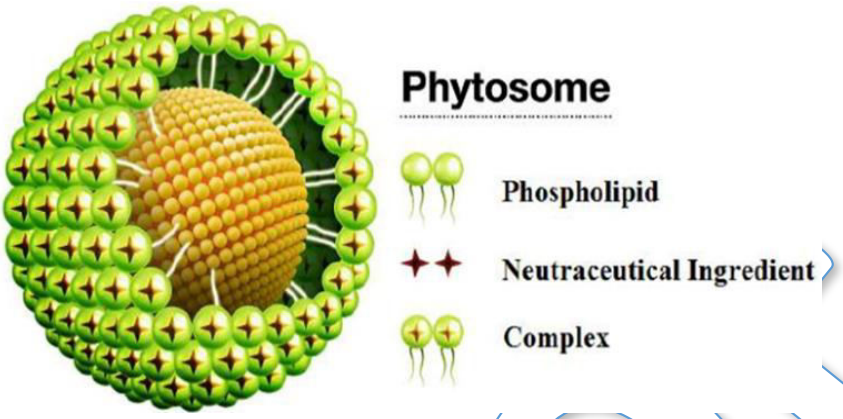
Novel Drug delivery System (NDDS) refers to the formulations, systems and technologies for transporting a pharmaceutical compound in the body as it is needed to safely achieve its desired therapeutic effects. Drug delivery systems (DDS), are based on approaches that are interdisciplinary and that combine pharmaceutics, bio conjugate chemistry, and molecular biology. It is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of ayurveda whose potential is only doing realized in the recent years.

The therapeutic benefits of these new systems include: Increased efficacy of the drug, Site specific delivery, and decreased toxicity/side effects, increased convenience, viable treatments for previously incurable diseases, potential for prophylactic application, better patient compliance.

Phytosomes

Phytosomes are also known as herbosomes, are recently added herbal formulations that are betterabsorbed than extracts. Phytosomes are prepared through the attachment of individual ingredients of herbal extracts to phosphatidyl-choline, resulting in a formulation having higher solubility and hence better absorption leading to promoted pharmacokinetic and pharmacodynamic properties compared to the conventional herbal extracts. Various popular herbal extracts including *Ginkgo biloba*, grape seed, hawthorn, green tea, and ginseng have been incorporated in phytosomes. The active components of these herbal extracts were successfully bound to phosphatidyl choline. Phytosomes, also known as phospholipid complexes, are well- known delivery systems that are closely related to liposomes in terms of their structure and configuration.

Phytosomes have a higher capacity for nutraceutical compounds to be added to them, as they have a quite stable, chemically bound structure. Plant extracts can bind quite easily to phosphatidylcholines due to the presence of terpenoids and flavonoids. As delivery systems, phytosomes have proved to be superior to liposomes. The chemical bonding ensures the stability of phytosomes, enhances the encapsulation efficiency and stability of bioactives, generally at a stoichiometric molar ratio of 1:1 or 1:2 (phospholipids: phytochemicals) Phytosomes were found to improve solubility, permeability rate and bioavailability of active compounds in various cases and inhibit or delay physical and chemical degradation and could be implemented without generating any toxic effects. The choline head of the phosphatidylcholine molecule binds to these compounds while the fat-soluble phosphatidyl portion comprising the body and tail envelops the choline-bound material. The phytosome process also intensifies the action of herbal compounds by improving absorption, increasing biological activity, and enhancing delivery to the target tissue.



Method of preparation: For the preparation of phytosomes the phytoconstituents like bioflavonoids, flavolignan and polyphenolic compounds reacting drop by drop by the solution of natural or synthetic phospholipids like phosphatidycholine with vigorous stirring. Phytosomes of ginsenoside, puerarin and kushenin are prepared in this manner. Another example is the Curcumin phospholipids complexes which can be prepared when the ethanol solution of the hydro-alcoholic extract of turmeric rhizomes adding the phospholipids, under reflux and with stirring. Phytosomes which are prepared by the non-solvent, freeze drying, spray drying or vacuum drying are called the prepared complex phytosome.

Advantages of phytosomes

- ✓ Improve the absorption of lipid insoluble polar phytoconstituents, enhance the bioavailability.
- ✓ Appreciable drug entrapment which becomes very beneficial.
- ✓ Reduce the dose due to increased absorption.
- ✓ Phosphatidylcholine shows synergistic effect, because it is a hepatoprotective also.
- ✓ Phytosomes are more stable because of the chemical bonding between the phytoconstituents and carrier i.e., phophatidylcholine.
- ✓ Effective in cosmetics.

Phytosomes are a type of advanced formulation used to improve the bioavailability and absorption of plant-based compounds, particularly phytochemicals, in the body. These formulations are commonly used in dietary supplements and herbal medicines to enhance the effectiveness of herbal extracts.

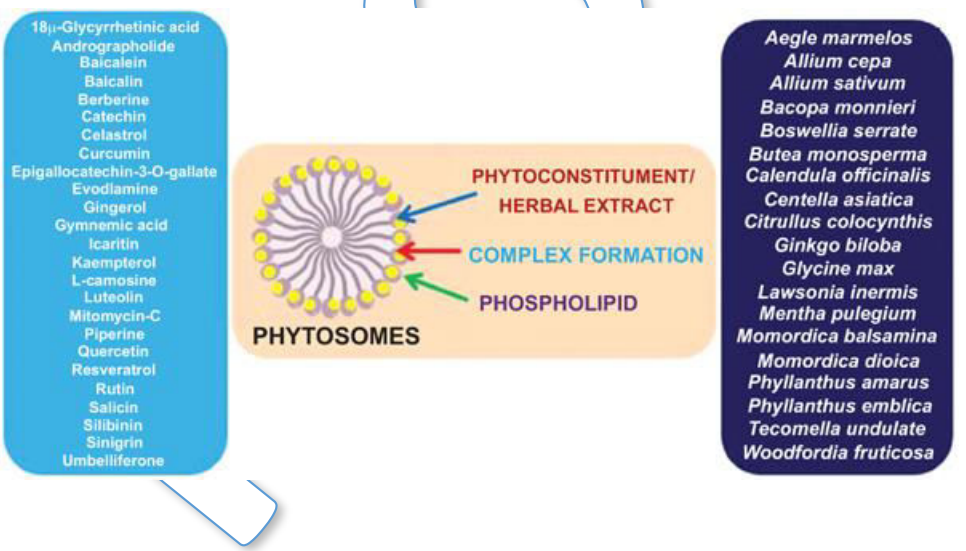
Phytosomes are created by combining plant extracts with phospholipids, which are natural substances found in cell membranes. Phospholipids have a hydrophilic (water-attracting) "head" and hydrophobic (water-repellent) "tail," which allows them to interact with both water and fats. When plant extracts are complexed with phospholipids, they form phytosomes, which have several benefits:

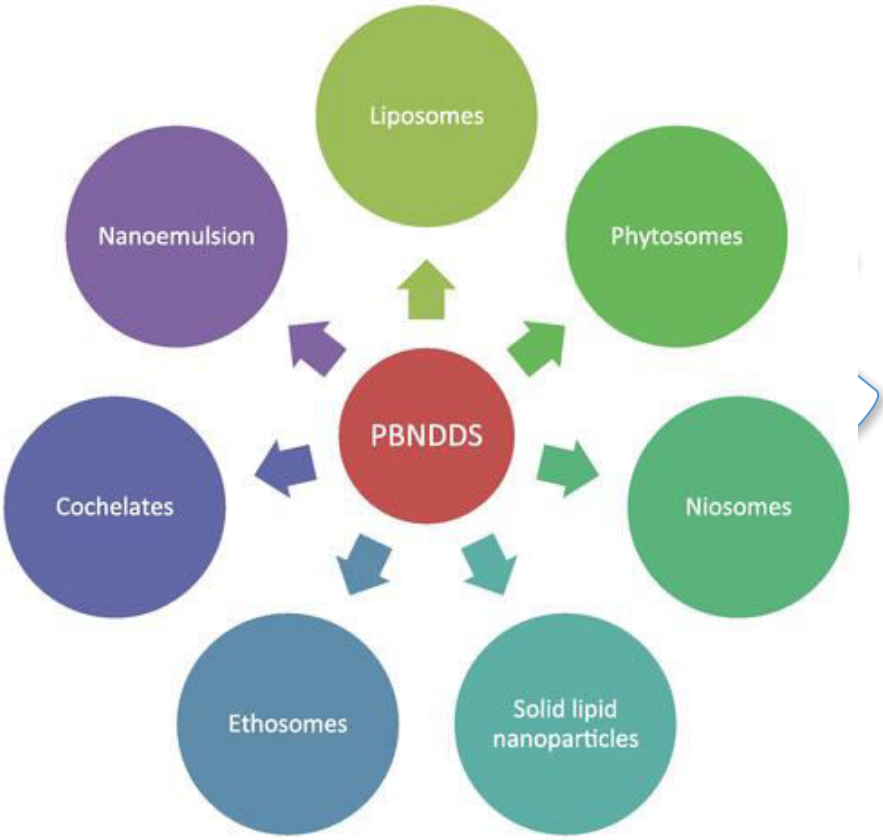
- Improved Bioavailability: Phytosomes enhance the solubility of plant compounds that are often poorly soluble in water. This improved solubility leads to better absorption in the gastrointestinal tract, allowing the body to more effectively utilize the active compounds.
- Enhanced Absorption: The phospholipid structure of phytosomes resembles the natural cell membranes in the body. This similarity facilitates easier penetration of cell membranes, leading to enhanced absorption of the encapsulated phytochemicals.
- Targeted Delivery: Phytosomes can be designed to target specific tissues or organs. This can be particularly useful in herbal medicine, where the goal is to deliver the active compounds to a specific part of the body.
- Reduced Degradation: Phytosomes can protect delicate phytochemicals from degradation by enzymes and harsh conditions in the digestive system, increasing their stability and preserving their efficacy.
- Stabilization of Compounds: Some phytochemicals are sensitive to light, heat, and oxygen. Phytosomes can provide a protective shield, preventing these compounds from undergoing degradation.
- Consistent Dosage: Using phytosomes can lead to more consistent dosing of herbal extracts, as their improved absorption allows for a more

predictable response in the body.

- Potential for Lower Dosages: Due to the enhanced absorption and bioavailability, lower doses of plant extracts might be needed to achieve the desired therapeutic effects.
- Phytosome technology has been applied to a variety of plant compounds, including flavonoids, polyphenols, terpenoids, and more. Some common phytosome formulations include extracts from herbs like *Ginkgo biloba*, Milk thistle (*Silybum marianum*), and green tea (*Camellia sinensis*).

It's important to note that while phytosomes can enhance the bioavailability of plant compounds, the overall effectiveness of an herbal product also depends on the quality of the starting plant material, the extraction process, and the specific health condition being addressed. If you're considering using phytosome-based supplements or products, it's advisable to consult a healthcare professional to ensure that they are appropriate for your needs.




Liposomes
Nanoemulsion
Phytosomes
PBNDDS
Cochelates
Niosomes
Ethosomes
Solid lipid nanoparticles

UNIT – IV

EVALUATION OF HERBAL DRUGS

Introduction

The safety and efficacy of herbal drugs remain major issues of concern especially in the developing world where the use is high. The evaluation of herbal drugs involves confirmation of its identity, quality, purity and detection of nature of adulteration. Thus, the evaluation parameters are based upon chemical, physical, microbiological, therapeutic and toxicological studies. It also serves as an important tool in stability studies.

