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EMERGING TRENDS OF BIORESEARCH

# EMERGING TRENDS OF BIORESEARCH

**First Edition**

**Editors**

**Dr. R.B. Tripathi,**
**Dr. Taniya Sengupta Rathore,**
**Mrs. J. Suguna, Dr. S. Priya**

**THANUJ INTERNATIONAL PUBLISHERS,**
**TAMIL NADU, INDIA**

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**Tamil Nadu, India**

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# Preface

Emerging Trends of Bioresearch have brought about remarkable progress in various fields, including evolution of bioresearch, biosensors, pediatrics, phytochemicals, endocrine, bioinformatics, enzymes, environmental pollution, plant biotechnology, clinical dermatology, food science and nutrition, cellbiology, microtomy, artificial intelligence, toxicology, biomedical informatics, neurobiotechnology, stem cell technology, phytomedicines, bioresource technology, biostatistics, immunology, environmental microbiology and molecular neurobiology. We aim to foster scientific curiosity, inspire further researchand contribute to the advancement of knowledge in these fields.

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# About Editors

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**Dr. Taniya Sengupta Rathore** is an Associate Professor in the Department of Biotechnology at O.P. Jindal University, Raigarh, bringing over 13 years of expertise in academic research and instruction. She holds a Ph.D. in Life Science from Devi Ahilya University, Indore. She has established herself as a prolific scholar with 14 research papers, 6 book chapters, and one authored book to her credit. Her research specializations include Environmental Microbial Biotechnology, Enzymology and Enzyme Kinetics, Biostatistics, and Molecular Biology Techniques. A recognized leader in her field, Dr. Rathore has received numerous accolades, including the Young Scientist Award (2018), the Senior Scientist Award from the Zoological Society of India (2020), and the award for best oral presentation at a 2023 international conference. Demonstrating leadership in organizing scientific events, she recently served as the Convener for the 2024 International Conference organized by the School of Science at O.P. Jindal University. In addition to her editorial contributions as a reviewer for the Advances in Science and Technology and Emerging Systems Journal, she is a dedicated mentor who has successfully guided students toward success in government-based bootcamps and various competitive scientific events.

Mrs. J. Suguna is currently serving as an Assistant Professor and Head (In-Charge) of the Department of Biochemistry at Vivekanandha Arts and Science College for Women (VIAAS), Salem. With 8 years of teaching experience, she has established herself as an expert in clinical biochemistry and intermediary metabolism. She has published 4 research papers in reputed national and international journals, contributed 3 book chapters, and has organized 3 national conferences and various workshops for the academic and professional development of students and faculty. Furthermore, her contributions to research and education highlight her significant role in advancing the field of biochemistry.

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# Transformative Technologies Steering the Evolution of Bioresearch

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## Abstract

Bioresearch is undergoing a technological revolution driven by breakthroughs in genome editing, multi-omics sciences, machine learning, synthetic biology, and advanced biotechnology. These approaches are reshaping our understanding of biological systems, enhancing healthcare, transforming agriculture, and supporting environmental conservation. This chapter outlines key emerging trends such as CRISPR-based gene editing, omics technologies, artificial intelligence, nanobiotechnology, and personalised medicine. Each section integrates in-text citations to support scientific validity. These innovations promise precise, efficient, and large-scale biological investigations that advance scientific discovery and global sustainability.

**Keywords:** Bioresearch, CRISPR, Multi-omics, AI in biology, Nanobiotechnology, Personalised medicine, Synthetic biology.

## Introduction

Bioresearch has entered an era of unprecedented innovation, driven by interdisciplinary integration and high-throughput experimentation (Hood & Flores, 2012). Advances such as CRISPR, artificial intelligence, and omics technologies have significantly accelerated biological discovery while reducing cost and improving accuracy (Goodwin, McPherson, & McCombie, 2016). These emerging trends have applications in medicine, agriculture, environmental science, industry, and conservation. This chapter discusses the major trends shaping the future of bioresearch with scientific references embedded throughout.Bioresearch is undergoing a profound transformation driven by rapid technological innovations, interdisciplinary approaches, and data-intensive methodologies. Over the last two decades, biological sciences

have transitioned from traditional observational studies to advanced, high-throughput, and computationally integrated systems. This shift has been accelerated by breakthroughs such as CRISPR-based genome editing, multi-omics platforms, artificial intelligence (AI), nanobiotechnology, and laboratory automation (Doudna & Charpentier, 2014; Goodwin, McPherson, & McCombie, 2016). These emerging tools are expanding the frontiers of bioresearch and enabling deeper insights into complex biological processes across medicine, agriculture, environmental sciences, and biotechnology.A major driver of this progress is the integration of molecular biology with computational sciences. High-throughput sequencing technologies and big-data analytics have made it possible to process and interpret large biological datasets with remarkable accuracy. Machine learning and computational modeling further enhance this capacity by predicting protein structures, identifying biomarkers, and accelerating drug discovery (Topol, 2019). Similarly, multi-omics approaches—such as genomics, proteomics, and metabolomics—allow researchers to study biological systems holistically, linking molecular events to phenotypes and disease mechanisms (Kell & Oliver, 2016).Technological advancements are also reshaping applied biological research. Synthetic biology enables the design of novel biological circuits, engineered organisms, and bio-based materials (Silver, Way, & Arnold, 2019). Nanobiotechnology supports precision diagnostics, targeted drug delivery, and nanoscale imaging (Jain, 2020). Environmental genomics, aided by metagenomics and environmental DNA (eDNA), provides non-invasive tools for monitoring biodiversity and ecosystem health (Gilbert, Jansson, & Knight, 2014). Additionally, laboratory automation and robotics increase experimental reproducibility, reduce human error, and support high-throughput experimentation (Goodwin et al., 2016).Collectively, these emerging trends are redefining how scientists explore, understand, and manipulate biological systems. As bioresearch advances, ethical considerations, responsible innovation, and interdisciplinary collaboration will be crucial for maximising societal benefits while minimising risks.

## CRISPR and Advanced Gene-Editing Technologies

CRISPR-Cas technologies have revolutionised molecular biology by enabling precise genome manipulation (Doudna & Charpentier, 2014). New versions such as Cas12, Cas13, base editors, and prime editors have broadened the scope of gene-editing applications (Zhang, Wen, & Guo, 2014).

CRISPR is used to:

1. Develop disease-resistant crops
2. Correct genetic disorders
3. Modify vector populations using gene drives
4. Create CRISPR-based diagnostics like SHERLOCK (Doudna & Charpentier, 2014)

While powerful, CRISPR technology faces ethical and regulatory issues, including concerns about germline manipulation and off-target effects (Zhang et al., 2014).

## Multi-Omics Technologies in Systems Biology

### Integration of Omics Layers

Multi-omics platforms—including genomics, transcriptomics, metabolomics, and proteomics—enable comprehensive understanding of biological systems by integrating multiple layers of biological information (Kell & Oliver, 2016). Multi-omics tools aid in:

1. Discovering disease biomarkers
2. Cancer classification
3. Mapping metabolic pathways
4. Studying ecological interactions (Gilbert, Jansson, & Knight, 2014)

Omics approaches produce large, quantitative datasets that allow predictive modelling and systems-level interpretation of biological phenomena (Alon, 2019).

### Artificial Intelligence and Machine Learning in Bioresearch

Artificial intelligence has become central to modern bioresearch, particularly for analysing large biological datasets and predicting biomolecular structures (Topol, 2019).

AI is used for:

1. Protein structure prediction (e.g., Alpha Fold)
2. Drug discovery and molecular docking
3. Genome annotation
4. Disease surveillance and epidemic forecasting (Topol, 2019)

AI increases speed, accuracy, and scalability of biological analyses and reduces human error, enabling automated and reproducible research pipelines.

## Synthetic Biology and Biomolecular Engineering

Synthetic biology applies engineering principles to modify or create biological systems (Silver, Way, & Arnold, 2019). It aims to design organisms with predictable functions.

1. Production of bioplastics and biosynthetic chemicals
2. Development of biofuels
3. Engineering probiotics for health applications
4. Creating artificial tissues and organs (Silver et al., 2019)

Issues include biosafety risks, ecological impacts, and the dual-use problem where technology might be misapplied (Silver et al., 2019).

## Nanobiotechnology and Biosensors

Nanotechnology improves biological research by enabling nanoscale imaging, targeted drug delivery, and precision diagnostics (Jain, 2020).

1. Nanoparticle-mediated drug delivery
2. Nano-biosensors for detecting pathogens
3. Imaging using quantum dots
4. Development of antimicrobial nanomaterials (Jain, 2020)

Nanobiotechnology allows high sensitivity, specificity, and real-time monitoring of biological processes.

## Automation, Robotics, and High-Throughput Technologies

Robotics and automation have transformed laboratories by enabling high-throughput experiments and minimizing human error (Goodwin et al., 2016).

1. Lab-on-a-chip microfluidics
2. Next-generation sequencing systems
3. Robotic sample handling systems

Automation accelerates research, increases reproducibility, and allows real-time data generation for big-data analyses.

## Environmental and Conservation Genomics

Environmental genomics employs eDNA, metagenomics, and molecular markers to assess biodiversity and ecological function (Gilbert et al., 2014).

1. Monitoring endangered species
2. Microbial community studies
3. Climate change impact assessment
4. Bioprospecting for novel enzymes

eDNA provides a non-invasive, efficient, and high-resolution tool for biodiversity assessment (Gilbert et al., 2014).

## Personalized and Regenerative Medicine

Genomics and pharmacogenomics enable individualized treatments tailored to genetic profiles (Topol, 2019).

1. Cancer immunotherapy
2. Predictive risk profiling
3. Drug response prediction

Regenerative biotechnologies—such as stem cell therapy, 3D bioprinting, and tissue engineering—have the potential to replace damaged tissues and organs (Silver et al., 2019).

### Future Prospects

Future bioresearch will be shaped by:

1. Quantum biology
2. Full-scale pan-omics integration
3. AI-driven biological design
4. Eco-friendly industrial biotechnology
5. Advanced neurotechnologies

These innovations will support sustainability, global health, and precision science.

## Conclusion

The landscape of bioresearch is expanding at an unprecedented pace, driven by transformative technologies that are reshaping the way scientists investigate, manipulate, and apply biological systems. The convergence of molecular biology, computational sciences, engineering, and nanotechnology has created a powerful ecosystem of tools and methodologies that enhance precision, efficiency, and scalability in scientific inquiry. As demonstrated throughout this chapter, innovations such as CRISPR gene-editing, multi-omics platforms, artificial intelligence, synthetic biology, nanobiotechnology, and environmental genomics have collectively revolutionized biological research across disciplines. CRISPR and advanced genome-editing tools have opened possibilities for precise genetic modifications, disease modeling, and therapeutic interventions. Multi-omics technologies have enabled holistic understanding of biological complexity by integrating genetic, molecular, metabolic, and cellular data. Artificial intelligence and machine-learning algorithms now serve as indispensable partners in modern research, offering predictive insights, accelerating drug discovery, and enhancing diagnostic accuracy. At the same time, synthetic biology and engineered biological systems are shaping the future of sustainable biotechnology, bio-based manufacturing, and innovative therapeutic approaches.Nanobiotechnology has enhanced diagnostics and targeted therapeutics by allowing manipulation at the nanoscale, while environmental and conservation genomics provide powerful, non-invasive means to monitor ecosystems, biodiversity, and climate-related biological shifts. Laboratory automation, robotics, and high-throughput systems have significantly improved reproducibility, reduced human error, and

expanded the capacity for large-scale experimentation. Despite these advancements, bioresearch faces important challenges that must be addressed. Ethical considerations surrounding genome editing, data privacy, engineered organisms, and AI-driven decision making require robust governance and global dialogue. Ensuring equitable access to emerging technologies, particularly in low-resource regions, remains essential for promoting global scientific progress. Environmental safety, biosurveillance, and long-term ecological impacts must also be continuously evaluated. Overall, the emerging trends in bioresearch represent a paradigm shift from traditional biological investigation toward a more integrated, predictive, and engineering-driven approach. These advancements hold immense potential to address critical global issues related to health, agriculture, sustainability, and environmental protection. As bioresearch continues to evolve, nurturing interdisciplinary collaboration, fostering responsible innovation, and maintaining strong ethical frameworks will be essential to harness its full potential for the benefit of science and society.

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# Microbial Enzyme Biosensors for Sustainable Environmental Monitoring and Remediation

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## Abstract

Environmental monitoring is vital for measuring ecosystem health, tracking pollution, and supporting sustainable resource management. Among the advanced tools developed for this purpose, microbial enzyme-based biosensors have emerged as promising candidates due to their high sensitivity, specificity, and rapid response capabilities. These biosensors employ microorganisms—either naturally occurring or genetically engineered—as biological sensing elements to detect a wide array of environmental contaminants, including heavy metals, organic pollutants, and toxic gases.Microbial biosensors can be categorized into various types, such as whole-cell biosensors, enzyme-based systems, genetically engineered microorganism biosensors, microbial fuel cells, and ion-selective or optical biosensors. Each variant operates through distinct transduction mechanisms—electrochemical, optical, piezoelectric, or amperometric—to convert microbial responses into measurable signals.Applications span across air, water, and soil quality monitoring, with the ability to detect specific pollutants like arsenic, lead, pesticides, hydrocarbons, and even pathogens. Additionally, these biosensors are pivotal in monitoring bioremediation processes and ecosystem restoration by providing near-real-time feedback on pollutant degradation. The integration of microbial biosensors with remote sensing and digital platforms further enhances their utility for large-scale environmental surveillance.Despite challenges like maintaining microbial viability and sensitivity to external factors (e.g., pH, temperature), ongoing advancements in synthetic biology, nanotechnology, and data analytics continue to expand the scope and robustness of microbial biosensing platforms. This paper provides a comprehensive overview of microbial enzyme-based biosensors, highlighting their mechanisms, applications, advantages, and limitations in environmental monitoring and remediation efforts.

**Keywords:** Microbial Biosensors, Environmental Monitoring, Whole-Cell Biosensor, Bioremediation, Enzyme-Based Detection

## Introduction

A systematic process of collection, analysis and interpretation of data to assess the state of environment and to track the changes is called Environmental monitoring. This process is necessary to understand the natural processes, impact of human activities and climate change for ensuring the sustainability and health of our environment.

Environmental monitoring involves various parameters such as monitoring air pollutants such as hazardous gases, particulate matter and volatile organic compounds, assessment of water conditions by measuring physic-chemical and biological parameters, evaluation of soil properties, nutrient levels, pH, salinity and contamination with heavy metals, pesticides, organic and inorganic pollutants, tracking the abundance and distribution of flora and fauna, study of climate change by monitoring temperature, humidity, precipitation and other meteorological data, measuring sound level to assess noise pollution, analyzing ionizing and non-ionizing radiation levels, studying the health and behavior of wildlife and aquatic organisms and detecting the qualitative and quantitative presence of hazardous chemicals and industrial pollutants

Effective environmental monitoring processes are crucial for decision making, sustainable resource management and addressing environmental challenges such as pollution, climate change, loss of habitat and biodiversity decline. Continuous monitoring helps to protect ecosystem, public health and wellbeing of future generations.

Advances in sensor technology, data analytics and remote sensing have improved the accuracy and efficiency of environmental monitoring.

### Biosensors for Environmental monitoring

Biosensors have proved to be a valuable tool for environmental monitoring for their ability to provide real time data on specific analytes of the environment. The advantages such as rapid response, sensitivity and specificity make them well suited for various environmental applications.

With improvement in sensor technology, genetic engineering techniques and data analysis methods, the development and deployment of biosensors for environmental monitoring are continued to advance. These have become essential tools for assessing and mitigating the impact of human

activities on the environment and ensuring the health and sustainability of ecosystem.

Some of the applications of biosensors in environmental monitoring are as follows:

### 1. Water Quality Monitoring:

a. The biosensors based on living cells are used to detect waterborne contaminants like heavy metals, toxins and pathogens. They are used to provide real time information about water quality.

b. Changes in enzyme activity due to presence of pollutant could be detected through enzyme based biosensors for example acetylcholinesterase enzyme biosensors are used to detect pesticides and other chemical agents in water bodies.

c. Antigen coated surfaces or antibodies are used to detect specific waterborne pathogens like *Escherichia coli* or *cryptosporidium* in drinking water.

### 2. Air Quality Monitoring:

a. Enzyme based gas biosensors uses enzymes to detect gases like $CO_2$ and CO and other volatile organic compounds in the air. The electrical or optical signals used in these biosensors which changes with the change in enzyme activity.

b. Engineered bacteria produce luminescence or fluorescence in response to specific air pollutants like nitrous oxide, nitric oxide or volatile organic compounds used for monitoring air quality.

### 3. Assessment of Soil Quality:

a. Genetically engineered bacteria respond to the presence of soil pollutant such as heavy metals, pesticides and hydrocarbons.

b. Enzyme immobilized on electrodes can be used to detect specific soil contaminants such as phenols, organophosphate and pesticides.

### 4. Monitoring of Bioremediation:

Biosensors are used to monitor the progress of bioremediation processes in which microorganisms are employed to neutralize or break down

the pollutants of contaminated sites. These biosensors are used to track the changes in pollutant level and the microbial activity.

**5. Monitoring of Natural Ecosystems:**

Generally biosensors using whole cell or enzyme based approaches are used to assess the quality of natural ecosystem. They can detect the presence of contaminants and changes in environmental parameters.

**6. Remote Sensing:**

Biosensors equipped with satellite based remote sensor provide large scale and real time information on environmental parameters like chlorophyll concentration in ocean or deforestation rates.

**7. Climate Monitoring:**

In wetlands and forests, biosensors are used to monitor climate relevant gases like methane and carbon dioxide.

**8. Biological Oxygen Demand Measurement:**

BOD biosensors are used to measure the amount of oxygen required by microorganisms to biodegrade organic matter in water, indicating water pollution levels.

**9. Oil spill Detection:**

Whole cell biosensors are used to detect hydrocarbons from oil spills in water, resulting rapid response to environmental disasters.

10. Hazardous Waste Management:

Biosensors are applied to monitor hazardous waste sites, provide information on the movement of contaminants and the effectiveness of remediation efforts.

**Structural components of Biosensors**

Biosensors behave as analytical devices that combine a biological component with a physicochemical detector to provide specific, quantitative and often real time information about the presence or concentration of a target

analytes in a sample. Biosensors are categorized on the basis of the type of biological component, the transduction mechanism and their applications.

The components of Biosensor are:

### 1. Biological Recognition Element:

This biological element is responsible for interacting with target analyte. It includes enzymes, antibodies, nucleic acids or whole cells. It could be a synthetic receptor designed to mimic biological recognition.

### 2. Transducer:

The biological responses or interactions are converted into a measurable signal by transducers. Commonly in electrochemical biosensors, electrodes are used as transducers, in optical biosensors and piezoelectric biosensors, optical systems and piezoelectric crystals are used as transducers respectively.

### 3. Signal Processing and Output

Biosensors include signal amplification, processing and output components to provide a clear interpreting signal. These involve electronic circuits, software and display.

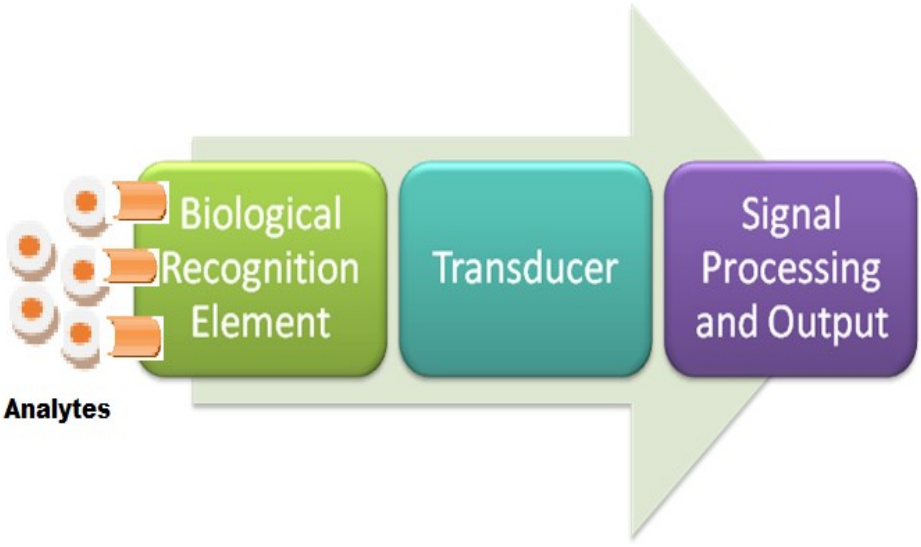


**Fig 01: Operation of Biosensors**

## Microbial Biosensors

Microbial biosensors use microorganism such as bacteria, yeast or algae as sensing elements to detect specific environmental factors or analytes. These biosensors bind the natural abilities of microorganisms to interact with and further respond to target substances, thus making them an efficient valuable tool in various sectors such as in biotechnology, environmental monitoring, medical diagnostics, food safety etc.

Naturally isolated microorganisms or genetically engineered are selected as biological recognition element according to their ability to interact with the target analyte. They carry the reporter genes that produce detectable signal for e.g. bioluminescence, fluorescence or electrochemical signals in response to the qualitative presence or quantitative concentration of the target substances. The microorganisms may be a whole cell, cell extracts or isolated enzymes. To enhance the sensitivity, selectivity or response toward the target analytes, genetic modifications are also applicable.

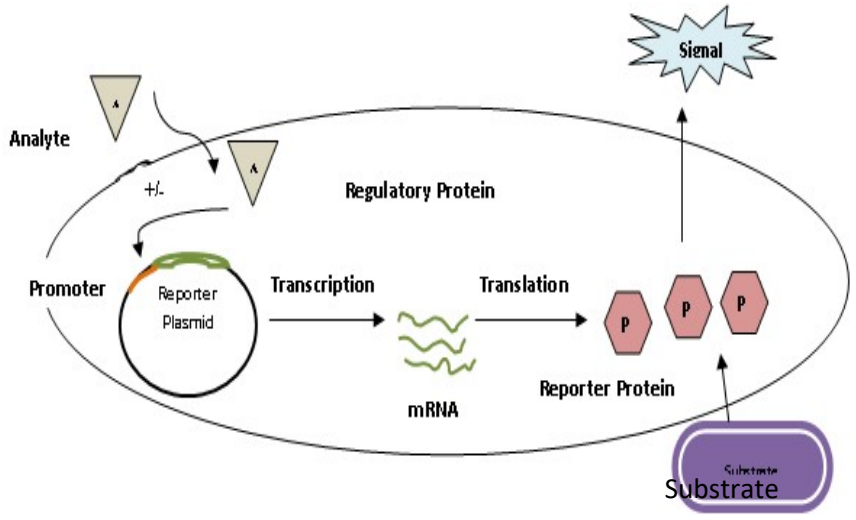


**Fig 02: General Mechanism of Biosensor's Microbes**

Common transducers for microbial biosensors include generally simple electrodes, photo detectors and ion selective electrodes. Signal processing components are used to amplify, filter or digitize the output signal and the results are displayed or recorded for interpretation.

Microbial Biosensors have several advantages such as they are highly sensitive and are capable of detecting low concentrations of target substances. They offer real time monitoring capabilities, allowing rapid response to

environmental changes. By genetically engineering, microorganisms with their specific receptors are made selective for their target compounds. They are generally cost effective especially for continuous monitoring as compared to traditional analytical methods.

## Types of Microbial Biosensors

Based on specific analytes or environmental parameters, various types of microbial biosensors have been designed. The choice of microbial biosensors depends upon the desired sensitivity, its application and the target analytes. The common types of microbial biosensors are:

1. **Whole Cell Biosensors:**

In such types of biosensors, intact microorganisms such as bacteria or yeast work as the sensing element. Whole cell biosensors respond to analytes by producing measurable signal, based on changes in their cellular metabolism, gene expression or enzyme activity. These types of biosensors are generally used to detect heavy metals, organic pollutants and pathogens. Different transducers have integrated with different tpes of microbes nd work in different principle such as amperometric, conductometric, potentiometric, colorimetric, luminescent and fluorescent(Chung & Dhar., 2021). As compared to conventional techniques microbial biosensors are more sensitive to environmental factors (Bilal et al., 2019). There are several advantages of whole cell biosensors such as they are highly selective and sensitive. They are able to detect very low concentration of pollutants, thus are applicable to various fields of environmental monitoring and monitoring of bioremediation activities (Naresh & Lee., 2021). Microbial cells are immobilized on the transducers or support matrices by using physical or chemical methods. Physical methods include adsorption and entrapment whereas chemical methods involve are covalent bonding and cross linking. The immobilized technique chosen must guarantee cell viability, mechanical stress, safe handling and long storage capacity (Moraskie et al., 2021).

Beside several advantages, microbial whole cell biosensors also have few limitations such as difficulty in maintaining prolonged cell viability, long response period and sensitivity to other environmental factors such as temperature, pH (Lim et al., 2015;Chang et al .,2017). Several papers have been reported with the use of microbial whole cell biosensors for environmental monitoring such as heavy metals, organic wastes and other toxic pollutants (Gupta et al., 2019; Do et al., 2021; Chung et al 2021).

**Table 01: The feature of whole cell microbial biosensors.**

| S. no. | Microorgamisms (analyteinteracting element) | Analytes | Immobilized Method | Tranducers | Environment under consideration |
|---|---|---|---|---|---|
| 1 | *Shewanella oneidensis* (Genetically engineered) | $AS^{3+}$ | Formation of biofilm | Electrochemical | All (air, water, soil) |
| 2 | *Saccharomyces cerevisiae* | $Cu^{2+}$, $Ni^{2+}$, $Pb^{2+}$, $Cd^{2+}$ | Adsorption | Amperometric | Water (Waste) |
| 3 | *Escherichia coli* | $AS^{3+}$, $Cd^{2+}$, $Pb^{2+}$, $Zn^{2+}$ | Micro fluidic device with microbial culture | Fluorescent | Water |
| 4 | *Bacillus megaterium* VR1 | $Cu^{2+}$, $Cd^{2+}$, $Zn^{2+}$ | Entrapped in sol-gel matrix | Fluorescent | Soil |
| 5 | *Escherichia coli*DH5α | $Pb^{2+}$ | Entrapped in sol-gel matrix | Fluorescent | All (air, water, soil) |
| 6 | *Escherichia coli*(Genetically engineered) | Parathion, methyl parathion, paraoxon | Formation of biofilm | Amperometric | All (air, water, soil) |
| 7 | *Saccharomyces cerevisiae* | $Cu^{2+}$ | Entrapped in alginate beads | Colorimetric | Water |
| 8 | *Anabaena Variabilis* | Herbicide (Antrazine) | Entrapped in alginate beads | Amperometric | All (air, water, soil) |

2. **Enzyme based Biosensors:**

Enzymes extracted from microorganisms, or genetically engineered are immobilized on the sensor surface. These biosensors are based on the mechanism of enzyme-substrate reactions, resulting in production of a detectable signal such as in form of electrochemical or optical response.

3. **Genetically Engineered Microorganisms (GEMs):** GEMs are genetically modifies microorganisms which express specific reporter genes in response to target analytes. When activated in presence of target compounds it produces signals like bioluminescence, change in colour etc.

4. **Microbial Fuel Cells (MFCs):** In presence of organic pollutant or waste water, MFCs use microbes as biocatalyst which metabolize these organic matters and generate electrical power. The electrical outputs are used to measure microbial activity and thus the concentration of the organic waste. These types of biosensors are generally used in environmental monitoring and wastewater treatment.

5. **Ion- Selective Microbial Biosensors (ISMBs):** ISMBSs use microbes that respond to changes in ion concentrations in the environment. In these biosensors ion sensitive electrodes are used to measure changes in ion concentrations and the microorganisms act as ion carriers. These biosensors are generally used in ion specific measurements in soil, water and other biological samples.

6. **Optical Biosensors:** Optical microbial biosensors use microorganisms labeled with luminescent or fluorescent markers. These biosensors are used in pathogen detection and monitoring microbial growth.

7. **Piezoelectric Biosensors:** The microorganisms or microbial components re immobilized on piezoelectric crystal in piezoelectric biosensors. Binding events between immobilized microbes and target analytes cause changes in crystal vibrations results in measurable frequency shifts. These biosensors are applicable broadly including antibodies and antigens.

8. **Amperometric Biosensors:** Amperometric microbial biosensors based on immobilized microbes or their enzymes on electrodes. Redox reaction between analyte and the immobilized components changes the current flow, which is measured to detect specific chemicals, gases etc.

With several advantages and limitations, each type of microbial biosensors has different applications. Workers select the appropriate type on the basis of their sensitivity, selectivity, response time and environmental conditions.

## Microbial Biosensors for environmental Monitoring

Microbial biosensors leverage the unique abilities of microorganisms to detect and respond the specific environmental factors. These biosensors provide real time or generally near real time data on different environmental parameters making them valuable for a wide range of applications such as detection of hazardous compounds, water quality monitoring , pollution monitoring etc.

Microbial biosensors are widely used to monitor water quality by detecting the pollutants and their levels such as heavy metals, organic compounds and pathogens, they provide rapid and on site assessments of water quality. These biosensors are also adapted to detect airborne pollutants, hazardous gases associated to industrial emissions and volatile organic compounds. They also help to assess soil quality by detecting contaminants such as hydrocarbons, pesticides and heavy metals. They are also used to monitor natural ecosystem like oceans, rivers and forests by detecting any changes in environmental parameters. In addition to monitoring, microbial biosensors are also employed to guide bioremediation efforts by identifying heavy pollutant areas as well as change in pollutant concentration by bioremediation approach.

**Fig 02: Overview of application of Biosensors in Environment**

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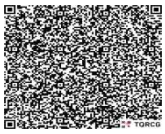
|  | Subject: Biosensors |
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# Inborn Errors of Metabolism

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## Introduction

Inborn errors of metabolism are a group of genetic conditions that affect the function of your metabolism. Your metabolism runs chemical processes that convert food into energy and removes toxins from your body. Treatment includes changes to your diet or taking medicines to help your body process certain foods.

Inborn errors of metabolism, also known as inherited metabolic disorders or hereditary metabolic disorders, are a group of conditions that affect your ability to convert food into energy and remove waste and unhealthy substances from your body.

### Etiology

Inborn errors of metabolism are inherited disorders caused by mutations in genes coding for proteins that function in metabolism. Most are inherited as autosomal recessive. Rarely, they are autosomal dominant and X-linked. Environmental, epigenetic, and microbiome factors and additional genes are potential modifying etiologic factors in those with inborn errors of metabolism.

### Epidermiology

Inborn errors of metabolism occur in 1 out of 2500 births. Because of their heterogeneity, different disorders have different distinct epidemiologies, presentations, and heritabilities. For instance, mitochondrial disorders are inherited from mother to 100% of her offspring, while other disorders may have variable penetrance or be sex-linked. The disorder may cause complete dysfunction of the involved enzyme, or it may be partial or incomplete. Although neonatal birth screens seek to identify many inborn errors of metabolism early, different states and even different hospitals have differing

panels through which they screen. Neonatal screens may identify 8 to 50 different diseases, but unfortunately, there are thousands of diseases.

## Treatment/Management

Initial treatment in these patients is aggressive resuscitation via the PALS/ACLS algorithm. Do not give anything by mouth (NPO) to patients in whom inborn errors are suspected. Since the emergency provider cannot know which portion of the metabolic pathway is deranged, it is prudent to prevent the patient from utilizing his or her native pathways for carbohydrate metabolism, clearance of metabolites, or accessing of stored energy. Therefore, the patient should receive pure substrate (glucose) at a volume that obviates the need for the patient to break down glycogen or fatty acids. This should be accomplished with 10% dextrose solution at a one and a half maintenance rate.

## Differential Diagnosis

- Emergent management of pediatric patients with fever
- Heart failure
- Imaging in restrictive cardiomyopathy
- Migraine headache
- Multiple sclerosis
- Pediatric apnea
- Pediatric pyloric stenosis
- Pediatric urinary tract infection
- Pediatrics crying child
- Pediatrics, hypoglycemia

There are many different types of inborn errors of metabolism.

### 1. *Glycosuria*

Glycosuria refers to the presence of glucose in the urine, which is caused by a variety of etiologies that either cause elevated blood sugar levels (diabetes mellitus) in the bloodstream or prevent glucose reabsorption in the renal tubules.

## Risk Factor

Increased age is a risk factor due to the increased risk of developing chronic disease conditions like diabetes mellitus and hypertension. This

condition leads abnormal reabsorptive capacity but also increase the risk for renovascular damage, leading to subsequent leakage of glucose and proteins into the urine.

### Symptoms

- Excessive Urination, more than usual
- Extreme hunger
- Extreme thirst associated with dehydration
- Fatigue
- Unexplained Weight loss
- Difficulty in seeing
- Diabetic ketoacidosis
- Urinary Tract Infections

### Diagnosis

- Urinalysis
- Blood sugar
- HbA1C test

### Treatment

- Lifestyle modifications
- Exercise
- Balanced diet
- Pharmacologic modalities

### *2. Fructosuria*

Essential fructosuria, caused by a lack of the enzyme hepatic fructokinase, is a clinically benign disorder defined by the inadequate metabolism of fructose in the liver, leading to its excretion in urine. Fructokinase (also known as ketohexokinase) is the first enzyme in the liver that converts fructose to fructose-1-phosphate.

Fructose is either eliminated unchanged in the urine or converted to fructose-6-phosphate by other pathways in the body, most commonly through hexokinase in adipose tissue and muscle, resulting in minimal clinical signs. Essential fructosuria is a genetic disorder that is passed down through the generations in an autosomal recessive pattern and hence, is also referred to as Hereditary Fructosuria. The prevalence is about 1 in 130,000 births.

### Essential Fructosuria Symptoms

A positive routine test for lowering sugars in the urine is usually used to diagnose essential fructosuria. Because a positive test for reducing sugars is most typically a result of glucosuria owing to diabetes mellitus, an additional test with glucose oxidase must be performed (with a negative result suggesting essential fructosuria). The amount of fructose excreted in the urine is not constant, and it is mostly determined by food intake.

### Essential Fructosuria Diagnosis

Essential Fructosuria is diagnosed accidentally when a non-glucose reducing substance is spotted in the urine by a positive test.