Evaluating herbal drugs, also known as herbal medicines or phytotherapeutic agents, involves assessing their safety, efficacy, quality, and proper usage. Herbal drugs are derived from plant sources and have been used for centuries in traditional medicine systems worldwide. However, modern scientific evaluation methods are essential to ensure their safety and effectiveness.

It's important to note that not all herbal products on the market undergo rigorous evaluation, and the quality and safety of these products can vary widely. Consumers should exercise caution, consult healthcare professionals, and choose products from reputable manufacturers when considering herbal remedies. Additionally, regulatory agencies in different countries may have varying requirements for the evaluation and approval of herbal drugs.

WHO guidelines

The WHO guidelines present general consideration on potentially hazardous contaminants and residues in herbal medicines. It includes guiding principles of assessing quality of herbal medicines in terms of major contaminants and residues. It also recommends analytical methods for qualitative and quantitative determination of such contaminants and residues. The objectives of these guidelines are to provide:

a. Quality control of crude drugs material, plant preparations and finished products.

b. Stability assessment and shelf life.

c. Safety assessment; documentation of safety based on experience or toxicological studies.

d. Assessment of efficacy by ethno-medical information and biological activity evaluations.

The scope of these guidelines does not cover issues of adulteration of herbal medicines. It should be noted that these methods need to be validated for the material that is to be tested and also for each type of instruments. The other WHO documents and publications relating to the quality assurance of herbal medicines with regard to safety should include the following steps:

1. Authentication (Stage of collection, parts of the plant collected, regional status, botanical identity like phytomorphology, microscopical and

histological analysis, taxonomical identity, etc.)

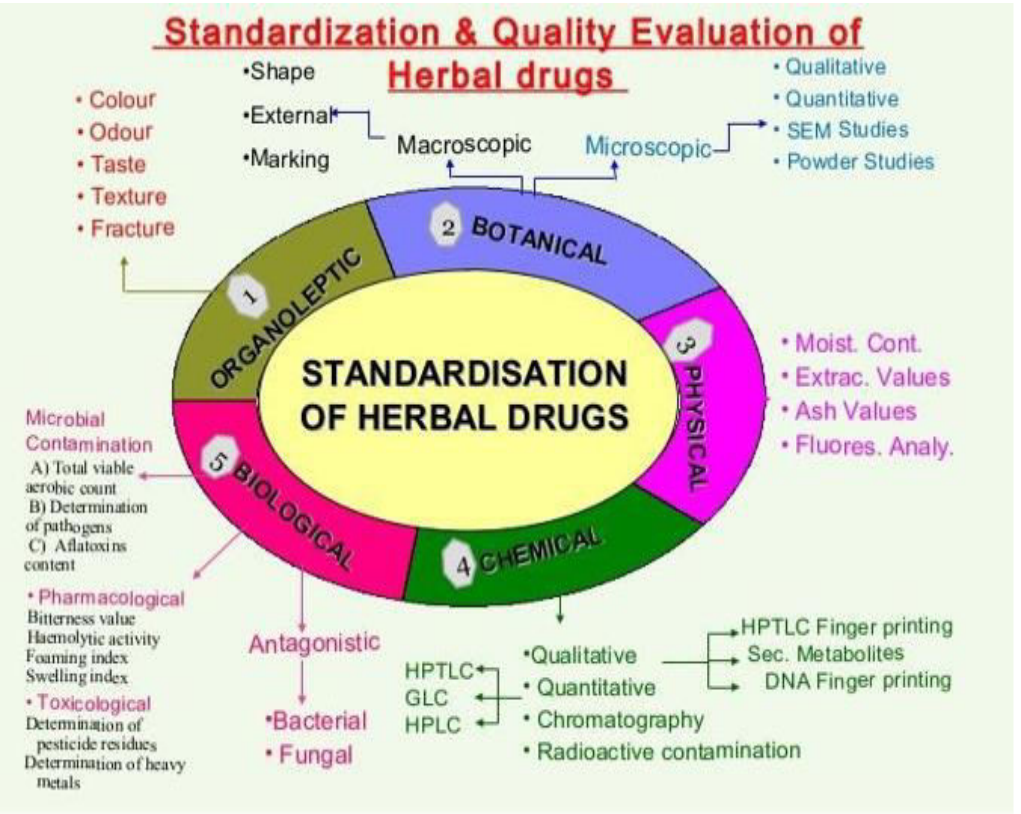
2. Foreign matter (herbs collected should be free from soil, insect parts or animal excreta, etc.)
3. Organoleptic evaluation (sensory characters – taste, appearance, odor, feel of the drug, etc.)
4. Tissues of diagnostic importance present in the drug powder.
5. Ash values and extractive values.
6. Volatile matter
7. Moisture content determination
8. Chromatographic and spectroscopic evaluation-TLC, HPTLC, HPLC methods will provide qualitative and semi quantitative information about the main active constituents present in the crude drug as chemical markers in the TLC fingerprint evaluation of herbals (FEH). The quality of the drug can also be assessed on the basis of the chromatographic fingerprint.
9. Determination of heavy metals - e.g., cadmium, lead, arsenic, etc.
10. Pesticide residue – WHO and FAO (Food and Agricultural Organization) set limits of pesticides, which are usually present in the herbs. These pesticides are mixed with the herbs during the time of cultivation. Mainly pesticides like DDT, BHC, toxaphene, aldrin cause seriousside-effects in human beings if the crude drugs are mixed with these agents.
11. Microbial contamination – usually medicinal plants containing bacteria and molds are coming from soil and atmosphere. Analysis of the limits of E. coli and molds clearly throws lighttowards the harvesting and production practices. The substance known as afflatoxins will produce serious side-effects if consumed along with the crude drugs. Afflatoxins should be completely removed or should not be present.
12. Radioactive contamination – Microbial growth in herbals is usually avoided by irradiation. This process may sterilize the plant material but the radioactivity hazard should be taken into account. The radioactivity of the

plant samples should be checked accordingly to the guidelines of International Atomic Energy (IAE) in Vienna and that of WHO.

The quality of the raw materials can be tested according to the following format:

- Name of the drug (English, Regional names, Exact botanical nomenclature)
- Part of the plant used
- Area of collection
- Distribution details
- Season of Crop
- Time and year of collection
- Pesticide and insecticides
- Condition of the drug (fresh or dry)
- Form of the drug (powdered or intact or cuttings like etc.)

In order to obtain quality oriented herbal products care should be taken right from the proper identification of plants; season and area of collection, extraction, isolation and verification process. Chemical and instrumental analyses are routinely used for analyzing synthetic drugs to confirm its authenticity. In the case of herbal drugs, however the scene is different especially for polyherbal formulation, as there are no chemical or analytical methods available. The herbal formulations in general can be standardized schematically as to formulate the medicament using raw materials collected from different localities and a comparative chemical efficacy of different batches of formulation are to be observed. The preparation with better clinical efficacy is to be selected. After all the routine physical, chemical and pharmacological parameters are to be checked for all the batches to select the final finished product and to validate the whole manufacturing process.



Flow chart on standardization and evaluation of herbal drugs

Stability testing of herbal drugs

It is a challenging risk, because the entire herb or herbalproduct is regarded as the active matter, regardless of whether constituents with defined therapeutic activity are known. The most important aspect in the evaluation of the stability study of a product and its storage condition. The purpose of a stability testing is to provide proof on how the quality of the herbal products varies with the time under the influence of environmental factors such as temperature, light, oxygen, moisture, other ingredient or excipients in the dosage form, particle size of drug, microbial contamination, trace metal etc.

Stability studies should be performed on at least three production batches of the herbal products for the proposed shelf-life, which is normally denoted as

long-term stability and is performed under natural atmospheric conditions. With the help of modern analytical techniques like spectrophotometry, HPLC, HPTLC and by employing proper guidelines it is possible to generatea sound stability data of herbal products and predict their shelf-life, which will help in improving global acceptability of herbal products.

Shelf-life

The determination of shelf life of herbal medicinal drug products is same as chemically defined APIs, but special nature of herbal product should be taken into consideration. It is recommended that in case of an herbal medicinal product containing a natural product or a herbal drug preparation with constituents of known therapeutic activity, the variation in component during the proposed shelf-life should not exceed ±5% of the initial assay value, unless justified to widen the range up to ±10 per cent or even higher. The low marker concentration in the finished product, justify the wider range.

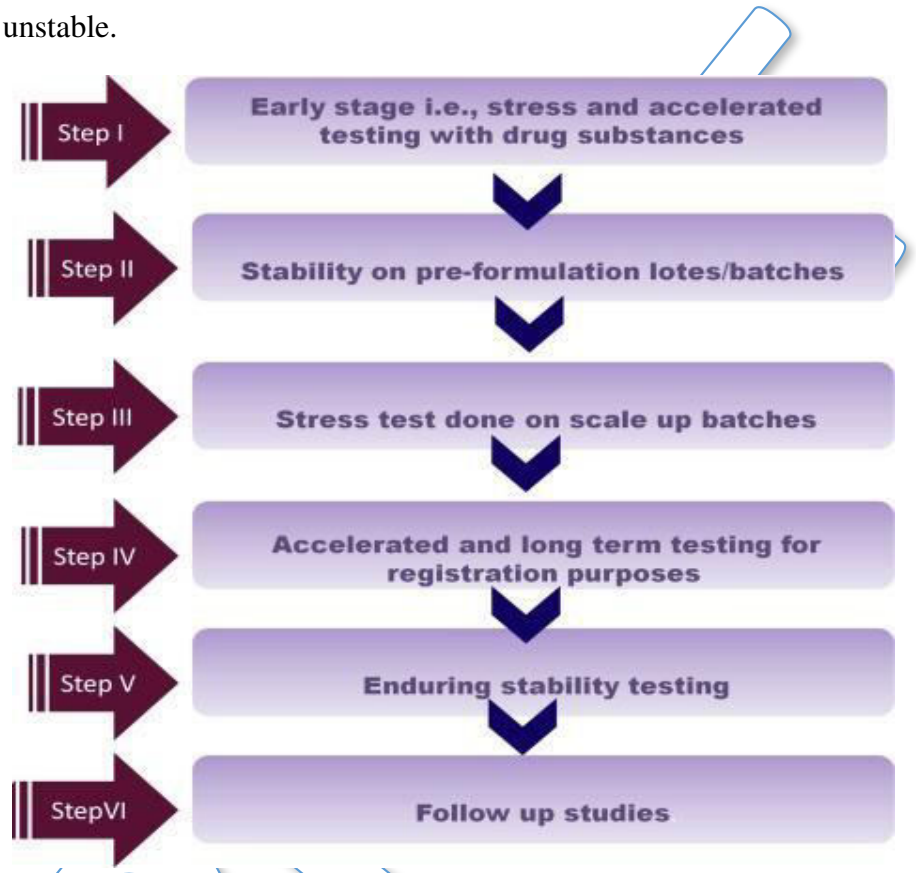
Additionally, due to the influences of climate, harvesting and biological variance, the natural variation of the marker content needs to be taken into account.For example, the linearity of the method may be tested over a range of 40-160 per cent of the marker's expected content in the extract and/or product. During stability testing, a setting up of the limits to ±10 per cent is accepted for the finished product, by the justification of matrix effects (placebo), the lack of precision and selectivity (combination products) and the lowanalyte concentrations. Considering that the marker content cannot be defined to a specified level, the relative changes from the starting value are specified (95-105 per cent or 90-110 per cent from the initial value).

Challenges in stability testing of herbal medicinal product:

1. Active substances (herbal substances and/or herbal preparations) in HMPs (herbal medicinal products) consist of complex mixtures of constituents and in most cases the constituents responsible for the therapeutic effects are unknown.

2. The situation is further complicated when two or more herbal substances and/or herbal preparations are combined in an herbal formulation.

3. In addition, many herbal substances/herbal preparations are known to be unstable.



Taking into account these special features of Herbal Medicinal Products, adequate quality concepts have been established. As part of a total control strategy for herbal substances, herbal preparations and herbal medicinal products, a set of test criteria including qualitative andquantitative parameters has been recognized as quality indicating. With regard to stability tests, chromatographic fingerprints as well as appropriate methods of assay via marker substances represent the fundamental part of this concept, laid down in shelf-life specifications. Notwithstanding the appropriateness of this approach, its realization is often associated with analytical problems and high costs.

Mechanisms involved in change product: Loss of activity, change in concentration of active component, alteration in bioavailability, loss of content uniformity, loss of elegance, formation of toxic degradation product, loss of packaging integrity.

Importance of stability testing: It evaluates the efficacy of a drug. Stability studies are used to develop suitable packaging information for quality, strength, purity & integrity of product duringits shelf life. It is used for determination of the shelf life.

Stress testing: Stress testing help to identify the degradation product, which can help to establish the degradation pathway. Stress tests are usually considered unnecessary for herbal drug & its preparation.

1) For herbal drugs and herbal drug preparations, a testing under accelerated or intermediate conditions may be omitted. This should apply to finished products as well, because it is known that most products fail at 30 ^{0}C/65 per cent relative humidity (RH) and at 40 ^{0}C/75 per cent RH in particular. Herbal drug substances at only 25 ^{0}C/60 per cent RH, with no requirement for intermediate/ accelerated testing.
2) If intermediate conditions are tested, the three-month time-point is omitted (that is 0, 6, 9 and 12 months). In some cases of combination products, it is hardly possible to provide the required two batches of each extract at the same time due to different harvesting times.

Selection of batches: Long-term testing is to be provided with on at least two batches of the drugsubstance and three batches of drug product. In some cases of combination products, it is hardly possible to provide the required two batches of each extract at the same time due to different harvesting times. This should be taken into consideration when planning the schedule for stability study.

Predictable changes in herbal medicinal product: Following predictable changes may occurs in herbal medicinal product during storage and in shelf-

life determination: hydrolysis, oxidation, racemization, geometric isomerization, temperature, moisture and light.

Hydrolysis: Reaction with water takes place results in degradation of product.

Oxidation: Due to addition of electro negative atom, removal of electro positive atom, radicals' formation results in decomposition of natural products.

Racemization: Racemization is the process in which one enantiomer of a compound, such as an L-amino acid, converts to the other enantiomer. The compound then alternates between each form while the ratio between the (+) and (–) groups approaches 1:1, at which point it becomes optically inactive.

Geometric isomerization: Products can be change in trans or cis form. One form may be more therapeutically active.

Polymerization: There is combination of two or more identical molecule to form much larger and more complex molecule.

Temperature: The rate of most chemical increase with increase in temperature. So that "Tropical" area must be taken in consideration during preparation of the formula of the herbal substance.

Moisture: Moisture absorbed on to the surface of solid drug will often increase the rate of decomposition, if it is susceptible to the hydrolysis.

Light: Many types of chemical reaction induced by exposure to light of high energy. Autoxidation of volatile oil/fixed oil takes place and substance becomes coloured.

Patenting and regulatory requirements of natural products

Patent

A patent is a monopoly right, which is granted to a patentee for a limited period of time during which he is given the exclusive right to hinder anyone else from using her invention without consent. Thus, it is a negative right as it doesn't

grant anyone the right to produce or do anything, simply the right to hinder others from doing or producing what is covered by the patent. Patents as a legal institution have evolved over hundreds of years. The scope, length and purpose for protection has changed many times and it is of value to this paper to examine the developments in relation to the developments occurring in the Southern countries but at a much more accelerated pace as a means of mirroring the development.

A patent can be granted for an invention which may be related to any process or product. The word "Invention "has been defined under the Patents Act 1970 as amended from time to time. "An invention means a new product or process involving an inventive step and capable of industrial application. A patent gives its owner the right to exclude other from making, using, selling and importing an invention for a limited period of time, usually 20 years. The patent rights are granted in exchange for an enabling public disclosure of the invention.

Intellectual property rights (IPRs)

These are rights to make, use, and sell a new product or technology that are granted, usually for a period of 17-20 years, solely to the inventor or the corporation which files a claim on the inventor's behalf. IPRs are meant to reward innovators, inventors and researchers. It is a driving force behind rapid industrial growth and progress.Under intellectual property law, owners are granted certain exclusive rights to a variety of intangible assets, such as musical, literary, and artistic works, discoveries and inventions, words, phrases, symbols, and designs. Common types of intellectual property include copyrights, trademarks, patents, industrial design rights and trade secrets in some jurisdictions. Among various kinds of IPRs patents and trademarks are more important to pharmaceutical industries. IPR does not provide protection for inventions that are based on prior existing knowledge.

A patent is a set of exclusive rights granted by a state (national government) to an inventor or their assignee for a limited period of time in exchange for a public disclosure of an invention. The association of patents and thievery has

a long history. When Columbus sailed out to "discover" a world that was new to him, he was carrying letters patent from the King and Queen of Spain. The procedure for granting patents, the requirements placed on the patentee, and the extent of the exclusive rights vary widely between countries according to national laws and international agreements. Typically, however, a patent application must include one or more claims defining the invention which must be new, inventive, and useful or applicable. In most countries, both natural persons and corporate entities may apply for a patent. The grant and enforcement of patents are governed by national laws, and also by international treaties.

Pharmaceutical companies have been making use of traditional knowledge of tribal people to identify plants and their ingredients for developing new medicines. Researchers, screening plantsfor useful substances can cut down time taken, by getting information from tribal healers on variety of plants used for treating ailments. Many pharmaceutical corporations are misusing traditional knowledge and making huge profits in form of what is known as biopiracy. Trade secret is an IPR which provides simplified protection. It does not require registration with government and is not bound by time. It is useful in countries like India in managing heavy cost of IP protection.

Farmers right

Farmers may have little or no understanding of the scientific basis of genetic diversity, but they certainly understand its paramount importance to agriculture, and the need for promoting variability in agricultural practices. The autonomy that every farmer exercises in selecting, saving and maintaining seed for re-sowing has been fundamental for the agronomic transformation of plant species into crops, and their further selection.

Farmers' rights and intellectual property rights: The basic principle underlying IPR on plant varieties is the recognition of human innovation in developing a new plant variety through selection, with or without recombination, which is novel and distinct from the pre-existing varieties.

Unlike the innovations that are made in many non-biological domains, life forms such as crop varieties are not completely invented, but are always created from pre-existing life forms and propagated by natural processes. Thus, the creation of a new variety has two components:the use of pre-existing varieties and the knowledge required to select a new variety by recombining the pre-existing ones or by other processes. Equity demands that the recognition of innovations made on the newly bred varieties should also include the similarly innovativecomponent invested in the source varieties (i.e., plant genetic resources).

The latter essentially represent the far greater cumulative intellectual inputs contributed by generations of farming communities over a long period. The fact that those communities lack identity and institutional backing, unlike the present commercial plant breeders, should not mean that they are given less importance or recognition for their intellectual inputs. While IPR on plant varieties are upheld, the demand for free access to varieties developed by farmers, without the payment of royalties applicable to varieties protected by intellectual property (IP), can be seen as a double standard concerning rights. Moreover, the granting of exclusive rights over the seed or propagatingmaterial of an IP-protected variety marks a turning point from the traditional unrestricted right farmers had enjoyed over seed. This restriction on the seed of a patent-protected variety is rigorous, allowing no flexibility for farmers and minimal flexibility for breeders, depending on the jurisdiction.

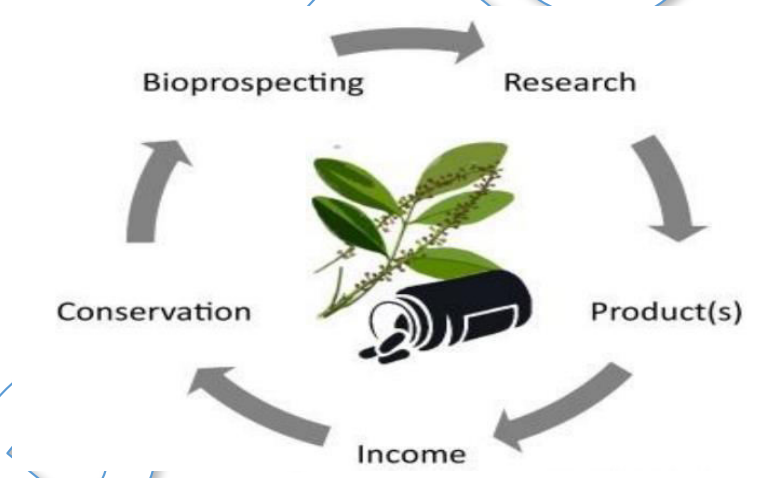
Plant Breeders Rights (PBR): These are also known as plant variety rights (PVR). These are the rights granted to the breeder of a new variety of plant that give the breeder exclusive control over the propagating material and harvested material of a new variety for a number of years. With these rights, the breeder can choose to become the exclusive rights, a variety must be new, distinct, uniform and stable. PBRs allow a plant breeder to exclude others from the production, processing, stocking, distribution, marketing, sale, export and import of propagating material of aprotected variety for a specified number of years. It also allows the breeder to license such rights to others, and to receive

royalties generated from the authorized use of the propagating material. These rights may in some countries also include harvested material, such as cut flowers, fruits or foliage of the protected variety, in cases where the breeders do not have reasonable opportunities to exercise their rights over the planting materials. The legal space available to farmers concerning the seed of a protected variety under such a system for plant varietal protection takes the form of farmers' rights, together with PBRs; or that of the farmers' privilege within PBRs.

Biopiracy: When researchers use traditional knowledge without permission, or exploits the cultures they're drawing from - it's called biopiracy. Biopiracy happens when researchers or research organisations take biological resources without official sanction, largely from lessaffluent countries or marginalised people. Biopiracy is not limited to drug development. It also occurs in agricultural and industrial contexts. Indian products such as the neem tree, tamarind, turmeric, and Darjeeling tea have all been patented by foreign firms for different lucrative purposes.

The term biopiracy was coined by Pat Mooney, to describe a practice in which indigenous knowledge of nature, originating with indigenous peoples, is used by others for profit, without authorization or compensation to the indigenous people themselves. For example, when bio prospectors draw on indigenous knowledge of medicinal plants which is later patented by medical companies without recognizing the fact that the knowledge is not new or invented by the patentor, this deprives the indigenous community of their potential rights to the commercial product derived from the technology that they themselves had developed. Critics of this practice, such as Greenpeace, claim these practices contribute to inequality between developing countries rich in biodiversity, and developed countries hosting biotech firms. In the 1990s many large pharmaceutical and drug discovery companies responded to charges of biopiracy by ceasing work on natural products, turning to combinatorial chemistry to develop novel compounds.

Bioprospecting: It is the process of discovery and commercialization of new products based on biological resources. Despite indigenous knowledge being intuitively helpful, bioprospecting has only recently begun to incorporate such knowledge in focusing screening efforts for bioactive compounds. During 1981-2010, one third of all small molecule new chemical entities approved by the U.S. Food and Drug Administration (USFDA) were either natural products or compounds derived from natural products. Despite indigenous knowledge being intuitively helpful, bioprospecting has only recently begun to incorporate such knowledge in focusing screening efforts for bioactive compounds. Bioprospecting may involve biopiracy, the exploitative appropriation of indigenous forms of knowledge by commercial actors, and can include the patenting of already widely used natural resources, such as plant varieties, by commercial entities.