### Essential Fructosuria Treatment

Essential fructosuria requires no therapy, and while the severity of the condition is determined by dietary fructose intake, it has no clinical signs. The amount of fructose lost in urine is insignificant. Other fructose metabolism problems are more clinically significant. A lack of aldolase B, the second enzyme involved in fructose metabolism, causes hereditary fructose intolerance, or the presence of fructose in the blood (fructosemia).

This enzyme deficit leads to a buildup of fructose-1-phosphate, which slows glucose synthesis and reduces adenosine triphosphate regeneration. Patients with inherited fructose intolerance are far more severely impacted clinically than those with essential fructosuria, with increased uric acid, growth anomalies, and, if left untreated, unconsciousness.

Essential Fructosuria is a rare condition.

### *3. Pentosuria*

The disorder is caused by mutations (changes) in the dicarbonyl and L-xylulose reductase (DCXR) gene. This gene provides instructions for making the DCXR protein which is responsible for converting a sugar called L-xylulose into a molecule called xylitol. This is part of the process in which the body uses sugars for energy.

These mutations (changes) in the DCXR gene cause the production of distorted DCXR proteins that are broken down very quickly. Without the DCXR protein, L-xylulose is not transformed into xylitol and the leftover sugar is released in the urine.

**Types of Pentosuria:**

1. ***Essential Pentosuria*** *(most common type):*
   - Benign condition
   - More common in individuals of **Ashkenazi Jewish** descent
   - No treatment needed
2. ***Alimentary Pentosuria****:*
   - Caused by high intake of fruits rich in pentose sugars (e.g., apples, cherries)
   - Temporary condition
3. ***Drug-induced Pentosuria***:
   - Certain drugs may interfere with sugar metabolism
   - Also reversible

**Clinical Features:**

- **No symptoms** – it's usually **asymptomatic**
- Discovered incidentally during urine sugar tests
- **Urine may test falsely positive** for glucose (reducing sugar), leading to confusion with diabetes

**Treatment:**

- **No treatment is required** for essential pentosuria
- It is a **benign** and harmless condition

***4. Galactosemia***

Galactosemia is a disorder that affects how the body processes a simple sugar called galactose. A small amount of galactose is present in many foods. It is primarily part of a larger sugar called lactose, which is found in all dairy products and many baby formulas. The signs and symptoms of galactosemia result from an inability to use galactose to produce energy. Classic galactosemia, also known as type I, is the most common and most severe form of the condition.

If infants with classic galactosemia are not treated promptly with a low galactose diet, life-threatening complications appear within a few days after birth. Affected infants typically develop feeding difficulties, a lack of energy

(lethargy), a failure to gain weight and grow as expected (failure to thrive), yellowing of the skin and whites of the eyes (jaundice), liver damage, and abnormal bleeding. Other serious complications of this condition can include overwhelming bacterial infections (sepsis) and shock. Affected children are also at increased risk of delayed development, clouding of the lens of the eye (cataract), speech difficulties, and intellectual disability. Females with classic galactosemia may develop reproductive problems caused by an early loss of function of the ovaries (premature ovarian insufficiency).

Galactosemia type II (also called galactokinase deficiency) and type III (also called galactose epimerase deficiency) cause different patterns of signs and symptoms. Galactosemia type II causes fewer medical problems than the classic type. Affected infants develop cataracts but otherwise experience few long-term complications. The signs and symptoms of galactosemia type III vary from mild to severe and can include cataracts, delayed growth and development, intellectual disability, liver disease, and kidney problems.

Incidance of galactosemia is 1 in 30,000 to 60,000 newborns. Galactosemia type II and type III are less common; type II probably affects fewer than 1 in 100,000 newborns and type III appears to be very rare.

## Causes

- The accumulation of galactose occurs due to the deficiency of the enzyme **Galactose-1-phosphate uridyltransferase (GALT),** which is necessary for converting galactose-1-phosphate into glucose.
- As a result, galactose and galactose-1-phosphate build up in the body, leading to toxicity, especially in the liver, kidneys, and brain.

Symptoms:

- Jaundice
- Vomiting after milk feeding
- Poor feeding or weight gain
- Diarrhea
- Liver enlargement (hepatomegaly)
- Cataracts
- Lethargy
- Risk of **sepsis** (especially with E. COLI)

- Intellectual disability (if untreated)

Diagnosis:

- **Newborn screening** (blood test for GALT activity)
- Measuring **galactose-1-phosphate** levels in red blood cells
- **Urine test** for reducing sugars (but not glucose)
- Genetic testing for **GALT gene mutations**

Treatment:

- **Lifelong elimination of galactose and lactose from the diet**
  - Avoid **milk, dairy products,** and foods containing **lactose**
  - Use lactose-free formulas (e.g., soy-based)
- **Monitoring:**
  - Regular follow-up for developmental, speech, and growth issues
  - Monitor for speech delays, motor problems, and learning disabilities

### *5. Glycogen Storage Diseases*

Glycogen storage diseases (GSDs) are inherited inborn errors of carbohydrate metabolism that result in abnormal glycogen storage. The onset can range from neonatal life to adulthood, and clinical manifestations result either from a failure to convert glycogen into energy or the toxic accumulation of glycogen.

Glycogen is a branched polymer comprised of glucose monomers (see **Image**. Glycogen, Free Glucose Release, and Glycogen Storage Diseases, Figure 1). After a meal, the plasma glucose level rises, stimulating the storage of the excess in cytoplasmic glycogen.

The liver contains the highest percentage of glycogen by weight (about 10%), whereas muscles can store about 2% by weight. Nevertheless, since the total muscle mass is greater than the liver mass, the total mass of glycogen in muscles is about twice that of the liver. When needed, the glycogen polymer can be broken down into glucose monomers and utilized for energy production. Defects in the enzymes and transporters for these processes cause GSDs. An increasing number of GSDs are being identified, but most are very rare. These subtypes are classified numerically in the order of recognition and identification of the enzyme defect causing the disorder.

## Classification of Glycogen Storage Disorder

GSDs that primarily affect the liver include the following:

- Glycogen synthase-2 deficiency (GSD type 0a)
- Glucose-6-phosphatase deficiency (GSD type Ia)
- Glucose-6-phosphate transporter deficiency (GSD type Ib)
- Glycogen debrancher deficiency (GSD type III)
- Glycogen branching enzyme deficiency (GSD type IV)
- Liver phosphorylase deficiency (GSD type VI)
- Phosphorylase kinase deficiency (GSD type IXa)
- GLUT2 deficiency or Fanconi-Bickel disease

GSDs that primarily affect the skeletal muscles include the following:

- Muscle phosphorylase deficiency (GSD type V)
- Phosphofructokinase deficiency (GSD type VII)
- Phosphoglycerate mutase deficiency (GSD type X)
- Lactate dehydrogenase A deficiency (GSD type XI)
- Aldolase A deficiency (GSD type XII)
- β-enolase deficiency (GSD type XIII)
- Phosphoglucomutase-1 deficiency (GSD type XIV)

GSDs that affect both skeletal and cardiac muscles include the following:

- Lysosomal acid maltase deficiency (GSD type IIa)
- Lysosome-associated membrane protein 2 deficiency (GSD type IIb)
- Glycogenin-1 deficiency (GSD type XV)
- Muscle glycogen synthase deficiency (GSD type 0b)

## Etiology

- The etiology of GSDs is best understood by following the metabolic events leading to glycogen synthesis (glycogenesis) and degradation (glycogenolysis).
- Excess dietary glucose is stored in glycogen, and the synthesis of this molecule is, in part, accomplished by glycogen synthase. As indicated in

Table 1, glycogen synthase has 2 distinct forms: one in the liver encoded by the *GYS2* gene and another in skeletal muscle encoded by the *GYS1* gene.

- Both enzyme forms work by attaching glucose monomers to growing glycogen polymers by creating α-1,4 links and glycogen has α-1,4 and α-1,6 bonds between glucose units.
- Glycogen synthase catalyzes the formation of α-1,4 glucose linkages in glycogen, but the glycogen branching enzyme (*GBE1*) is required to create the branching α-1,6 linkages. Mutations in *GBE1* lead to the production of abnormally structured glycogen, known as polyglucosan bodies, which is the hallmark of GSD type IV.
- These polyglucosan bodies accumulate in liver and muscle cells and do not effectively undergo glycogenolysis. In muscle tissue, this accumulation causes weakness and myopathy, while in the liver, it results in hepatomegaly.
- Glycogen is a branched polymer, with glycogen phosphorylase removing glucose from α-1,4 linkages but unable to act on α-1,6 linkages at branch points. A glycogen debranching enzyme (GDE) is required to remove these branch points. In mammals, this enzyme is called "amylo-α-1,6-glucosidase, 4-α-glucanotransferase," encoded by the *AGL* gene. Mutations in the *AGL* gene cause GSD type III, resulting in either a nonfunctional GDE (GSD type IIIa or IIIb) or a GDE with reduced function (GSD type IIIc or IIId).
- GSD type II is unique among glycogen storage diseases, as it is also classified as a lysosomal storage disease. Lysosomes are subcellular organelles responsible for recycling cellular macromolecules. Lysosomal storage diseases arise from the absence or dysfunction of a lysosomal enzyme.
- In GSD type II, the deficient enzyme is lysosomal acid α-glucosidase, encoded by the *GAA* gene. This enzyme breaks down glycogen into glucose for cellular energy. Mutations in the *GAA* gene lead to toxic glycogen accumulation within lysosomes.

## Epidemiology

The true incidence of metabolic diseases is difficult to determine, given the lack of uniform, universal screening at birth. While GSD type IX has been found to be the most common subtype, the individual incidence of specific

GSD types is further complicated due to overlapping symptoms and the lack of standardized specific testing in most areas of the world.

A study evaluating the incidence of inborn errors of metabolism in British Columbia in the 1990s reported that the incidence of these diseases was approximately 30 cases per 100,000 live births.

This figure represented a mix of metabolic disorders and was not restricted to GSDs. Approximately 2.3 children per 100,000 births were thought to have GSD in this study. Current literature suggests the incidence of GSDs is approximately 1 case per 20,000 to 43,000 live births, although incidence rates are found to be higher in specific population groups, such as non-Ashkenazi Jews.

## Pathophysiology

As mentioned, glycogen is the storage form of glucose and consists of long polymers of α-1,4-linked glucose, with branch points formed by α-1,6-linked glucose molecules. Glycogen's primary physiologic function is to provide glucose via glycogenolysis for glucose homeostasis. Liver stores are used to maintain glucose homeostasis in the serum, and muscle stores provide glucose for the muscles during periods of high demand, especially exercise, as a source of energy.

Hypoglycemia, hepatomegaly, muscle cramps, exercise intolerance, and weakness develop when these physiological functions are defective. Some disorders also affect the myocardial tissue and can lead to cardiomyopathy and cardiac conduction defects.[10] Failure to maintain glucose homeostasis triggers alternate pathways to meet metabolic demands. In GSD type 1, for example, failure of glycogenolysis in the liver results in increased lactic acid production, resulting in lactic acidosis due to the intracellular accumulation of glucose-6-phosphate, which stimulates the glycolytic pathway.

## Diagnosis

### a) Laboratory Testing

- Hypoglycemia should be documented by measuring serum glucose levels. In patients where hypoglycemia is suspected, a diagnostic fasting glucose test can be performed but should only be considered in a monitored inpatient setting.
- Hepatic GSDs (type 0, III, VI, and IX) are characterized by ketosis and usually yield a β-hydroxybutyrate level greater than 2.5 mmol/L. These

diseases also typically present with hypertriglyceridemia and elevated liver function tests.

- Patients with skeletal muscle-associated GSDs may also have elevated creatine kinase levels and urinary myoglobin levels. GSD type I is associated with elevated levels of lactic acid and acidosis.

### b) Biopsy

- Although specific genetic testing is now available for diagnosing most GSDs, histologic examination of liver or muscle biopsy is still used in specific scenarios. In GSD type 0, a liver biopsy typically shows decreased hepatic glycogen and can make a definitive diagnosis for this disease.
- In GSD type I, a liver biopsy should reveal pale-staining, swollen hepatocytes, steatosis and nuclear hyper-glycogenation. Fibrosis is another common finding on liver biopsy in patients with GSDs and is predominant in patients with GSD type III, IV, and VI. In GSD type III, periportal fibrosis and micronodular cirrhosis are often seen with distended hepatocytes due to excess glycogen accumulation.
- Muscle biopsies typically reveal diastase-sensitive vacuoles that yield a positive staining result with periodic acid-Schiff (PAS) and acid phosphatase in GSD type IV. In GSD type V, a muscle biopsy should demonstrate negative histochemical staining for phosphorylase activity.
- In the absence of phosphorylase activity, the specimen remains brown instead of taking up a deep blue hue. In addition, the biopsy should reveal subsarcolemmal deposits of glycogen detected by PAS staining.
- In patients with GSD type XV, muscle biopsies often show PAS-positive inclusions that are not digested with α-amylase treatment and, on electron microscopy, may be seen as filamentous material corresponding to polyglucosan bodies.

### c) Molecular Testing

- Molecular genetic testing is noninvasive and, for the most part, available for diagnosing these rare genetic disorders. In some cases, genetic tests have eliminated the need for invasive muscle and liver biopsies. The table below outlines the genetic foci of mutations for these disorders.

## Treatment

- GSDs currently have no cure, and most treatments aim to alleviate signs and symptoms. Critical goals include preventing and managing hypoglycemia, hyperlactatemia, hyperuricemia, and hyperlipidemia.
- Hypoglycemia may be avoided through starch consumption, with a commercially available, physically modified form now in use. In patients with GLUT2 deficiency, maintaining an antiketogenic diet leads to a significant decrease in liver size and glycogen content.
- Hyperuricemia is managed with allopurinol, while hyperlipidemia is treated with statins. Some GSDs, such as GSD type II, can now be treated with enzyme replacement therapy (ERT) using recombinant alglucosidase alfa, which helps degrade lysosomal glycogen. Ongoing research explores the potential use of ERT for other forms of GSD.
- Liver transplantation should be considered for patients with certain GSDs that have progressed to hepatic malignancy or failure. While this procedure can correct hepatic failure and hypoglycemia, it does not address the cardiomyopathy associated with the GSD, which may continue to progress.
- The immediate management of acute hypoglycemia involves rapid correction with oral carbohydrates or parenteral glucose. Glucagon is effective only in insulin-mediated hypoglycemia and will not help patients with hypoglycemia caused by a GSD.

## Prognosis

The prognosis of GSDs varies widely and depends on the enzyme defect and the type of GSD. Severe infantile forms are often associated with early mortality, while milder adult-onset cases have normal life spans. With early diagnosis and proper management, the prognosis of most GSDs remains favorable. The advent of ERT is expected to further improve outcomes in these patients.

## Complications

- Even with appropriate dietary modifications, GSDs are associated with a wide range of serious complications. In early childhood, individuals with GSDs are at risk of hypoglycemia-associated seizures and cardiac arrest.
- In patients with GSD type Ia, growth delay with short stature, osteopenia, renal dysfunction, hypertriglyceridemia, and hepatocellular carcinoma can

occur. In GSD type Ib, recurrent bacterial infections secondary to neutropenia may be seen.

- In GSD type IV, progressive liver failure with cirrhosis can occur. Cardiomyopathy and limb-girdle dystrophy can be seen in patients with GSD type II. Hypertrophic cardiomyopathy is a classic complication of GSD type III.
- Growth retardation and short status are also seen in GSD types IX (a, b, c, d) and XII, but a cognitive-developmental delay is also a feature of the latter. In GSD types V and XIII, exercise intolerance and rhabdomyolysis with an associated renal injury can occur. Rarely, end-stage renal disease requiring kidney transplantation may develop in patients with GSD type Ib.

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# "*Psidium guajava* L.-Based Phytochemicals and Chitosan Nanocarriers in Triple-Negative Breast Cancer Treatment: A Comprehensive Review"

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## Abstract

Breast cancer is a heterogeneous malignancy and a leading cause of cancer-related mortality among women worldwide. Triple-negative breast cancer (TNBC), characterized by the absence of estrogen, progesterone, and HER2 receptors, is an aggressive subtype with poor prognosis and limited treatment options. Conventional therapies for TNBC are often associated with drug resistance and systemic toxicity. Phytochemicals have emerged as promising anticancer agents due to their multi-targeted actions and reduced side effects. *Psidium guajava* L. contains bioactive compounds with demonstrated anticancer potential; however, their clinical application is limited by low bioavailability. Nanoencapsulation, particularly using chitosan nanoparticles, offers an effective strategy to enhance targeted delivery and therapeutic efficacy in TNBC treatment.

**Keyword:** Cancer, Breast Cancer, Triple-negative breast cancer, *Psidium guajava* L., Chitosan

## 1. Introduction

Cancer is a serious health problem in clinical sectors, worldwide. It was characterized through irregular growth of cell that occurred due to genetic or epigenetic modification of somatic cells. These irregular growths of cells are known as neoplasm or tumour, whereby it forms a huge lump or mass, which may be disseminated from one part of body to other parts of the body (Saini *et al*., 2020). As stated by World Health Organization (WHO), cancer have

become the topmost health issues, which significantly affect 244.6 million DALYs individuals, globally with high mortality rates. In 2012, nearly 14.1 million individuals were reported to have cancer with 8.2 million deaths. Nevertheless, this could be estimated to increase to 21.3 million by the year 20230. Among various cancer, breast cancer is most diagnosed in hospitals, and these impose a significant mortality risk. However, breast cancer ranks first common cancer diagnosed at higher proportion followed by lung cancer (Buffart*et al*., 2014; Mattiuzzi& Lippi, 2019).

## 2. Breast cancer and its epidemiology

Breast cancer is recognized through the profound growth of cells within ducts, lobules, nipples, connective tissue, or lymphatic tissue. However, it was frequently diagnosed in the lobular region of breast. It is generally considered as heterogenous owing to their etiology and pathological features (Winters *et al*., 2017). It was reported that about 14 million women diagnosed with breast cancer annually, worldwide. Of which 4,50,000 individuals were died out of breast cancer. As per the report of the American Cancer Society, out of eight women one women is diagnosed with breast cancer. In 2013, about 2,32,340 individuals were reported for breast cancer with a mean death rate of 32,620, globally. Nevertheless, in India about 1,80,000 individuals were diagnosed with breast cancer in 2016. It was gradually increased to 5,26,000 cases which was found to be the highest number that was reported in clinical sectors. Subsequently, it was estimated that in 2020 tentatively 3.2 million would be diagnosed for breast cancer. According to the GLOBOCAN, breast cancer would be accounted for 13.5% cases with 10% death rate, annually (Tao *et al*., 2014; Ban *et al*., 2014; Mehotra& Yadav, 2022). Thus, breast cancer has become a significant health concern in medical communities which needs to be addressed.

## 3. Classification of Breast Cancer

Breast cancer is mainly classified into invasive and non-invasive carcinoma. The non-invasive breast cancer is restricted to its location (i.e.,) lobular or ductal region of breast. This non-invasive breast cancer is further categorized into *in situ* ductal breast cancer pertained to the ductal region of breast, whereas *in situ* lobular breast cancer pertained to the lobular region of the breast. In contrast, invasive breast cancer eventually spreads to fatty and connective tissues that surrounds lobular or ductal region of breast.This invasive type of breast cancer can also affect different organs like brain, bones, lungs, and liver and thus it also characterized as metastatic breast cancer. It was also divided into infiltrating/invasive ductal cancer, infiltrating/invasive lobular

carcinoma, medullary cancer, mucinous cancer, and tubular cancer. The infiltrating/invasive ductal cancer originate from the ductal region of breast and further infect other parts of the body. Similarly, invasive/infiltrating lobular carcinoma arise from lobular region of breast and extends to fatty tissues initially and further spreads to the other parts of the body. However, medullary cancer mainly creates a boundary between tumour tissue and normal tissue, whereas mucinous/colloidal cancer are characterized by mucus forming cancer cells. Nevertheless, tubular cancer is recognized by their tubular cancer cell structure, which plays a crucial feature in differentiating subtype of invasive cancer. Among these invasive tumours, both mucinous and tubular cancer will have better prognosis than the other cancer (Sharma *et al*., 2010; Malhotra *et al*., 2010; Akram *et al*., 2017).

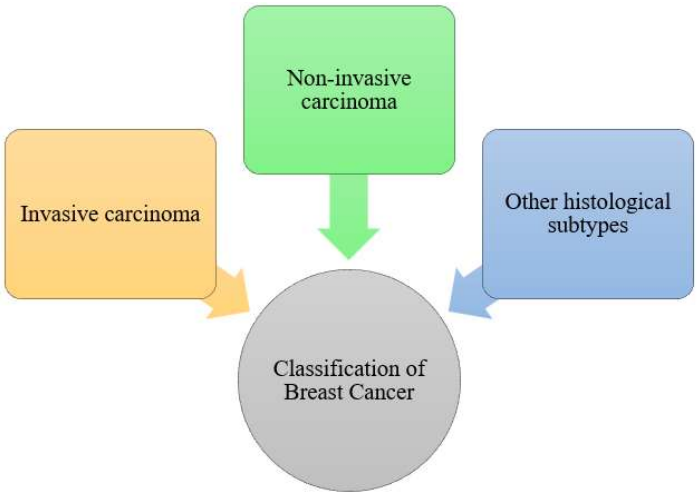


**Figure 1. General Classification of Breast Cancer**

Based on immunohistochemical properties, breast cancer is sub-classified as hormone receptor-positive, HER2 positive (HER2+), and triple-negative breast cancer. The hormone receptor-positive are generally characterized through estrogen receptor-positive/ progesterone receptor-positive, which contributes about 85% of breast cancer. HER2+ are recognized based on the human epidermal growth factor receptor 2 positive and negative to hormonal receptor, which accounts appropriately 20% of breast cancer. However, triple-negative breast cancers are characterized where both hormonal receptor and human epidermal growth factor 2 receptor are found to be negative, which influences 15% of breast cancer (Tang *et al*., 2016; Lukasiewicz *et al*., 2021). Among all these breast cancer types, triple-negative

breast cancer poses a serious threat,which requires more attention as they do not possessany specific or efficient therapies for prognosis.

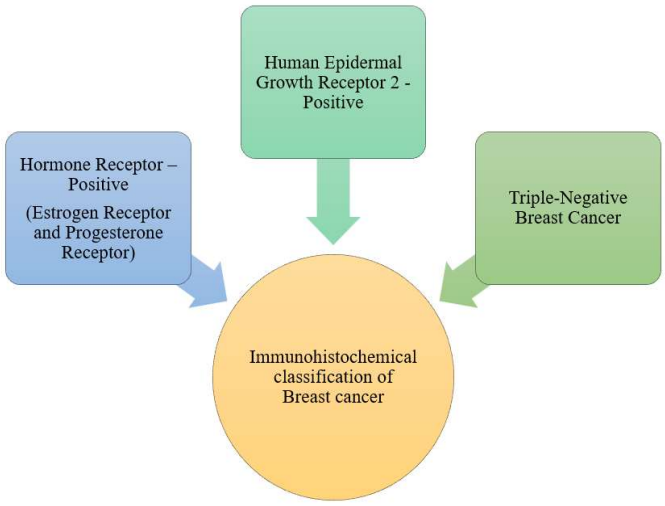


**Figure 2. Classification of Breast Cancer based on Immunohistochemical properties**

## 4. Triple-negative breast cancer and its epidemiology

Triple-negative breast cancers (TNBC) are the peculiar form of epithelial breast cancer that are immunohistochemically negative for the expression of the hormone receptor, i.e., estrogen receptor (ER) and progesterone receptor (PR) and negative for human epidermal growth factor receptor 2 (HER2) (O'Reilly *et al*., 2015; Podo *et al*., 2010). It is highly diagnosed in younger and older women who have the higher expression of BRCA mutation. These TNBC individuals reported with an increased incidence of recurrence within first three years of therapy and significant mortality observed in first five years of therapy (De Laurentiis *et al*., 2010; Almansour, 2022). Globally, African American women are reported with TNBC with high mortality rate. However, in India, about one lakh women are diagnosed with breast cancer, of which 20-43% are diagnosed with TNBC. Based on the data, prevalence of TNBC was high in Indian women which accounts for about 27.9% when compared to other countries. In India, the high incidence of TNBC was diagnosed and reported in Nagpur, Srinagar, Mumbai, Chennai, Bangalore, Delhi, Pune, and Hyderabad. Hence, it was evidenced that Indian women who have TNBC poses a high risk, where it contributes to higher mortality among individuals who resides within India (Thakur *et al*., 2018; Jha *et al*., 2020).

## 5. Diagnosis of TNBC

To diagnose TNBC in individuals, a two-step diagnosis procedure isgenerally used, i.e., imaging and immunohistochemistry (IHC) analysis. For imaging, three different techniques were adopted to diagnose TNBC, which includes a mammogram, an ultrasound of the breast and magnetic resonance imaging (MRI). In mammographic data, the presence of tumour is determined based on the white spots (calcification), irregular growth and lump formation. The main advantage of mammogram is that it requires only a limited radiation dose, where the radiation cannot significantly enter the breast tissues and cause further damage. However, false positive and false negative results may be reported, which considered a major challenge faced in tumour diagnosis. Moreover, a minor radiation also contributes to the development of cancer in high-risk individuals who carries BRCA genes (Kojima & Tsunoda, 2011; Dogan & Turnbull, 2012). Next significant diagnosis method used to detect TNBC is ultrasound. Whenever, mammogram fails to produce accurate results, alternatively ultrasound will be performed where the breast cyst (fibroadenoma) can be differentiated from the tumour cells. The accurate biopsy collection of tumour cells will be based on the ultrasound diagnosis (Tian *et al*., 2020; Chen & Lee-Felker, 2023).

The high-risk cancer individuals who carry BRCA mutation and having the family of breast cancer can be diagnosis using MRI, where the severity of breast cancer can be identified and thus it could be used for comparing the results obtained in mammogram or ultrasound. In MRI, the presence or absence of tumour can be detected but the type of breast cancer cannot be diagnosed (Li & Han, 2014; Uematsu, 2011; Wekking*et al*., 2023). To detect the type of breast cancer, Immunohistochemistry (IHC) is required, where the cellswere stained with the biomarkers such as hormone receptor (progesterone receptor (PR) and estrogen receptor (ER)) and human epidermal growth factor receptor two (HER2) markers. To enhance the efficacy and accuracy of IHC staining, the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) have also provided a standard guideline for the identification of histological group of breast cancer. These guidelines would help to avoid the errors made in the false positive and false negative test individuals. According to this ASCO/CAP guideline, ER and PR is considered positive only if immunoreactive cancer cells present at a minimum value of 1%. However, HER2 positive can be identified through fluorescent *in situ* (FISH) after initial IHC confirmation to avoid the false-positive and false-negative results (Penault-Llorca & Viale, 2012; Bonacho*et al*., 2020; Dass *et al*., 2021).

## 6. Treatment options available for TNBC and its limitations

TNBC are biologically aggressive, and it is already known that the individuals having TNBC cannot be cured from hormonal or trastuzumab-based therapy, as they lack the expression of hormonal and human epidermal growth factor 2 receptors.Hence, surgery and chemotherapy, discretely or in combination may help the individuals to recover from the disease. It was well documented that TNBC individuals are more likely to prefer mastectomy than lumpectomy owing to the possibilities of recurrence. However, the surgical removal of the breast can be appropriate choice for the individuals who are at the young age. Even though TNBC is found to be a dreadful, aggressive disease, the surgical choice relies on the clinicopathological variables, patients'choice, and severity of the dissemination of tumour cells (Al-Mahmood *et al*., 2018).Nevertheless, radiotherapy is recognized as conventional therapeutic option for the TNBC individuals, as the surgical option is not highly preferred by the diseased individuals. However, it is not an appropriate therapeutic choice for the individuals who exhibit BRCA mutation, as they are highly sensitive to radiation. These radiosensitive individuals lag functional genes in double-stranded DNA break repair, which should normally occur through homologous recombination (Chang-Qiang *et al*., 2020).

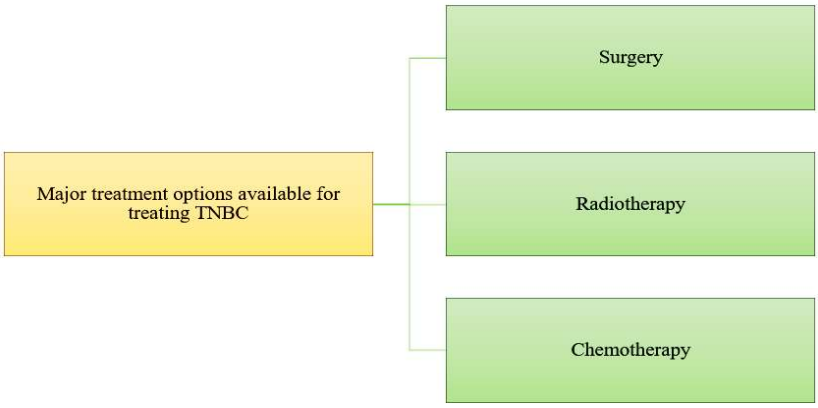


**Figure 3. Primary treatment options available for TNBC**

In addition to this, the combinatorial effect of novel therapeutic compound with the standard chemotherapeutic compound such as anthracycline, taxanes, antimetabolites, platinum agents and novel microtubule stabilizing agents are also found to be efficient in TNBC treatment according to the neoadjuvant studies. It was also observed that specific adjuvant treatments that are highly efficient in treating TNBC can also limits their usage in earlier and advanced phase of disease, and it is more suitable for intermediate phaseof

TNBC. Hence to treat the advanced phase of TNBC, third-generation chemotherapy using dose dense or metronomic polychemotherapy could be used (Wahba & El-Hadaad, 2015).To overcome the limitations, targeted therapy is widely adopted for the management and treatment of TNBC, which includes DNA repair agents,Epidermal Growth Factor Receptor (EGFR) inhibitors, antiangiogenic agents, poly-ADP-ribose-polymerase (PARP) inhibitors, or checkpoint kinase 1 inhibitors (with or without chemotherapy). All these have been considered for the treatment of metastatic TNBC, but still these agents have not produced desired improvements in TNBC outcomes (Khosravi-Shahi *et al*., 2018). It was well evidenced that there is no standard care in the first-line therapy is available for treating advanced TNBC individuals. Hence, researchers should focus more on finding an efficient alternative which targets the tumour cells and make the individuals free from the cancer.

## 7. Phytochemicals in Breast Cancer treatment

Globally, the researchers of medical communities have been significantly involved on the cancer research, where they haunt to find an effective alternative in treating the TNBC individuals. The emergence of technological advancement has made the researchers to shift drastically from traditional plant-based therapeutics to synthetic chemotherapeutic drugs for the treatment of dreadful diseases, including cancer. However, the emergence of drug resistance and toxicity behaviour of synthetic therapeutic drugs may urge us to make a paradigm shift back to adopt natural therapeutic compounds for the effective treatment of breast cancer. Recently, many researchers have already been reported with the potential phytochemical compounds that could be used for the treatment of various diseases and disorders, including Triple-negative breast cancer. These plant-based phytochemical compounds are promising therapeutic options, as they minimise or exhibit no toxic side effects in individuals even used for longer duration and thus it could be a better therapeutic option in treating breast cancer patients (Shrihastini*et al*., 2021).

The term “phytochemicals” refers to the bioactive non-nutritious compounds present in the plant-based diet. It is well documented that various phytochemicals have different categories of nutrients, vitamins, minerals, and fibres which often exhibit many disease-preventive properties. It has been knownfrom various researchthat phytochemicalspossess anticancer and antimutagenic properties, where they can play a substantial role in the treatment of the various groups of breast cancer (Kapinova*et al*., 2018).These phytochemicals are known to contain carotenoids, phenolics, alkaloids,

nitrogen-containing compounds, and organosulfur compounds as a significant bioactive compound, which are responsible for its anticancer potential in medical sectors. Of various phytochemicals, phenolic compounds are frequently encountered in preclinical studies of various chronic diseases, including cancer. In addition to this, bioactive phytochemicals exhibit anti-inflammatory, antioxidant, antimicrobial, and neuroprotective properties, which are often crucial in the treatment of breast cancer. Based on the earlier reports, phytochemicals have potential anticancer ability in targeting breast cancer and inhibiting the proliferation of breast cancer growth by mediating various cell signallingprocess (Solanki *et al*., 2022).

## 8. *Psidium guajava* L.

*Psidium guajava* L., generally called as guava, which is a fruit-bearing tree categorized under the familyMyrtaceae. It is a small shrub-like tree (reaching up to 10 meters tall) with a peculiar copper-coloured bark and green colour internal layer. The tree has trivial roots and a widely distributed crown that contains evergreen, parallelogram leaves which release fragrance upon crushing it. In addition, the white flowers that bear its fruit have four to five petals and a tuft of around 250 white stamens with pale yellow anthers. The guava fruit is round, oval, or pear shaped with a size that ranges from 1 to 48 ounces and when ripe has a strong sweet and musky odour. The outer peel is green or yellow and the flesh has a variety of colours, including white, yellow, pink, salmon, and red with numerous small hard white seeds. The fruit flavour also differs depending on the cultivar and can range from sweet to acidic. *Psidium guajava* L., or apple guava, is the guava species that is most eaten and traded. Many cultivars of this species have been developed, selecting for traits, such as sweetness, aroma, colour, and lack of seeds (Jameison *et al*., 2022).

**Figure 4. Fruit peel of *Psidium guajava* L.(Guava)**

Guava has been grown and considered an important fruit in tropical areas, including India, Indonesia, Pakistan, Bangladesh, and South America. Various parts of the guava tree, i.e., roots, leaves, bark, stem, and fruits, have been employed for treating stomach-ache, diabetes, diarrhoea, and other diseases and disorders (Kumar *et al*., 2021). Among various parts, fruits of guava contain many important biochemical phytoconstituents like alkaloids, terpenoids, flavonoids, tannins, carotenoids, lectins, vitamins, carbohydrate, phenols, saponins,fibres, fatty acids, and glycosides. Pharmacological studies on *Psidium guajava* L. revealed that it possesses antimutagenic, analgesic, anti-hyperglycaemic effect, anti-inflammatory, adaptogenic, antidiabetics, antidiarrheal, anti-angiogenesis, hepato-protective, antioxidant, anticancer, antimicrobial, cardioprotective, anti-hypertensive, antiparasitic properties, etc., (Ugbogu*et al*., 2022).This paves a way on using the fruit peel extract of *Psidium guajava L.* for the effective treatment option for the management of breast cancer.