Traditional knowledge (TK): The concept of traditional knowledge is too varied to havea single definition as such a definition would be prejudicial to the various forms of knowledge that are held by traditional communities. No superficial legal definition will sufficiently encompass the complex social and legal systems that sustain traditional knowledge within the original communities. Nonetheless it is very necessary to arrive at certain demarcating standards defining traditional knowledge if such knowledge is to be protected.

The most practical method of protection is the prevention of unauthorized use by third parties beyond the traditional circle.

This form of protection focuses on the use of any indigenous knowledge as technical, ecological, scientific, medical or cultural by a traditional community. A report by WHO says that about 80%of World's population is depending on the traditional knowledge on the ancient methods for curing disease. The traditional knowledge is based on indispensable for its primary health care uses. For example, the Neem and its uses can be registered under traditional knowledge by indigenous people of India for its medical uses which includes first aid, cosmetic nature and for curing inflammation and redness caused by any medical issue. This is based on herbal plant usedfor medical purpose and it is called "arogyapaacha".

"Traditional knowledge refers to the knowledge, innovations and practices of indigenous and local communities around the world. Developed from experience gained over the centuries and adapted to the local culture and environment, traditional knowledge is transmitted orally from generation to generation. It tends to be collectively owned and takes the form of stories, songs, folklore, proverbs, cultural values, beliefs, rituals, community laws, local language, and agricultural practices, including the development of plant species and animal breeds. Traditional knowledge is mainly of a practical nature, particularly in such fields as agriculture, fisheries, health, horticulture, forestry and environmental management in general.

Case study of Neem

The Neem tree (*Azadirachta indica*) is a large tropical evergreen that can grow up to 30 meters tall and 2.5 meters in girth. The tree carries a yellow or greenish yellow fruit, which holds a seed. The exact origin of the tree is unknown, it is found in many different countries but it is in India that the tree is most widely spread; the subcontinent is estimated to contain approximately 18 million Neem trees. The tree has been shown to be useful in many different areas including contraception, dental hygiene and pesticides, as well as being

part of many traditional Indian medicines and cures. The widespread growth of the Neem treeand its many practical uses has made the Neem tree very dear to the Indian people to whom it represents an integral part of their traditional and even religious heritage. Indian scientists have been researching the Neem tree as a natural pesticide since the 1920's but Western awareness of its qualities wasn't raised until 1959 when German entomologist Heinrich Schmutterer witnesseda locust plague in the Sudan and noticed that the Neem trees were the only ones that had withstood the onslaught. He immediately started studying the Neem tree and his work in turn generated a great deal of western scientific interest in its pesticidal qualities.

That the Neem tree could withstand locust infestations had been common knowledge among Indian farmers for centuries. Both the seeds and to a lesser extent the leaves contain the active substance azadirachtin, which is a powerful insecticide that is not harmful to human beings. Even beforethe discovery of the active substance in the latter half of the 20th century, Neem seeds had been used by Indian farmers as a natural pesticide. The most common practice was to break up the seeds, soak them in water or alcohol, and then apply the resulting emulsion on their crops. The efficiency of this practice was however limited by the rapid degradation of the chemical solution which usually only lasted a couple of days.

The first U.S. patent on a storage stable composition for Neem seed extract was issued in 1985 to inventor Robert O. Larsson W.R. Grace in partnership with The United States of America as represented by The Secretary of Agriculture jointly filed a Patent Application for the formulation with the (European Patent Office) EPO, who after a long-drawn-out examination process granted the applicants the patent in 1994. The main claim of the patent had however been restricted by the EPO in relation to the patent granted in the U.S. The aim of the opponents was to revoke the patent, and more specifically on the grounds of prior use and TK so as to gain an important case law precedent in their battle against biopiracy. The decision of the opposition division followed along the lines of what they were after. The claim was

rejected on the grounds of lacking novelty and the evidence upon which this decision was taken was the testimony of a witness who had worked with the process himself and who could verify its use among Indian farmers.

The decision of the Board of appeal to leave open whether prior art had been proven or not changed the whole focus of the case. In choosing the article as the closest prior art they relied on a scientific study published in a Western journal. Thereby the question of novelty and inventive step wasn't truly judged on the grounds of TK. The decision was taken on the basis of comparing two scientific documents, the lack of inventive step wasn't judged againstIndian traditional practices but the scientific studies of two scholars. The board shied away from dealing with the issue of prior use and decided the case on materials with which they were more comfortable. Another interesting aspect of the change is that the patentees who had declined an oral hearing provided no defence against the article on the grounds of inventive step and only a fleeting remark regarding the article in relation to novelty. Even if the significance of the inadequate defence presented by the patentees is hard to discern, it cannot be ignored as a potential factor in the decision.

Case study of Turmeric

Turmeric is a tropical herb grown in east India. Turmeric powder is widely used in India as a medicine, a food ingredient and a dye to name a few of its uses. For instance, it is used as a blood purifier, in treating the common cold, and as an anti-parasitic for many skin infections. It is also used as an essential ingredient in cooking many Indian dishes. In 1995, the United States awarded patent on turmeric to University of Mississippi Medical Center for wound healing property.

The claimed subject matter was the use of "turmeric powder and its administration", both oral as well as topical, for wound healing. An exclusive right has been granted to sell and distribute. The Indian Council for Scientific and Industrial Research (CSIR) had objected to the patent granted and provided documented evidences of the prior art to United States Patent and Trademark Office (USPTO). Though it was a well-known fact that the use of turmeric was known in every householdsince ages in India, it was a herculean task to find published information on the use of turmeric powder through oral as well as topical route for wound healing. Due to extensive researches, 32 references

were located in different languages namely Sanskrit, Urdu and Hindi. Therefore, the USPTO revoked the patent, stating that the claims made in the patent were obvious and anticipated, and agreeing that the use of turmeric was an old art of healing wounds. Therefore, the Traditional Knowledge that belonged to India was safeguarded in Turmeric case.

(1993) Patent application by University of Mississippi Medical Center

(1995) USPTO granted patent for use of turmeric in wound healing

Opposed by India's Council of Scientific and Industrial Research(CSIR)

1997 Patent cancelled

Regulatory issues in India

Herbal drug regulation in India:

Drug regulation is a public policy response to the demandsof public health and the changing needs of pharmaceutical industry. Thus, the objective of regulatory control is a question of achieving a 'balance' between protecting and promoting public health and facilitating the industry vis-a-vis compliance with regulatory standards. Consequently, although the regulatory objectives seem clear, the actual quantum of regulatory oversight, the mechanism for achieving regulatory compliance and the actions needed to deal with non-compliance have to be designed in a manner that is sensitive to the characteristics ofthe regulatory space, and specifically, the actors operating in that space.

This is the basic premise in the conceptual approach proposed by 'Smart or Responsive Regulation'. The rationale behind this is to design a regulatory system where the choice of regulatory instruments not only match the imperatives/objectives of regulation, but also take into consideration the range and the intrinsic characteristics of each of the regulatory stakeholders. Provision related to the manufacture and control of Ayurvedic, Sidha and Unani (ASU) drugs have been prescribed in the Drugs and cosmetics acts 1940. This act described the formation of Drugs Technical Advisory Board (DTAB), which consist of various nominated members and Drugs Consultative committees(DCC). DTAB is the highest constitutional decision-making body

on technical matters related to the drugs in the country. It is a part of central drug Standard Control Organisation (CDSCO) in the ministry of Health and family welfare. The drug and cosmetic act provide the establishment of following agencies:

1. Advisory
2. Analytical
3. Executive

Administration of the act and rules:

Advisory

- Drugs Technical Advisory Board (DTAB)
- Drugs Consultative committees (DCC)

Analytical

- Central Drugs Laboratory
- Drug Control Laboratory
- Government Analysts

Executives

- Drug Inspector
- Licensing Authorities
- Controlling Authorities

Drugs and Cosmetics Act 1940

The Drugs and Cosmetics Act, 1940 is an Act of the Parliament of India which regulates the import, manufacture and distribution of drugs in India. The primary objective of the act is to ensure that the drugs and cosmetics sold in India are safe, effective and conform to state quality standards. The related Drugs and Cosmetics Rules, 1945 contains provisions for classification of drugs under given schedules and there are guidelines for the storage, sale, display and prescription of each schedule. The term "drug" as defined in the

act includes a wide variety of substance, diagnostic and medical devices. The act defines "cosmetic" as any product that is meant to be applied to the human body for the purpose of beautifying or cleansing. The definition however excludes soaps. In 1964, the act was amended to include Ayurveda and Unani drugs.

Provisions related to Ayurveda, Siddha and Unani drugs (ASU):

- The Drugs Technical Advisory Board (DTAB)
- The Central Drugs Laboratory (CDL)
- The Drugs Consultative Committee (DCC)

The Drugs Technical Advisory Board (DTAB)

(1) The Central Government shall, as soon as may be, constitute a Board (to be called the Drugs Technical Advisory Board) to advise the Central Government and the State Governments on technical matters arising out of the administration of this Act and to carry out the other functions assigned to it by this Act.

(2) The Board shall consist of the following members, namely:

i. The Director General of Health Services, ex officio, who shall be the Chairman;
ii. The Drugs Controller, India, ex officio;
iii. The Director of the Central Drugs Laboratory, Calcutta, ex officio;
iv. The Director of the Central Research Institute, Kasauli, ex officio;
v. The Director of the Indian Veterinary Research Institute, Izatnagar, ex officio;
vi. The President of the Medical Council of India, ex officio;
vii. The President of the Pharmacy Council of India, ex officio;
viii. The Director of the Central Drug Research Institute, Lucknow, ex officio;
ix. Two persons to be nominated by the Central Government from among

personswho are in charge of drugs control in the States;

x. One person, to be elected by the Executive Committee of the Pharmacy Council of India, from among teachers in pharmacy or pharmaceutical chemistry or pharmacognosyon the staff of an Indian university or a college affiliated thereto;

xi. One person, to be elected by the Executive Committee of the Medical Council of India, from among teachers in medicine or therapeutics on the staff of an Indian university or a college affiliated there to.

The Central Drugs Laboratory (CDL)

The Central Government shall, as soon as may be, establish a Central Drugs Laboratory under the control of a Director to be appointed by the Central Government, to carry out the functions entrusted to it by this Act or any rules made under this Chapter.

The Drugs Consultative Committee (DCC)

The Central Government may constitutean advisory committee to be called "the Drugs Consultative Committee" to advise theCentral Government, the State Governments and the Drugs Technical Advisory Board onany matter ending to secure uniformity throughout [India] in the administration of this act. The Drugs Consultative Committee shall consist of two representatives of the Central Government to be nominated by that Government and one representative of each state Government to be nominated by the State Government concerned. The Drugs Consultative Committee shall meet when required to do so by the Central Government and shall have power to regulate its own procedure.

Manufacture for sale of Ayurvedic, Siddha and Unani drugs:

(1) The Central Government shall, by notification in the Official Gazette and with effect from such date as may be specified therein, constitute a Board (to be called the [Ayurvedic, Siddha and Unani Drugs Technical Advisory Board] to advise the Central Government and the

State Governments on Technical matters arising out of this Chapter and to carry out the other functions assigned to it by this Chapter.