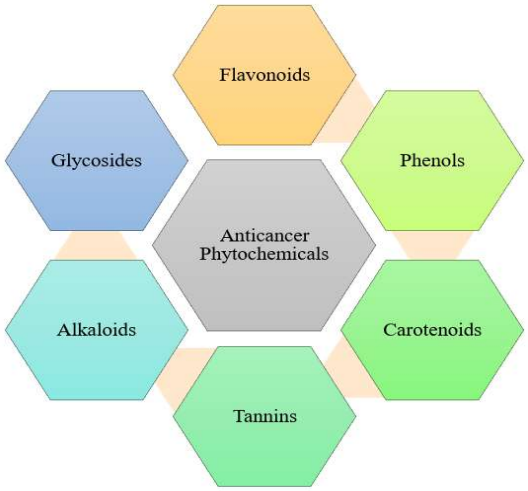


**Figure 5. Phytochemicals of *Psidium guajava* L.**

## 9. Challenges in using*Psidium guajava* L.for breast cancer treatment

The extensive metabolism of bioactive phytochemicals would limit the bioavailability and bioactivity in*in vivo*and thus their usage in anticancer treatment may hindered. The metabolization of bioactive phytochemical constituents occurs in the small and large intestine, and in the liver through associated phase I and II metabolism. Moreover, the absorption, distribution, metabolism, and elimination of phytochemicals and thus the circulating

concentrations, elimination, and tissue exposure to the phytochemical are affected based on the age, gender, genotype, diet intake, medications, and the presence of gut microbiome. Despite the role of the factors on the side of the individual, the metabolism of phytochemicals is also affected by the structural complexity of phytochemicals alone (Garcia-Oliveira *et al*., 2021; Mazurakova*et al*., 2022). Hence, the bioactive phytochemicals should be conserved to use in the health care sector, especially for cancer treatment.

## 10.Nanoencapsulation of bioactive compounds for breast cancer treatment

Nanotechnology has played a crucial role inassisting the effective anticancer drug development. When compared with free phytochemical constituents, the bioactive phytochemicals entrapped in the nanoparticles not only exhibit enhanced solubility of drug molecules, but also it adds other advantages. For instance, upon encapsulation of active phytochemicals in nanoparticles may cause an alteration in pharmacokinetic properties and biodistribution profiling, which ultimately leads to the improvement in the therapeutic index of the bioactive phytochemicals by reducing its toxicity and subsequently enhance their efficacy (Xie *et al*., 2016; Enrico *et al*., 2019). To deliver drug effectively in the targeted sire, nanocarriers like liposomes, dendrimers, micelles, metal nanoparticles, mesoporous, polymers, and even protein-drug conjugates have been used. However, the use of polymeric nanoparticles as drug carrier molecule will be more advantageous. The significance of using polymeric nanoparticles is that the modification of surface is easier, straightforward ornamentation and design, biologically compatible, and non-toxic in nature. The conventional method used for effective delivery of drug at target site for breast cancer treatment is encapsulating phytochemicals in polymeric nanoparticles. In the modern drug delivery systems, polysaccharides like chitosan, dextran, alginates, and hyaluronic acid are widely employed. These polysaccharides may be obtained from the natural sources are used frequently because of their biocompatibility and biodegradability, which exhibit little accumulation of byproducts after the administrationof anticancer drug molecules (Sartaj *et al*., 2021; Chavda *et al*., 2023).

## 11. Chitosan nanoparticles for effective drug delivery

Chitosan is a deacetylation process derived from chitin and is composed of d-glucosamine and N-acetyl-d-glucosamine units linked to β-(1→4). Chitosan is one of the possible drug carrier nanoparticles (NPs) because of its biodegradability and biocompatibility and displayed non- or minimal toxicity. The cationic nature, which increased adhesion through electrostatic interaction to the negatively charged mucosal surface, is one of the most significant chitosan characteristics, resulting in improved drug internalization into targeted cells. A significant barrier to its implementation is only soluble in an acidic medium. The extensive groups of aminos and hydroxyl serve as the target groups for chemical changes to improve solubility. The biocompatibility, low immunogenicity and biodegradability of CS are good. Under the *in vivo* enzyme, Chitosan will break down into water and carbon dioxide and become an endogenous species, ensuring no harmful effects from the products of degradation. Due to its increased solubility at slightly acidic pHs, such as those present in the microenvironment of the tumour, chitosan is generally used to develop pH-sensitive drug delivery system (Rostami, 2020; Herdiana *et al*., 2021; Wang *et al*., 2021).

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# Modern Trends in Fish Endocrine Research

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## Abstract

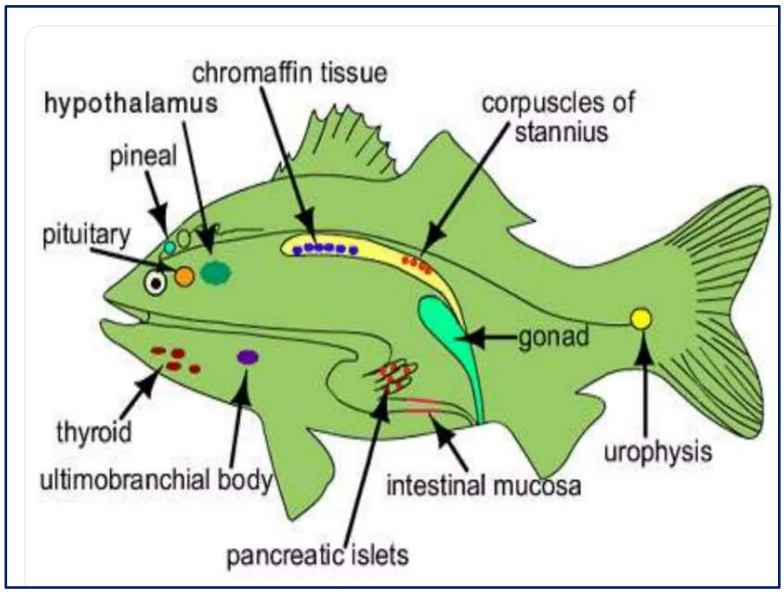
Fish possess a sophisticated endocrine system that regulates growth, reproduction, metabolism, stress response, osmoregulation, and behaviour. Classical studies of fish endocrinology focused on anatomy, histology, and hormone assays, but rapid technological advancement has transformed the field. High-throughput sequencing, multi-omics approaches, CRISPR-Cas9 genome editing, epigenetics, microbiome research, endocrine-disruptor bioassays, AI-driven ecological modelling, and non-invasive hormone detection are reshaping our understanding of endocrine function in teleosts. This chapter provides an overview of all major endocrine glands in fish—pituitary, thyroid, interrenal tissue, pancreas, gonads, ultimobranchial gland, urophysis, and diffuse neuroendocrine tissues—along with a detailed discussion of emerging trends in fish endocrinology. By integrating classical physiology with modern molecular bioresearch, the chapter highlights current breakthroughs and their implications for aquaculture, conservation, evolutionary biology, and environmental toxicology.

**Keywords:** Fish endocrine glands, CRISPR, Multi-omics, Aquaculture biotechnology

## Introduction

The endocrine system of fishes plays a central role in regulating growth, reproduction, stress responses, osmoregulation, metabolism, and behavior, making it a foundational subject in both classical and modern ichthyological research. Fish endocrine glands—such as the pituitary, thyroid, pancreas, interrenal tissue, ultimobranchial gland, and gonads—function through a network of hormones that coordinate physiological processes essential for survival across diverse aquatic environments (Mommsen & Walsh, 2019). The hypothalamic–pituitary axis, particularly the hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–interrenal (HPI) axes, forms the structural and functional core of endocrine regulation in teleosts. As

environmental changes accelerate globally, the study of fish endocrinology has become increasingly important for aquaculture, conservation biology, and ecotoxicology (Norris & Carr, 2020).Recent decades have witnessed major advancements in bioresearch technologies that have transformed our understanding of fish endocrine mechanisms. Traditional histological and biochemical approaches are now supplemented with high-resolution imaging, molecular diagnostics, omics technologies, and genome editing. These innovations enable precise identification of hormones, receptors, signaling pathways, and environmental influences on endocrine function. For example, transcriptomics and proteomics allow researchers to map global gene and protein changes in response to stressors, reproductive cues, or pollutants, providing a broader systems-level understanding of endocrine regulation (Qian et al., 2021). Metabolomics has further enhanced the ability to track metabolic shifts induced by endocrine-disrupting chemicals (EDCs), facilitating early detection of sub-lethal physiological impacts in fish populations (Gonzalez & Tarazona, 2022).




Additionally, CRISPR/Cas9 gene editing has emerged as a transformative tool for functional endocrinology. It enables targeted knockout or modification of hormone-related genes, helping elucidate their roles in growth, reproduction, and behavior (Hsu et al., 2020). This has paved the way for developing improved aquaculture strains with enhanced growth rates, stress tolerance, and reproductive control. Advances in endocrine biomarkers,

combined with next-generation sequencing, have also strengthened environmental monitoring programs by enabling detection of chemically induced endocrine disruption in wild fish populations (Kidd et al., 2019).Another emerging trend is the integration of neuroendocrinology with climate change research. Studies on temperature-dependent sex determination (TSD), altered spawning cycles, and stress endocrine responses contribute to predicting fish adaptation under warming oceans and freshwater systems (Pankhurst & Munday, 2018). Moreover, in aquaculture, biotechnological tools such as hormone analogs, recombinant gonadotropins, and controlled-release implants have improved induced breeding, larval survival, and reproductive synchronization in commercially important species (Zohar et al., 2019).Thus, the convergence of classical endocrine physiology with cutting-edge bioresearch technologies marks a new era in fish endocrinology. These advancements not only deepen scientific understanding but also address practical challenges in fisheries management, aquaculture sustainability, and environmental protection. As the field continues to evolve, integrated, multi-omics approaches and genome editing promise to further unravel the complex endocrine networks that govern fish biology.

## Major Endocrine Glands and Hormone-Secreting Tissues in Fish

### Hypothalamus–Pituitary Axis

The hypothalamus integrates neural and endocrine signals and regulates pituitary hormone release through releasing factors.
The pituitary (hypophysis) consists of neurohypophysis and adenohypophysis, secreting:

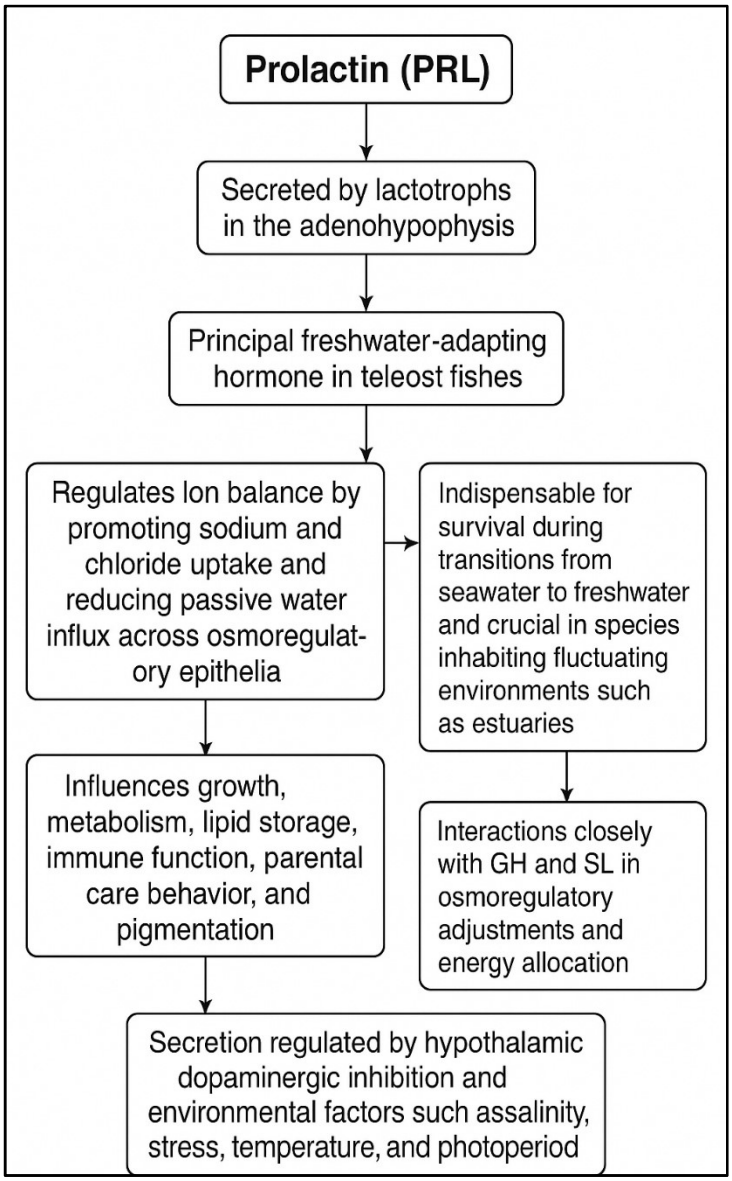
### Growth hormone (GH)

Growth hormone (GH) is one of the most important adenohypophyseal hormones in fish, produced by somatotrophs located primarily in the proximal pars distalis. GH regulates somatic growth, protein synthesis, lipid metabolism, and energy allocation and acts through both direct tissue effects and indirect pathways mediated by insulin-like growth factors (IGFs) (Björnsson, 1997). In teleosts, GH has an additional and uniquely significant role in osmoregulation, particularly during seawater adaptation, where it enhances gill chloride cell activity and upregulates ion transporters such as $Na^+/K^+$-ATPase (McCormick, 2001). GH also affects immune function, behavior, and stress tolerance, interacting with prolactin and somatolactin to maintain physiological homeostasis.Environmental factors such as temperature, salinity, photoperiod, food availability, and stress modulate GH secretion. Nutritional status is a major regulator, with fasting increasing GH levels while reducing IGF-I,

indicating a shift in the GH/IGF axis for metabolic conservation. GH has been widely explored in aquaculture for its growth-promoting potential, including through genetic engineering, recombinant hormone injection, and selective breeding. However, ecological and ethical concerns have limited the widespread use of GH-transgenic fish.Recent trends in GH research include genomics, transcriptomics, receptor-specific studies, and CRISPR/Cas9-mediated gene editing, which help clarify GH receptors, signaling pathways, and species-specific physiological roles. GH is also being studied as a biomarker for climate resilience, stress adaptation, and developmental plasticity. Its multifunctional nature and evolutionary diversification make GH one of the most intensely researched hormones in fish endocrinology.

## Prolactin (PRL)

Prolactin (PRL), secreted by lactotrophs in the adenohypophysis, is the principal **freshwater-adapting hormone** in teleost fishes. It plays a central role in regulating ion balance by promoting sodium and chloride uptake and reducing passive water influx across osmoregulatory epithelia (Manzon, 2002). PRL is indispensable for survival during transitions from seawater to freshwater and is crucial in species inhabiting fluctuating environments such as estuaries. Fish exhibit **multiple PRL isoforms**, resulting from gene duplication events, enabling functional diversification across species (Kawauchi et al., 2002).Beyond osmoregulation, PRL influences **growth, metabolism, lipid storage, immune function, parental care behavior**, and even pigmentation. It interacts closely with GH and SL in osmoregulatory adjustments and energy allocation. PRL secretion is regulated by hypothalamic dopaminergic inhibition and environmental factors such as salinity, stress, temperature, and photoperiod.In aquaculture, PRL research facilitates freshwater acclimation of euryhaline species, larval rearing, and broodstock management. Molecular advances such as **PRL receptor cloning, RNA-seq studies, and CRISPR/Cas9 gene knockouts** have expanded understanding of PRL's intracellular signaling pathways. PRL also serves as a sensitive biomarker for endocrine disruption because pollutants such as heavy metals, pesticides, and pharmaceuticals can alter its secretion.




## Somatolactin (SL)

Somatolactin (SL) is a unique pituitary hormone found only in fish and produced by the melanotrophs of the pars intermedia. Structurally related to GH and PRL, SL performs multiple functions including **pigmentation control, reproductive modulation, lipid metabolism, calcium regulation, ion balance, and stress adaptation** (Kawauchi & Sower, 2006). One of its most recognized roles is in **chromatophore regulation**, where SL affects

background adaptation and seasonal color changes. It also influences reproductive cycles through interactions with the gonadal steroids and photoperiodic cues.SL secretion is influenced by various environmental stimuli such as temperature, salinity, UV exposure, and pollutants. During sexual maturation, especially in salmonids, SL levels rise and modulate calcium mobilization and energy allocation for gametogenesis (Rand-Weaver et al., 1991).Recent molecular studies, including SL receptor identification, gene knockouts, and transcriptome profiling, have advanced understanding of SL's specific roles and evolutionary relationships with the GH/PRL family. In aquaculture, SL has practical relevance in managing stress, enhancing pigmentation of ornamental fish, and optimizing broodstock conditioning.

## Thyroid-stimulating hormone (TSH)

Thyroid-stimulating hormone (TSH), produced by thyrotrophs in the adenohypophysis, is responsible for stimulating synthesis and release of thyroid hormones (T3 and T4) by the thyroid follicles. These thyroid hormones regulate **metabolism, development,metamorphosis, growth, and thermogenesis** in fishes (Power et al., 2001). TSH activity is tightly controlled by the hypothalamic thyrotropin-releasing hormone (TRH) and negative feedback from circulating thyroid hormones.

In larval and juvenile fishes, thyroid hormones influence key developmental transitions such as **metamorphosis in flatfishes**, smoltification in salmonids, and larval morphogenesis across teleost species. Environmental factors—such as temperature, iodine availability, salinity, and pollutants—regulate TSH secretion and thyroid responsiveness. Endocrine-disrupting chemicals (EDCs), including PCBs and pesticides, can impair TSH signaling and thyroid gland function.Recent advances include molecular characterization of TSH subunits, receptor studies, transcriptomics of thyroid-regulated gene networks, and hormonal biomarkers for environmental monitoring. TSH is also important in aquaculture, where thyroid modulation helps improve larval development, survival, pigmentation, and metamorphosis timing in several species.

## Gonadotropins (FSH, LH)

Teleost fish possess two gonadotropins: **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**, produced by distinct gonadotrophs in the adenohypophysis. Together they regulate **gametogenesis, gonadal maturation, steroidogenesis, and spawning** through the hypothalamic–pituitary–gonadal (HPG) axis (Zohar et al., 2010).FSH primarily supports **early gametogenesis**, including ovarian follicular growth and spermatogonial

proliferation. LH regulates **final gamete maturation**, ovulation in females, and spermiation in males. Seasonal breeders rely heavily on photoperiod and temperature cues, which modulate gonadotropin levels through hypothalamic GnRH stimulation.Advances in biotechnology—such as **recombinant FSH and LH**, **GnRH analogues**, and controlled-release hormone implants—have significantly improved induced breeding in aquaculture. Molecular approaches include gonadotropin receptor studies, transcriptomics, and CRISPR-mediated gene knockouts to explore reproductive disorders and endocrine disruption.

## Adrenocorticotropic hormone (ACTH)

ACTH is secreted by corticotrophs in the adenohypophysis and regulates the synthesis of cortisol by the interrenal tissue, forming the central axis of the **hypothalamic–pituitary–interrenal (HPI) stress axis**. Cortisol influences metabolism, osmoregulation, immune responses, and stress adaptation (Mommsen et al., 1999). ACTH release is controlled by hypothalamic corticotropin-releasing hormone (CRH), environmental stressors, and feedback inhibition by cortisol.Chronic stress affects ACTH signaling, leading to impaired growth, reproductive dysfunction, and immunosuppression. ACTH and cortisol are widely used as biomarkers of environmental stress in wild fish populations, especially in polluted, hypoxic, or temperature-stressed environments. Modern tools such as ELISA assays, transcriptomics, and endocrine-disruption studies have expanded understanding of ACTH dynamics.

## Melanocyte-stimulating hormone (MSH)

Melanocyte-stimulating hormone (MSH), produced by melanotrophs in the pars intermedia, regulates pigmentation, background adaptation, stress, behavior, appetite, and energy balance (Fujii, 2000). MSH controls the dispersion of melanin within chromatophores, enabling rapid color adaptation to environmental backgrounds. In some species, MSH also influences feeding behavior and seasonal physiological changes.Environmental factors such as light, background color, temperature, stress, and pollutants modulate MSH secretion. Its role in stress is mediated through interaction with cortisol and somatolactin. MSH levels also change during reproduction and migration.Modern research includes MSH receptor characterization, molecular studies of chromatophore signaling pathways, and applications in ornamental fish pigmentation.

## Thyroid Gland

The thyroid tissue in fish is structurally unique because it is not organized into a single compact gland, as observed in mammals, but instead

exists in a diffuse form. It is composed of numerous spherical follicles that are scattered predominantly around the pharyngeal region, often extending along the ventral aorta or distributed within the branchial cavity. Each follicle is lined by epithelial cells responsible for synthesizing and storing thyroid hormones. The principal hormones secreted are thyroxine (T4) and triiodothyronine (T3), which play central roles in regulating a wide spectrum of physiological and developmental processes in fish.Thyroid hormones are essential for growth, influencing protein synthesis, cellular differentiation, and overall metabolic balance. They are also key regulators of metamorphosis, particularly in species such as flatfishes, where larval transformation involves extensive morphological reorganization, including eye migration and body asymmetry. In addition, T3 and T4 modulate basal metabolic rate, oxygen consumption, and energy utilization, enabling fish to adapt to diverse ecological conditions. Another significant function of thyroid hormones in fish is osmoregulation. They interact with gill ion-transport systems and metabolic pathways to facilitate transitions between freshwater and marine environments, thereby maintaining ionic and osmotic stability.Recent advances in bioresearch have brought increased attention to environmental and physiological factors influencing fish thyroid function. A major contemporary concern is the impact of thyroid-disrupting chemicals (TDCs) such as industrial pollutants, pesticides, heavy metals, and pharmaceutical residues, which can impair hormone synthesis, release, or receptor sensitivity, ultimately affecting growth and reproduction. Breakthroughs in metabolomics have enhanced understanding of iodothyronine pathways, enabling detection of subtle biochemical alterations. Additionally, studies on temperature-induced thyroid plasticity reveal that climate-driven thermal fluctuations significantly influence thyroid activity, metabolic rate, and developmental timing across diverse fish species, underscoring the system's environmental sensitivity.

## Interrenal Tissue (Analogous to Adrenal Cortex)

In fish, the interrenal tissue—functionally equivalent to the adrenal cortex of mammals—is located within the head kidney, a major hematopoietic and endocrine organ. The interrenal cells embedded in this region are chiefly responsible for synthesizing and secreting cortisol, the primary corticosteroid and central stress hormone in teleosts. Cortisol plays a pivotal role in maintaining homeostasis by coordinating a broad range of physiological functions that enable fish to respond efficiently to internal and external challenges.One of the most critical roles of cortisol lies in the regulation of stress responses. Activation of the hypothalamic–pituitary–interrenal (HPI) axis triggers rapid cortisol release during environmental, social, or

physiological stress, allowing fish to adjust behavioral patterns, enhance alertness, and mobilize energy reserves. Cortisol is also essential for osmoregulation, especially in euryhaline species undergoing transitions between freshwater and marine environments. It influences ion transporter activity in the gills, kidneys, and intestine, ensuring ionic balance and maintaining appropriate plasma osmolarity.In addition to osmoregulatory functions, cortisol significantly modulates energy metabolism. It facilitates gluconeogenesis, lipid mobilization, and protein turnover, thereby providing the metabolic fuel required during periods of stress, fasting, or increased activity. Cortisol also exerts immunomodulatory effects, promoting immune readiness under mild stress while suppressing immune function under chronic exposure, which can increase susceptibility to disease.Contemporary bioresearch in fish endocrinology increasingly focuses on understanding the regulation and plasticity of the HPI axis. Studies are examining the long-term impacts of chronic aquaculture stressors—such as crowding, handling, noise, and fluctuating water conditions—on cortisol rhythms, growth, and welfare. Another emerging trend is the use of waterborne cortisol measurements as a non-invasive biomarker. This method enables monitoring of fish stress levels without physical restraint, offering valuable applications in conservation, environmental toxicology, and sustainable aquaculture practices.

## Chromaffin Tissue (Analogous to Adrenal Medulla)

Chromaffin tissue in fish represents a key neuroendocrine system analogous to the adrenal medulla of higher vertebrates. Unlike mammals, where the adrenal gland is a compact organ, fish possess chromaffin cells scattered mainly along the posterior cardinal veins, head kidney, and perivascular regions. These cells, derived from the neural crest, function as endocrine effectors of the sympathetic nervous system and play a crucial role in maintaining physiological homeostasis (Wendelaar Bonga, 1997).The primary function of chromaffin tissue is the synthesis and secretion of **catecholamines**, including **adrenaline (epinephrine)** and **noradrenaline (norepinephrine)**. Catecholamines are stored in granulated vesicles and released in response to acute stressors such as hypoxia, handling, crowding, and temperature fluctuations. Their release is mediated by direct innervation from sympathetic cholinergic fibers, forming the functional **hypothalamus–sympathetic–chromaffin (HSC) axis** (Reid et al., 1998).Adrenaline is the major hormone that facilitates the **acute stress response**, enhancing cardiac output, stimulating gill ventilation, and increasing oxygen uptake. It also promotes glycogenolysis and elevates blood glucose levels, thereby supporting rapid energy mobilization essential for survival during “fight-or-flight”

situations (Mommsen et al., 1999). Noradrenaline, on the other hand, plays a dominant role in **cardiovascular regulation**, particularly by inducing vasoconstriction, modulating blood pressure, and redistributing blood flow to vital organs.Catecholamines also contribute significantly to **emergency metabolism**, helping fish maintain ionic and osmotic balance, especially during environmental disturbances such as salinity shifts or pollutants. Their interaction with corticosteroids further amplifies the stress response, highlighting the integrated nature of endocrine regulation in fish.Thus, chromaffin tissue acts as a vital stress-response system in fish, reflecting evolutionary conservation of adrenal-like functions across vertebrates.

## Pancreatic Islets (Brockmann Bodies)

In teleost fish, the endocrine pancreas is organized into discrete clusters known as **Brockmann bodies**, named after the German anatomist Karl Brockmann. These islets are scattered throughout the pancreas, often in association with blood vessels, facilitating rapid hormonal release into circulation. They play a central role in maintaining metabolic homeostasis and regulating energy balance in fish (Heller et al., 1981).Brockmann bodies contain several specialized endocrine cell types: **β-cells** that secrete **insulin**, **α-cells** producing **glucagon**, and **δ-cells** releasing **somatostatin**. Insulin lowers blood glucose by promoting uptake and storage in liver, muscle, and other tissues, while glucagon counteracts insulin's action, mobilizing glucose through glycogenolysis and gluconeogenesis. Somatostatin serves as a modulatory hormone, inhibiting both insulin and glucagon secretion to fine-tune glucose homeostasis. Collectively, these hormones regulate **carbohydrate metabolism**, energy availability, and feeding behavior, allowing fish to adapt to variable nutrient environments.Recent research highlights that **diet composition and feeding regimes** can significantly influence pancreatic endocrine activity. For example, high-protein or carbohydrate-enriched diets induce differential insulin and glucagon responses, affecting growth and metabolic efficiency (Polakof et al., 2012). Additionally, the **gut microbiome** has emerged as a critical factor influencing metabolic regulation in fish, modulating endocrine signaling and energy balance through microbial metabolites and nutrient absorption pathways.Overall, Brockmann bodies represent an evolutionarily conserved endocrine system that integrates nutritional status, energy demand, and metabolic adaptation in fish. Understanding their physiology not only sheds light on fundamental metabolic processes but also informs aquaculture practices aimed at optimizing growth, feed efficiency, and health in cultured species.

## Gonads (Testis and Ovary)

In fish, the **gonads**, comprising **testes** in males and **ovaries** in females, serve as primary reproductive organs and endocrine centers. Beyond gamete production, they secrete vital **sex steroids**, including **estrogens (E2)**, **androgens (testosterone [T] and 11-ketotestosterone [11-KT])**, and **progestogens**. These hormones orchestrate key reproductive processes such as **sexual differentiation**, **gametogenesis**, **reproductive behavior**, and **spawning cycles** (Nagahama, 1994).In females, estrogens, primarily 17β-estradiol (E2), stimulate **vitellogenesis**, the liver-mediated production of yolk proteins necessary for oocyte maturation. Progestogens regulate **final oocyte maturation** and ovulation. In males, testosterone and its more potent derivative 11-ketotestosterone promote **spermatogenesis**, secondary sexual characteristics, and mating behaviors. The dynamic interplay of these hormones ensures synchronization of reproductive timing with environmental cues such as photoperiod, temperature, and food availability.Modern research in fish reproductive endocrinology has expanded to include **molecular and genetic tools**. **CRISPR/Cas9-mediated gene editing** is increasingly applied to study mechanisms of sex differentiation, identify key regulators of steroidogenesis, and manipulate sex ratios for aquaculture improvement. Additionally, the effects of **endocrine-disrupting chemicals (EDCs)**, such as pesticides and industrial pollutants, are under intense investigation due to their potential to impair gonadal development, steroid production, and reproductive success (Schulz et al., 2010).Overall, fish gonads are central to both reproductive and endocrine physiology. Insights into their hormonal regulation, combined with advanced molecular techniques, provide critical understanding of fish biology and have practical implications for aquaculture, conservation, and environmental monitoring.

## Ultimobranchial Gland

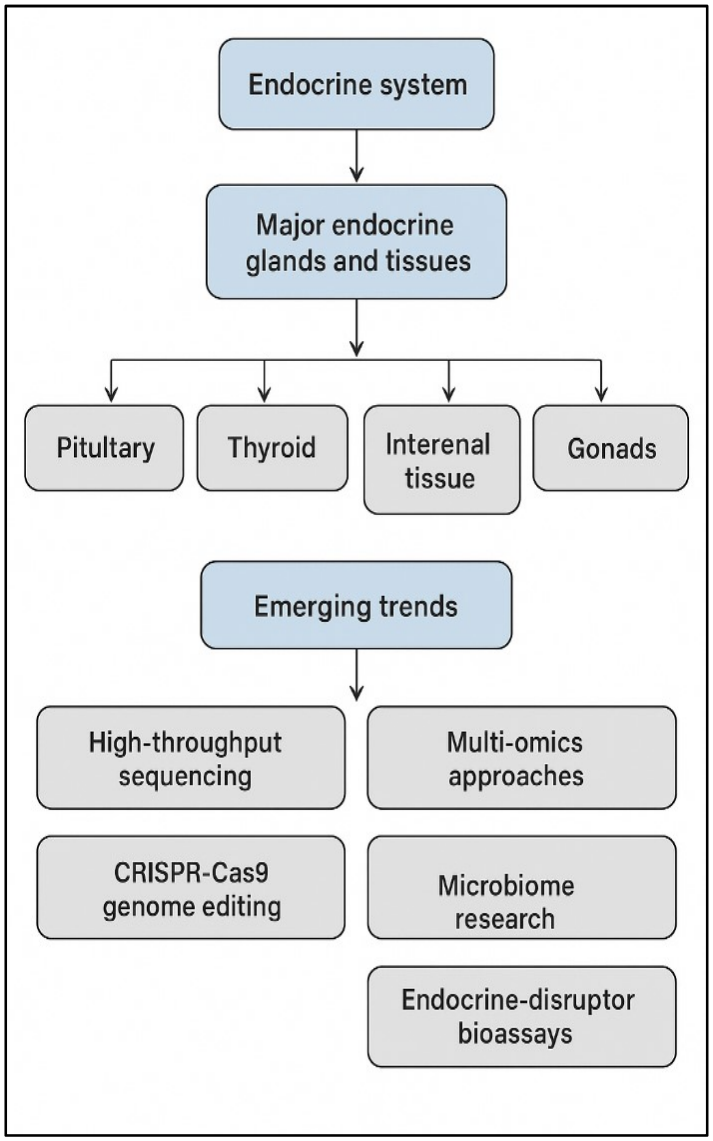
The **ultimobranchial gland** is a distinctive endocrine organ in fish, anatomically located near the thyroid or in association with the gill arches. It is unique to fish and some lower vertebrates and plays a crucial role in **calcium homeostasis**. The gland contains specialized **C-cells** that produce **calcitonin**, a peptide hormone that lowers blood calcium levels by inhibiting bone resorption and enhancing calcium deposition in skeletal tissues (Brown, 1991).Calcitonin secretion is responsive to circulating calcium concentrations, acting as a rapid regulator of mineral balance. This function is particularly important in fish, as calcium is critical not only for skeletal development but also for muscle contraction, nerve transmission, and overall metabolic stability.Recent research

has extended the understanding of the ultimobranchial gland beyond classical calcium regulation. Studies now explore the **integration of calcitonin signaling with bone metabolism** and its role in modulating **osmoregulatory mechanisms**, allowing fish to adapt to variations in water salinity and ionic composition (Baker et al., 2007). Investigations also examine how environmental factors, diet, and hormonal interactions influence calcitonin activity, providing insights into endocrine control of mineral homeostasis in aquatic vertebrates.Overall, the ultimobranchial gland exemplifies a specialized endocrine system in fish, linking mineral balance, skeletal integrity, and environmental adaptation.

## Urophysis and the Caudal Neurosecretory System

The **urophysis** is a unique neuroendocrine structure located in the **tail region** of teleost fish, forming a key component of the **caudal neurosecretory system (CNSS)**. It consists of neurosecretory terminals of **Dahlgren cells**, which synthesize and release peptide hormones directly into the circulation. The principal secretions of the urophysis include **urotensin I** and **urotensin II**, which are critical modulators of physiological homeostasis (Peter & Dubois, 1991).These neuropeptides perform diverse functions. **Urotensin I** primarily regulates **cardiovascular activity**, influencing heart rate and vascular tone, while **urotensin II** contributes to both **osmotic balance** and **stress responses**, including adaptation to salinity changes and acute environmental stressors. Collectively, the urophysis plays a pivotal role in **osmoregulation**, **cardiovascular regulation**, and **stress modulation**, integrating sensory inputs with endocrine outputs to maintain internal equilibrium.Recent research has highlighted the potential of urotensins as **biomarkers for environmental stress** in aquatic ecosystems. Elevated urotensin levels are observed in fish exposed to pollutants, hypoxia, or abrupt salinity shifts, reflecting their involvement in neuroendocrine adaptation to environmental challenges (Martos-Sitcha et al., 2017). Such studies underscore the functional importance of the CNSS and urophysis in monitoring fish health and assessing ecological stressors.Overall, the urophysis exemplifies an evolutionarily specialized endocrine system, critical for both internal physiological regulation and environmental responsiveness in teleosts.

## Diffuse Neuroendocrine System




The diffuse neuroendocrine system (DNES) in fish comprises scattered endocrine cells located in various peripheral tissues, including the gills, gastrointestinal tract, and skin. Unlike discrete glands, these cells are widely distributed, forming a network that allows rapid local and systemic hormonal signaling. They secrete a variety of peptides and biogenic amines, such as serotonin, neuropeptide Y (NPY), and substance P, which collectively modulate multiple physiological processes (Barker & Peter, 1992).Serotonin in

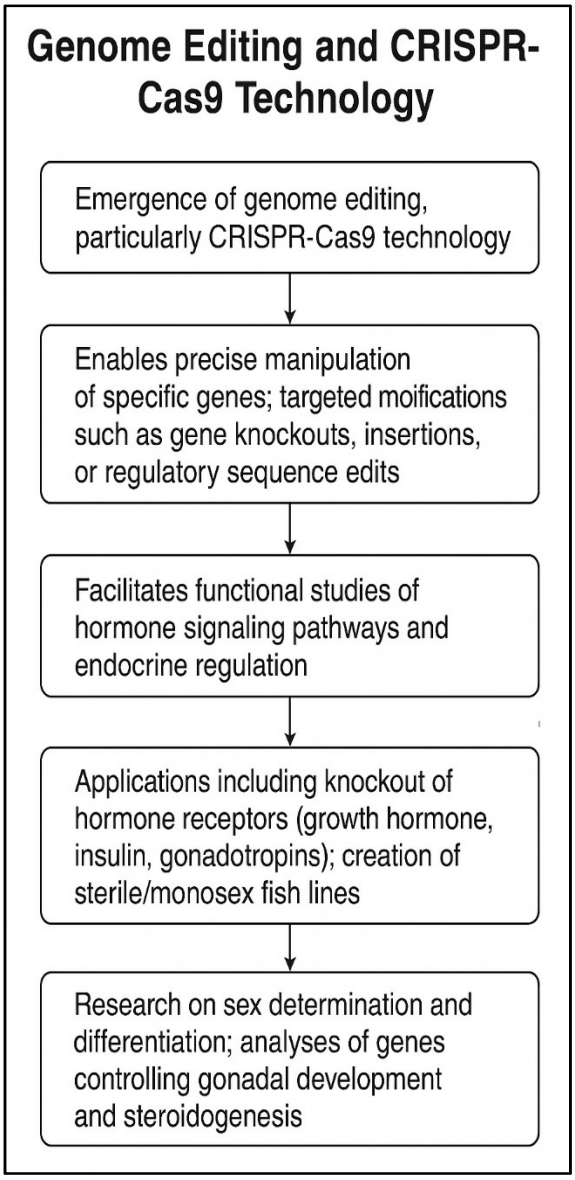
the DNES primarily regulates mood-like states, locomotor activity, and feeding behavior. Neuropeptide Y is a potent orexigenic signal that stimulates appetite and coordinates energy balance, while substance P is involved in nociception, defense responses, and modulation of mucus secretion on the skin and gills. The secreted peptides act both locally and systemically, integrating environmental cues with behavioral and physiological adaptations.In the gills, DNES cells help adjust respiratory efficiency and ionic balance by influencing vascular tone and mucus production. In the gut, they regulate digestive motility, enzyme secretion, and nutrient absorption. In the skin, they contribute to mucus secretion, which serves as a first-line defense against pathogens and environmental stressors.Overall, the diffuse neuroendocrine system in fish represents an evolutionarily conserved mechanism that links behavior, metabolism, and environmental adaptation. Its widespread distribution allows fish to rapidly respond to changes in feeding conditions, stress, and pathogen exposure, highlighting its critical role in survival and ecological fitness.

## Emerging Trends in Bioresearch in Fish Endocrinology

### Multi-Omics Approaches

The advent of **multi-omics technologies** has transformed the study of fish endocrinology, offering unprecedented insights into the molecular and systemic regulation of physiological processes. Multi-omics integrates **genomics, transcriptomics, proteomics, metabolomics, lipidomics, and epigenomics**, providing a holistic view of endocrine function and regulation in fish (Hasan et al., 2020).**Genomics** allows identification of genes involved in hormone synthesis, receptor signaling, and stress responses, while **transcriptomics** provides dynamic information on gene expression patterns under different environmental or developmental conditions. **Proteomics** complements these by quantifying hormone-related proteins, enzymes, and signaling molecules, and **metabolomics** reveals changes in metabolites associated with endocrine activity, energy metabolism, and stress adaptation. **Lipidomics** helps in understanding steroidogenesis and membrane-associated hormone signaling, whereas **epigenomics** uncovers regulatory modifications that influence hormone gene expression and long-term physiological adaptation.By integrating these datasets, researchers can **discover novel endocrine pathways**, identify **biomarkers of stress, reproduction, and metabolic states**, and perform **systems-level analyses** of neuroendocrine and gonadal regulation. For example, multi-omics has been applied to study the hypothalamus–pituitary–gonad (HPG) and hypothalamus–pituitary–interrenal (HPI) axes under environmental stressors, revealing interactions between gene

expression, protein signaling, and metabolic outputs (Kong et al., 2021).Overall, multi-omics approaches enable a comprehensive understanding of **endocrine networks in fish**, bridging molecular, cellular, and physiological scales. These methodologies not only advance fundamental research but also offer practical applications in aquaculture, environmental monitoring, and conservation biology.



## Genome Editing and CRISPR-Cas9 Technology

The emergence of **genome editing**, particularly **CRISPR-Cas9 technology**, has revolutionized fish endocrinology and aquaculture research by enabling precise manipulation of specific genes. This technology allows targeted modifications such as **gene knockouts**, insertions, or regulatory sequence edits, facilitating functional studies of hormone signaling pathways and endocrine regulation (Hwang et al., 2013).One major application is the **knockout of hormone receptors**, such as those for growth hormone, insulin, or gonadotropins, which helps elucidate their roles in growth, metabolism, and reproduction. CRISPR-Cas9 is also used to **create sterile or monosex fish lines**, a valuable strategy in aquaculture to prevent uncontrolled breeding, improve growth efficiency, and enhance product quality.Additionally, CRISPR facilitates in-depth research on **sex determination and differentiation**, allowing functional analysis of genes such as dmrt1, foxl2, and cyp19a1, which govern gonadal development and steroidogenesis. This has provided new insights into the genetic control of **neuroendocrine regulation**, including the hypothalamus–pituitary–gonad (HPG) axis. Moreover, functional genomics studies using CRISPR have illuminated the **pituitary and thyroid hormone regulation**, enabling a better understanding of endocrine control over growth, metabolism, and stress responses in teleosts (Liu et al., 2020).

Overall, genome editing through CRISPR-Cas9 represents a **powerful tool for both basic and applied fish research**, bridging molecular biology, endocrinology, and aquaculture biotechnology. Its applications promise improved fish health, production efficiency, and conservation strategies while expanding fundamental knowledge of vertebrate endocrine systems.

## Epigenetics and Environmental Endocrinology

Epigenetic mechanisms, including **DNA methylation, histone modifications, and microRNA (miRNA) regulation**, have emerged as critical modulators of endocrine function in fish. These processes allow gene expression to be dynamically regulated without altering the underlying DNA sequence, providing **physiological plasticity** in response to environmental cues (Vandegehuchte& Janssen, 2014).Environmental factors such as **stress, temperature fluctuations, pollution, and endocrine-disrupting chemicals (EDCs)** can induce epigenetic changes in key genes controlling hormonal pathways, reproductive processes, and metabolic regulation. For example, chronic stress or exposure to high cortisol levels can modify DNA methylation patterns in the hypothalamus–pituitary–interrenal (HPI) axis, altering stress responsiveness and energy metabolism. Temperature shifts during critical

developmental windows can influence sex-determining gene expression through histone acetylation or methylation, impacting **sexual differentiation**.Pollutants and EDCs, including pesticides and industrial chemicals, have been shown to disrupt endocrine signaling by modifying miRNA expression, which in turn regulates hormone synthesis, receptor sensitivity, and reproductive function. These epigenetic modifications can be **transient or persistent**, sometimes affecting multiple generations, highlighting the long-term consequences of environmental exposure on fish populations (Mirbahai& Chipman, 2014).By integrating **epigenetics with environmental endocrinology**, researchers can better understand how external stressors influence endocrine plasticity, reproductive health, and metabolic adaptation in fish. This approach also provides valuable biomarkers for ecological monitoring and conservation management.

## Endocrine-Disrupting Chemicals (EDCs)

Fish are highly sensitive indicators of **aquatic pollution** and serve as **sentinel species** for monitoring environmental contaminants that interfere with endocrine function. **Endocrine-disrupting chemicals (EDCs)**, such as industrial pollutants, pesticides, pharmaceuticals, and heavy metals, can mimic or block natural hormones, leading to altered growth, reproduction, and behavior in aquatic organisms (Kime, 1999).Modern research employs advanced **bioassays and molecular tools** to detect and study EDC effects in fish. **Zebrafish embryo assays** provide rapid, high-throughput platforms for evaluating developmental and endocrine toxicity, allowing visualization of morphological and molecular endpoints. **Vitellogenin induction**, the abnormal synthesis of egg yolk precursor proteins in male fish, serves as a widely used biomarker of estrogenic contamination.In addition, **Adverse Outcome Pathways (AOPs)** models integrate molecular initiating events with organism-level outcomes, linking chemical exposure to reproductive, developmental, and behavioral consequences. **Toxicogenomics** approaches, combining transcriptomics, proteomics, and metabolomics, allow identification of disrupted endocrine pathways and stress-response genes, offering a systems-level understanding of EDC effects (Scholz & Mayer, 2008).Overall, fish-based EDC research not only provides insights into endocrine regulation and environmental toxicology but also informs **risk assessment, ecological monitoring, and conservation strategies**, highlighting the critical role of aquatic vertebrates in understanding human and ecosystem health.

## Microbiome–Endocrine Interactions

In fish, the **gut microbiome** plays a pivotal role in modulating endocrine function, influencing growth, metabolism, and stress responses. Microbial communities interact closely with the **growth hormone (GH)/insulin-like growth factor (IGF) axis**, affecting somatic growth, nutrient utilization, and energy balance. They also impact **stress hormones**, such as cortisol, and metabolic hormones regulating carbohydrate and lipid homeostasis, thereby integrating nutritional status with physiological adaptation (Ringø et al., 2016).Studies indicate that specific gut microbes can enhance GH/IGF signaling by producing short-chain fatty acids, vitamins, or other bioactive metabolites that influence hormone secretion and receptor sensitivity. Similarly, microbiota can modulate hypothalamic–pituitary–interrenal (HPI) axis activity, altering cortisol levels and stress resilience. Disruption of microbial balance, through antibiotics, poor diet, or environmental stressors, may impair endocrine regulation, growth, and reproductive performance in fish.Emerging bioresearch focuses on **probiotic and prebiotic strategies** to optimize microbiome composition, thereby supporting endocrine health in aquaculture. Supplementation with beneficial bacteria has been shown to enhance growth, improve feed conversion, modulate stress responses, and stabilize metabolic hormone levels, offering sustainable approaches to enhance fish productivity and welfare (Gómez &Balcázar, 2018).Overall, the **microbiome–endocrine axis** represents a critical interface between environmental inputs, diet, and hormonal regulation in fish, providing novel opportunities for aquaculture optimization and fundamental research in vertebrate physiology.

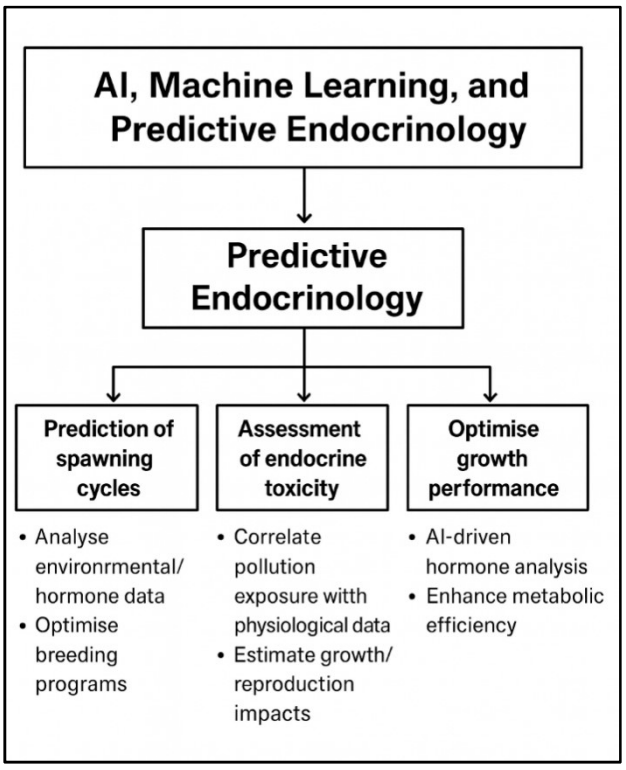
## Climate Change and Endocrine Plasticity

Climate change poses significant challenges to fish physiology, particularly impacting **endocrine plasticity**, the ability of hormonal systems to adapt to environmental fluctuations. Rising water temperatures can alter **temperature-dependent sex determination (TSD)** in many teleost species, leading to skewed sex ratios and potentially affecting population sustainability. Shifts in temperature also influence **thyroid hormone levels**, which regulate metabolism, growth, and developmental timing, as well as **reproductive hormones** such as gonadotropins and sex steroids, affecting gametogenesis and spawning cycles (Pankhurst & Munday, 2011).Ocean **acidification** resulting from increased $CO_2$ levels disrupts **cortisol regulation** in fish, impairing stress responses and osmoregulatory efficiency. Similarly, changes in water **salinity** necessitate hormonal adaptation involving the hypothalamus–pituitary–

interrenal (HPI) and hypothalamus–pituitary–thyroid (HPT) axes to maintain ionic balance, growth, and metabolic homeostasis. These endocrine adjustments exemplify the plasticity of fish hormonal systems, enabling short-term survival under environmental stress but potentially compromising long-term reproductive success and growth performance.Recent studies highlight the importance of understanding climate-induced endocrine alterations for **conservation and aquaculture**, as hormonal responses serve as sensitive biomarkers of environmental stress. Integrating endocrinology with climate research helps predict species resilience, adapt management strategies, and develop mitigation approaches to maintain healthy fish populations in changing aquatic ecosystems.

## Non-Invasive Hormone Assessment

Non-invasive hormone assessment has emerged as a transformative approach in fish endocrinology, enabling **stress-free monitoring of physiological status**. Traditional blood sampling can induce handling stress, potentially altering hormone levels and confounding results. Modern techniques allow measurement of hormones such as **cortisol, sex steroids, and other metabolites directly from water samples**, reflecting the endocrine activity of individual fish or populations without physical interference (Sumpter, 2005).These methods rely on the fact that fish continuously excrete hormones and their metabolites into the surrounding water. By collecting and analysing water samples, researchers can track **stress responses, reproductive status, and metabolic changes** in a naturalistic setting. This approach is particularly valuable in aquaculture and ecological studies, where minimizing animal disturbance is crucial for accurate welfare assessment and behaviour observation.Recent advances also integrate **artificial intelligence (AI) and machine learning tools** to interpret hormone dynamics in real time. AI can analyse temporal patterns, predict stress events, and correlate hormonal fluctuations with environmental factors such as temperature, salinity, or pollutants. This provides a **systems-level understanding of fish physiology**, enhances management practices, and supports proactive welfare monitoring (Delezie et al., 2020).Overall, non-invasive hormone assessment represents a significant advancement in fish endocrinology, combining **precision, animal welfare, and real-time analytics**, and opening new avenues for research in stress biology, reproduction, and environmental monitoring.




## AI, Machine Learning, and Predictive Endocrinology

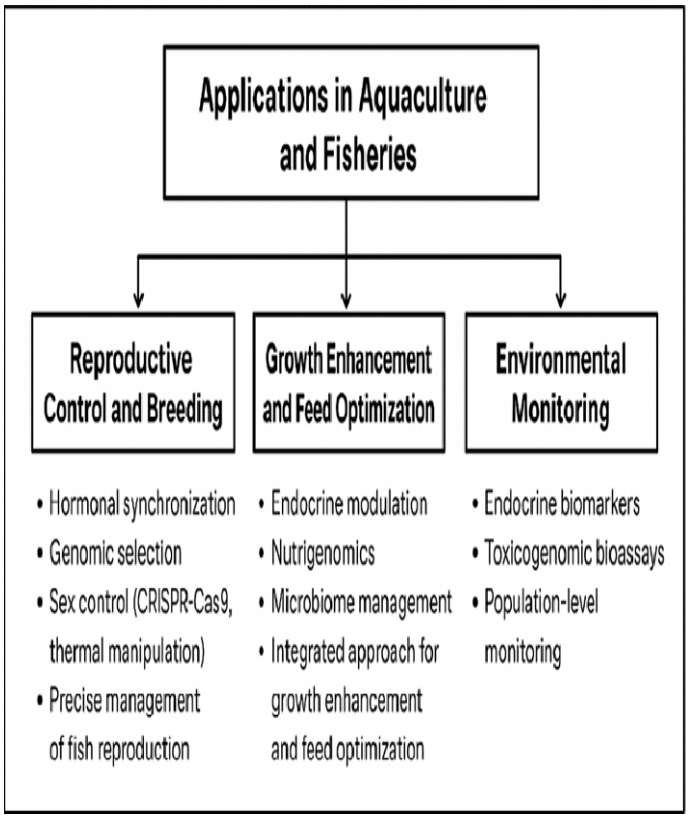
The integration of **artificial intelligence (AI)** and **machine learning (ML)** in fish endocrinology has ushered in a new era of **predictive biology**, enabling data-driven insights into complex hormonal and physiological processes. By combining large-scale **environmental and physiological datasets**, these computational tools can model and forecast key endocrine-mediated outcomes with high accuracy (Li et al., 2021).One major application is the prediction of **spawning cycles**, where ML algorithms analyse patterns in water temperature, photoperiod, hormone levels, and nutritional status to anticipate reproductive timing, thereby optimising breeding programs in aquaculture. Similarly, AI models can forecast **stress events** by integrating cortisol measurements, environmental fluctuations, and behavioural data, allowing proactive interventions to improve fish welfare.Predictive endocrinology also facilitates the assessment of **endocrine toxicity**. By correlating exposure to pollutants, endocrine-disrupting chemicals, or pharmaceuticals with multi-omics and physiological data, ML algorithms can identify early biomarkers of disruption and estimate long-term impacts on growth, reproduction, and survival. Furthermore, AI-driven analysis of

hormone and growth data helps optimise**growth performance**, feeding regimes, and metabolic efficiency under variable environmental conditions.Overall, the application of AI and ML provides a **systems-level understanding of endocrine dynamics** in fish, bridging environmental, physiological, and molecular data. These approaches support sustainable aquaculture, environmental monitoring, and conservation strategies, marking a paradigm shift toward **precision endocrinology** in aquatic research.

## Applications in Aquaculture and Fisheries

### Reproductive Control and Breeding

Endocrine research and modern biotechnologies have revolutionized **reproductive management in aquaculture and fisheries**, enhancing productivity, sustainability, and genetic improvement. One key approach is **hormonal synchronization**, which involves administering exogenous hormones such as gonadotropins, gonadotropin-releasing hormone analogs (GnRHa), or pituitary extracts to synchronize **spawning and ovulation**. This enables precise control over breeding cycles, facilitates seed production, and improves the efficiency of hatchery operations (Mylonas et al., 2010).**Genomic selection** is increasingly applied to accelerate selective breeding by identifying fish with desirable traits, including growth rate, disease resistance, and reproductive performance. Integration of genomics and endocrine phenotyping allows breeders to select individuals with optimal hormone profiles, enhancing both reproductive success and aquaculture productivity.Advanced molecular tools, including **CRISPR-Cas9**, are now employed for **sex control**, allowing targeted gene edits in sex-determining pathways to produce monosex populations, which can improve growth efficiency and reduce unwanted breeding. Similarly, **thermal manipulation** during early development can influence sex ratios in temperature-sensitive species, providing an environmentally guided approach to sex control.Together, these techniques enable precise management of fish reproduction, combining endocrine regulation, molecular genetics, and environmental modulation. Their application supports **sustainable aquaculture practices**, improves yield, and provides insights into the fundamental biology of fish reproduction.




## Growth Enhancement and Feed Optimization

Optimizing growth and feed efficiency is a central focus in aquaculture, and endocrine research provides critical strategies to achieve these goals. **Growth hormone (GH) and insulin-like growth factor (IGF) signaling** play a pivotal role in regulating somatic growth, nutrient partitioning, and metabolism in fish. Modulating the GH/IGF axis through selective breeding, dietary interventions, or genetic approaches can significantly enhance growth rates and feed conversion efficiency (Gahr et al., 2013).**Nutrigenomics** is increasingly applied to link diet composition with gene expression patterns related to growth, metabolism, and endocrine regulation. By understanding how specific nutrients, such as amino acids, fatty acids, or micronutrients, influence hormone production and metabolic pathways, feed formulations can be optimized to maximize growth while minimizing waste and environmental impact (Panserat et al., 2017).The **gut microbiome** also plays a crucial role in growth performance by modulating nutrient absorption, energy metabolism, and hormonal signaling. **Microbiome engineering**, through probiotics,

prebiotics, or synbiotics, can improve digestive efficiency, enhance GH/IGF responsiveness, and stabilize metabolic hormone levels, contributing to improved growth and health in cultured fish (Ringø et al., 2016).Overall, integrating endocrine modulation, nutrigenomics, and microbiome management enables a **systems-level approach** to growth enhancement and feed optimization, supporting sustainable aquaculture practices and improving the economic and ecological efficiency of fish production.

### Environmental Monitoring

Fish serve as critical **sentinel species** for assessing the health of aquatic ecosystems, particularly through **endocrine biomarkers** that indicate exposure to pollutants and environmental stressors. Hormones such as **vitellogenin, cortisol, and sex steroids** are widely used to detect estrogenic compounds, heavy metals, and other endocrine-disrupting chemicals (EDCs), providing early-warning signals of ecological contamination (Kime, 1999).

**Toxicogenomic bioassays** integrate genomics, transcriptomics, proteomics, and metabolomics to evaluate molecular responses of fish to chemical exposure. These approaches allow the identification of **disrupted endocrine pathways**, predict adverse outcomes, and provide mechanistic insights into how pollutants affect growth, reproduction, and stress physiology (Scholz & Mayer, 2008). By analyzing gene expression profiles in exposed fish, researchers can detect sublethal effects before population-level consequences occur.Monitoring endocrine disruption in **wild fish populations** is essential for ecological risk assessment. Sampling hormone levels, receptor activity, and biomarker expression across multiple species and habitats helps track the impact of industrial effluents, agricultural runoff, and urban pollutants. Such monitoring not only informs **environmental policy and regulation** but also aids in conservation strategies to protect biodiversity and ecosystem services.Overall, the integration of **endocrine biomarkers, toxicogenomics, and population-level monitoring** makes fish indispensable tools for environmental surveillance, enabling proactive detection and mitigation of ecological threats.

## Conclusion

The study of fish endocrine glands and the expanding field of fish endocrinology represent a vital frontier in biological research, aquaculture, and environmental conservation. Fish, as highly diverse vertebrates, possess adaptive endocrine systems that regulate growth, reproduction, metabolism, osmoregulation, immune function, and stress physiology. Understanding these

mechanisms is essential not only for advancing scientific knowledge but also for addressing practical challenges such as sustainable fisheries, aquaculture productivity, and environmental change. Classical endocrinology has established the structural and functional roles of key glands including the pituitary, thyroid, interrenal tissue, pancreas, ultimobranchial gland, urophysis, and gonads, which operate through coordinated networks like the HPG and HPI axes.Recent technological advances, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, have transformed fish endocrinology by revealing new hormone isoforms, receptor subtypes, signaling pathways, and gene–environment interactions. Integration of multi-omics approaches provides insights into how environmental stressors—such as pollutants, temperature shifts, hypoxia, and salinity changes—affect endocrine function. Genome editing tools like CRISPR/Cas9 further allow targeted studies of hormone-related genes, enhancing growth, stress tolerance, reproductive control, and aquaculture efficiency.Monitoring endocrine biomarkers in wild populations also enables the detection of endocrine-disrupting chemicals and assessment of ecological health. Overall, fish endocrinology integrates physiology, molecular biology, and biotechnology, supporting sustainable aquaculture, conservation, and ecosystem management while addressing global environmental challenges.

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# Navigating the Bioinformatics Landscape: An Update on Currently Active Web Tools and Databases

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## Abstract

Large-scale biological data management, analysis, and interpretation present an urgent need for effective computational resources due to the explosive rise of high-throughput technologies in genomics, transcriptomics, proteomics, and cheminformatics. Many bioinformatics databases and web applications tackle the challenges of molecular and systems biology. Annotation tools like UniProt and Ensembl provide precise functional gene and protein details. Evolutionary and phylogenetic interfaces clarify the relationships and variations in species. Reactome and KEGG are databases that focus on networks and pathways, helping study molecular and cellular processes related to disease. Tools like ENCODE and GEO offer extensive databases on the epigenomics and transcriptomics of gene regulatory elements and expression. Metagenomic tools such as MG-RAST and QIIME support microbial ecology. Additionally, cheminformatics and drug discovery technology modules speed up lead suggestions, molecular docking, and drug action predictions using in-silico methods. Covering precision medicine, translational medicine, and basic biology, these systems create a unified network that combines approaches from various fields of life science research. This study highlights the diversity, usefulness, and recent developments in essential bioinformatics areas to support data-driven discoveries in the post-genomic era.

## Introduction

In modern biological and biomedical research, for bioinformatics is the computational support for the organization, evaluation, and interpretation of huge sets of data generated by high-throughput technology. The gradual

evolution of NGS, structural biology, and systems biology has contributed to researchers becoming more dependent on web-based bioinformatics tools and software programs for processing, visualization, and interpretation of the result data. In bringing the unprocessed data closer to biologically meaningful insights, these platforms enable faster drug discovery, proteomics, transcriptomics, metabolomics, and genome work [1-2].

In the past decade, thousands of bioinformatics web tools have been created to tackle problems spanning many areas of research, such as sequence alignment, functional annotation, pathway analysis, protein structure prediction, and molecular docking. Over time many of these tools tend to become inactive, either due to insufficient maintenance, lack of funding, or technological obsolescence. As a result, researchers find it difficult to identify timely resources suitable for their research work [3-4].

The purpose of this review is to furnish a comprehensive update on bioinformatics web tools that are actively maintained and extensively employed in several domains of life science research. Thus, by categorizing and summarizing these resources, we intend it to stand as an operational manual for researchers seeking dependable tools for their analyses in 2025 and beyond.

## Proteomics & Structural Biology

Wet-lab research is no longer necessary in modern bioinformatics, which studies biological sequences, structures, and interactions using in-silico databases or web applications. For example, NCBI BLAST is used to search for sequence similarity [5]. Genome annotation and visualization are made possible by programs such as the Ensembl Genome Browser [6] and the UCSC Genome Browser [7]. There are some curated, priceless protein-level repositories, like UniProtKB [8], and organizations like the Protein Data Bank or PDB [9]. SWISS-MODEL [10] and I-TASSER [11] can be used for prediction-like studies on protein shape determination. These tools are explained in the below.

### *I. Ncbi Blast*

The Basic Local Alignment Search Tool (BLAST) is used to identify regions of local similarity between sequences. The significance of the matches between protein or nucleotide sequences and sequence databases is gauged using this technique. In addition to suggesting functional and evolutionary relationships between sequences, BLAST can assist in identifying members of gene families.The Blast tool is available at the site

https://blast.ncbi.nlm.nih.gov/blast/Blast.cgi?CMD=Web&PAGE_TYPE=BlastHome. [12]

### *II. The University of California Santa Cruz (UCSC) Genome Browser*

The UCSC Genome Browser (genome.ucsc.edu) is a well-known online resource that may be used to rapidly show a desired section of a genome at any scale along with a number of aligned annotation "tracks." The annotations, which were produced by the UCSC Genome Bioinformatics Group and outside partners, show simple nucleotide polymorphisms, phenotype and variation data, expression and regulatory data, pairwise and multiple-species comparative genomics data, gene predictions, and mRNA and expressed sequence tag alignments. Biological analysis and interpretation are made easier by the presentation of all pertinent information about a location in a single window (https://genome.ucsc.edu/index.html) .Another Web-based tool, the UCSC Table Browser, allows you to see, download, and change the database tables that underlie the Genome Browser tracks. In both browsers, users can upload data as custom annotation tracks for use in teaching or research. This lesson explains how to download the underlying database tables, create and see custom annotation tracks, and perform genomic analysis using the genomic Browser and Table Browser [13].

### *III. Ensembl Genome Browser*

Ensembl is a browser for vertebrate genomes (https://asia.ensembl.org/index.html). It promotes studies in transcriptional regulation, evolution, sequence variation, and comparative genomics. Ensembl gathers disease information, predicts regulatory function, computes multiple alignments, and annotates genes. BLAST, BLAT, BioMart, and the Ensembl Variant Effect Predictor (VEP) for every supported species are among its resources [14].

### *IV. UniProtKB*

The UniProtKB is the main source for information about protein functions. It provides clear and detailed annotations. Each UniProtKB entry has key data like the amino acid sequence, protein name or description, taxonomic data, and citation information. We also include as much annotation information as possible.
The UniProt Knowledgebase has two sections. One section has manually

annotated records based on information from literature and reviewed computer analysis (UniProtKB/Swiss-Prot). The other section contains records that have been analyzed by computers and are waiting for full manual annotation (UniProtKB/TrEMBL)(https://www.uniprot.org/uniprotkb).\ [15]

### Protein Data Bank (PDB)

The Protein Data Bank (PDB; http://www.rcsb.org/pdb/) is the only global repository for biological macromolecule structural data. The global Protein Data Bank (PDB) library of 3D structure data for big biological molecules (proteins, DNA, and RNA) is housed at RCSB PDB (RCSB.org), the US data center. This data is crucial for basic biology, health, energy, and biotechnology research and teaching. The first open access digital data resource in biology and medicine was the Protein Data Bank (PDB) (Historical Timeline). It is currently a top worldwide source of experimental data essential to scientific advancement. Through a downloadable data archive and online information portal, PDB offers access to 3D structure data for the molecules of life that are present in all living things on Earth [16].

### *1. I-TASSER*

The I-TASSER server(https://zhanggroup.org/I-TASSER/about.html) is an online platform that predicts the structure and function of proteins using I-TASSER algorithms. From amino acid sequences, it allows researchers to automatically produce high-quality 3D structure models and biological function predictions. The I-TASSER server compares the projected 3D models to proteins in three different libraries in order to determine a protein's biological function. Proteins having known ligand-binding sites, gene ontology (GO) keywords, and enzyme classification (EC) numbers can be found in these libraries. The consensus of the best structural matches yields the final function projections [11].

### 2. SWISS-Model

The Swiss Model https://expasy.org/swissmodel was the first protein homology modeling server that was completely automated, and it has undergone constant improvement over the past 25 years [17-19]. With the amino acid sequences of the interaction partners as a starting point, its modeling capabilities have recently been expanded to enable the modeling of homo- and heteromeric complexes. Other recently announced innovations include the development of a new modelling engine, ProMod3,

with higher accuracy of the created models, and an improved local model quality estimation approach (QMEANDisCo) based on a novel version of QMEAN [20].

## Functional Annotation & Protein Domains

Understanding protein function, recognizing conserved motifs, and analyzing biological sequences rely on functional annotation and protein domain analysis. To predict functional domains and sort proteins into families, InterPro provides an integrated platform that combines several protein signature databases [21]. The study of signaling and regulatory proteins greatly benefits from using SMART (Simple Modular Architecture Research Tool). This tool focuses on identifying genetically mobile domains and modular designs in proteins [22]. STRING is a database that combines known and expected protein-protein interactions from computational, experimental, and literature sources, along with domain analysis. It helps researchers examine functional relationships [23]. Researchers can also use DAVID (Database for Annotation, Visualization and Integrated Discovery) to extract biological insights from large gene or protein databases [24]. This tool supports enrichment analysis.

## InterPro

Functional analysis of proteins is made possible by InterPro (https://www.ebi.ac.uk/interpro/), which classifies proteins into families and predicts their domains and important locations. It provides this by using signatures, which are predictive models contributed by several InterPro consortium member databases. InterPro uses the advantages of each member database to provide a comprehensive resource and reliable diagnostic tool by combining these signatures into a single, searchable platform**[21].**. To identify conserved protein domains, Pfam's well-managed protein family models are also commonly used. These models are based on hidden Markov models and multiple sequence alignments.Pfam data and new releases are available through InterPro[25].

## SMART

Domain architecture analysis and the identification and annotation of genetically movable domains are possible through SMART, a Simple Modular Architecture Research Tool (http://SMART.embl-heidelberg.de). About 400 domain families can be identified in chromatin-associated, extracellular, and signaling proteins. These domains are well annotated with phyletic distributions, functional classes, tertiary structures, and

functionally important residues. A relational database system stores search parameters, taxonomy data, and every domain identified in a non-redundant protein database. The user interfaces of this database allow users to search for proteins in specific taxa that contain certain domain combinations [26].

### STRING

Protein-protein interactions, including both functional associations and physical interactions, are gathered and compiled by the STRING database (https://string-db.org/). The information is derived from a number of sources, including databases of interaction studies, automatic text mining of scientific literature, predictions based on co-expression and conserved genomic context, and curated sources of known complexes and pathways. Each of these contacts is carefully assessed and graded. Then, utilizing hierarchical orthology knowledge, they are automatically applied to creatures that have received less attention [27].