(2) The Board shall consist of the following members, namely:

i. The Director General of Health Services ex officio;

ii. The Drugs Controller, India, ex officio;

iii. The principal officer dealing with Indian systems of medicine in the Ministry of Health, ex officio];

iv. The Director of the Central Drugs Laboratory, Calcutta ex officio;

v. One person holding the appointment of Government Analyst under section 33F, to be nominated by the Central Government;

vi. One Pharmacognocist to be nominated by the Central Government;

vii. One Phyto-chemist to be nominated by the Central Government;

(3) The Central Government shall appoint a member of the Board as its Chairman.

(4) The nominated members of the Board shall hold office for three years but shall be eligible for renomination.

(5) The Board may, subject to the previous approval of the Central Government, make bye-laws fixing a quorum and regulating its own procedure and conduct of all business to be transacted by it.

(6) The functions of the Board may be exercised notwithstanding any vacancy therein.

(7) The Central Government shall appoint a person to be Secretary of the Board andshall provide the Board with such clerical and other staff as the Central Governmentconsiders necessary.

The Ayurvedic, Siddha and Unani Drugs Consultative Committee (ASU)

1) The Central Government may constitute an Advisory Committee to be called the Ayurvedic, Siddha and Unani Drugs Consultative Committee to advise the Central Government, the State Governments and the Ayurvedic, Siddha and Unani Drugs Technical Advisory Board on any matter for the purpose of securing uniformity throughout India in the administration of this Act in so far as it relates to Ayurvedic, Siddha or Unani drugs.

2) The Ayurvedic, Siddha and Unani Drugs Consultative Committee shall consist of twopersons to be nominated by the Central Government as representatives of that Government and not more than one representative of each State to be nominated by the State Government concerned.

3) The Ayurvedic, Siddha and Unani Drugs Consultative Committee shall meet whenrequired to do so by the Central Government and shall regulate its own procedure.

Prohibition of manufacture and sale of certain Ayurvedic, Siddha and Unani Drugs

From such date as the State Government may, by notification in the Official Gazette, specify in this behalf, no person, either by himself or by any other person on his behalf, shall-

(a) Manufacture for sale or for distribution-

i. Any misbranded, adulterated or spurious Ayurvedic, Siddha or Unani drug;

ii. Any patent or proprietary medicine, unless there is displayed in the prescribed manner on the label or container thereof the true list of all the ingredients contained in it;

iii. Any Ayurvedic, Siddha or Unani drug in contravention of any of the provisions of this Chapter or any rule made there under;

(b) Sell, stock or exhibit or offer for sale or distribute any Ayurvedic, Siddha or Unani drug which has been manufactured in contravention of any of the provisions of this Act, or any rule made there under,

(c) Manufacture for sale or for distribution, any Ayurvedic, Siddha or Unani drug except under, and in accordance with the conditions of, a license issued for such purpose under this Chapter by the prescribed authority: Provided that nothing in this section shall apply to Vaidyas and Hakims who manufacture Ayurvedic, Siddha or Unani drug for the use of their own patients : Provided further that nothing in this section shall apply to themanufacture, subject to the prescribed conditions, of small quantities of any Ayurvedic, Siddha or Unani drug for the purpose of examination, test or analysis.

Schedule Z (Proposed): Requirements and guidelines for permission to manufacture of ASU drugs for sale or to undertake clinical trials. The Ayurvedic Drug Manufacturers' Association (ADMA) wants the Department of Ayush to take a gradual approach while implementing the proposed draft notification on Schedule Z after considering requisite change as suggested by the stakeholders. This demand was projected in the representationthat they recently sent to the government which elaborately highlighted the industry issues and concerns over adopting the proposed draft notification. The association stressed that industry is not against any progressive ideas offered by the government provided that they are taken after considerable discussion and deliberation with thestakeholders.

The industry pointed out that they are open to consider the proposition, however implied that the industry needs time to adjust to these changes. ADMA in their representation suggested that the government should take a calculative approach focusingon gradually implementing the so called changed in an organised and phased manner so that the industry will not be forced to face the brunt of the changes. The association stated that prior to coming out

with regulatory changes the government should also take into account the ability of the small-scale industry in adopting to those proposed changes.

In brief these guidelines consist of information on the protocol, ethical issues, safety considerations, informed consent process, data management, quality assurance, record keeping, statistics and areas on special concern like studies with contraceptives, surgical procedures, medical devices etc. Draft of this schedule is under consideration.

UNIT-V

GENERAL INTRODUCTION TO HERBAL INDUSTRY

Introduction

Herbs are those remedial agents which are created by nature for curing human illness. Herbal extracts have been used since ancient times in traditional medicine. This system of medicine (Ayurveda, Unani and Siddha) is 5000-year-old recommends a combination of lifestyle management and treatment with specific herbs and minerals to cure various diseases. Approximately 1250 Indian medicinal plants are being used to formulate beneficial measures according to Ayurveda. WHO define Traditional herbal medicines as naturally occurring, plant derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices. Traditional herbal medicine and their preparationshave been widely used for the thousands of years in developing and developed countries due toits natural origin and lesser side effects.

These medicines initially used in the form of crude drugssuch as tinctures, teas, poultices, powders, and other herbal formulations. The use of plants for healing purposes predates human history and forms the origin of much modern medicine. Clinical, pharmacological, and chemical studies of these traditional medicines, which werederived predominantly from plants, were the basis of most early medicines such as aspirin (Willow bark), digitoxin (Fox glove leaves), morphine (Opium poppy), quinine (Cinchona bark), and pilocarpine (Jaborandi). Herbal medicine is still the mainstay of about 75-80% of the world population, mainly in the developing countries, for primary health care. This is primarily becauseof the general belief that herbal drugs are without any side effects besides being cheap and locally available. According to the WHO, the use of herbal remedies throughout the world exceeds that of the conventional drugs by two to three times.

Recently WHO classified herbal medicines into four different classes according to their origin, evolution and forms of current usage.

- Indigenous herbal medicines
- Herbal medicines in systems
- Modified herbal medicines
- Imported products with an herbal medicine base.

Indigenous herbal medicines are those which historically used in a local community or region and are very well known through long usage by the local population in terms of its composition, treatment and dosage. It can be used freely by the local community or in the local region. However, if the medicines in this category enter the market or go away from the local community or region, they have to meet the requirements of safety and efficacy as per the national regulations for herbal medicines. Herbal medicines in systems have been used for a longtime and are documented with their special theories and concepts, and accepted by the countries such as Ayurveda, Unani and Siddha.

Modified herbal medicines have been modified in shape, or form including dose, dosage form, mode of administration, herbal medicinal ingredients, methods of preparation and medical indications. They have to meet the national regulatory requirements of safety and efficacy of herbal medicines. Imported products with herbal medicine base covers all imported herbal medicines including raw materials and products. Imported herbal medicines must be registered and marketed in the countries of origin. The safety and efficacy data have to be submitted to the national authority of the importing country and need to meet the requirements of safety and efficacy of regulation in the recipient country.

Past and present status of herbal medicines

Plants and natural products were used by humankind over the years as food and medicines to cure and prevent diseases. It is very difficult to point out an exact time when the use of plants was started as medicine, the carbon dating from ancient Babylon (Iraq) records that plants were cultivated as medicines 60,000 years ago. Written Materia medica of medicinal herbs go back approximately 5,000 years in India, China and Egypt and at least 2,500 years in Greece and Asia Minor. Neanderthal remains have been found to contain the remnants of medicinal herbs. Ancient Ayurveda was meant essentially to promote health, however, rather than fight disease. Charak Samhita (1000 BC) and Sushrut Samhita (100 AD) are the main text available. Ayurveda Materia medica gives detailed descriptions of over 1500 herbs and 10,000 formulations.

Currently more than 80% of the world population depends on traditional and plant derived medicine because plants are important sources of medicines and presently about 25% of pharmaceutical prescriptions in the United States contain at least one plant derived ingredient. In the last century, roughly 121 pharmaceutical products were formulated based on the traditional knowledge obtained from various sources. In fact, it is now believed that nature contributes up to 90% to the new drug molecule. Nature has provided many of the effective agent such as dactinomycin, bleomycin, and doxorubicin, vinblastine,

irinotecan, topotecan, etoposide, and paclitaxel (anti-cancer), mefloquine, chloroquine, amodiaquine, artemisinin, artemether, and arteether (anti-malarial), metformin and eventually the other biguanide, harunganin, cryptolepine, maprouneacin (anti-diabetic), calanolide A, curcumin, phenoxodiol (anti-HIV drugs) etc. India has around 25,000 effective plant-based formulations used traditionally with over 1.5 million practitioners of traditional medicinal system and 7800 medicinal drug manufacturing units in India, which consume about 2000 tons of herbs annually.

Traditional medicine in most regions of the world takes place after WHO Traditional Medicine Strategy 2002-2005, state member also developed their own documentation and safety concern. The diversity of regulations and regulatory categories for Traditional medicinal products makesit difficult to assess the size of the market for products across member states accurately. However, available data suggests that the Traditional medicine have significant market in member states. Indian herbal market is nearly 50 billion rupees with 14% annual growth. One billion rupees worth of herbal product are being exported. The demand for medicinal plants is increasing every day and WHO has projected that global herbal market will grow up to $ 5 trillion in 2050 from the current level of $ 62 billion. India and China produce more than 70% of the global diversity. The significant global herbal export market includes EU, USA, Canada, Australia, Singapore, and Japan while Brazil, Argentina, Mexico, China and Indonesia are new emerging market.

Future prospects of herbal medicine

It is estimated that there are about 350,000 species of existing plants (including seed plants, bryophytes, and ferns), among which 287,655 species havebeen identified as of 2004. Relatively small percentages (1 to 10%) of these are used as foods by both humans and other animal species. It is possible that even more are used for medicinal purposes. WHO has shown great interest in documenting the use of medicinal plants used by tribes from different parts of the world. Many developing countries have intensified their efforts in documenting the ethno-medicinal data on medicinal plants. Research to find

out scientific evidence for claims by tribal healers on Indian herbs has been intensified. Once these local ethno-medicinal preparations are scientifically evaluated and disseminated properly, people will be better informed regarding efficacious drug treatment and improved health status.

The traditional knowledge system needs to be studied, documented, preserved and used for thebenefit of humankind, before it is lost forever. This will require a holistic approach, and involvement and participation of local inhabitants. The Associated Chambers of Commerce and Industry of India (ASSOCHAM) has projected that the market size of herbal industry which is currently estimated at Rs. 7,500 crores (Rs.75 billion) will double to levels at Rs.15,000 crores by 2015 since this industry would be growing at a compounded annual growth rate of over 20% hence forth. In a study brought out by ASSOCHAM on herbal industry and global market 2015, it is pointed out that India's rich resource of medicinal plants and traditional treasure of knowledge in this area, its share at present is considered very meager. A quick estimate of the potential reveals that India can generate raw stock of around Rs. 300 billion and easily achieve around Rs.150 billion value added products. Thus, India is hardly able to exploit less than 50% ofits potential. Interestingly both raw materials (herbs) and herbal products have ready market globally.

The future prospects of herbal medicine are promising and can be viewed from various angles, including scientific research, healthcare trends, and societal shifts. Here are some potential directions in which herbal medicine may evolve:

1. Scientific Research and Validation: As interest in natural and holistic approaches to health grows, there's likely to be increased scientific research into the medicinal properties of various herbs. This could lead to a better understanding of the active compounds in herbs, their mechanisms of action, and their potential interactions with conventional medications. With more rigorous scientific studies, certain herbal remedies may gain recognition as viable options for

specific health conditions.