### DAVID (Database for Annotation, Visualization and Integrated Discovery)

A web server (https://davidbioinformatics.nih.gov/ ) for functional annotation and enrichment analysis of gene lists are part of the well-known bioinformatics resource system DAVID. It includes a collection of tools for functional analysis as well as an extensive knowledge base. The taxonomy coverage grew from 17 399 to 55 464 after the DAVID Gene system was redesigned to include new organisms. Based on the new DAVID Gene system, all current annotation types have been updated, if they are available. In the revised Knowledgebase, there are much more gene-term data for the majority of annotation categories than in the previous edition.Moreover, new annotations have been added to the Knowledgebase. These consist of pathways from WikiPathways and PathBank, disease information from DisGeNET, tissue expression data from the Human Protein Atlas, and small molecule-gene interactions from PubChem and DrugBank. Specific types were assigned to eight of the ten subgroups that separated from the Uniprot Keyword annotation. These modifications have greatly increased the Knowledgebase's size and enhanced DAVID's capacity for discovery [28].

## Evolutionary & Phylogenetic Analysis

Evolutionary and phylogenetic analytical techniques are crucial in studies of comparative genomics and molecular evolution. They help us understand how species relate to one another and how they have diverged over

time. MEGA (Molecular Evolutionary Genetics Analysis) is a popular tool for constructing phylogenetic trees, determining divergence times, and assessing evolutionary theories [29].For the purpose of studying orthologous genes across species, OrthoDB provides an extensive catalog of orthologous groups from a diverse range of genomes. This supports both functional and evolutionary analysis [30].

## MEGA (Molecular Evolutionary Genetics Analysis)

Molecular Evolutionary Genetics Analysis (MEGA) is a popular method for phylogenetic and molecular evolution research (Kumar 2022). It offers various computational tools, such as Bayesian techniques, traditional least squares, distance-based methods, maximum likelihood (ML), and maximum parsimony (MP). Some of MEGA's standout features include reconstructing ancestral sequences, evaluating phylogenies with the bootstrap technique, selecting appropriate models for nucleotide and amino acid replacement, determining evolutionary relationships, and calculating sequence divergences and timeframes. In order to find delicate clades and related sequences in evolutionary trees derived from phylogenomicinvestigations, new version MEGA12 incorporates an evolutionary sparse learning technique. This version also features an improved Tree Explorer, support for high-resolution monitors, and fine-grained parallelization for machine learning analysis. The download link for MEGA12 is https://www.megasoftware.net. (31).

## Ortho DB

OrthoDB (https://www.orthodb.org) expands our understanding of gene function in newly sequenced genomes. It provides evolutionary and functional details of orthologous genes across a wide range of viruses, prokaryotes, and eukaryotes. We define gene orthology hierarchies and annotate orthologous groups (OGs) with their evolutionary and functional traits. We also collect gene annotations. OrthoDB aims to include the most diverse and well-studied organisms with high-quality genomic data, making it the top database on species diversity. This update adds 5,827 eukaryotic genomes. We have also included coordinates for gene loci and coding DNA sequences (CDSs). OrthoDB is accessible through REST API, SPARQL/RDF, and, more recently, API packages for R Bioconductor and Python (32).

## Pathways & Systems Biology

A framework for combining omics data and understanding complex biological networks at the systems level is provided by pathways and systems biology tools. One of the most popular resources is KEGG (Kyoto Encyclopedia of Genes and Genomes). It offers carefully curated pathway

maps that connect functional, chemical, and genomic data to support the study of metabolic and signaling networks [33]. Comparative analyses between species and pathway enrichment studies are also possible with Reactome, an open-source, expert-curated knowledge base of human biological pathways [34]. Cytoscape features a vast ecosystem of network biology and data integration plugins. It provides a flexible framework for modeling and visualizing biomolecular interaction networks for integrative investigations [35]. To support pathway over-representation and enrichment analyses, **Gene Ontology (GO)** resources remain indispensable, providing a structured vocabulary for gene functions across species [36]. Collectively, these tools form the backbone of in-silico systems biology, enabling researchers to move from gene lists to mechanistic insights of biological processes and networks.

## KEGG

The KEGG (Kyoto Encyclopedia of Genes and Genomes; https://www.kegg.jp/) is a large, manually curated resource that brings together data from 18 connected databases. These databases focus on systems biology, genomics, chemistry, and health. KEGG helps interpret genome sequences and other molecular datasets by reconstructing molecular networks from basic building blocks. It uses the concept of functional orthologs and provides mapping tools for this purpose. With the addition of the KEGG NETWORK database, the resource now links various diseases to network variations. These variations are disruptions in molecular pathways caused by infections, viruses, environmental factors, or changes in human genetics. For example, network variation maps illustrate how different viruses can either stimulate or inhibit specific signaling pathways. They do this by showing aligned images of connected networks and their effects on biological systems. Moreover, KEGG route maps are being integrated with network variation maps from the NETWORK database and modular functional units (including both KEGG and response modules) from the MODULE database. We now have a better grasp of how viruses interact with their hosts and can forecast how viruses will affect cellular systems thanks to recent additions to viral ortholog groups. Continuous improvement is being made to the KO (KEGG Orthology) database, which finds functional orthologs [33].

## Reactome Knowledgebase

Molecular knowledge related to signal transduction, transport, DNA replication, metabolism, and other cellular functions can be found in the Reactome Knowledgebase (https://reactome.org). An expanded form of a conventional metabolic map, it displays an ordered network of molecular

changes within a single, consistent data model. Reactome is a tool for identifying functional relationships in data, such as gene expression profiles or lists of somatic mutations from tumor cells, and it also acts as an archive of biological processes [37].

## Cytoscape

Cytoscape is an open-source software (https://cytoscape.org/) platform for visualizing molecular interaction networks and biological pathways. It also integrates these networks with annotations, gene expression profiles, and other relevant data. While Cytoscape was initially created for biological research, it has now become a general platform for analyzing and visualizing complex networks. The core distribution of Cytoscape offers a basic set of features for data integration, analysis, and visualization[36].

## Gene Ontology (GO)

An integrated, standardized way to convey biological knowledge is the Gene Ontology (GO) (https://geneontology.org/). Concepts (also called terms or formally classes) that are linked to one another through formally defined relations are described by GO. In order to facilitate the annotation of gene products throughout the entire tree of life, the GO is made to be species-agnostic. Consistent gene annotation, function comparison across organisms, and knowledge integration across various biological databases are made possible by the GO's computational framework [38].

## Epigenomics& Regulation

Epigenomics and regulatory databases offer valuable tools for examining chromatin states, DNA methylation, histone modifications, and transcription factor (TF) binding. They help us understand gene regulation. The ENCODE (Encyclopedia of DNA Elements) Portal is one of the largest resources available. It provides detailed maps of functional elements in the human and mouse genomes, including enhancers, promoters, and TF binding sites [39]. The Roadmap Epigenomics Project supports this work by creating large-scale reference epigenomes from different human tissues and cell types. This project reveals insights into specific chromatin patterns for various cell types and their regulatory landscapes [40]. To study transcription factor regulation, JASPAR offers an open-access repository of curated TF binding profiles from various species. This supports motif enrichment and predictions of TF binding sites [41]. Together, these resources create a strong in-silico toolkit for integrative epigenomic analysis and regulatory genomics.

- ***The ENCODE (Encyclopedia of DNA Elements)***

The human and mouse genomes contain instructions that specify RNAs and proteins and control when, how much, and where they are produced. To clarify these elements, phase III of the Encyclopedia of DNA Elements (ENCODE) Project has broadened the analysis of RNA transcription, chromatin structure and modification, DNA methylation, chromatin looping, and the binding of transcription factors and RNA-binding proteins in different cells and tissues. Here, we summarize these efforts, which resulted in 5,992 new experimental datasets, including detailed observations from mouse fetal development. All data are accessible through the ENCODE data portal (https://www.encodeproject.org), which includes phase II ENCODE1 and Roadmap Epigenomics2 data. We have created a registry of 926,535 human and 339,815 mouse candidate cis-regulatory elements, representing 7.9 and 3.4% of their respective genomes. This was achieved by integrating selected data types related to gene regulation. We also built a web-based server (SCREEN; http://screen.encodeproject.org) to give users flexible access to this resource. Together, the ENCODE data and registry offer a valuable resource for the scientific community to improve their understanding of the organization and function of the human and mouse genomes [39].

- ***The Roadmap Epigenomics Project***

The Roadmap Epigenomics project (https://maayanlab.cloud/Harmonizome/resource/Roadmap+Epigenomics) is a genome mapping initiative that measures the genomic distribution of nucleoproteins like histones, DNA binding factors, and accessory proteins. It also examines the genomic patterns of reversible chemical changes on DNA and nucleoproteins. The goal of the Roadmap Epigenomics project is to create reference epigenomic maps for stem cells, differentiated cells, and primary tissues. The project maps DNA methylation sites, histone modification sites, transcription factor binding sites, and chromatin accessibility sites. Additionally, it measures RNA transcripts using RNA-seq [40].

- ***JASPAR***

The JASPAR CORE database(https://jaspar.elixir.no/ ) includes a carefully selected, non-redundant group of profiles. These profiles come from published collections of experimentally defined transcription factor binding sites for eukaryotes. The main differences from similar resources, like TRANSFAC, are the open data access, lack of redundancy, and high quality [41].

## Metagenomics & Microbiome

Metagenomics and microbiome analysis platforms are essential for studying microbial communities, their diversity, and their potential functions. MG-RAST (Metagenomics Rapid Annotations using Subsystems Technology) is one of the most established web resources. It offers automated quality control, annotation, and comparison of metagenomic sequences against several reference databases [42]. For community profiling, QIIME2 provides a flexible framework for analyzing microbiome data.It covers raw sequencing, taxonomic classification, diversity estimation, and statistical visualization. It also provides strong support for plugins and web-accessible workflows [43]. For strain-level taxonomic and functional description, MetaPhlAn (Metagenomic Phylogenetic Analysis) delivers high-resolution profiling of microbial communities using unique clade-specific marker genes from metagenomic shotgun data [44]. Together, these tools create a strong in-silico toolkit for uncovering microbial diversity and ecological interactions in complex environments.

### *a. MG-RAST*

The open-source metagenomics RAST service offers a new way to annotate and analyze metagenomes. It supports multiple data sources and has a back end that accommodates abstract data types. The metagenomics RAST is stable, flexible, and freely available to all researchers. This service has eliminated one of the main challenges in metagenome sequence analysis, which is the need for high-performance computing to annotate the data (http://metagenomics.nmpdr.org) [42]

### b. QIIME 2

QIIME 2 is an open-source platform for microbiome bioinformatics. It lets users analyze microbiome data in a reproducible, scalable, and interactive way. The latest version features a plugin-based structure with many tools for processing sequences, classifying taxonomy, analyzing diversity, and visualizing data. This system tracks data lineage and automatically records each step of the analysis. QIIME 2 provides interactive visualization tools and supports both command-line and graphical interfaces, which makes it user-friendly for researchers with different skill levels. Its flexible framework allows for easy addition of new methods from the microbiome research community. Overall, QIIME 2 acts as a complete ecosystem for microbiome data science. It enables workflows that cover everything from raw sequence data to statistical and biological interpretations [43].

### c. MetaPhlAn 4.0

MetaPhlAn is a tool (https://huttenhower.sph.harvard.edu/metaphlan/ )) that profiles the makeup of microbial communities, including Bacteria, Archaea, and Eukaryotes, using data from metagenomic shotgun sequencing instead of 16S, at the species level. With Strain PhlAn, users can perform strain-level microbial profiling. MetaPhlAn 4 uses about 5.1 million unique clade-specific marker genes found in around 1 million microbial genomes, including 236,600 references and 771,500 metagenomic assembled genomes. This data covers 26,970 species-level genome bins, with 4,992 of them not identified at the species level [44].

## Drug Discovery & Molecular Docking

In-silico drug discovery platforms are important for speeding up lead identification, molecular docking, virtual screening, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) predictions. AutoDockVina is one of the most popular open-source docking programs. It provides better speed and accuracy for studying ligand-receptor interactions [45]. For ligand screening, **PubChem** serves as the world's largest open chemical database, hosting over 100 million compounds with integrated bioassay, drug, and safety data, making it a vital resource for cheminformatics and drug repurposing [46]. For ADME profiling, SwissADME offers free online predictions of physicochemical properties, lipophilicity, solubility, drug-likeness, and pharmacokinetics. It has become an important tool for early-stage drug design [47]. Additionally, PASS (Prediction of Activity Spectra for Substances) predicts biological activity profiles based on chemical structure, assisting in drug repurposing and lead optimization [48]. Together, these tools form an integrated framework that speeds up the drug discovery process from molecular docking to safety evaluation.

## AutodockVina

One of the simplest and most widely used open-source molecular docking programs is AutoDockVina. However, in contrast to other AutoDock Suite programs, it does not support modeling certain features like explicit water molecules or macrocycles. Here, we describe the addition of this feature to AutoDockVina 1.2.0. Additionally, AutoDockVina 1.2.0 has a batch mode for docking numerous ligands at once, supports the AutoDock4.2 scoring function, and permits multiple ligands to be docked simultaneously[49].

## I. *PubChem*

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A widely used source of chemical information for the general public and scientific community, PubChem (https://pubchem.ncbi.nlm.nih.gov) draws millions of unique users every month. PubChem has significantly improved in the past two years. PubChem now has data from more than 100 new sources. These include links to Thieme Chemistry's chemical literature, SpringerMaterials' chemical and physical property links, and the World Intellectual Property Organization's (WIPO) patent links. Updates were made to PubChem's homepage and individual record pages to make it easier for users to locate the information they require [46]

## II. SWISS ADME

To be effective, a strong molecule must reach its target in the body at a sufficient concentration and remain there in a biologically active form long enough for the expected biological events to take place. Drug development involves evaluating absorption, distribution, metabolism, and excretion (ADME) earlier in the discovery process. At this point, many compounds are considered, but access to physical samples is limited. In this context, computer models offer valid alternatives to experiments. The new SwissADME web tool provides free access to a range of fast and reliable predictive models for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness. It includes advanced methods like the BOILED-Egg, iLOGP, and Bioavailability Radar. The user-friendly interface ensures easy input and interpretation through the login-free website http://www.swissadme.ch. Specialists and those without expertise in cheminformatics or computational chemistry can quickly predict key parameters for a collection of molecules to aid their drug discovery efforts[47].

## *III. PASS Prediction*

The idea of the biological activity spectrum was created to explain the characteristics of biologically active substances. The PASS software predicts over 300 pharmacological effects and biochemical mechanisms based on the structural formula of a substance. It can effectively help discover new targets for certain ligands and reveal new ligands for some biological targets. We have created a web interface for the PASS software (https://www.way2drug.com/index.php) [48].

### IV. Pymol

PyMOL is a cross-platform molecular graphics program that has been widely used to visualize proteins, nucleic acids, small molecules, electron densities, surfaces, and trajectories in three dimensions (3D).In addition, it has the ability to create videos, alter molecules, and trace rays [50].The latest Version 3.1.6.1 - Updated June 9th 2025 (https://www.pymol.org/ ).

## Future Prospects

Future perspectives in bioinformatics highlight the rapid development of web tools and databases for better interoperability, sustainability, and computational integration. The constant rise of new and updated resources, noted in the Nucleic Acids Research annual Web Server and Database Issues [51-52], emphasizes the need for timely evaluations and organized reviews.There is an increasing focus on FAIR (Findable, Accessible, Interoperable, and Reusable) principles. These principles aim to guarantee the lasting value and consistency of bioinformatics resources [53]. At the same time, global initiatives such as the Global Alliance for Genomics and Health (GA4GH) promote standards for data sharing and workflow portability [54]. Moreover, the use of artificial intelligence and machine learning in bioinformatics platforms improves tool performance and predictive abilities. However, these technologies also create challenges for benchmarking and validation [55]. Future reviews should not only list active resources, but they should also evaluate sustainability models, community-driven curation, and the use of new technologies. This will help researchers navigate the growing digital ecosystem.

## Conclusion

Databases and web tools for bioinformatics are crucial for today's biological research. They offer solid options for integrating, analyzing, and storing data. Future developments will emphasize FAIR principles, AI integration, and community-driven curation, but challenges such as sustainability, redundancy, and standardization still exist. With these efforts, bioinformatics resources will remain reliable, accessible, and useful for advancing life sciences research.

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## Ethics Statement

Not applicable

## Conflict of Interest

The authors did not have any conflict of interest to disclose.

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# Enzyme: The black horse driving the future of Clinical research

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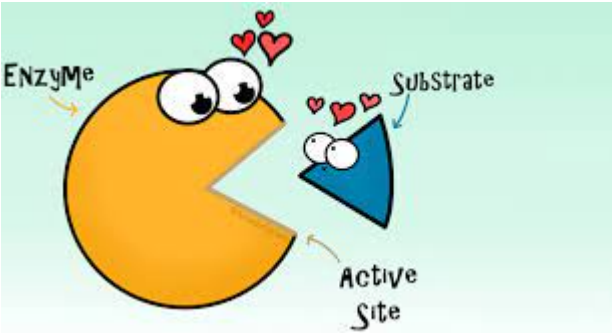
## Introduction

Life is possible due to the coordination of numerous metabolic reactions inside the cells. Virtually all reactions in the body are mediated by enzymes. Enzymes are biological catalyst which are mostly proteins in nature, used to enhance a reaction without changing the equilibrium. They are essential for carrying out various life processes such as digestion, respiration, and metabolism. Each enzyme acts on a specific substance called a substrate and works best under certain conditions of temperature and pH. The cleft or crevice present on the enzyme to which the substrate binds is called the ACTIVE SITE. Without enzymes, most biochemical reactions in our body would be too slow to sustain life.




### Characteristics of Enzymes

i. Almost all enzymes are proteins. Enzymes follow the physical and chemical reactions of proteins.
ii. They are heat labile.
iii. They are water-soluble.
iv. They can be precipitated by protein precipitating reagents (ammonium sulfate or trichloroacetic acid).
v. They contain 16% weight as nitrogen.

vi. They are required in small quantities.
vii. They are not used up completely in a reaction.

All this is well explained by a wonderful story:

Once upon a time there was a rich merchant. In his last will and testament, he put aside his 17 white horses to his 3 sons to be shared thus; 1/2 for the1st son, 1/3 for the 2nd son and 1/9 for the 3rd son. After his death, the sons started to quarrel, as the division could not produce whole number. Then their brother-in-law told them that they should include his black Horse also for the sharing purpose. Thusnow they had 17 + 1 = 18 horses, and so division was possible; 1st son got one-half or 9 horses; 2nd son got 6 and 3rd son 2 horses. Now all the 17 white horses were correctly divided among the sons. The remaining black horse was taken back by the brother-in-law. Catalysts are similar to this BLACK HORSE.

## Historical background

Berzelius in 1835 showed hydrolysis of starch by malt extract and put forward the theory of enzyme catalysis.

In 1878, Willy Kuhne coinedthe word enzyme, which in Greek means "in yeast".

Eduard Buchner (Nobel Prize 1907) showed that cell-free extract of yeast could catalyzethe fermentation of sucrose to ethanol. He named this active principle as Zymase.

Sir Arthur Harden in 1897 (Nobel Prize 1929) showed that Zymase is a complex mixture of enzymes, each catalyzing a separate step in the degradation of sucrose.

The rate of chemical reactions, chemical equilibrium and catalysis were studied by Ostwald (Nobel Prize 1909).

In 1926, James Sumner (Nobel Prize 1946) was the first to crystallize the enzyme urease.

In 1930, John Northrop (Nobel prize, 1946) crystallized a number of proteolytic enzymes from gastrointestinal tract and proved that they are all proteins.

Eduard Buchner NP 1907 1860–1917 | Arthur Harden NP 1929 1865–1940 | James Sumner NP 1946 1887–1955 | John Northrop NP 1946 1891–1987 | Wilhelm Ostwald NP 1909 1853–1932

## Nomenclature and classification of enzymes

When early workers isolated certain enzymes, whimsical names were given. Some of these, such as Pepsin, Trypsin, Chymotrypsin, etc. are still used. Later, it was agreed to callthe enzymes by adding the suffix "-ase" to the substrate. Thus, enzyme Lactase acts on the substrate lactose, and the products glucose and galactose are formed. Enzymes that hydrolyse starch (amylose) are termed as amylases; those that dehydrogenate the substrates are called dehydrogenases. These are known as the TRIVIAL NAMES of the enzymes.

## IUBMB System of Classification

The International Union of Biochemistry (IUB) appointed an Enzyme Commission in 1961. This committee made a thorough study of the existing enzymes and devised some basic principles for the classification and nomenclature of enzymes. Since 1964, the IUB system of enzyme classification has been in force. Enzymes are divided into six major classes (in that order). Each class on its own represents the general type of reaction brought about by the enzymes of that class International Union of Biochemistry and Molecular Biology (IUBMB) in 1964, (modified in 1972 and 1978), suggested the IUBMB system of nomenclature of enzymes. It is complex and cumbersome; but unambiguous. As per this system, the name starts with EC (enzyme class) followed by 4 digits.

First digit represents the class

Second digit stands for the subclass

Third digit is the sub-sub class or subgroup

Fourth digit gives the number of the particular enzyme in the list.

The enzymes are grouped into following six major classes.

### Class 1: Oxidoreductases

This group of enzymes will catalyze oxidation of one substrate with simultaneous reduction of another substrate or co-enzyme. This may be represented as

$AH_2 + B \; A + {}_{BH2}$

for example,

Alcohol + NADAldehyde + NADH + H+

The enzyme is Alcohol dehydrogenase; IUB name is

Alcohol-NAD-oxidoreductase; Code number is EC.1.1.1.1.

Oxidoreductases may also oxidize substrates by adding oxygen, e.g. oxidases, oxygenases and dehydrogenases

### Class 2: Transferases

This class of enzymes transfers one group (other than hydrogen) from the substrate to another substrate. This may be represented as

A-R + B → A + B-R, For example,

Hexose + ATP → Hexose-6-phosphate + ADP

The name of enzyme is Hexokinase and systematic name is ATP-Hexose–6-phosphate-transferase.

### Class 3: Hydrolases

This class of enzymes can hydrolyze ester, ether, peptide or glycosidic bonds by adding water and then breaking the bond.

Acetylcholine + H2O → Choline + acetate

The enzyme is Acetylcholine esterase or Acetylcholine hydrolase (systematic). All digestive enzymes are hydrolases.

### Class 4: Lyases

These enzymes can remove groups from substrates or break bonds by mechanisms other than hydrolysis. For example,

Fructose-1,6-bisphosphate → Glyceraldehyde-3-phosphate+dihydroxy acetone phosphate

The enzyme is Aldolase.

### Class 5: Isomerases

These enzymes can produce optical, geometric or positional isomers of substrates.Racemases, epimerases, cis-trans isomerases are examples.

Glyceraldehyde-3-phosphate → Dihydroxy acetonephosphate

Enzyme is Triose phosphate isomerase.

### Class 6: Ligases

These enzymes link two substrates together, usually withthe simultaneous hydrolysis of ATP, (Latin, Ligare = tobind). For example,

Acetyl CoA + CO2 + ATP → Malonyl CoA + ADP +Pi

Enzyme is Acetyl CoA carboxylase.

### Chemical nature and properties of enzymes

All the enzymes are invariably proteins. In recent years, however, a few RNA molecules have been shown to function as enzymes(RIBOZYMES). Each enzyme has its own tertiary structure and specific conformation which is very essential for its catalytic activity. The functional unit of the enzyme is known as HOLOENZYME which is often made up of APOENZYME (the protein part) and a COENZYME (non-protein organic part).

HOLOENZYME → APOENZYME + COENZYME

(active enzyme) (protein part) (non-protein part)

The term prosthetic group is used when the non-protein moiety tightly (covalently) binds with the apoenzyme. The coenzyme can be separated by dialysis from the enzyme while the prosthetic group cannot be.

The word MONOMERIC ENZYME is used if it is made up of a single polypeptide e.g. ribo-nuclease, trypsin. Some of the enzymes which possess more than one polypeptide (subunit)chain are known as OLIGOMERIC ENZYMES eg.lactate dehydrogenase, aspartate trans-carbamoylase etc. There are certain MULTIENZYME COMPLEXES possessing specific sites to catalyse different reactions in a sequence. Only the native intact multienzyme complex is functionally active and not the individual units, if they are separated.e.g. pyruvate dehydrogenase, fatty acid synthase, prostaglandin synthase etc. The enzymes exhibit all the general properties of proteins.

## Co-enzymes

i. Enzymes may be simple proteins, or complex enzymes, containing a non-protein part, called the prosthetic group. The prosthetic group is called the co-enzyme. It is heat stable. Salient features of co-enzymes are

1. The protein part of the enzyme gives the necessary three-dimensional infrastructure for chemical reaction; but the group is transferred from or accepted by the co-enzyme

2. The co-enzyme is essential for the biological activity of the enzyme

3. Co-enzyme is a low molecular weight organic substance. It is heat stable

4. Generally, the co-enzymes combine loosely with the enzyme molecules. The enzyme and co-enzyme can be separated easily by dialysis

5. Inside the body, when the reaction is completed, the co-enzyme is released from the apo-enzyme, and can bind toanother enzyme molecule.

6. One molecule of the co-enzyme is able to convert a largenumber of substrate molecules with the help of enzyme.

7. Most of the co-enzymes are derivatives of vitamin B complexsubstances.

Co-enzymes may be divided into two groups

a. Those taking part in reactions catalyzed by oxidoreductases by donating or accepting hydrogen atoms or electrons.

b. Those co-enzymes taking part in reactions transferring groups other than hydrogen.

# Coenzymes

Coenzymes of B- complex vitamins

| Coenzyme | Vitamin from which it is derived | Atom or group transferred | Dependent enzyme (one example) |
|---|---|---|---|
| Thiamine pyrophosphate (TPP) | Thiamine ($B_1$) | Aldehyde or keto | Transketolase |
| Flavin mononucleotide (FMN) | Riboflavin ($B_2$) | Hydrogen and electron | L-aminoacid oxidase |
| Flavin adenine dinucleotide (FAD) | Riboflavin ($B_2$) | Hydrogen and electron | D-aminoacid oxidase |
| Nicotinamide adenine dinucleotide ($NAD^+$) | Niacin | Hydrogen and electron | Lactate dehydrogenase (LDH) |
| Nicotinamide adenine dinucleotide phosphate ($NADP^+$) | Niacin | Hydrogen and electron | Glucose-6-phosphate dehydrogenase |
| Lipoic acid | Lipoic acid | Hydrogen and electron | Pyruvate dehydrogenase complex (PDH complex) |
| Biocytin | Biotin | $CO_2$ | Pyruvate carboxylase |
| Pyridoxal phosphate (PLP) | Pyridoxine ($B_6$) | Amino | Alanine transaminase (ALT) |
| Coenzyme A (CoA) | Pantothenic acid | Acyl | Pyruvate dehydrogenase complex |
| Tetrahydrofolate ($FH_4$) | Folic acid | One carbon unit | Formyl transferase |
| Methylcobalamine | Cobalamine ($B_{12}$) | Methyl | Homocysteine methyl transferase |
| Deoxyadenosyl cobalamine | Cobalamine ($B_{12}$) | Isomerisation | Methylmalonyl CoA mutase |

## Coenzymes which are not related to vitamins

| Coenzyme | Biochemical role |
|---|---|
| Adenosine triphosphate (ATP) | Donor of phosphate, adenosine and adenosine monophosphate (AMP) moieties |
| Cytidine diphosphate (CDP) | Serves as a carrier of choline and ethanolamine in phospholipid synthesis |
| Uridine diphosphate (UDP) | Serves as a carrier of glucose in glycogen synthesis |
| S-Adenosylmethionine (SAM) | Donor of methyl groups (transmethylation reactions) |
| Phosphoadenosine phosphosulphate (PAPS) | Donor of sulphate groups (e.g., in the synthesis of mucopolysaccharides) |

## Genetic engineering and modified enzymes

Recent advances in biotechnology have made it possible to modify the enzymes with desirable characters-improved catalytic abilities, activities under unusual conditions. This approach is required since enzymes possess enormous potential for their use in medicine and industry.

**Hybrid Enzymes:** It is possible to rearrange genes and produce fusion proteins. e.g. a hybrid enzyme (of glucanase and cellulase) that can more efficiently hydrolyse barley E-glucans inbeer manufacture.

**Site-Directed Mutagenesis:** This is a technique used to produce a specified mutation at a predetermined position in a DNA molecule.The result is incorporation of a desired amino acid (of one's choice) in place of the specified amino acid in the enzyme. By this approach, it is possible to produce an enzyme with desirable characteristics. e.g. tissue plasminogen activator (used to lyse blood clots in myocardial infarction) with increased half-life. This is achieved by replacing asparagine (at position 120) by glutamine.

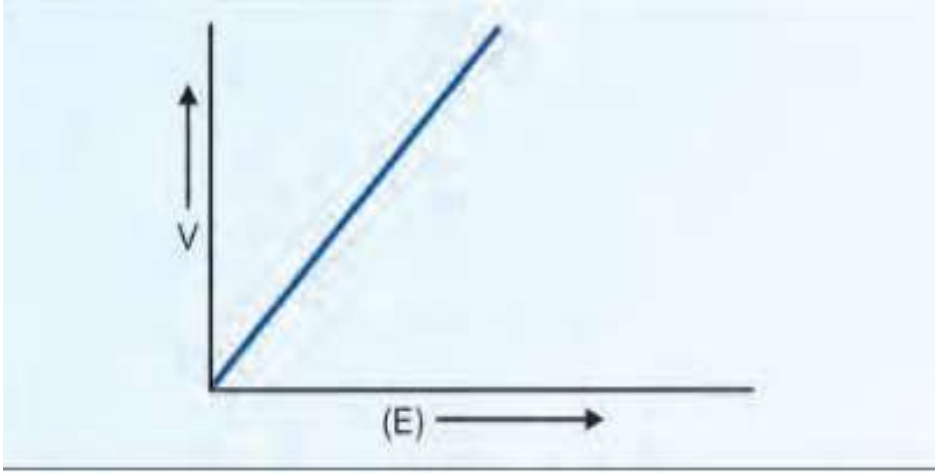
In recent years, it has also become possible to produce hybrid enzymes by rearrangement of genes. Another innovative approach is the production of Abzymes or catalytic antibodies, the antibody enzymes.

## Factors affecting enzyme activity

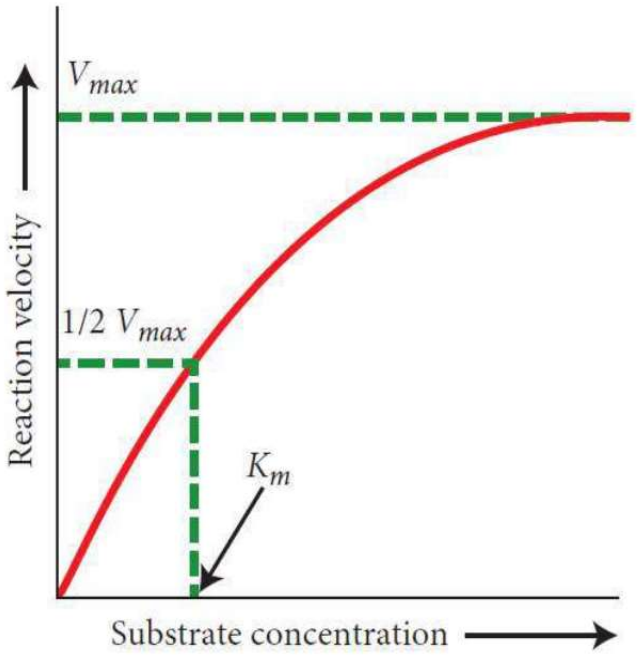
The various factors that influence enzyme activity are

1. Concentration of enzyme
2. Concentration of substrate
3. Concentration of product
4. Temperature
5. pH

**Effect of Concentration of Enzyme on Enzyme Velocity**

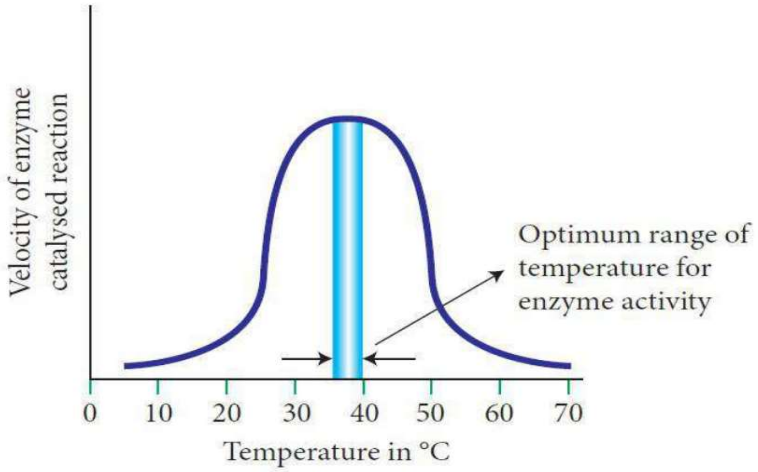



**Effect of Concentration of Substrate on Enzyme Velocity**

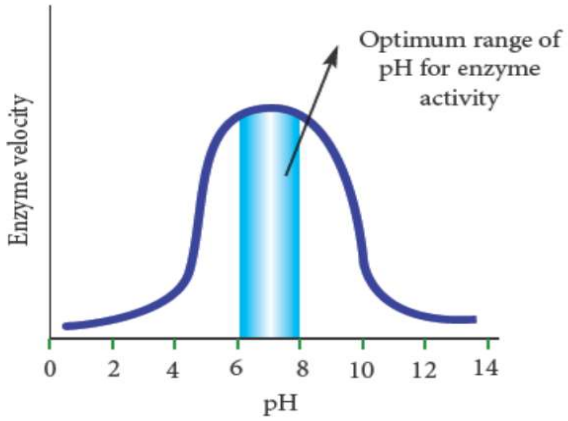


The rate of an enzyme catalysed reaction increasesas the substrate concentration increases until it reaches a maximal rate, which remains constant despite further increases in substrate concentration. The substrate concentration (expressed in moles/ L)required to produce half- maximum velocity (1/ 2Vmax) is known as Km or Michaelis–Menten constant.

## Effect of Temperature on Enzyme Velocity



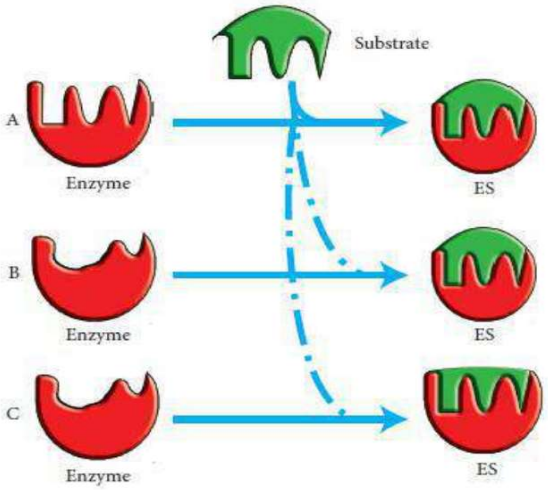

## Effect of pH on Enzyme Velocity



## Mechanism of enzyme action

1. Lock and key model
2. Induced fit theory
3. Substrate strain theory

## Different models explaining enzyme–substrate (ES) complex




(A) Lock and key model
(B) Induced fit theory
(C) (C) Substrate strain theory

## Clinical Enzymology

Plasma contains many functional enzymes, which are actively secreted into plasma. For example, enzymes of blood coagulation. On the other hand, there are a few non-functional enzymes in plasma, which are coming out from cells of various tissues due to normal wear and tear. Their normal levels in blood are very low; but are drastically increased during cell death (necrosis) or disease .Therefore, assays of these enzymes are very useful in diagnosis of diseases. Sources of Plasma Enzymes: They can be:

- Plasma derived, and
- Cell derived.

(a) Plasma derived enzymes: These act on substrates in plasma, and their activity is higher in plasma than in cells, e.g. coagulation enzymes. This group will not be further considered.

(b) Cell-derived enzymes: These have a high activity in cells and overflow into the plasma. They are further subdivided into:

• Secretory: These are mainly derived from digestive glands and function in the extracellular space

• Metabolic: These are concerned with intermediary metabolism and function in the cells and those enzymes found in the plasma are mainly derived from the soluble and microsomal fractions of the cells.

The cell-derived enzymes enter the plasma in small amounts as a result of:

• Continuous normal ageing of the cells, or

• Owing to diffusion through undamaged cell membranes.

They leave the plasma through:

• Inactivation.

• Catabolism in general protein pool.

• Rarely excretion in bile and urine.

Possible Mechanisms Responsible for Abnormal Levels: Serum level of a particular enzyme may be increased by diseases that provoke: (a) an increase in its rate of release, or (b) a decrease in rate of disposition or excretion.

### 1. Increase Serum Level

### (a) Increased Release

• Necrosis of cells: Due to damage to cells of the tissue. The resultant pattern will depend on:

– Normal enzyme content of the tissue/organ.

– On the extent and type of necrosis.

• Increased permeability of cell membrane without necrosis of cells: Increased permeability without gross cellular damage/necrosis can increase the enzyme level, e.g.

• In early stage of viral hepatitis, before jaundice appears. There is “ballooning” degeneration of liver cells, leading to elevated levels of transaminases (S-GPT).

• Progressive muscular dystrophy-elevated levelsof Aldolase, GOT and CPK.

• Increased production of the enzyme within cell:

Such a situation may be seen in treatment of whichpatients with protein anabolic drugs, results inincreased synthesis of liver cell transaminases andserum transaminases will increase by overflow.

• An increase in tissue source of enzymes due toeither:

• Increased rate of production in cells as mentioned above, or

• Increase in the number of cells/and cell mass,as seen in malignancies, e.g. alkaline phosphataseincrease in patients with osteoblastic bonelesions, or acid phosphatase increase in patientswith carcinoma prostate.

**(b) Impaired Disposition/excretion**

• Increased levels of serum LAP and ALP seen inpatients with obstructive jaundice

• Certain increased enzyme levels in cases of renalfailure.

**2. Decreased Serum Levels**

(a) Decreased formation of the enzyme which may be:

**1. Genetic**

• Hypophosphatasia, with decreased ALP levelin serum,

• Wilson's disease with decrease in serumceruloplasmin.

**2. Acquired**

• In hepatitis: Decreased serum level of pseudo-cholinesterase due to decreased production.

• Decreased serum amylase in patients withchronic hepatic, or pancreatic diseases, or those who are severely malnourished.

(b) Enzyme inhibition: Decreased serum pseudo-cholinesterase in insecticide poisoning.

(c) Lack of cofactors: Decreased serum GOT level inpregnancy and cirrhosis.

## Enzyme patterns (enzyme profiles) in diseases

I. **Hepatic diseases**
   1. *Alanine amino transferase (ALT)*
      Marked increase in parenchymal liver diseases
   2. *Aspartate amino transferase (AST)*
      Increase in muscle disease; not specific
   3. *Alkaline phosphatase (ALP)*
      Marked increase in obstructive liver disease
   4. *Gamma glutamyl transferase (GGT)*
      Increase in obstructive and alcoholic liver
   5. *Nucleotide phosphatase (NTP)*
      Elevated in liver dysfunction with cholestasis

II. **Myocardial infarction**
   1. *Creatine kinase (CK-MB)*
      Starts to rise within 3–6 hours
   2. *Cardiac troponins (cTnT and cTnI)*
      Starts to rise within 4–6 hour
   3. *High sensitive TnT (hsTnT)*
      Starts to rise within 3 hours
   4. *BNP and NTproBNP*
      Indicate heart failure
   5. *AST and LDH*
      Have only historical importance

III. **Muscle diseases**
   1. *Creatine kinase (CK-MM)*
      Marked increase in muscle diseases
      CK-MM fraction is elevated
   2. *Aldolase (ALD)*
      Earliest enzyme to rise, but not specific

IV. **Bone diseases**
   1. *Alkaline phosphatase (ALP)*
      Marked elevation in rickets and Paget's disease
      Heat labile bone isoenzyme (BAP) is elevated

V. **Prostate cancer**
   1. *Prostate specific antigen (PSA)*
      Marker for prostate cancer.
      Mild increase in benign prostate enlargement
   2. *Acid phosphatase (ACP)*
      Marker for prostate cancer. Metastatic bone disease especially from a primary from prostate. Inhibited by L tartrate.

**Therapeutic use of enzymes**

| *Enzyme* | *Therapeutic application* |
|---|---|
| 1. Asparaginase | Acute lymphoblastic leukemia |
| 2. Streptokinase | To lyse intravascular clot |
| 3. Urokinase | Do |
| 4. Streptodornase | DNAse; applied locally |
| 5. Pancreatin (trypsin and lipase) | Pancreatic insufficiency; oral administration |
| 6. Papain | Anti-inflammatory |
| 7. Alpha1-antitrypsin | AAT deficiency; emphysema |

**Enzymes used for diagnostic purpose**

| *Enzyme* | *Used for testing* |
|---|---|
| Urease | Urea |
| Uricase | Uric acid |
| Glucose oxidase | Glucose |
| Peroxidase | Glucose; Cholesterol |
| Hexokinase | Glucose |
| Cholesterol oxidase | Cholesterol |
| Lipase | Triglycerides |
| Horse radish peroxidase | ELISA |
| Alkaline phosphatase | ELISA |
| Restriction endonuclease | Southern blot; RFLP |
| Reverse transcriptase | Polymerase chain reaction (RT PCR) |

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# A Brief Insight on Prevalence and Global Perspective of Pesticide

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## Introduction

Pesticide is "any substance or mixture of substances intended for preventing, destroying or controlling any pests including vectors of human or animal. The unwanted species of pest in plants or animals causing harm during the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs". Pesticides are often referred as "super chemicals" or "agrochemicals" and are employed globally, especially in agrarian economy countries like India, to meet the increasing food demand of growing population. The world's population has been growing faster than cereal production since the early 1980s, between now and the year 2025, the human population is expected to rise from about 6 billion to 8 billion. India produces an average of 250 million tons of grain a year, nevertheless it also loses 11-15% of its total output, orabout 27.5-37.5 million tonnes a year, due to pests and other causes (Walter *et al*. 2016). Hence, many pesticides have been registered since 1985 in order to meet out the demand of food in future (Zhang *et al.* 2011).

Meeting out the demand of food and fiber for the increasing global population is a challenge to the mankind. The lower production of agricultural products is not only because of diminishing cultivable lands due to heavy industrialization, and also due to the climatic change which severally affects the production of agricultural products (Shetty *et al.* 2008). In order to enhance the production of the agricultural products, without encountering heavy loss due to pests and insects, various pesticides are used worldwide. Pesticides, in common, is defined as a substance or mixture of substances mitigating any pest (insects, mites, nematodes, weeds, rats etc.) including

insecticides, fungicides, herbicides and various other substances used to control pests (EPA 2012).

## Classification of Pesticide

Pesticides include a wide range of chemical compounds of different chemical formulations. Pesticides can be classified in many ways on the basis of its use, toxicity, mode of entry, mode of action, chemistry and formulation. Pesticide can be broadly classified as insecticides (used against insect pests), herbicides (for destroying and controlling weeds), fungicides (against diseases) and others. Based on chemical composition of the pesticides, they are classified as organophosphate, organochlorine, synthetic pyrethroids and carbamates. Biopesticides are of different types- insecticide which are used against insect pest, nematicides used against nematodes, fungicides used against fungi, weedicides used against weed pests (Hamza *et al.* 2016). The flowers of chrysanthemum contain compounds called pyrethrins which are esters of cyclopropane carboxylic acid and a cyclopentenone alcohol. Natural pyrethrins are found to have very good pesticidal activity, however, exhibits least stability in the environment especially to direct sunlight. Synthetic Pyrethroids, popularly known as "emergency insecticides", a synthetic version of pyrethrins have been designed to increase insecticidal potency and extend longevity in the presence of water, moisture, and sunlight. Based on their toxicological and physical properties, pyrethroids are categorized into two separate classes- type I and type II pyrethroids. Type I pyrethroids do not contain a cyano-group in their molecules. Example, allethrin, tetramethrin, permethrin, and phenothrin, whereas, type II pyrethroids contain a cyano group in their structure eg. deltamethrin, cyfluthrin, cypermethrin, and fenvalerate.

## Pesticide Usage in India

Globally, approximately 9,000 species of insects and mites; 50,000 species of plant pathogens, and 8,000 species of weeds damage crops. An average 45% crop loss occurs annually in India was due to pest infestation while, 35% of crop production is lost during storage (Abhilash & Singh 2009). Food is endangered by pests during its natural growth or storage. India produces an average of 250 million tons of grain a year, and it also loses 11–15% of its total output, or about 27.5–37.5 million tons a year, due to pests and other causes (Walter *et al*. 2016). One of the best ways to increase the crop productivity is effective pest management by using chemical pesticides. Without pesticide application the loss of fruits, vegetables and cereals from pest injury would reach 78%, 54% and 32% respectively. Crop loss from pest's

declined to 35% from 42% when pesticides are used (Pimentel 2009). Pesticides are essential in the production of agricultural products. About one-third of the agricultural products are produced by using pesticides. The usage of chemical pesticide has increased with an increasing demand of food production for the rapidly growing world population. From the end of the 20$^{th}$ century to the present, the total global grain output has increased from 500 million tonnes to 700 million tons now (FAO 2018).

United States of Environmental Protection Agency (USEPA) documented more than 1180 pesticides have been registered worldwide out of which, 435 are herbicides, 335 are insecticides and 410 are fungicides (Nollet & Rathore 2009). Worldwide usage of pesticides has increased upto 50-fold since 1950 and annually, 2.5 million tonnes of pesticides are used (Mahmoud &Loutfy 2012). About two million tonnes of pesticides are consumed per year throughout the world. Among the two million tonnes, 24% is consumed in United States of America (USA), 45% in Europe and 25% in rest of the world. Among the Asian countries, pesticide consumption is highest in China followed by Korea, Japan and India. Globally, India stands at 10th position in pesticide consumption (Huang *et al*. 2018).

India, being an agricultural country is the largest producer of pesticides in Asia. The Indian pesticide industry is ranked second in Asia (behind China) with 82000 MT of production and ranks twelfth in the world for the use of pesticides with an annual production of 90,000 tonnes. From the end of the 20$^{th}$ century to the present, the total global grain output has increased from 500 million tons to 700 million tons now (FAO 2018). Among them, cereals account for 80% of human consumption of food (Sola *et al*. 2018). Food is endangered by pests during its natural growth or storage. Pyrethroids contribute more than 25% of the world's total pesticide market. Synthetic pyrethroids reached an estimated 1.3-1.4 billion dollars worldwide and account for 17% of global insecticide sales.

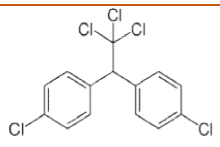
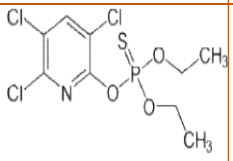
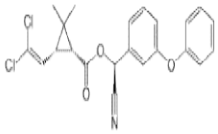
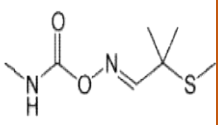
According to Section 9(3) of the insecticide act 1968, amended on 20th August 2014, 246 pesticides have been registered in India for usage. Among which consumption of insecticides, herbicides, fungicides, and other pesticides is 65%, 16%, 15% and 4% respectively. But, unfortunately, Maximum Residual Limit (MRL) of some pesticides have not been notified yet (Nollet & Rathore 2009). The consumption of herbicide was highest compared to insecticides, fungicides, and other pesticides throughout the globe, whereas, in India it is pesticide consumption overtakes herbicide. This might due to the

increased insect pest attack caused mainly by the prevailing warm humid climatic conditions in the sub-tropical region (Greeshma & Vasudevan 2015).

In developing country like India, where agriculture has the major share in Gross Domestic Product (GDP), crop production needs to be increased to match the growing demand. Agricultural production is increasing rapidly thus the consumption of pesticides is also increases. In India, the average pesticide consumption is much lesser than the developed countries, nonetheless pesticide residue problem is comparatively higher. Thus, incidences of pesticide contamination are increasing day by day. Samples of fruit, vegetables, cereals, wheat flour, oils, pulses, grains, meat, fishes, bovine milk collected from all over India were found to be having sizable amount of pesticide residues. All the samples were found to be contaminated with four major pesticide groups, organophosphorus, carbamates, pyrethroids and organochlorine among which maximum residues were related to organophosphorus and pyrethroid pesticides (Nollet & Rathore 2009). Ahmadi (2017) reported that 50% vegetables were found to be contaminated by various pesticides, from which, 16% were above MRL limit.

Among the various pesticides registered for use in India, the most commonly used pesticides include atrazine, chlorpyrifos, cypermethrin, fenalverate, diazinon, endosulfan, lindane, deltamehtrin, ethion, carbofuran, simazine, permethrin, monocotrophos etc. The usage of pesticide in India is about 0.5 kg/ha of which major contribution is from organochlorine pesticides. Organochlorine, carbamate and pyrethroids pesticide are used against insect pest like lepidoptera, hemiptera and diptera. In turn, organophosphorus insecticides are mostly used against aphids and viral diseases (Table.1). Insect pest of various crops like rice, wheat, cotton, plantation crops, vegetables and fruits are the major targets of these pesticides which exhibited larvicidal, adulticidal and ovicidal activity. The decline of organochlorine pesticides in the late 1960s, organophosphorus, then carbamates and finally synthetic pyrethroids arrived (Nollet & Rathore 2009).

**Table.1 Illustration of molecular structure of pesticides and its uses**

| S. No | Pesticide group (Example) | Chemical name | Molecular structure | MW g/Mol | Usage | Reference |
|---|---|---|---|---|---|---|
| 1. | Organochlorine (DDT) | 1-chloro-4-[2,2,2-trichloro-1-(4-chloro phenyl)ethyl] benzene |  | 354.48 | Acaricide and Insecticide | Jayaraj *et al.* 2016 |
| 2. | Organo Phosphate (Chlorpyrifos) | O,O-Diethyl O-3,5,6-trichloropyridin-2-yl phosphorothioate |  | 350.57 | Insecticide and Miticide | Giesy & Solomon 2014 |
| 3. | Pyrethroid (Cypermethrin) | Cyano-(3-phenoxy phenyl)methyl] 3-(2,2-dichloro ethenyl)-2,2-dimethyl cyclopropane -1 -carboxylate |  | 416.30 | Termiticide and Insecticide | Laskowski 2002 |
| 4. | Carbamate (Aldicarb) | 2-Methyl-2-methylthio) propanalO-(N-methyl carbamoyl) oxime |  | 190.26 | Nematicide and Insecticide | Basheer *et al.* 2009 |

Note: MW- Molecular Weight.

## Accumulation of Pesticide

The loss of food has been reduced a lot after the use of pesticides, however, these pesticides are widely distributed in the soil, water, air, and agricultural products (Fenner *et al*. 2013). Due to their extensive use, synthetic pyrethroids residues have been frequently detected in soils, sediments, natural waters and agricultural products. Due to their highly hydrophobic properties, pyrethroids strongly bind to soil particles and organic matter, which allows

them to leach into the groundwater and to form residues of these compounds, thereby adversely affecting the ecosystem (Hu *et al*. 2019). Intense and frequent use of these chemicals has led to the persistence of pesticides in soil due to lack of timely degradation. Less solubility and highly stable structure of the pesticide limits their degradation in soil via physico-chemical processes and less availability to plants and microbes limits the biochemical process (Odukkathil& Vasudevan 2013).The inappropriate discharge of pesticides from industries and agriculture widely contaminate air, soil, and water So, the wide use of pesticides causes a great potential threat to the environment (Chen *et al*. 2007; Fenner *et al*. 2013).

Several studies have reported the presence of synthetic pyrethroids in soil and water throughout India. Kumar *et al*. (2008) showed the status of insecticide contamination of soil and water in Haryana, India. The pollution of pyrethroids in farm soil and water collected from Karnataka, India evidenced increased concentration level ranges from 0-44.6 µg/kg of synthetic pyrethroid in soil. Conversely, a lesser range between 0.25 and 34.12 µg/L was found in water and the residual content was observed to be more than the rice field water (0.15-4.65 µg/L). The primary mode of disposal of synthetic pyrethroids are the receding waters from agricultural, urban and industrial applications through runoff from sprayed fields, lawns, parking lots, etc., during rainstorm events, and, to a lesser extent through spray drift.

Pyrethroid insecticides (cypermethrin and deltamethrin) were also detected in liver, brain and ovary of captured catfish *Bagariusbagarius* from unpolluted ponds of Gujarat, Jaunpur and polluted river Gomti, Jaunpur during pre-monsoon or breeding phase. As well, the surveillance study on synthetic pyrethroids and organophosphate in different brands of soft drinks was well documented. The residues of synthetic pyrethroids (deltamethrin, fenvalerate, cypermethrin and Permethrin) were recorded as 25%, 7%, 18%, and 3% of the total pesticide concentration in soft drink samples of different brands (Vengayil*et al*. 2011). In 2024, Somon et al., reported that chlorpyrifos and chlorpropham were the most detected pesticides with a detection frequency of 33% and 25%, respectively. Except for vegetables and fruits, the levels pesticides in all other food types were significantly higher in samples from Delhi, India.

## Toxicity of Pesticide

Highest pesticide consuming states of India in comparison to other states are Andhra Pradesh, Karnataka, Maharashtra, Gujarat and Punjab (Govt. of India, Eleventh Five-Year plan: 2008-2012). Organochlorine pesticides such as atrazine, Dichloro Diphenyl Trichloroethane (DDT), Benzene Hexa Chloride (BHC), lindane and endosulfan were much problematic and can cause serious environmental concern (Pandit *et al*. 2001). Extreme exposure of pesticide and their residues, directly or indirectly, had resulted in several toxicological problems on living beings. A significant concern about pesticide is that they are likely to be neurotoxic to humans, possibly by utilizing the similar mechanisms that target the nervous system of insects. This property is very dangerous to the developing human brain of the fetus, which is much more vulnerable to any injury caused by toxic chemicals (Zhang *et al.* 2014).The mechanism of pesticide is based on the acetylcholine esterase enzyme inhibition, which is essential for the functioning of the CNS. Due to the pesticide attack, acetylcholine neurotransmitter gets accumulated, interfering with the muscular response. The interference in muscular response causes respiratory and myocardial malfunctions and even death in extreme cases (Lionetto *et al.* 2013). Pesticide poisoning leads to cardiac complications such as cardiac arrest, arrhythmia and pulmonary edema (Abdelnaby 2018).

Although the reliance on chemicals in green revolution agriculture has contributed to the remarkable gains in the production of grains in the world, especially in developing countries, the extensive use of fertilizers and pesticides has caused serious public health and environmental problems. Pyrethroids are extremely toxic to aquatic organisms, with lethal concentration ($LC_{50}$) values less than 1.0 ppb. The toxicity of an individual pyrethroid varies widely depending on the route of administration and the vehicle used for dosing. Pyrethroids cause neuronal hyper excitation, resulting in repetitive synaptic firing and persistent depolarization. The molecular targets of the pyrethrins and pyrethroids are similar in mammals and insects, and include voltage-gated sodium, chloride, and calcium channels, γ-aminobutyric acid (GABA) -gated chloride channels, nicotinic Acetyl Choline receptors, and intercellular gap junctions. Exposure to these substances can modify histone modifications and DNA methylation patterns, which can disrupt gene expression and increase vulnerability to neurological illnesses (Oyovwi et al., 2025).

World Health Organization (WHO) has been categorized each pesticide according to its toxicity. Based on their toxicity expressed in terms of $LD_{50}$ value WHO categorized all the pesticides into IA: Extremely hazardous, IB: Highly hazardous, II: Moderately hazardous and III: Slightly hazardous (WHO 2004). The $LD_{50}$ and $LC_{50}$ values for the four toxicity categories and their associated signal word was summarizes in Table 2.2. Being labelled as slightly toxic or nontoxic, these pesticides can be hazardous to humans, other living beings and environment, if they are misused. These active ingredients are diluted by a carrier or diluent and are made available in various formulations like dust, granule, emulsifiable concentrate, wettable powder, fumigants, smokes, vapours and aerosol. Their dosage depends on the nature and extent of pest attack. Formulation and dosage also vary depending on the type of pest, nature of crop, parts of plant where the pest had caused damage (Jayaraj *et al*. 2016).

**Table .2 Route of exposure and toxicity category of pesticides**

| Routes of Exposure | Toxicity Category | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Oral $LD_{50}$ | Upto 50 mg/kg | 50-500 mg/kg | 500-5,000 mg/kg | >5,000 mg/kg |
| Inhalation $LC_{50}$ | Upto and including 0.2 mg/L | 0.2 – 2 mg/L | 2-20 mg/L | >20 mg/L |
| Dermal $LD_{50}$ | Upto and including 200 mg/kg | 200-2,000 mg/kg | 2,000-20,000 mg/kg | >20,000 mg/kg |
| Eye Effects | Corrosive corneal opacity not reversible within 7 d | Corneal opacity reversible within 7 d, irritation persisting for 7 d | No corneal opacity, irritation reversible within 7 d | No irritation |
| Skin Effects | Corrosive | Severe irritation | Moderate irritation at 72 h | Mild or slight irritation at 72 h |
| Signal word | Danger Poison | Warning | Caution | Caution |

Note: Lethal Dose $LD_{50,}$ Source: (Damalas and Koutroubas, 2016)

## Conclusion

The need for a more comprehensive understanding of their safety profile is highlighted by their neurotoxic potential, which is mainly caused by prolonged opening of voltage-gated sodium channels, as well as new information on oxidative stress, endocrine disruption, reproductive toxicity, and immunological effects. Long-term research is necessary to address the increasing risk of chronic low-dose exposure, especially in susceptible groups like children and agricultural labourers. Concerns regarding the ecological sustainability of pyrethroids are raised by their persistence in sediments and harm to aquatic creatures and pollinators. Clarifying dose-response relationships, improving exposure and effect biomarkers, and using cutting-edge molecular and omics-based techniques to elucidate mechanisms of toxicity should be the top priorities for future study. Additionally, regulatory regimes need to change in response to new data, supporting the development of next-generation pests and safer application techniques.

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# Biotechnological Frontiers in Mangrove Species: Conservation, Molecular Understanding, and Sustainable Application

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## 1. Introduction

Mangrove forests are strong and distinct coastal ecosystems. They live where land and sea meet. Mangroves in the tropics and subtropics live in high salt, high flooding frequency, and low soil oxygen (Tomlinson, 2016). True mangroves encompass the Avicennia, Rhizophora, Sonneratia, and Bruguiera genera. Such plants possess unique characteristics such as vivipary, in which seeds develop. At the same time, they are still attached to the parent tree, aerial roots for gas exchange, salt-excreting leaves, and stilt or prop roots that support soil during tidal stress (Parida & Jha, 2010). True mangroves are ecologically significant in many ways. They supply natural barriers that reduce coastal erosion impacts and lessen the consequences of storms, cyclones, and tsunamis (Kathiresan & Rajendran, 2005). Their roots provide sediment capture, filtering of water, and critical nursery habitats for many fish, crustaceans, and mollusks, which sustain coastal fisheries and industries (Nagelkerken& Faunce, 2021). Conservation strategies like creating protected areas, restoring plant life, and managing communities are all important. However, they cannot tackle

emerging challenges (Ragavan et al., 2022). Biotechnology can provide a new method to conserve mangroves. There is potential for large-scale regeneration of endangered species through in vitro regeneration and tissue culture. Mangroves are also "blue carbon" ecosystems that can sequester more carbon than specific terrestrial forest ecosystems. They sequester substantial carbon in their above-ground biomass and deep waterlogged soils (Alongi, 2015). Sadly, mangrove systems are rapidly threatened globally. In the last five decades, 20-35% of mangrove cover globally has been destroyed because of aquaculture, urbanization, agriculture, and coastal development (Giri & Long, 2016). Climate change enhances these pressures.Sea-level rise, increased storm frequency, and salinity changes slow mangrove growth and resistance (Duke, 2017).

While the local significance of mangroves cannot be overstated, they provide important roles globally as blue carbon ecosystems for climate control. Molecular and genomic studies uncover the genetic mechanisms of stress tolerance and adaptation.It opens the door to creating stress-resistant mangrove populations. Metabolomic and microbial investigations show that mangroves are tremendous sources of bioactive compounds for pharmacological, agricultural, and industrial use (Bandaranayake, 2002; Choudhury et al., 2021). This chapter gives an overview of the recent advancements in mangrove biotechnology and biology, including advancements in propagation, molecular and genomic research, secondary metabolite analysis, mangrove-microbe interactions, scalability, and ecological hazards. Bringing biotechnology knowledge together with conservation science and local ecological knowledge, this chapter shows how these methods can effectively collaborate to conserve genuine mangrove species and aid global sustainability and climate resilience.

## 2. Mangrove Species: Variation and Ecological Role

True mangroves possess a special ecological function as salt-physiological forests in intertidal areas with adaptations that enable them to survive in tidal, salty, and low-oxygen conditions.They are distinct from mangrove associates since they possess exclusive habitat requirements, osmoregulation processes, and features facilitating survival in harsh coastal environments (Sheue et al., 2003). Almost 70 known mangrove species worldwide, about 30 are True mangroves from genera like Avicennia, Rhizophora, Bruguiera, Sonneratia, and Laguncularia (Duke, 2017). They have significant adaptations like pneumatophores and lenticels that help with gas exchange in wet soils. They also have salt glands to regulate ion balance and vivipary and grow propagules before dispersing. These traits show how they

have evolved differently from other plant families (Parida & Jha, 2010). True mangroves are "green infrastructure," providing many regulating, supporting, and provisioning services. Extensive root systems dissipate wave energy, stabilize sediments, and defend coastlines against erosion, storms, and tsunamis (Kathiresan & Rajendran, 2005). They store carbon in their above-ground woody structures and deep, poorly oxygenated soils, which makes them even more potent in the battle against climate change than most terrestrial forests (Alongi, 2015). True mangroves, however, suffer from human activities and stress caused by climate change. Their large-scale conversion into agriculture, aquaculture, and urbanization has resulted in high rates of mangrove loss on a global scale. Pollution, over-exploitation of resources, and changed water flow debilitate the resilience of the ecosystem (Giri & Long, 2016). Climate change exacerbates these threats.

Increased sea levels, salinity changes, and storm surges impede natural recovery and species survival (Duke, 2017). These dangers lower mangrove cover and threaten their ecological functions and values. Enhanced conservation efforts are needed because of their ecological value and growing vulnerability. Biotechnology offers new ways to improve traditional methods through mass propagation, maintaining genetic diversity, and understanding molecular adaptation mechanisms. Using these techniques along with ecosystem management can boost the resilience of true mangroves and support sustainable applications.

## 3. Biotechnological Interventions for Mangrove Conservation

Biotechnology holds promise for true mangrove species conservation, particularly in addressing low natural regeneration, habitat fragmentation, and climatic stress. These approaches aim at long-term conservation and propagation of genetic resources, significantly enhancing restoration on the ground.

### *In Vitro Propagation*

Scientists in mangrove species have widely researched tissue culture methods such as somatic embryogenesis, organogenesis, and callus induction.In plants such as Avicennia marina and Rhizophora apiculata, successful in vitro regeneration produces high-quality genotypes with desirable characteristics such as stress tolerance (Das & Ghose, 2019).These methods solve a significant problem for mangroves: poor seed dispersal and low rates of natural recolonization, particularly in areas that have been damaged.Tissue culture represents a method of propagation all year round in controlled

conditions and reduces dependence upon the variability of seasonal seed availability. However, there are limitations. Not all species of mangroves readily adopt tissue culture. Some species show poor regeneration results, root issues, and high rates of somaclonal variation (Abhijith et al., 2020). Most wild mangrove species have poor seed dispersal, low recruitment in nature, and fragmented habitat, making them hard to conserve (Polidoro et al., 2010). The roots of mangrove ecosystems filter organic matter, improve nutrient cycling, and form complex ecosystem parts for fish, crustaceans, and mollusks, thereby increasing food security and livelihoods (Nagelkerken& Faunce, 2021).This method entails preserving tissues at ultra-low temperatures to maintain dormancy, and it holds potential for plants such as Avicennia marina and Rhizophora mucronata (Rao et al., 2019). In addition, another serious issue to contend with is the acclimatization of plantlets to ex vitro, which requires seedlings to acclimatize from sterile laboratory conditions to a dynamic, salt-laden, anoxic coastal environment. More attention should be directed towards promoting explant choice, optimizing combinations of growth regulators, and preconditioning stress acclimatization for improving transplant survivability. New technologies like temporary immersion bioreactors and stress micropropagation can aid mass propagation.

### *Germplasm Storage and Cryopreservation*

The conservation of genetic diversity beyond the propagation process is crucial for adapting mangroves. Cryopreservation was investigated as a possible storage technique for embryos, seeds, and authentic mangrove tissues for long-term storage. These processes safeguard against habitat destruction, climactic catastrophes, and genetic deterioration.There is variability among species in terms of cryopreservation effectiveness. Some mangrove species have recalcitrant seeds, experience freezing and desiccation difficulties, and have poor viability on thawing. Recent studies show better cryoprotectant protocols, vitrification techniques, and encapsulation-dehydration techniques, as they will increase the inactivity of tissue to damage from ice crystal formation. Advances in molecular markers and viability assays further cement the cause of germplasm preservation. Combining in vitro culture and cryopreservation could result in a valid ex situ conservation regime for mangroves.These technologies offer quality genetic resources for subsequent restoration programs and provide consistent access to quality genotypes for ecological and biotechnological utilizations.

## 4. Molecular and Genomic Insights

Advances in molecular biology and omics tools have revolutionized our concept of mangrove biology. These recent advances focus on how mangrove species adapt to cope with the most hostile intertidal conditions. True mangroves encounter extreme salinity, tidal flooding, low oxygen, and poor-nutrient conditions. Genomic and molecular understanding of these adaptations is essential for conservation and biotechnological uses (Parida & Jha, 2010). Genomics Whole-genome sequencing of Avicennia marina and Rhizophora mucronata has unveiled crucial genetic elements associated with salt tolerance, ion homeostasis, and vivipary (Li et al., 2019). Genes related to the coding of ion transporters, sodium-proton antiporters, aquaporins, and the biosynthetic pathways for compatible solutes are relevant in signaling osmotic pressure adjustment in cells during salt stress.Additionally, vivipary, important for mangrove reproduction, is related to genes involved in hormonal pathways, within the pathways controlled by abscisic acid and gibberellin to promote propagule formation while still attached to the parental plant.

Comparative genomics in mangroves reflects common and species-specific adaptations, revealing evolutionary adaptations promoting abrasiveness to intertidal surfaces (Choudhury et al., 2021). The use of transcriptomics and proteomics Transcriptomic and proteomic profiling has revealed the molecular processes through which mangroves have developed the capacity to mount responses to stresses. Plasticity in using aquaporins and regulation of late embryogenesis abundant protein play a role in water transport and cellular protection against salinity fluctuations and drought stress. In conditions of oxidative stress due to high salinity and tidal exposure, plants have been found to activate antioxidative enzymes, like superoxide dismutases, catalases, and peroxidases (Choudhury et al., 2021).Proteomic analysis has identified post-translational modifications stabilizing stress-associated proteins.Integrating transcriptomic data with metabolomicdata increasingly gives a comprehensive picture of how mangroves respond to stress.Functional Genomics and Future Directions The emergence of functional genomics and genome-editing technology opens up new avenues in mangrove science. CRISPR-Cas tools can validate candidate genes' functions associated with salinity stress, vivipary, and stress signaling. Synthetic biology has the potential to generate stress-tolerant crops or the yield of beneficial metabolites (Zhou et al., 2022).