2. Integration with Conventional Medicine: Herbal medicine may become more integrated with conventional medical practices. Some healthcare providers are already incorporating herbal remedies as complementary therapies alongside conventional treatments. Collaboration between herbalists and medical professionals could lead to more personalized and comprehensive healthcare plans.
3. Preventive Healthcare: Herbal medicine's emphasis on preventive care and maintaining overall well-being aligns with the growing focus on preventive healthcare. Herbs with antioxidant, anti-inflammatory, and immune-boosting properties could play a role in preventing chronic diseases and supporting the body's natural defenses.
4. Natural Product Development: The pharmaceutical industry might explore the development of new drugs based on herbal compounds. Extracting and isolating specific active ingredients from herbs could lead to the creation of novel pharmaceuticals with fewer side effects compared to synthetic drugs.
5. Cultural and Traditional Revival: Many traditional healing practices and knowledge of herbs have been passed down through generations. There could be a resurgence of interest in these practices as people seek more holistic and culturally rooted approaches to healthcare.
6. Personalized Herbal Medicine: Advances in genetics and personalized medicine might lead to the development of tailored herbal remedies based on an individual's genetic makeup, health history, and specific health needs.
7. Regulation and Safety: As herbal medicine gains popularity, regulatory bodies might establish clearer guidelines for quality control, labeling, and safety standards. This could ensure that herbal products on the market are accurately labeled and meet certain quality criteria.
8. Environmental Sustainability: Increased demand for herbs could raise concerns about overharvesting and the impact on plant populations.

Sustainable and ethical practices for cultivating and harvesting medicinal plants could become more important.

9. Consumer Education: With easy access to information, consumers are becoming more proactive in their healthcare choices. As interest in herbal medicine grows, there may be a greater focus on educating the public about proper usage, potential interactions, and the importance of consulting qualified professionals.
10. Global Collaboration: As traditional herbal knowledge varies across cultures, there might be greater international collaboration to share information, experiences, and best practices related to herbal medicine.

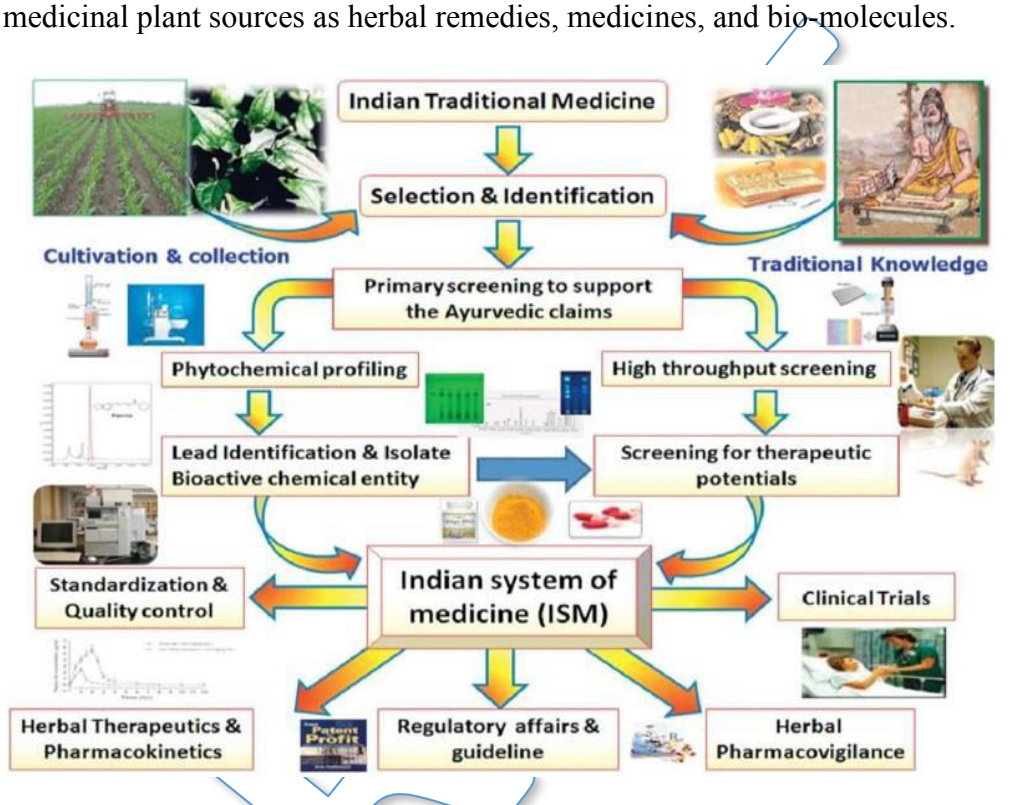
It's important to note that while herbal medicine has numerous potential benefits, there will also be challenges to address, including standardization, quality control, regulation, and bridging the gap between traditional knowledge and modern scientific research. As with any healthcare approach, informed decision-making and collaboration with qualified healthcare professionals are crucial.

Global overview of medicinal plants

The current and recent trends all over the world have clearly shown that for one reason or the other people are not only willing to try natural medicine especially those of plant origin but alternatively are seeking nonconventional remedies. As a result of this situation there is a global resurgence in the trade of herbal medicines. International market for medicinal plants is reported to be over 62 billion US dollars per year during 2000-2001, which is growing steadily at the rate of 7% annually. The botanical retail market, inclusive of herbs and medicinal plants, in USA, is estimated to be approximately 1.6 billion US dollars annually.

It is estimated that countries in Europe annually imports about 400,000 tonnes of medicinal plant material with an average market value of 1 billion US dollars from countries in Africa and Asia. A growing awareness of this new and recent contributor to the foreign exchange reserves of several national

treasuries is beginning to emerge globally. To satisfy the growing market demands for medicinal plants, surveys worldwide are being conducted by the pharmaceutical industries and research organization to unearth and unveil new medicinal plant sources as herbal remedies, medicines, and bio-molecules.



Trade of medicinal plants/Indian scenario

India is one of the richest regions as far as the diversity of plant species is concerned. India is the largest exporter, next to China, accounting for about 13% of the global exports. If we look at the socio-economic scenario of Asian and African countries, modern medicine is neither affordable nor within the reach of many villagers and tribes inhabiting remote areas and deep forests. There are certain pockets in a country like India where the tribal people have no access to modern amenities like roads, telecommunicationsor electricity, and therefore, these communities rely only on their traditional knowledge of medicine for day-today requirements.

It is well established that industrialisation has many direct and indirect effects on the human population. Increased stress is the most evident, although this is offset by increased health awareness among the people and better medical facilities. Nevertheless, increases in the incidence of diseases (mostly in urban populations) such as coronary heart disease, diabetes, hyperlipidaemia, AIDS and cancer cannot be denied. There are many examples where medicines have been obtained from plants known to traditional healers. With the development of modern analytical tools, interest in natural product chemistry has led to the isolation by serturner of morphine alkaloid from opium, a mixture of plentiful alkaloids. This in turn was obtained from the opium poppy (*Papaver somniferum*) by processes that have been used for over 5000 years.

Quinine isolated from the Cinchona tree had its origin in the Royal household of South American Incas. Long before the first European explorers arrived, the native people of South America had developed medical systems with complete diagnosis and treatment of various maladies. The leaves of the coca tree have been primarily chewed by Andean people to obtain well-known benefits. In 1860, Carl Koler isolated cocaine from the coca tree, the chemical responsible for its biological activity, and has become infamous as a drug of abuse. The other botanicals include atropine, hyoscine, digoxin, colchicine and emetine.

Medicinal and aromatic plant-based industries and institutions in India

In India, it is estimated that there are about 25,000 licensed pharmacies of Indian system of medicine. Presently about 1000 single drugs and 3000 compound formulations are registered. Herbal Industry in India uses about 8000 medicinal plants. In India, herbal Research institute andmanufacturer of herbal formulations. However, none the pharma has standardized herbal medicine using active compounds as markers linked with confirmation of bioactivity of medicinal plants. There are about 8000 drug manufactures in India, there are however not more than 25 manufactures that can be classified as large-scale manufactures.

A large number of academic, industrial and government institutes are conducting research on the medicinal plants of India. There has been no systematic review of the massive work that is available from this nation. Many international data-bases and web-sites do not cover even the work published in the Indian Journals. Hence, there is a global lack of awareness of the mass and nature of work carried out on diverse aspects viz. ethnobotany, phytochemistry, pharmacognosy, pharmacology, clinical trials, safety studies and formulation-research. Following Figure provides a short list of some of the eminent institutes which are active in research on medicinal plants and in Ayurveda.

Schedule T-good manufacturing practices of Indian systems of medicine

Components of GMP and its objectives

Good Manufacturing Practice (GMP) is a production and testing practice that helps to ensure a quality product. GMP guidelines are not prescriptive instructions on how to manufacture products. These are a series ofgeneral principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfil GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process. The Good Manufacturing Practices for ASU Drugsas described in Rule 157 of Drugs & Cosmetics Rules 1945 with conditions as specifiedin Schedule T/GMP are to ensure that:

I. Raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination.

II. The manufacturing process is as has been prescribed to maintain the standards.

III. Adequate quality control measures are adopted.

IV. The manufactured drug which is released for sale is of acceptable quality.

V. To achieve the objectives listed above, each licensee shall evolve methodology and procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection. However,under IMCC Act, 1970 registered Vaidyas, Siddhas and Hakeems who prepare medicineson their own to dispense to their patients and not selling such drugs in the market are exempted from the purview of Good Manufacturing Practice (GMP).

Basic principles of GMP

Many countries have legislated that pharmaceutical and medical device companies must follow GMP procedures, and have created their own GMP guidelines that correspondwith their legislation. Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicine. Although there are a number of them, all guidelines follow a few basic principles:

- Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
- Manufacturing processes are controlled, and any changes to the process areevaluated.
- Changes that have an impact on the quality of the drug are validated as necessary.
- Instructions and procedures are written in clear and unambiguous language.
- Operators are trained to carry out and document procedures.
- Records are made manually or by instruments during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected

- Deviations are investigated and documented.
- Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.

Duties regarding regulation of manufacture for sale of ASU drugs: Subject to the provisions of section 23 and of any rules made by the Central Government in this behalf, an Inspector may, within the local limits of the areafor which he is appointed

1. Inspect;

i. Any premises wherein any ASU drugs is being manufactured and the means employed for standardizing and testing the ASU drugs;

ii. Any premises wherein any ASU drugs is being sold, or stocked or exhibited oroffered for sale, or distributed.

2. Take samples ofc any ASU drug

i. Which is being manufactured or being sold or is stocked or exhibited or offered for sale, or is being distributed;

ii. From any person who is in the course of conveying, delivering or preparing to deliver such ASU drugs to a purchaser or a consignee.

3. At all reasonable times, with such assistance, if any, as he considers necessary

i. Search any person, who, he has reason to believe, has secreted about his person, any ASU drugs in respect of which an offence under Chapter IV-A of D&C Act has been, or is being, committed; or

ii. Enter and search any place in which he has reason to believe that an offence under Chapter IV-A of D&C Act has been, or is being committed; or

iii. Stop and search any vehicle, vessel, or other conveyance which, he has reason to believe, is being used for carrying any ASU drug in respect of which an offence under Chapter IV-A of D&C Act has been, or is being, committed, and order in writing the person in possession of the ASU

drugs in respect of which the offence has been, or is being, committed, not to dispose of any stock of such ASU drugs for a specified period not exceeding twenty days, or, unless the alleged offence is such that the defect may be removed by the possessor of the ASU drugs, seize the stock of such ASU drugs and any substance or article by means of which the offence has been ,or is being, committed or which may be employed for the commission of such offence. (Clause c of Section 22 of D&C Act 1940).