Researchers can promptly detect superior genotypes for restoration and sustainable utilization using high-throughput sequencing and bioinformatics.However, there are also concerns. Importantly, socio-ecological risks of releasing genetically engineered mangroves must be carefully assessed for their direct impacts on intertidal communities, microbial communities, and evolutionary processes. Ethical and legal frameworks must be established to balance conservation needs with future biotechnology opportunities. Genomic research is also limited primarily to a few species, demonstrating a significant need for expanded sequencing initiatives and multi-omics approaches in varying mangrove species.All these genomic and molecular data lay the groundwork for a deeper comprehension of the true mangrove species' complicated adaptations. By integrating genomics, transcriptomics, proteomics, and functional genomics, researchers may refine basic ecological data, elevate conservation practice, enhance restoration effectiveness, and assess the biotechnological potential in pharmaceuticals, agriculture, and environmental management.

## 5. Secondary Metabolites and Bioprospecting

Mangroves synthesize secondary metabolites and bioactive compounds like flavonoids, terpenoids, alkaloids, phenolics, and tannins.These compounds function in defense functions such as antioxidative protection, antimicrobial function, and UV protection to help mangroves cope with harsh conditions (Bandaranayake, 2002). Such metabolites also represent potentially exploitable pharmaceutical, nutraceutical, and industrial resources. Bioactive compounds and pharmacological potential Avicennia, Rhizophora, Bruguiera flavonoids and terpenoids possess many antioxidant, anti-inflammatory, and anticancer activities (Schaeffer-Novelli et al., 2020). Free radical scavenging by phenolic compounds protects plant and potentially human cells against oxidative damage. Mangrove alkaloids and glycosides have been assessed for anticancer activity and cardioprotective effects. In addition, the extracts have cosmetic, food preservation, and biopesticide or growth regulator applications in agriculture.

### *Biotechnological Approaches to Metabolite Synthesis*

Seasonal variations, poor productivity, and environmental stresses compromise conventional approaches to material extraction from natural sources.Biotechnology provides alternative means of production, including cell suspension culture, hairy root culture, and metabolic pathway engineering to produce high-value metabolites in aseptic conditions (Schaeffer-Novelli et al., 2020).Metabolic engineering allows scientists to modify biosynthetic pathways

to enhance yields, change the structure of compounds, and improve production efficiency.Advancements in the application of elicitors, bioreactor design, and genome editing enhance scalability and reproducibility.Despite abundant evidence for bioactivity, the commercialization of mangrove-derived metabolites is low. This is related to limitations in abundance in nature, some challenges to maintain stable in vitro cultures, and the regulatory challenges that are associated with bioprospecting in sensitive ecological contexts (Krishnamurthy & Sasidharan, 2020). Mangrove populations are also threatened by over-harvesting for the extraction of metabolites, which calls for combining sustainable methods with biotechnological means. Ethical and Environmental Considerations: Bioprospecting in mangrove habitats also creates ethical issues regarding access to biodiversity, benefit sharing, and conservation priorities. Fair benefit-sharing from genetic resources and limitation of ecological effects are fostered by national and international legislation such as the Nagoya Protocol.

Utilizing in vitro production, synthetic biology, and microbial co-cultures, the dependency on wild harvesting can be minimized, thereby facilitating sustainability.In summary, mangroves are a rich and under-exploited reservoir of bioactive metabolites with promising applications in pharmaceuticals, agriculture, and industry.Biotechnological strategies provide scalable, controlled, and sustainable means of producing valuable compounds, correlating environmental protection with economic and health gains for humankind.Increased research that combines genomics, metabolomics, and processing technologies will be essential to unlock the full value of these ecosystems.

## 6. Potential for climate change and environmental mitigation.

Mangroves were globally identified as essential blue carbon ecosystems capable of sequestering carbon above ground and in waterlogged sediments with more carbon than most terrestrial forests (Nagelkerken& Faunce, 2021). Its unique root structure stores sediments and organic matter in a stable carbon sink, and thus contributes a substantial amount towards climate change mitigation. Mangroves provide more than carbon sequestration; they also have consequential ecosystem services. These are coastal protection, nutrient cycling, and habitat for fisheries and other flora/fauna, and these ecosystem services support mangroves' antecedent function of environmental sustainability and socio-economic resilience (Alongi, 2015). Integrating biotechnological instruments, recent advancements in biotechnology, and remote sensing is improving the effectiveness of estimating and monitoring

mangrove carbon stocks. Stable isotope tracing (providing specificity of carbon sources and sediment turnover). Genomic and transcriptomic information (these applications could provide specificity of species and genotype with high carbon sequestration potential) (Alongi, 2015).

### *Geospatial analysis - Bioremediation Capability*

Mangroves also help minimize pollution from the environment. They are resistant to, and can store, heavy metals in their roots and the respective microbial communities, which can degrade hydrocarbons and detoxify organic xenobiotics (Basyuni et al., 2017). These intrinsic capabilities can be further developed by biotechnological processes such as cranberry toxin-pathway degradation or the utilization of beneficial bacteria, which could also supply natural remediation agents to contaminated coastal environments. Functional genomics, metabolomics, and microbial consortia design can empower these bioremediation processes.

### *Climate Resilience and Restoration Uses*

Mangroves are an essential buffer between land and sea to help ameliorate sea-level rise and enhance resilience to storm surges. Ecosystem restoration, which relies on suitable, more stress-tolerant genotypes based on genomic and physiological research, could assist in achieving restoration objectives planned for coastal ecosystems that are currently under threat. Biotechnological advancements in the areas of propagule production and genotypic selection could have a direct influence on survival and recovery rates, and ensure the restoration of mangrove stands that are functional and support ecosystem functions and services. Some significant issues are precise carbon estimation in multi-species ecosystems, co-prehension of stress responses at the species level, and avoiding interference with native biodiversity during restoration. Integrating omics strategies, biochemical quantification, and satellite monitoring methodologies will improve carbon accounting. Sustainable management will be ensured by involving the community and policy structures. Synthesizing biotechnology with conservation and ecosystem service evaluation will make mangroves valuable climate mitigation measures and models for nature-based solutions.Finally, mangroves are critical assets for climate change adaptation and ecological sustainability. Biotechnology can optimize organisms' cultivation, survivability, and functions in ecosystems. It can also create bioremediation technologies, enhance monitoring, and assist with precise carbon accounting to make mangroves critical contributors to global climate adaptation.

## 7. Mangrove–Microbe Interactions: A Biotechnological Perspective

The rhizosphere and the root systems of mangrove trees are filled with diverse microorganisms, including nitrogen-fixers, phosphorus-solubilizers, and hydrocarbon degraders, among many others. These microbes are important in nutrient recycling, soil health, and environmental remediation (Krishnamurthy & Sasidharan, 2020).Endophytic fungi and bacteria in mangrove tissues produce bioactive molecules such as antimicrobial peptides, enzymes, and secondary metabolites.These are of tremendous potential for application in the pharmaceutical sector, industrial biotechnology, and agriculture (Bandaranayake, 2002).

Emerging technologies in the omics, such as metagenomics, metatranscriptomics, and metabolomics, reveal new enzymes and pathways that broaden the uses of mangrove-associated microbiomes.For instance, hydrocarbon-degrading bacteria isolated from mangrove sediments are proving helpful in remediating oil-contaminated shores.Plant growth-promoting bacteria also provide mangrove seedlings with salt tolerance and nutrient acquisition efficiency (Choudhury et al., 2021).While these advances have been made, transferring laboratory results to field conditions remains challenging. Functional description of microbial metabolites, scale-up amplification of inocula, and determination of ecological effects demand a multidisciplinary effort. A strategy involving synthetic biology, metabolic engineering, and field tests can speed up the applicability of mangrove–microbe systems in ecological restoration, sustainable agriculture, and climate change abatement. Microbial metagenomic studies and precision biotechnology tools like CRISPR genome editing and high-throughput screening can identify genes related to environmental stress tolerance and the production of bioactive compounds. The mangrove microbiome mainly supports ecosystem functions, improves carbon storage, and promotes sustainable biotechnology practices in coastal areas.

## 8. Challenges, Research Gaps, and Future Directions

Despite the significant progress in mangrove biotechnology, some gaps and challenges restrict research for larger-scale applications. Technical difficulties still exist, such as poor reproducibility of tissue culture methods, incomplete transcriptomic and genomic databases, and high cost of operations. These issues limit large-scale propagation and commercialization (Das & Ghose, 2019). There remain gaps in knowledge about intricate stress adaptation

mechanisms; genomics, proteomics, metabolomics, and phenomics integration is still in its infancy (Choudhury et al., 2021). This gap confines our knowledge of the molecular networks involved in salinity tolerance, heavy metal detoxification, and fast growth under environmental stress.

Ecological risks also represent a considerable risk if the genetically improved or selectively bred mangroves are not thoroughly risk-analyzed; they can destabilize ecosystems, alter microbial interactions, and their collaborations with non-microbials (Zhou et al., 2022). The social and economic aspects of biotechnology need further research, too, as research must address social aspects like public perceptions about biotechnology, policies surrounding biotechnology, and equitable sharing of these benefits. The goal is to rationalize emerging biotechnologies with traditional ecological knowledge (TEK) to develop targeted conservation approaches, predict how mangroves may respond to environmental pressures, and develop big-data analysis. Predictive modelling also involves identifying genes or metabolites for biotechnology applications, as well as developing global databases of mangrove genomic, transcriptome, and metabolome, which can enhance international collaborative science, enable comparative analysis, and assist in informed restoration and sustainable management of mangroves (Ragavan et al., 2022). It is also necessary to create a strategy for judicious investment in technology for environmentally sustainable and scalable propagation, field monitoring, and community engagement to transition laboratory success into successful coastal conservation strategies.

## 9. Conclusion

Mangrove ecosystems are significant ecological and economic resources, providing shoreline protection, biodiversity, and important carbon sinks. Mangrove ecosystems are threatened as ever through urbanization and aquaculture, pollution, and climate change, affecting ecosystems and people's livelihoods. Biotechnology provides robust interventions that promote mangrove conservation, explore their molecular and metabolic possibilities, and promote sustainable use. Developments in in vitro culture methods, cryopreservation, profiling of metabolites, and omics strategies present new opportunities for restoration, lead compound identification, and climate-resilient strategies. Major challenges remain. The technical limitations of scaling tissue culture processes, reproducibility, the limited availability of comprehensive aligned genomic assets, and possible ecological effects limit their application. The solution to these challenges needs a continuum of approaches that combine biotechnology, a robust and analytical consideration

of ecological risk, robust policy approaches, and community engagement. By combining scientific research with ecologically based approaches, we can help stakeholders develop intact, diverse, resilient mangrove ecosystems that preserve the potential for climate change mitigation, sustainable livelihoods, and natural product banks for pharmaceutical and industrial use. Finally, natural mangrove conservation requires an integrated approach to conservation, ecosystem restoration, and the sustainable innovation of biotechnology as a tool to turn rainforests into climate-resilient coastal ecosystems for generations to come.

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# Comprehensive Insights into Wounds: Classification, Healing Pathways, and Dressing types

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## 1. Wound

The skin provides a life-protective barrier between the body and the external environment against physical damage, pathogens, fluid loss, and has immune-neuroendocrine functions that contribute to the maintenance of body homeostasis. Its structure is composed of two layers: the epidermis and the dermis. The epidermis contains keratinocytes, melanocytes, dendritic cells, Langerhans cells and other immune cells, sensory axons, and the epidermal-dermal basement membrane. The dermis has the skin appendages, mast cells, fibroblasts, antigen presenting dermal cells, resident and circulating immune cells. Additionally, the dermis includes the extracellular matrix complex that provides support to intercellular connections, cellular movement, and regulates cytokine and growth factor functions.Skin innervation consists of a dense network of sensory and autonomic fibers that form tight junctions with keratinocytes and transmit sensations of pain, temperature, pressure, vibration, and itch.

A wound is defined as a break in the normal structure and function of the skin or underlying tissues caused by physical, chemical, thermal, or pathological factors. It disrupts the protective barrier of the skin, exposing internal tissues to the external environment. This causes pain and bleeding and increases the risk of infection, fluid loss, and delayed healing. Wounds can vary in severity, depth, and cause, ranging from minor cuts to life-threatening injuries. Proper classification of wounds is essential to determine appropriate treatment and to promote effective healing.

## 2. Types of wound

Wounds can be classified using several criteria such as etiology (cause), cleanliness, depth, or healing pattern. Understanding these categories helps healthcare professionals select the right dressing and treatment strategy.

### 2.1 Based on Etiology (Cause)

a) **Incised Wounds** – These are caused by sharp objects like knives, blades, or glass. They have clean-cut edges and usually bleed profusely, but heal relatively quickly when properly managed.

b) **Lacerated Wounds** – Caused by blunt trauma that tears the skin and underlying tissue. The edges are irregular, often accompanied by bruising, and healing may take longer due to tissue damage.

c) **Abrasion** – A superficial wound where the skin is scraped off due to friction against a rough surface. Common examples are road rashes or grazes. They are often painful because nerve endings are exposed, but they heal without major complications if kept clean.

d) **Puncture Wounds** – Created by pointed objects like nails, needles, or animal bites. These wounds may appear small on the surface but can be deep, increasing the risk of infection and tetanus.

e) **Contusion (Bruise)** – Caused by blunt trauma without breaking the skin. Blood vessels under the skin rupture, leading to discoloration, swelling, and tenderness.

f) **Avulsion** – A more severe type where a portion of tissue is torn away from its normal position. It may involve skin, muscle, or even bone, requiring surgical intervention.

g) **Gunshot Wounds** – Result from projectiles such as bullets. The severity depends on the velocity, angle, and location of entry, often involving significant tissue destruction

### 2.2 Based on Cleanliness

a) **Clean Wounds** – These are uninfected wounds created under sterile conditions, such as surgical incisions. The risk of infection is minimal.

b) **Contaminated Wounds** – Wounds exposed to foreign particles, dirt, or bacteria. For example, road traffic accident injuries.

c) **Infected Wounds** – These contain pus, necrotic tissue, or show signs of infection such as redness, swelling, warmth, and foul-smelling discharge

### 2.3 Based On Depth

a) **Superficial Wounds** – Involving only the epidermis or outermost skin layers. Example: minor abrasions.

b) **Partial-Thickness Wounds** – Extend into the dermis but do not involve the full skin thickness. They are commonly seen in burns.

c) **Full-Thickness Wounds** – Involve destruction of the epidermis, dermis, and may extend into subcutaneous tissue, muscle, or even bone. Such wounds require advanced management and longer healing time

### 2.4 Based On Healing Process

a) **Acute Wounds** – Heal within a predictable and timely manner, usually within 4–6 weeks, such as surgical incisions or minor cuts.

b) **Chronic Wounds** – Fail to progress through normal healing stages and persist for months or years. Examples include diabetic ulcers, venous leg ulcers, and pressure sores. Chronic wounds often require specialized care and advanced dressings

### 2.5 Special Types Of Wounds

a) **Burns** – Caused by heat, chemicals, electricity, or radiation. Classified into first, second, and third degree depending on tissue damage.

b) **Pressure Ulcers (Bedsores)** – Occur due to prolonged pressure on bony areas, common in bedridden patients.

c) **Diabetic Ulcers** – Develop in patients with uncontrolled diabetes due to poor circulation and neuropathy.

d) **Surgical Wounds** – Intentionally created under sterile conditions but may become complicated by infection

## 3. Phases of wound healing

Wound healing is a dynamic and complex mechanism of tissue regeneration and development that occurs in four stages: (i) coagulation and haemostasis (immediately after injury); (ii) inflammatory phase (shortly after tissue injury); and during which swelling occurs; (ii) the proliferation phase, during which new tissues and blood vessels are formed; and (iv) the maturation phase, during which new tissue remodelling occurs These processes appear in a logical order, combining and intertwining in a well-connected cascade is shown in Figure 1.

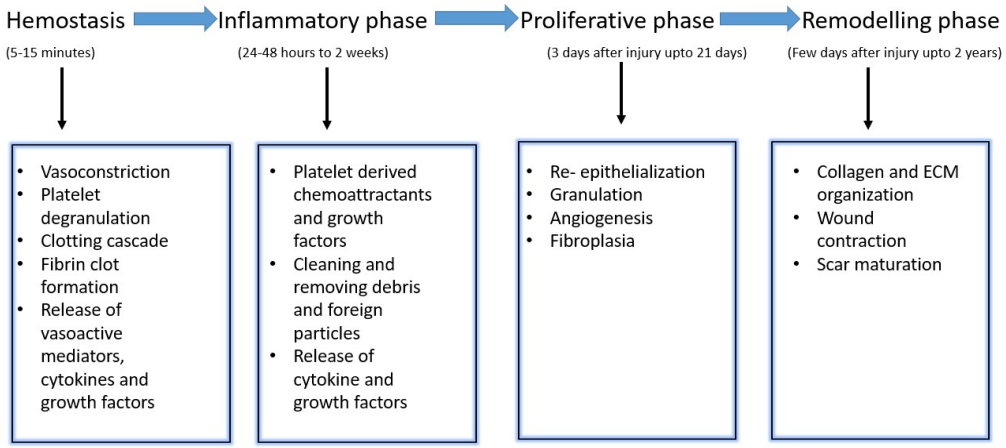


**Figure 1: Phases of Wound healing process**

## 3.1 Phases of Wound Healing:

### a) The Inflammatory phase:

The inflammatory process starts quickly after the injury which lasts between 24 and 48 hours, in some cases lasting up to two weeks. The inflammatory phase activates the haemostatic pathways immediately, which avoid blood loss from the wound site. This results in clinically recognizable cardinal signs of inflammation: rubor, calor, tumour, dolour, and function. This process is indicated by vasoconstriction and platelet accumulation to trigger blood clotting, followed by vasodilation and phagocytosis to cause wound inflammation.

### b) Fibroblastic phase:

The fibroblastic phase of wound healing follows the inflammatory phase, which will last anywhere from 2 to 3 weeks. Granulation, contraction, and epithelialization are the three stages in this process. Fibroblasts produce a collagen bed and new capillaries during the granulation process. Glycosaminoglycans and collagen are produced by fibroblasts, which are essential for wound healing. In the second step, wound edges pull together to eliminate defects, and in the third step, epithelial tissues form around the wound site.

### c) Epithelization phase:

Epithelial cell migration is one of the vital processes of wound healing. The stem cells of the epithelium must detach from the edges of the wound and

migrate into the wound. Normally, dermal basal cells adhere to each other and to the underlying basal layer of the dermis. Following mobilization, epithelial cells begin to enlarge and migrate down and across the wound. Transected hair follicles also contribute to the number of migrating epithelial cells. Epithelial cells migrating across a wound usually move along the basal lamina or fibrin deposits; this phenomenon is called contact guidance and is an important factor in epithelial migration. Epithelial migration is followed by increased mytosis of epithelium. Recent literature reveals that chalcone, a water-soluble heat-labile substance secreted at the wound site, is responsible for mytosis regulation.

### d) Proliferative phase

The Proliferative Phase (which lasts between two and three weeks) involves the following activities: Fibroblasts lay a collagen bed during the granulation period. Fills the cavity and creates new capillaries. Step of contraction: Wound edges draw together to minimise the defect. Crosses moist surface cells migrate about 3 cm from the point of origin in all directions during the epithelialization stage.

### e) Contraction phase:

Differentiated fibroblasts (myofibroblasts) in the granulation tissue, which contain smooth muscle actin filaments, trigger wound contraction. The wound margins migrate toward the centre of the wound as these fibroblasts contract.

Wound contraction is caused by the action of differentiated fibroblasts (myofibroblasts) in the granulation tissue, which contain filaments of smooth muscle actin. Contraction of these fibroblasts makes the wound margins move toward the center of the wound.

### f) Remodelling phase:

This phase will last from 3 weeks to 2 years. During this process, new collagen is formed. Collagen intermolecular cross-linking through vitamin-C-dependent hydroxylation increases tissue tensile strength. The wound flattens out, and the scar tissue becomes 80 per cent stronger than before.

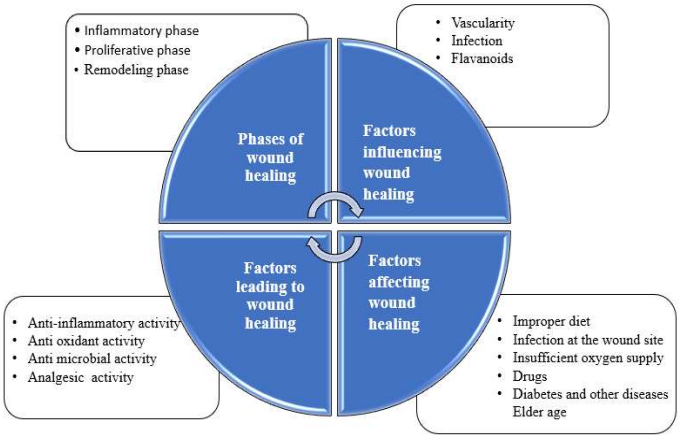


**Figure 2: Factors affecting, influencing and leading to wound healing**

## 4. Wound dressing

A **wound dressing** is a material applied to a wound to protect it, promote healing, and prevent infection. The main functions of a wound dressing include **shielding the wound from microbes and physical injury, absorbing excess exudate, maintaining a moist environment, reducing pain, and supporting tissue regeneration.** Proper dressing is crucial to avoid complications such as delayed healing, infection, or excessive scarring. Wound dressings can be broadly classified into **traditional and modern dressings.** The choice of dressing depends on the**wound type, depth, exudate level, and infection risk**. Proper selection and regular monitoring ensure faster healing, minimize pain, and improve overall patient outcomes.

### 4.1 Characteristics of an ideal wound dressing

An ideal wound dressing should have the following qualities:

a) Be economical and safe for patients (non-toxic and non-allergenic)
b) Act as a barrier to dirt, microbes, and foreign matter
c) Control or eliminate unpleasant odours from the wound
d) Reduce or prevent pain during use and removal
e) Provide physical protection against injury and friction
f) Maintain a moist environment that promotes faster healing
g) Absorb excess exudate without becoming oversaturated
h) Allow oxygen and carbon dioxide exchange through the material
i) Prevent infection by blocking microbial invasion

j) Help keep the wound at an optimal temperature and pH level
k) Be comfortable to wear, apply, and remove
l) Have an acceptable appearance and be cosmetically safe
m) Avoid leaving behind fibres or particles that may contaminate the wound
n) Encourage blood vessel growth and connective tissue formation
o) Not adhere to the wound surface, avoiding trauma during removal
p) Support white blood cell migration and enzyme activity for natural defense and repair

### 4.2 Types of wound dressings:

#### 4.2.1 Traditional wound dressings

Gauze, lint, plasters, bandages (natural or synthetic), and cotton wool are all dry wound dressings that are used as primary or secondary dressings to protect the wound from infection. Gauze dressings made of cotton, rayon, and polyester woven and nonwoven fibres provide protection against bacterial infection. With the aid of fibres in these dressings, certain sterile gauze pads are used to absorb exudates and fluid in an open wound. To avoid maceration of healthy tissues, these dressings must be changed frequently. The cost of gauze dressings is higher. Dressings become moistened and adherent to the wound as a result of prolonged wound drainage, rendering removal painful**.**

Bandages made of natural cotton wool and cellulose, synthetic bandages made of polyamide materials, serve different purposes. Cotton bandages, for example, are used to keep light dressings in place, while high compression bandages and short stretch compression bandages provide sustained compression in the case of venous ulcers.

Traditional dressings are usually used as secondary dressings for clean and dry wounds with moderate exudate levels. Traditional dressings have been replaced by modern dressings with more advanced formulations because they fail to provide a moist atmosphere for the wound.

#### 4.2.2 Modern dressings

Modern dressings act as a barrier to bacterial penetration into the wound environment. Modern dressings differ significantly from traditional dressings in that they maintain and create a moist environment around the wound, facilitating wound healing**.**They are primarily classified as hydrocolloids, alginates and hydrogels, films, and foams and are based on synthetic polymers. Modern wound dressings have been developed to aid in the function of the wound rather than simply covering it. These dressings are designed to keep the wound from drying out and to promote healing. Modern

wound dressings are typically made of synthetic polymers and can be classified as passive, interactive, or bioactive. Non-occlusive products, such as gauze and tulle dressings, are used to cover the wound and restore its function underneath. Interactive dressings are semi-occlusive or occlusive and come in films, foam, hydrogel and hydrogel forms.

## Hydrogel

Hydrogels are water-based cross-linked starch polymers that contain up to 96% water.Sheets, amorphous gels (dry or pre-mixed), and impregnated gauze all have the advantage of being available in a variety of physical states. Hydrogels are the perfect choice for dry wounds as they can rehydrate and maintain the wound moist. They can have a cooling effect on the wound, which can help to reduce chronic pain. Their absorptive ability is reduced due to their high water content, and they will not be ideal for a wound with excess exudate. Since hydrogels do not bind to the skin, they require a secondary dressing to form a protective. Dressings should be replaced every 1–3 days, depending on the wound hydration conditions.In a recent Cochrane study on hydrogels in diabetic foot ulcers, pooled data from three trials revealed that the hydrogel-treated group had a higher number of ulcers healed than the standard contact gauze dressing**.** Hydrogel dressings healed partial-thickness burns faster than the normal counterparts (paraffin gauze, paraffin gauze with antibiotics, or silver sulfadiazine) in another meta-analysis on dressings for superficial and partial-thickness burns Hydrogels may have their physical and chemical properties changed to produce a dynamically sensitive material that is temperature responsive, drug delivering, and photoresponsive

## Hydrocolloid

Hydrocolloids are made up of cross-linked polymer macromolecules with integrated adhesives and starches, such as cellulose, gelatin, pectin, and guar. They are available as papers, pastes, and powders. Hydrocolloids absorb water and form gels as they come into contact with wound exudates. Hydrocolloids can be beneficial for wounds over joints because they provide mild cushioning. In addition, they promote autolytic debridement. One disadvantage is that the dressing is opaque, limiting frequent wound checks. The gel that forms can also be thick, yellow, and odorous, giving it the appearance of infection. These dressings are suitable for abrasions, post-operative wounds, superficial pressure ulcers, and shallow leg ulcers, and should be replaced every 2–4 days depending on the rate of saturation Hydrocolloid dressings are superior to saline gauze or paraffin gauze for complete wound healing.

## Alginate

Alginate dressings are polysaccharides derived from seaweed or kelp. Alginate gel is formed when calcium ions in the dressing react with sodium ions in wound exudate. The gel is more absorbent, making it the best choice for strongly exudative wounds. These dressings absorb 15–20 times their weight of fluid, which may help patients with draining ulcer live a healthier lifestyle. The calcium released from the dressing has hemostatic properties that promote the clotting cascade. If these dressings are not changed at least weekly, they may dry and adhere to the wound base, which can be very painful for patients if not monitored properly. Clinically, these dressings are excellent for deep pressure ulcers, pyodermagangrenosum, and exudative ulcers on the lower extremities.

## Foam

Foam dressings are typically made of a polyurethane or silicone core with a semi-occlusive outer layer. The outer layer is water vapour permeable and may have varying moisture vapour transmission rates depending on the manufacturer, it also protects against bacterial penetration or leakage, and the polyurethane core aids in the absorptive property of dressing . Their ability to cushion wounds can provide relief and comfort. Foam dressings can be adherent or non-adherent, and in the latter case, a secondary film may be required. Foam dressings are extremely effective over bony prominences or within exudative cavities, and should be replaced as often as the dressing becomes saturated with exudate, which may be as much as once or twice weekly.

## Film

Films are made up of polyurethanaesheests, which is self adhesive and transparent. Films are thin, elastic, permeable to gas and vapour, but impermeable to bacteria and fluids. Visualization of wound and flexibility to use as a primary or secondary dressing is an added advantage as the films are transparent. The non-absorbent property of film may sometimes lead to accumulation of exudates and maceration of wound edges. Exudates may leak open if the dressing is not tightly sealed. Film dressings can be replaced regularly and are often used in clinical situations such as intravenous access covers, donor sites for minor split-thickness skin grafts, and superficial lacerations.

### Hydrofiber

Hydrofiber dressings are sodium carboxymethylcellulose sheets or ribbons that are highly absorbent. When hydrofibers absorb wound exudate, they form gels that keeps the wound moist while promoting autolytic debridement. Hydrofibers can absorb three times the amount of water as alginates. Because of their ability to pack into deep concave spaces, hydrofiber ribbons are particularly useful in deep wounds. Since the dressing expands when transferred to gel form, it's good to only pack up to 80% of the wound space. These dressings have been shown to be effective in partial-thickness donor sites and partial-thickness burns, and they should be replaced every three days at the very least

### 4.2.3 Modern dressings used in clinical practice.

### Semi-permeable film dressings

These dressings are made of a clear and adherent polyurethane that allows for the transfer of water vapour, oxygen, and carbon dioxide from the wound, as well as autolytic eschar debridement and bacteria resistance..Initially, occlusive films were produced from nylon derivatives with adhesive polyethylene frameworks as the support.

Originally, nylon-derived film dressings were not used for strongly exuding wounds because of their poor absorption ability, which resulted in maceration of the wound and surrounding healthy tissues**.** dressings, on the other hand, are highly elastic and flexible, and can conform to any shape without the need for additional tapping.

Because of the clear films, it is also possible to inspect the wound closure without removing the wound dressing. As a result, these dressings, such as OpsiteTM, TegadermTM, and Biooclusive TM, are recommended for epithelializing wounds, superficial wounds, and shallow wounds with low exudates. Vapour permeability, adhesive properties, conformability, and extrusion properties of commercially available film dressings vary..

### Semi-permeable foam dressings

Foam dressings are made up of hydrophobic and hydrophilic foam, often with adhesive The outer layer's hydrophobic properties keep liquid out while allowing gaseous exchange and water vapor to pass through. Silastic, a silicon-based rubber foam, molds and contours to the form of the wound. Depending on the thickness of the wound, foam has the potential to absorb different amounts of wound drainage.Foam dressings are available in both

adhesive and non-adhesive varieties. Foam dressings are recommended for granulating wounds, lower leg ulcers, and mild to severely exuding wounds. Due to their high absorbency and moisture vapour permeability, they are typically used as primary dressings for absorption and secondary dressings are not needed.The disadvantage of foam dressing is that it is time consuming.Foam dressings have the disadvantage of requiring regular dressings and are not appropriate for low exudating wounds, dry wounds, or dry scars that depend on exudates for healing, such as LyofoamTM, AllevynTM, and TielleTM.

### 4.5 Bioactive wound dressings

The present state of modern wound dressing is bioactive dressings, which are made of biomaterials that aid in the healing process. These dressings are known for their biocompatibility, biodegradability, and non-toxic nature, and are made up of collagen, hyaluronic acid, chitosan, alginate, and elastin, among other materials. Depending on the nature and form of wound, polymers of these materials are used alone or in combination. To aid wound healing, biological dressings are often combined with growth factors and antimicrobials.Many researchers have discussed collagen, a major structural protein, for its active function in the natural healing process..When collagen comes into contact with wound tissue, it triggers the development of fibroblasts and speeds up endothelial migration.

Hyaluronic acid (HA) is a glycoaminoglycan portion of the extracellular matrix (ECM) with distinct biological and physical properties. HA, like collagen, is biocompatible, biodegradable, and naturally immunogenic. Biological dressings are shown to be superior to other types of dressings as compared to other types of dressings.

### Tissue engineered skin substitutes

There are two types of tissueengineered substitutes for human skin or dermal equivalent (HSE) available. The first mimics the layer of skin composed of Keratinocytes and fibroblasts on collagen matrix (Cell containing matrix).Second contains only the dermal elements with fibroblast on collagen matrix (Acellular matrix).Bioengineered gels can adapt to their surroundings and release growth factors and cytokines that are incorporated into dressings. Diabetic foot ulcers and venous leg ulcers can both benefit from bioengineered dressings. Apligraf is an FDA-approved skin substitute for venous ulcers composed of keratinocytes and fibroblast-seeded collagen.AllodermTM, which is made up of natural human fibroblasts stripped of all cellular materials, and IntegraTM artificial skin, which is made up of a collagen/chondroitin 6

sulphate matrix overlaid with a thin silicone sheet, are two commercially available skin substitutes. LaserskinTM, BiobraneTM, BioseedTM, and Hyalograft3-DTM are a few other options.

## Medicated dressings

The elimination of necrotic tissues by medicated dressings plays a vital part in the healing process, either directly or indirectly. Cleaning or debriding agents for necrotic tissue, as well as antimicrobials that prevent infection and stimulate tissue regeneration, have all contributed to this. Antimicrobial agents, growth hormones, and enzymes are some of the most often used compounds. CutisorbTM is a commercially marketed antimicrobial dressing.Fibrous hydrocolloid, Polyurethane foam film, and silicone gels are examples of silver-impregnated treatments. Antiseptic Iodine dressing acts on bacterial cells by inducing oxidative breakdown of cell components, which disrupts protein function and is very efficient against pathogens. Iodine use for a long time causes skin irritation and discoloration. Antimicrobials are used to prevent or treat infections, particularly in diabetic foot ulcers.

The normal tissue repair process in the body is regulated by cellular activity mediated by growth factors that are naturally present in our system. In the treatment of chronic wounds, growth factors and cells are trapped in the wound bed by clots, impairing the healing process. Exogenous administration of growth factors promotes wound healing. Platelet-derived growth factor (PDGF) is the most used growth factor, promoting chemotactic recruitment and cell proliferation, enhancing angiogenesis.

Enzymatic debridement of necrotic tissues without causing injury to healthy tissue is an important aspect of promoting normal recovery. To breakdown necrotic tissue, papain and collagenase-based ointments are used. Collagenase attacks native collagen and is mild on healthy collagen by gradually breaking down tissue, whereas papain destroys cystein residue and is associated with an inflammatory response. DebridaceTM is a commercially available dressing that boosts proteolytic activity.