Legal provisions for GMP certification

(Rules as in Drugs & Cosmetics Rules 1945 regarding) Manufacture for Sale of Ayurvedic (including Siddha) or Unani Drugs (Part XVI of D&C Rules 1945).

151. Manufacture on more than one set of premises: If Ayurvedic (including Siddha) or Unani drugs are manufactured on more than one set of premises, a separate application shall be made and a separate licence shall be obtained in respect of each such set of premises.

152. Licensing Authorities For this purpose of this Part the State Government shall appoint such Licensing Authorities and for such areas as may be specified in this behalf by notification in the Official Gazette.

153. Application for licence to manufacture Ayurvedic (including Siddha) or Unani drugs.

i. An application for the grant or renewal of a license to manufacture for sale any Ayurvedic (including Siddha) or Unani drugs shall be made in Form 24-D to the Licensing Authority along with a fee of rupees one thousand: Provided that in the case of renewal the applicant may apply for the renewal of the license before its expiry or within one month of such expiry: Provided further that the applicant may apply for renewal after the expiry of one month but within three months of such expiry in which case the fee payable for renewal of such license shall be rupees

one thousand and two hundred plus an additional feeof rupees six hundred.

ii. A fee of rupees three hundred shall be payable for a duplicate copy of a license issued under this rule, if the original license is defaced, damaged or lost.

153-A Loan Licence

i. An application for the grant or renewal of a loan license to manufacture for sale of any Ayurvedic (including Siddha) or Unani drugs shall be made in Form 24-E to the Licensing Authority along with a fee of rupees six hundred.

Explanation - For the purpose of this rule, a loan licence means a licence which a Licensing Authority may issue to an applicant who does not have his own arrangements for manufacture but intends to avail himself of the manufacturing facilities owned by a licence in Form 25-D:

PROVIDED that in the case of renewal the applicant may apply for the renewal of the licence before its expiry or within one month of such expiry:

PROVIDED further that the applicant may apply for renewal after the expiry of one month, but within three months of such expiry in which case the fee payable for renewal of such licence shall be rupees six hundred plus an additional fee of rupees three hundred.

ii. A fee of rupees one hundred and fifty shall be payable for a duplicate copy of a license issued under this rule, if the original license is defaced, damaged or lost.

154. Form of licence to manufacture Ayurvedic (including Siddha) or Unani drugs.

1. Subject to the conditions of rule 157 being fulfilled, a license to manufacture for sale any Ayurvedic (including Siddha) or Unani drugs shall be issued in Form 25-D. The license shall be issued within a

period of three months from the date of receipt of the application.

2. A license under this rule shall be granted by the licensing authority after consulting such expert in Ayurvedic (including Siddha) or Unani Systems of medicine as the case may be, which the State Government may approve in this behalf.

155. Certificate of renewal: The certificate of renewal of a licence in Form 25-D shall be issued in Form 26-D. 155-A Certificate of renewal of a loan licence The certificate of renewal of a loan licence in Form 25-E shall be issued in Form 26-E. 155-B Certificate of award of G.M.P. of Ayurveda, Siddha and Unani Drugs.

i. The certificate of Good Manufacturing Practices to manufacturers of Ayurveda, Siddha or Unani drugs shall be issued for a period of five years to licensees who comply with the requirements of Good Manufacturing Practices (GMP) of Ayurveda, Siddha and Unani drugs as laid down in Schedule T.

ii. The certificate referred to in sub rule (1) shall be issued for a period of five years from the date of issuance of the license.

156. Duration of licence: An original licence in Form 25-D or a renewed license in Form 26-D, unless sooner suspended or cancelled shall be valid for a period of five years from the date of its issue or renewed. PROVIDED that if the application for the renewal of a licence is made before its expiry

or within one month of its expiry, or if the application is made within three months of its expiry after payment of the additional fee of rupees five hundred, the licence shall continue to be in force until orders are passed on the application. The licence shall be deemed to haveexpired, if the application for its renewal is not made within three months of its expiry.

156. A Duration of loan licence

An original loan licence in Form 25-E or a renewed loan licence in Form 26-E, unless soonersuspended or cancelled, shall be valid for a period of five years from the date of its issue or renewed:

PROVIDED that if the application for the renewal of a loan licence is made in accordance with rule 153-A, the loan licence shall continue to be in force until orders are passed on theapplication. The licence shall be deemed to have expired, if the application for its renewal is not made within three months of its expiry.

157. Conditions for the grant or renewal of a licence in Form 25-D Before a licence in Form 25- D is granted or renewed in Form 26-D the following conditions shall be complied with by the applicant, namely-

1. The manufacture of Ayurvedic (including Siddha) or Unani drugs shall be carried outin such premises and under such hygienic conditions as are specified in Schedule T.

a) For issuing of the certificate of Good Manufacturing Practices, the Licensing Authority shall verify the requirements as per Schedule T and issue the Good Manufacturing Practices certificate in Form 26 E-I, simultaneously along with grant or renewal of License in Form 25-D.

2. The manufacture of Ayurvedic (including Siddha) or Unani drugs shall be conducted under the direction and supervision of competent technical staff consisting at least one person, who is a whole-time employee and who possesses the following qualifications, namely-

a) A degree in Ayurveda or Ayurvedic Pharmacy, Siddha or Unani system of medicine, as the case may be, conferred by a University, a State Government or Statutory Faculties, Councils and Boards of Indian Systems of medicines recognized by the Central Government or a State Government for this purpose, or

b) A diploma in Ayurveda, Siddha or Unani system of medicine granted by a State Government or an Institution recognised by the Central Government for this purpose, or

c) A graduate in Pharmacy or Pharmaceutical Chemistry or Chemistry or Botany of a Universityrecognized by the Central Government with experience of at least two years in the manufacture of drugs pertaining to the Ayurvedic or Siddha or Unani systems of medicines, or

d) A Vaid or Hakim registered in a State Register of Practitioners of indigenous systems of medicines having experience of at least four years in the manufacture of Ayurvedic or Siddha or Unani drugs, or

e) A qualification as Pharmacist in Ayurvedic (including Siddha) or Unani systems of medicine,possessing experience of not less than eight years in the manufacture of Ayurvedic or Siddha or Unani drugs as may be recognized by the Central Government.

3. The competent technical staff to direct and supervise the manufacture of Ayurvedic drugs shall have qualifications in Ayurveda and the competent technical staff to direct and supervise the manufacture if Siddha drugs and Unani drugs shall have qualification in Siddha or Unani, as the case may be.

Good Manufacturing Practices

Factory premises: The manufacturing plant should have adequate space for:

- Receiving and storing raw material;
- Manufacturing process areas;
- Quality control section;
- Finished goods store;
- Office;
- Rejected goods/drugs store.

General requirements:

(A) Location and surroundings - The factory building for manufacture of Ayurveda, Siddha and Unani medicines shall be so situated and shall have such construction as to avoid contamination from open sewerage, drain, public lavatory or any factory which produces disagreeable or obnoxious odour or fumes or excessive soot, dust or smoke.

1.1(B) Buildings - The building used for factory shall be such as to permit production of drugs under hygienic conditions and should be free from cobwebs and insects/rodents. It should have adequate provision of light and ventilation. The floor and the walls should not be damp or moist.The premises used for manufacturing, processing, packaging and labeling will be in conformity with the provisions of the Factory Act. It shall be located so as to be:

1. Compatible with other manufacturing operations that may be carried out in the same or adjacent premises.
2. Adequately provided with working space to allow orderly and logical placement of equipment and materials to avoid the risk of mix-up between different drugs or components thereof and control the possibility of cross- contamination by other drugs or substances and avoid the risk of omission of any manufacturing or control step.
3. Designed, constructed and maintained to prevent entry of insects and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks and permit easy cleaning and disinfection. The walls of the room in which the manufacturing operations are carried out shallbe impervious to and be capable of being kept clean. The flooring shall be smooth and even and shall be such as not to permit retention or accumulation of dust or waste products.
4. Provided with proper drainage system in the processing area. The sanitary fittings andelectrical fixtures in the manufacturing area shall

be proper and safe.

5. Furnace/Bhatti section could be covered with tin roof and proper ventilation, but sufficient care should be taken to prevent flies and dust.
6. There should be fire safety measures and proper exits should be there.
7. Drying space- There should be separate space for drying of raw material, in process medicine or medicines which require drying before packing. This space will be protected from flies/insects/dusts, etc., by proper flooring, wire-mesh window, glass pans or other material.

1.1(C) Water Supply - The water used in manufacture shall be pure and of potable quality. Adequate provision of water for washing the premises shall be made.

1.1(D) Disposal of Waste - From the manufacturing sections and laboratories the waste water and the residues which might be prejudicial to the workers or public health shall be disposed of after suitable treatment as per guidelines of pollution control authorities to render them harmless.

1.1(E) Containers' Cleaning - In factories where operations involving the use of containers suchas glass bottles, vials and jars are conducted, there shall be adequate arrangement separated from the manufacturing operations for washing, cleaning and drying of such containers.

1.1(F) Stores- Storage should have proper ventilation and shall be free from dampness. It shouldprovide independent adequate space for storage of different types of material, such as raw material, packaging material and finished products.

1.1(F)(A) Raw Materials - All raw materials procured for manufacturing will be stored in theraw materials store. The manufacture based on the experience and the characteristics of the particular raw material used in Ayurveda, Siddha and Unani system shall decide the use of appropriate containers which would protect the quality of the raw material as well as

prevent it from damage due to dampness, microbiological contamination or rodent and insect infestation, etc. If certain raw materials require such controlled environmental conditions, the raw materials stores may be sub-divided with proper enclosures to provide such conditions by suitable cabinization. While designing such containers, cabins or areas in the raw materials store, care may be taken to handle the following different categories of raw materials:

- ✓ Raw material of metallic origin.
- ✓ Raw material of mineral origin.
- ✓ Raw material from animal source.
- ✓ Fresh herbs.
- ✓ Dry Herbs or plant parts.
- ✓ Excipients etc.
- ✓ Volatile oils/perfumes & flavours.
- ✓ Plant concentrates/extracts and exudates/resins.

Each container used for raw material storage shall be properly identified with the label which indicates name of the raw material, source of supply and will also clearly state the status of raw material such as 'UNDER TEST' or 'APPROVED' or 'REJECTED'. The labels shall further indicate the identity of the particular supply in the form of Batch No. or Lot. No. and the date of receipt of consignment. All the raw materials shall be sampled and got tested either by the in- house Ayurvedic, Siddha and Unani experts (Quality control technical person) or by the laboratories approved by Government and shall be used only on approval after verifying. The rejected raw material should be removed from other raw materials store and should be kept in a separate room. Procedure of 'First in first out' should be adopted for raw materials wherever necessary. Records of the receipt, testing and approval or rejection and use of raw material shall be maintained.

1.1(F)(B) Packaging Materials - All packaging materials such as bottles, jars, capsules, etc. shall be stored properly. All containers and closures shall be adequately cleaned and dried beforepacking the products.

1.1(F)(C) Finished Goods Stores - The finished goods transferred from the production area afterproper packaging shall be stored in the finished goods stores within an area marked "Quarantine".After the quality control laboratory and the experts have checked the correctness of finished goods with reference to its packing/labelling as well as the finished product quality as prescribed, then it will be moved to 'Approved Finished Goods Stock" area.

1.1(G) Working Space - The manufacturing area shall provide adequate space (manufacture and quality control) for orderly placement of equipment and material used in any of the operationsfor which these are employed so as to facilitate easy and safe working and to minimize or to eliminate any risk of mix-up between different drugs, raw materials and to prevent the possibilityof cross-contamination of one drug by another drug that is manufactured, stored or handled in thesame premises.

1.1(H) Health, Clothing, Sanitation and Hygiene of Workers - All workers employed in the Factory shall be free from contagious diseases. The clothing of the workers shall consist of proper uniform suitable to the nature of work and the climate and shall be clean. The uniform shall also include cloth or synthetic covering for hands, feet and head wherever required. Adequate facilities for personal cleanliness such as clean towels, soap and scrubbing brushesshall be provided. Separate provision shall be made for lavatories to be used by men and women, and such lavatories shall be located at places separated from the processing rooms. Workers will also be provided facilities for changing their clothes and to keep their personal belongings.

1.1(I) Medical Services - The manufacturer shall also provide:

i. Adequate facilities for first aid;

ii. Medical examination of workers at the time of employment and

periodical checkup thereafter by a physician once a year, with particular attention being devoted to freedomfrom infections. Records thereof shall be maintained.

1.1(J) Machinery and Equipments - For carrying out manufacturing depending on the size of operation and the nature of product manufactured, suitable equipment either manually operatedor operated semi-automatically (electrical or team based) or fully automatic machinery shall be made available. These may include machines for use in the process of manufacture such as crushing, grinding, powdering, boiling, mashing, burning, roasting, filtering, drying, filling,labelling and packing, etc. To ensure ease in movement of workers and orderliness in operationsa suitably adequate space will be ensured between two machines or rows of machines. This machinery and equipments and machinery recommended is indicated in Part II-A. Proper standard operational procedures (SOPs) for cleaning maintaining and performance of everymachine should be laid down.

1.1(K) Batch Manufacturing Records - The licensee shall maintain batch manufacturing record of each batch of Ayurvedic, Siddha and Unani drugs manufactured irrespective of the type of product manufactured (classical preparation or patent and proprietary medicines). Manufacturingrecords are required to provide and account of the list of raw materials and their quantities obtained from the store, tests conducted during the various stages of manufacture like taste, colour, physical characteristics and chemical tests as may be necessary or indicated in the approved books of Ayurveda, Siddha and Unani mentioned in the First Schedule of the Drugsand Cosmetics Act, 1940 (23 of 1940). These tests may include any in-house or pharmacopoeial test adopted by the manufacturer in the raw material or in the process material and in the finishedproduct.

These records shall be duly signed by Production and Quality Control Personnel respectively. Details of transfer of manufactured drug to the finished products store including dates and quantity of drugs transferred along with

record of testing of the finished product, if any, and packaging, records shall be maintained. Only after the manufactured drugs have been verified and accepted quality shall be allowed to be cleared for sale. It should be essential to maintain the record of date, manpower, machine and equipments used and to keep in process record of various Shodhana, bhavana, burning in fire and specific grindings in terms of internal use.

1.1(L) Distribution Records - Records of sale and distribution of each batch of Ayurveda, Siddha and Unani drugs shall be maintained in order to facilitate prompt and complete recall of the batch, if necessary. The duration of record keeping should be the date of expiry of the batch, certain categories of Ayurvedic, Siddha and Unani medicines like Bhasma, Rasa, Kupi- pakva, Parpati, Sindura, Karpu/Uppu/Puram, Kushta, Asava-arista, etc. do not have expiry date, in contrast their efficacy increases with the passage of time. Hence, records need to be maintained up to 5 years of the exhausting of stock.

1.1(M) Record of Market Complaints - Manufacturers shall maintain a register to record all reports of market complaints received regarding the products sold in the market. The manufacturer shall enter all data received on such market complaints; investigations carried out by the manufacturers regarding the complaint as well as any corrective action initiated to prevent recurrence of such market complaints shall also be recorded. Once in a period of six months the manufacturer shall submit the record such complaints to the Licensing Authority. The Register shall also be available for inspection during any inspection of the premises. Reports of any adverse reaction resulting from the use of Ayurvedic, Siddha and Unani drugs shall also be maintained in a separate register by each manufacturer. The manufacturer shall investigate any ofthe adverse reaction to find if the same is due to any defect in the product, and whether such reactions are already reported in the literature or it is a new observation.

1.1(N) Quality Control - Every licensee is required to provide facility for quality control section in his own premises or through Government-approved

testing laboratory. The test shall be as per the Ayurveda, Siddha and Unani pharmacopoeial standard. Where the tests are not available, the test should be performed according to the manufacturer's specification or other information available. The quality control section shall verify all the raw materials, monitor in process, quality checks and control the quality of finished product being released to finished goods store/warehouse. Preferably for such quality control there will be a separate expert. The quality control section shall have the following facilities:

a. There should be 150 sq feet area for quality control section.
b. For identification of raw drugs, reference books and reference samples should be maintained.
c. Manufacturing record should be maintained for the various processes.
d. To verify the finished products, controlled samples of finished products of each batch will bekept till the expiry date of product.
e. To supervise and monitor adequacy of conditions under which raw materials, semifinished products and finished products are stored.
f. Keep record in establishing shelf life and storage requirements for the drugs.
g. Manufacturers who are manufacturing patent proprietary Ayurveda, Siddha and Unani medicines shall provide their own specification and control references in respect of such formulated drugs.
h. The record of specific method and procedure of preparation, that is, "Bhavana", "Mardana" and "Puta" and the record of every process carried out by the manufacturer shall be maintained.
i. The standards for identity, purity and strength as given in respective pharmacopoeias of Ayurveda, Siddha and Unani systems of medicines published by Government of India Shall be complied with.
j. All raw materials will be monitored for fungal, bacterial contamination with a view to minimize such contamination.
k. Quality control section will have a minimum of-

i) a) Expert in Ayurveda or Siddha or Unani who possess a degree qualification recognized under Schedule II of Indian Medicine Central Council Act, 1970.

b) Chemist, who shall possess at least a Bachelor Degree in Science or Pharmacy or Pharmacy (Ayurveda) awarded by a recognized University; and

c) A Botanist (Pharmacognosist) who shall possess at least a Bachelor Degree in Science (Medical) or Pharmacy or Pharmacy (Ayurveda) awarded by a recognized University.

ii) The manufacturing unit shall have a quality control section as explained underSection 35(ii). Alternatively, these quality control provisions will be met by getting testing, etc., from a recognized laboratory for Ayurveda, Siddha and Unani drugs; under Rule 160-A of the Drugs and Cosmetics Act. The manufacturing company will maintain all the record of various tests got done from outside recognized laboratory.

iii) List of equipment recommended is indicated in Part II-C.

Requirement for sterile product:

(A) Manufacturing Areas – For the manufacture of sterile Ayurvedic, Unani and Siddha drugs, separate enclosed areas specifically designed for the purpose shall be provided. These areas shall be provided with air locks for entry and shall be essentially dust free and ventilated with an air supply. For all areas where aseptic manufacture has to be carried out, air supply shall be filtered through bacteria retaining filters (HEPA Filters) and shall be at a pressure higher than in the adjacent areas. The filters shall be checked for performance on installation and periodically thereafter the record of checks shall be maintained. All the surfaces in sterile manufacturing areas shall be designed to facilitate cleaning and disinfection. For sterile manufacturing routine microbial counts of all Ayurvedic, Siddha and Unani drug manufacturing areas shall be carried out during operations. Results of such count shall be checked against established in-house standards and record maintained. Access to

manufacturing areas shall be restricted to minimum number of authorized personnel. Special procedure to be followed for entering and leaving the manufacturing areas shall be written down and displayed. For the manufacturing of Ayurvedic, Siddha and Unani drug that can be sterilized in their final containers, the design of the areas shallpreclude the possibility of the products intended for sterilization being mixed with or taken to be products already sterilized. In case of terminally sterilized products, the design of the areas shall preclude the possibility of mix-up between non-sterile products.

(B) Precautions against contamination and mix:

a. Carrying out manufacturing operations in a separate block of adequately isolated building or operating in an isolated enclosure within the building,

b. Using appropriate pressure differential in the process area.

c. Providing a suitable exhaust system.

d. Designing laminar flow sterile air system for sterile products.

e. The germicidal efficiency of UV lamps shall be checked and recorded indicating the burning hours or checked using intensity.

f. Individual containers of liquids and ophthalmic solutions shall be examined against black- white background fitted with diffused light after filling to ensure freedom from contamination with foreign suspended matter.

g. Expert technical staff approved by the Licensing Authority shall check and compare actual yield against theoretical yield before final distribution of the batch. All process controls as required under master formula including room temperature, relative humidity, volume filled, leakage and clarity shall be checked and recorded.

REFERENCES

1. W.C. Evans, Trease and Evans Pharmacognosy, 16th edition, W.B. Sounders & Co., London, 2009.
2. Mohammad Ali. Pharmacognosy and Phytochemistry, CBS Publishers & Distribution, New Delhi.
3. Text book of Pharmacognosy by C.K. Kokate, Purohit, Gokhlae (2007), 37th Edition, Nirali Prakashan, New Delhi.
4. Herbal drug industry by R.D. Choudhary (1996), 1st Edn, Eastern Publisher, New Delhi.
5. Essentials of Pharmacognosy, Dr. SH. Ansari, 2nd edition, Birla publications, New Delhi, 2007.
6. Herbal Cosmetics by H. Pande, Asia Pacific Business Press, Inc, New Delhi.
7. A.N. Kalia. Textbook of Industrial Pharmacognosy, CBS Publishers, New Delhi, 2005.
8. R Endress, Plant cell Biotechnology, Springer-Verlag, Berlin, 1994.
9. Pharmacognosy & Pharmacobiotechnology. James Bobbers, Marilyn KS, VE Tylor.
10. The formulation and preparation of cosmetic, fragrances and flavours. Remington's Pharmaceutical sciences.
11. Chopra, R.N., Nayar, SL., Chopar, I.C. Glossary of Indian Medicinal plants, 1956.
12. Nadkarni, K M., Indian Materia Medica, 1927, Vol (1), pg. 572.
13. Ikan Raphael, Natural Products, Academic Press-Elsevier, 2nd edn-2005.
14. Gogte VM, Ayurvedic pharmacology and therapeutic uses of medicinal plants (Dravyagunavignyam), India, Bharatiya Vidya Bhavan, 2000.
15. Khandewal KR. Practical Pharmacognocy. Nirali Prakashan, Pune, 2008.
16. Bartram T. Encyclopedia of Herbal Medicine, Grace, Dorset, 1995:1-25.
17. Textbook of Pharmacognosy and Phytochemistry by Jarald, Edwin E. and Edwin Jarald Sheeja.
18. Textbook of Industrial Pharmacognosy by Kalia A.N.
19. Pharmacognosy and Pharmacobiotechnology by Ashutosh Kar.

20. Pharmacognosy & Phytochemistry by V.D. Rangari.

21. Pharmacopoeial standards for Ayurvedic Formulation (Council of Research in Indian Medicine & Homeopathy).

22. Mukherjee PW. Quality Control of Herbal Drugs: An Approach to Evaluation of Botanicals. Business Horizons Publishers, New Delhi, India, 2002.

23. A Handbook on Practical Pharmacognosy and Phytochemistry by Kaveti Vamshi Sharathnath, Dr. B. Sree Giri Prasad, Narender Boggula.

24. Kohli KR. Ayurvedic medicines and heavy metals issue, Ayurveda Heritage. (Association of Manufacturers of Ayurvedic Medicines, AMAM, Ghaziabad). 2005; 1(3):5-6.

25. Adhamalla, Commentetor. Sharangdhara Samhita, Madhyama Khanda, 2/1, 5th edition, Chaukhamba Orientalia, Varanasi, 2005;144.

***** Good Luck *****