## Composite dressings

Composite dressings are flexible and comfortable for both partial and full thickness wounds. A composite or hybrid dressing is made up of multiple layers, each of which has a specific physiological function. The composite dressings are composed of three layers. As an adhesive border for composite dressings, nonwoven fabric tape or clear film can be employed. They can be used as a primary or secondary dressing on a variety of wounds and can be

utilised for topical medicines.The outermost layer protects the wound from infection, the intermediate layer has absorptive material to keep the wound moist and promote autolytic debridement, and the bottom layer is composed of non adherent material to prevent it from adhering to the young granulating tissues. Composite dressings are more expensive and less versatile.

| Dressing type | Description | Characteristics | Advantages | Disadvantages | Commercially available products | Suitable for |
|---|---|---|---|---|---|---|
| **Hydrogel** | Three-dimensional network of hydrophilic polymers | Moisturizing, removal of necrotic tissue, and monitoring of the wound without removing the dressing | Moisture retentive Nontraumatic removal | May over hydrate | Carrasyn, Curagel, Nu-Gel, Purilon, Restore, SAF-gel, XCell | Pressure ulcers, surgical wounds, burns, radiation dermatitis |
| **Hydrocolloid** | Hydrogel mixed with synthetic rubber and sticky materials | Excellent exudate absorption properties | Absorbent Occlusive protection from contamination | Opaque Fluid trapping malodorous discharge | Aquacel, Comfeel, DuoDERM, Granuflex, Tegasorb | Severe exudative wound |
| **Alginate** | Consists of polysaccharides derived from brown seaweed | Excellent exudate absorption properties, hemostasis | Highly absorbent Hemostatic Non-toxic, non allergenic | Fibrous debris | Algisite, Kaltostat, Sorbsan, Tegagen | Infected and non-infected wounds with a large amount of exudates |
| **Foam** | Consists of polyurethane or is silicone-based | Semipermeability, thermal insulation, antimicrobial activity | Absorbent Occlusive Thermal insulation | Opaque Malodorous discharge | 3M Adhesive Foam, Allevyn, Lyofoam, Tielle | Infected wounds |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Film** | Consists of adhesive, porous, and thin transparent polyurethane | Autolytic debridement properties, impermeable to liquids and bacteria | Transparent Occlusive moisture retentive protection from contamination Easy to inspect wounds | No absorption Fluid trapping skin stripping not for infected wounds | Bioclusive, Blisterfilm, Cutifilm, Flexigrid, OpSite, Tegaderm Occlusive, | Epithelializing wounds and superficial wounds with limited exudate |

**Table 1 : Types of modern wound dressings**

## 5. Conclusion

Effective wound management necessitates a comprehensive understanding of wound pathophysiology, classification, and the intricate phases of healing. The evolution of wound dressings—from traditional cotton and gauze to advanced hydrocolloid, hydrogel, foam, alginate, film, hydrofiber, bioactive, and composite systems—reflects a paradigm shift from passive coverage to active modulation of the wound microenvironment. Modern dressings not only maintain optimal moisture, absorb exudates, and prevent infection but also promote cellular migration, angiogenesis, and autolytic debridement, thereby accelerating tissue regeneration. Bioengineered and medicated dressings, particularly those incorporating growth factors, antimicrobial agents, and extracellular matrix components, further enhance healing in chronic, complex, and non-healing wounds. The selection of an appropriate dressing must be evidence-based, taking into account wound etiology, depth, exudate, microbial load, and patient-specific factors to optimize therapeutic outcomes. Overall, integrating advanced wound dressings with a mechanistic understanding of healing processes represents a sophisticated, patient-centered approach that improves tissue repair, minimizes complications, and enhances the overall quality of care in both acute and chronic wound management.

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# Efficacy of Eco Enzyme and Compost Tea on the Growth of Corriander (*Corriandrum sativum* .L)

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## Abstract

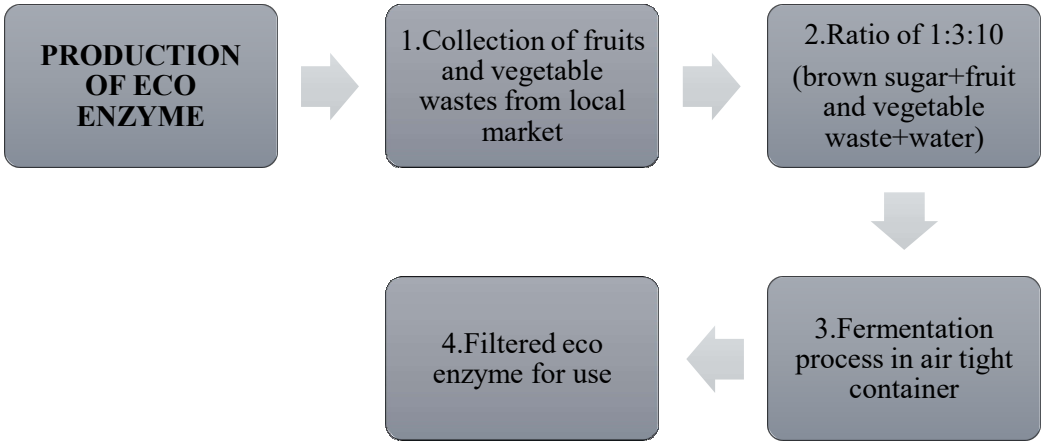
In the human diet vegetables and fruits play a major role. It is a healthy part in diet system of our body. There is no single fruit and vegetable will provides all the nutrients in the diet. There is lot of health benefits in consuming fruits and vegetables. There is some fruits and vegetables that can cure some diseases. Vegetable waste is a biodegradable material wasted in large amounts which is dumped on the land. It can be emits the foul odor. So the vegetable wastes such as peels, rotten, seeds are used for the fermentation process in many industries to produce alcohol which are used as a solvent system. Fruit and vegetable skin are contains many nutrients they are fiber, vitamins, minerals and anti oxidants. But the people eat only the pulp of the fruit. So the peels of the fruits were wasted. Fruit waste is also a bio degradable material which was wasted in large amounts now days. The fruit wastes such as skin of the fruits and seeds of some plants are used in the format of eco enzyme.Eco enzyme is a fermented solution from mixture of brown sugar ,waste and water in the ratio of 1: 3 : 10. Usually the eco enzyme is acidic in nature because the solution in the container will convert carbohydrates into volatile acids. So the pH of the solution should be maintained through the acidic condition .Brewed tea leaves make a fabulous fertilizer, both in your garden as well as helping potted plants indoors. The brewed leaves contain high levels of minerals, carbohydrates, and other nutrients that create a rich soil.In this study the eco enzymes are prepared from the vegetable and fruit waste and poured it into a soil to detect the nutrient level. At the same time the waste tea powder is collected then made up into compost and poured in the soil. After that the soil was taken for the experiment and evaluates the value of soil nutrients and then analyzed the plant growth. From the soil sample the best growth of the soil was characterized. The coriander plant was taken for the experiment.

## 1. Materials And Methods

### Phase I:

**1. Collection of Sample Material**

**2. Eco Enzyme Production**




### *Eco- Enzymes*

The eco enzyme solution was tested based on the parameters such as pH, total solids(TS), total dissolved soilds (TDS), total suspended solids (TSS), and chemical oxygen demand (COD), Bio-Chemical Oxygen Demand Test (BOD).

### Physio-Chemical Parameter Analysed in Eco Enzyme Solution

**Total Solids (TS)**

**Total Dissolved Solids (TDS)**

Water is a good solvent and picks up impurities easily. Pure water-tasteless, colorless and odorless – is often called the universal solvent. Any minerals metals, ions (i.e) cations and anions

**Total Suspended Solids (TSS)**

**Bio-Chemical Oxygen Demand (BOD)**

**Chemical Oxygen Demand (COD)**

## 1. Phytochemical Analysis in Eco Enzymes

**1.1 Test for Carbohydrates**

**1. 2. Test for Proteins**

**1.3. Test for Amino Acids**

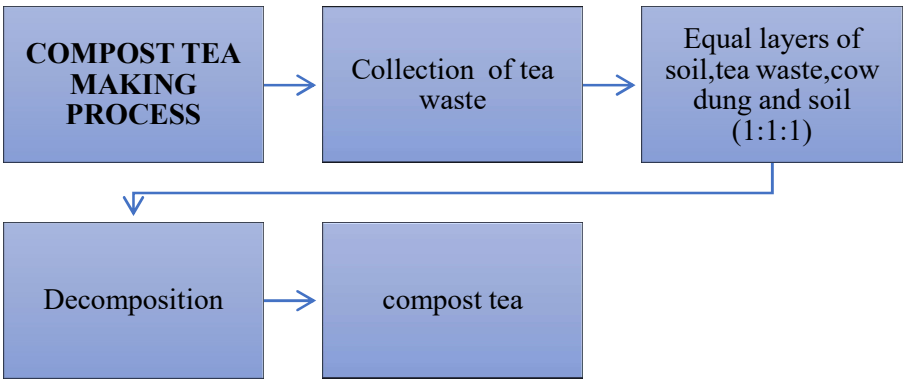
**1.4 Test for Saponins**

**1. 5. Test for Alkaloids**

### Phase II:-

## 2. Preparation of Compost Tea

The compost was prepared using the tea powder that was thrown away after the use. It was collected from houses and tea stalls. Equal layers of soil, tea waste, cow dung and the soil were laid at the top of the other. These are allowed to decompose for the period of three months and the temperature was monitored regularly. The temperature rise initially. When the decomposition process will takes place temperature of the compost was decreased. Decreased temperature showed that the compost was ready and the compost tea was taken for the further process. The following chart explains the process of compost making from tea waste.




## 2. Qualitative Phytochemical Analysis in Compost Tea

**2.1 Test for Tannins**

**2.2 Test For Flavonoids**

**2. 3. Test for Phenols**

**2.4. Test for Anthocyanins**

**2. 5. Test for Carbohydrates**

**Phase III:-**

**3.1. Soil Sample Testing**

Totally 3 samples were taken. Normal soil sample was taken as a control, eco enzyme with soil was sample 2 and compost tea with soil taken as a sample 3.These samples were tested to analyse the value of the macro nutrients.

**3.2. Test for The pH of Soil Sample**

**3.3 Test for Organic Carbon**

**3.4. Test for Available Phosphorus**

**3.5. Test for Available Potassium**

**3.6. Test for Available Nitrogen**

TABLE 1: Methods Used to Measure Physio Chemical Properties of Soil

| S.No | Parameter | Methods |
|---|---|---|
| **1.** | pH | Digital pH meter |
| **2.** | Organic carbon | Walkley and black Method |
| **3.** | Available phosphorus | Oslen P method |
| **4.** | Available potassium | Flame photometer (1954) |
| **5.** | Available nitrogen | Infrared sensors |

The above table indicates the methods used for measuring the various soil sample's organic matters. After the soil samples tested. It would be survived under the control for the plant growth. The three samples were taken separately. One is taken as a control 2$^{nd}$ one is with eco enzyme solution, and 3$^{rd}$ one is with tea decoction compost. Here the coriander seeds are used for the studies. About 30 coriander seeds are taken in an each soil sample. The growth of the plant was analysed in a weekly condition. On the second week, 25 seeds out of 30 seeds are germinate in the eco enzyme sample and 20 seeds are germinate in the compost tea sample. The normal soil will produce a slow germination.

After the plants were harvested and analysed for

1. Carbohydrate Estimination (Anthrone Method)
2. Starch Estimination
3. Chlorophyll Estimination in the grown plant samples.

## Results and Discussion

Lot of wastes from our society is dumped in the ground which will creates major pollution. Some wastes such as vegetable and fruit wastes, waste tea decoction are used in the horticulture in recent days.

### Phase I:-

Fruits and vegetable wastes (biodegradable) are collected from the Erode district and waste samples were allowed for fermentation. After the fermentation the filtered supernatant were collected.

### 5. 1. Physio-Chemical Properties During the Fermentation Process (30 Days Interval):

Temperature and pH observed during fermentation process:-

Physical parameters such as pH and temperature were analysed during the fermentation period. As shown in the above chart, pH was found to be about 3, which indicated the acidic nature of the eco enzyme. The temperature was observed, in the fermentation period which was increased.

### 5. 2. Characteristics Of Eco Enzyme

In the fermentation period, the carbohydrates from the vegetable waste and fruit wastes were converted into volatile acids. Due to the presence of volatile acids and organic acids eco enzymes shows acidic condition. (C.Arun and P.Sivashanmugan, 2015).

Table 2: Characteristics of Eco Enzyme

| S. No | Tests | Value |
|---|---|---|
| 1. | pH | 3.7 |
| 2. | TS | 2676.00 mg/l |
| 3. | TDS | 2215.00 mg/l |
| 4. | TSS | 110.00 mg/l |
| 5. | COD | 162000.00 mg/l |
| 6. | BOD | 38200.00 mg/l |

From the above table, the measured values of the pH, total solids, total dissolved solid (TDS), total suspended solids(TSS), chemical oxygen demand(COD), and biological oxygen demand(COD) are established. In this the pH of the eco enzyme is acidic in condition. The biological oxygen demand is in high level which means the eco enzyme contains more organic matters.

Chemical oxygen demand is one which is also used to measure the organic matter by using chemical reagents. Total dissolved solid (TDS) level was high so it denotes that the organic matters, calcium and minerals are present in the eco enzyme solution. The suspended solids (TSS) that were trapped by filters. Normal value were maintained in the TSS level. Total solids wasan combination of total dissolved solids and total suspended solids.

Table 3: Phytochemical Analysis in Eco Enzyme Solution

| Tests | Present | Absent |
|---|---|---|
| Test for Carbohydrates | - | + |
| Test for Proteins | + | - |
| Test for Amino Acids | + | - |
| Test for Saponins | + | - |
| Test for Alkaloids | + | - |

The phytochemicals that were present in the eco enzyme are proteins, amino acids, saponins and alkaloids. The above table indicated the presence of phytochemicals in eco enzyme solution. In the above table presence of proteins and amino acids indicates that the garbage solution posses the enzyme activity and the presence of saponins denotes that it will be capable for the saponification process and it will be used as a biological cleaner instead of chemical cleaners. Carbohydarates are absent in the samples.

**Phase II:-**

The waste tea powder (Tea decoction) were collected &taken in a wet format. The tea decoction was mixed with cow dung (1:1) and allowed for decomposition. The compost was prepared and used for plant growth.

Table 4: Qualitative Phytochemical Analysis in Compost Tea

| Tests | Present | Absent |
|---|---|---|
| Test for Tannins | + | - |
| Test for Flavonoids | + | - |
| Test for phenols | + | - |
| Test for Anthocyanins | + | - |
| Test for Carbohydrates | - | + |

Tea a calorie free beverage and it doesn't contain carbohydrate content. From the above table the carbohydrates are absent. The phytochemicals that were present in the compost tea were Tannins, Flavonoids, Phenols & Anthocyanins.

**Phase III:-**

The prepared eco enzyme and compost tea were mixed with soil and the soil was taken for the analysis of nutrient content.

Table 5:Nutrient Content in Different Samples

| **Parameters** | **Control ( soil)** | **Eco –Enzyme + soil** | **Compost tea + Soil** |
|---|---|---|---|
| ***pH*** | 7.89 | 7.78 | 8.04 |
| ***EC*** | 0.73ds/m | 0.91 ds/m | 0.72 ds/m |
| ***Organic Carbon*** | 0.32% | 0.21% | 0.19% |
| ***Available nitrogen*** | 228.1kg/hec | 272.2kg/hec | 253.3kg/hec |
| ***Available phosphorus*** | 11.4kg/hec | 11.8kg/hec | 11.4kg/hec |
| ***Available potassium*** | 254.5kg/hec | 274.2kg/hec | 268.3kg/hec |

From the above table the value of the pH,electrical conductivity,organic carbon, available nitrogen, available phosphorus and available potassium of the 3 different sampleswere identified. The pH of the control, eco enzyme and compost tea soil were 7.8, 7.8 and 8.02 respectively. The result demonstrate that the significant increase in the electrical conductivity (0.91 ds/m), Nitrogen (272.2 kg/hec), Phosphorus (11.8 kg/ hec) and potassium (274.2 kg/hec) in eco enzyme, when compared with control and compost tea soil sample.

ItwasobservedthatthegerminationtimeofseedlingwAs6dayswithEco-EnzymewhileseedlingstookdaystogerminatewithoutEco-Enzyme.

**pH:- Electrical Conductivity**:

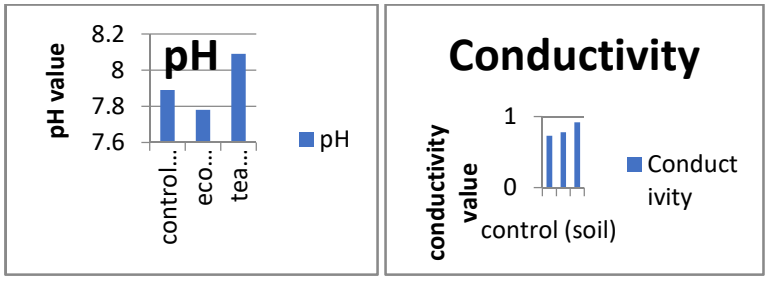
Soils can be naturally acid or alkaline, and this can be measured by testing their pH value.

Soils are classified according to their pH value:

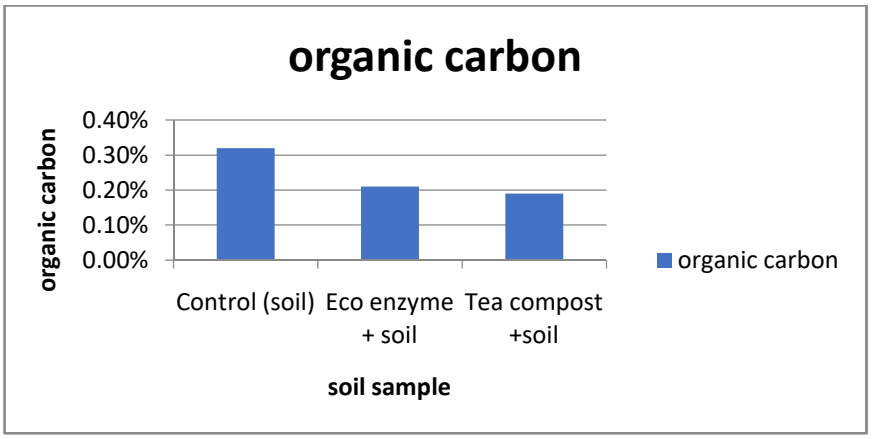
- 6.5 to 7.5—neutral

- above 7.5—alkaline
- less than 6.5—acidic, and soils with pH less than 5.5 are considered strongly acidic.

**pH ,ECLevel in the Control, Eco Enzyme + Soil and Tea Compost + Soil**



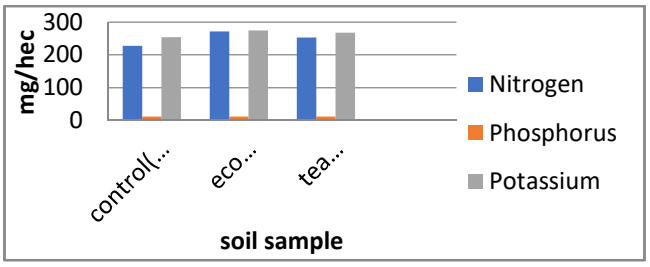

**Organic Carbon:-**




**Available Nitrogen, Phosphorus, Potassium**:

The normal range of the available nitrogen in soil is 180 – 450 kg/hectre. 1 hectre equals to 2 acre. On the above table the 3 soil samples have the available nitrogen. The normal range of the available phosphorus 11-22 kg / hectre. From the above table the phosphorus level doesn't exceed to the normal range. The normal range of the available potassium 118-280 kg / hectre. The eco enzyme made from the fruits and vegetable waste increase the soil nutrients level. Among them the compost tea has nearly same effect to soil macro nutrients.

## Macro Nutrients Level in 3 Samples




The above chart explains the net value of Available Nitrogen, Phosphorus, Potassium level in 3 samples. From that the Eco enzyme soil sample contains a more nutiritional value than other samples. The macro nutrients playsan major role in the soil environment. According to that soil analysis, Compost tea soil was more efficient than the control soil. Whereas the Eco enzyme soil sample is more efficient than the other 2 samples.

## Phase IV:-

The soil samples were used to grow plant. Here *Corriandrum sativum L.* plant seeds are taken for the process. The plants were grown and harvested. The harvested plants were go for an quantitative estimation.

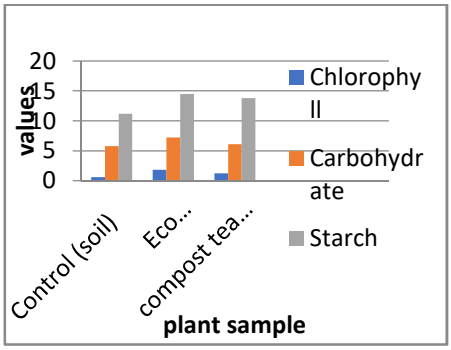
The Average HeightAnd Number of Leaves of*Corriandrum sativum LPLANT* Grownin Different Soil Samples

| | | **Control (soil )** | **Eco enzyme + Soil** | **Compost tea + Soil** |
|---|---|---|---|---|
| **Week 2** | Average height (in cm) | 3cm | 4cm | 5cm |
| | No. Of leaves | 2 | 2 | 2 |
| **Week 3** | Average height (in cm) | 4cm | 6cm | 5.8cm |
| | No. Of leaves | 2 | 6 | 5 |
| **Week 4** | Average height (in cm) | 5cm | 9cm | 7cm |
| | No. Of leaves | 3 | 12 | 10 |

The Average Height and Number of Leaves of *Corriandrum sativum L Plant* Grownin Different Soil Samples

| S. No | Parameters | Control ( soil ) | Eco enzyme + soil | Compost tea + Soil |
|---|---|---|---|---|
| 1. | Chlorophyll | 0.58 | 1.80 | 1.23 |
| 2. | Carbohydrate | 5.8 | 7.2 | 6.1 |
| 3. | Starch | 11.2 | 14.5 | 13.8 |

## Quantitative Phytochemical Analysis in Plants Grown Using 3 Samples




The table 6 showed that the coriander plant growth in eco enzyme soil was maximum 9 cm long along with the leaves of 12 as compared to the growth of coriander plants grown in compost tea 7cm long with 10 leaves respectively. The eco enzyme increased the amount of chlorophyll, carbohydrate content and starch content in the plant as well as the compost tea increased the chlorophyll, starch and carbohydrate content when compared to the control soil. The compost tea also acted as a pest control.

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# Cell Organelles

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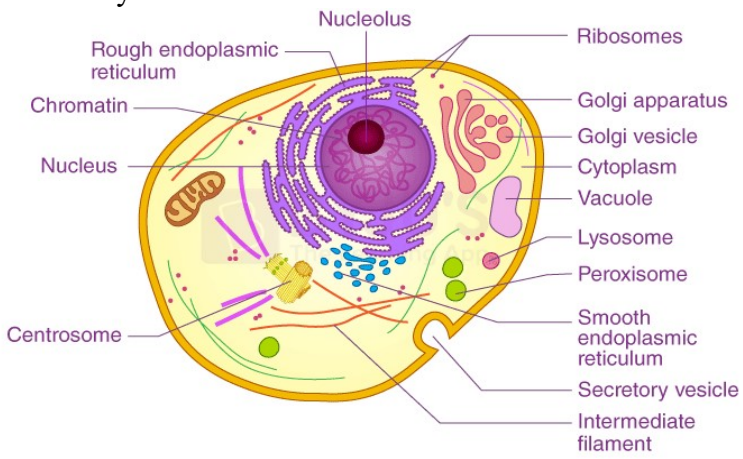
## Cell

A cell is the basic structural and functional unit of all living organisms. It is the smallest unit of life that can carry out all the processes necessary for life. Organisms can be unicellular (one cell) or multicellular (many cells). The cells provide shape, structure and carry out different types of functions to keep the entire system active. The cell contains different functional structures which are collectively called organelles.

- The Cell wall, Ribosomes, and Cytoskeleton are non-membrane-bound cell organelles. They are present both in the prokaryotic cell and the eukaryotic cell.
- **Single membrane-bound organelles:** Vacuole, Lysosome, Golgi Apparatus, Endoplasmic Reticulum are single membrane-bound organelles present only in a eukaryotic cell.
- **Double membrane-bound organelles:** Nucleus, mitochondria and chloroplast are double membrane-bound organelles present only in a eukaryotic cell.



## Cell Organelles

**Cell organelles** are specialized structures within a cell that perform distinct functions to keep the cell alive and functioning properly. Here are some major cell organelles and their functions:

### 1. Plasma Membrane

- The plasma membrane is also termed as a Cell Membrane or Cytoplasmic Membrane. It is a selectively permeable membrane of the cells, which is composed of a lipid bilayer and proteins.
- The plasma membrane is present both in plant and animal cells.
- It functions as the selectively permeable membrane, by permitting the entry of selective materials in and out of the cell according to the requirement.
- In an animal cell, the cell membrane functions by providing shape and protects the inner contents of the cell.
- Based on the structure of the plasma membrane, it is regarded as the fluid mosaic model.
- According to the fluid mosaic model, the plasma membranes are subcellular structures, made of a lipid bilayer in which the protein molecules are embedded.

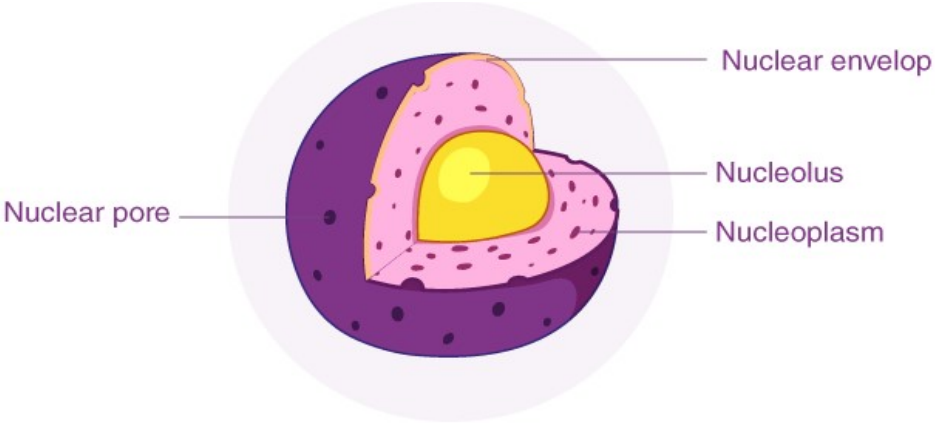
### 2. Cytoplasm

- The cytoplasm is present both in plant and animal cells.
- They are jelly-like substances, found between the cell membrane and nucleus.
- They are mainly composed of water, organic and inorganic compounds.
- The cytoplasm is one of the essential components of the cell, where all the cell organelles are embedded.
- These cell organelles contain enzymes, mainly responsible for controlling all metabolic activity taking place within the cell and are the site for most of the chemical reactions within a cell.

### 3. Nucleus

- The nucleus is a double-membraned organelle found in all eukaryotic cells.

- It is the largest organelle, which functions as the control centre of the cellular activities and is the storehouse of the cell's DNA.
- By structure, the nucleus is dark, round, surrounded by a nuclear membrane. It is a porous membrane (like cell membrane) and forms a wall between cytoplasm and nucleus.
- Within the nucleus, there are tiny spherical bodies called nucleolus. It also carries an essential structure called chromosomes.
- Chromosomes are thin and thread-like structures which carry another important structure called a gene.
- Genes are a hereditary unit in organisms i.e., it helps in the inheritance of traits from one generation (parents) to another (offspring).
- Hence, the nucleus controls the characters and functions of cells in our body.
- The primary function of the nucleus is to monitor cellular activities including metabolism and growth by making use of DNA's genetic information.
- Nucleoli in the nucleus are responsible for the synthesis of protein and RNA.




## 4. Endoplasmic Reticulum

- The Endoplasmic Reticulum is a network of membranous canals filled with fluid.

- They are the transport system of the cell, involved in transporting materials throughout the cell.
- There are two different types of Endoplasmic Reticulum:

### 1. Rough Endoplasmic Reticulum

They are composed of cisternae, tubules, and vesicles, which are found throughout the cell and are involved in protein manufacture.

### 2. Smooth Endoplasmic Reticulum

They are the storage organelle, associated with the production of lipids, steroids, and also responsible for detoxifying the cell.

## 5. Plastids

- Plastids are large, membrane-bound organelles which contain pigments. Based on the type of pigments, plastids are of three types:

### 5.1 Chloroplasts

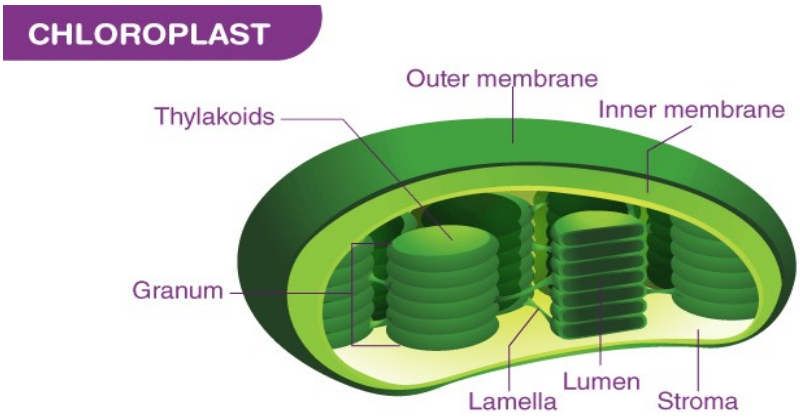
- Chloroplasts are double membrane-bound organelles, which usually vary in their shape – from a disc shape to spherical, discoid, oval and ribbon. They are present in mesophyll cells of leaves, which store chloroplasts and other carotenoid pigments.
- These pigments are responsible for trapping light energy for photosynthesis.
- The inner membrane encloses a space called the stroma.
- Flattened disc-like chlorophyll-containing structures known as thylakoids are arranged in a stacked manner like a pile of coins.
- Each pile is called a granum (plural: grana) and the thylakoids of different grana are connected by flat membranous tubules known as stromal lamella.
- Just like the mitochondrial matrix, the stroma of chloroplast also contains a double-stranded circular DNA, 70S ribosomes, and enzymes which are required for the synthesis of carbohydrates and proteins.

### 5.2 Chromoplasts

- The chromoplasts include fat-soluble, carotenoid pigments like xanthophylls, carotene, etc.
- In which provide the plants with their characteristic color – yellow, orange, red, etc.

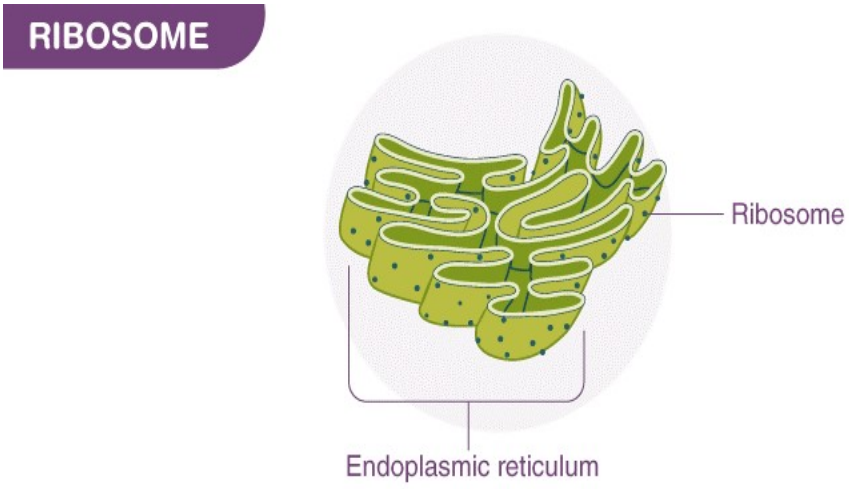
### 5.3. Leucoplasts

- Leucoplasts are colorless plastids which store nutrients.
- Amyloplasts store carbohydrates (like starch in potatoes), aleuroplasts store proteins, and elaioplasts store oils and fats.



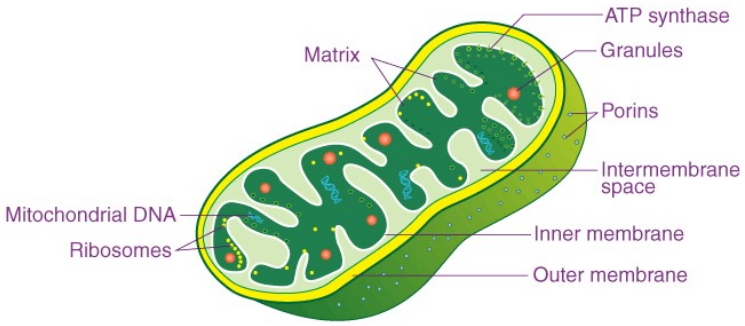

## 6. Ribosomes

- Ribosomes are non membrane-bound and important cytoplasmic organelles found in close association with the endoplasmic reticulum.
- Ribosomes are found in the form of tiny particles in a large number of cells and are mainly composed of 2/3rd of RNA and 1/3rd of protein.
- They are named as the 70s (found in prokaryotes) or 80s (found in eukaryotes) The letter S refers to the density and the size, known as Svedberg's Unit.
- Both 70S and 80S ribosomes are composed of two subunits.
- Ribosomes are either encompassed within the endoplasmic reticulum or are freely traced in the cell's cytoplasm.
- Ribosomal RNA and Ribosomal proteins are the two components that together constitute ribosomes.
- The primary function of the ribosomes includes protein synthesis in all living cells that ensure the survival of the cell.




## 7. Mitochondria:

- **"**Mitochondria are membrane-bound organelles present in the cytoplasm of all eukaryotic cells, that produce adenosine triphosphate (ATP), the main energy molecule used by the cell."
- Popularly known as the "**Powerhouse of the cell**," mitochondria (singular: mitochondrion) are a double membrane-bound organelle found in most eukaryotic organisms. They are found inside the cytoplasm and essentially function as the cell's "digestive system."
- They play a major role in breaking down nutrients and generating energy-rich molecules for the cell. Many of the biochemical reactions involved in cellular respiration take place within the mitochondria.
- The term 'mitochondrion' is derived from the Greek words "***mitos***" and "***chondrion***" which means "**thread**" and "**granules-like**", respectively.
- It was first described by a German pathologist named Richard Altmann in the year 1890.




## Structure of Mitochondria

- The mitochondrion is a double-membraned, rod-shaped structure found in both plant and animal cell.
- Its size ranges from 0.5 to 1.0 micrometre in diameter.
- The structure comprises an outer membrane, an inner membrane, and a gel-like material called the matrix.
- The outer membrane and the inner membrane are made of proteins and phospholipid layers separated by the intermembrane space.
- The outer membrane covers the surface of the mitochondrion and has a large number of special proteins known as porins.

### *Cristae*

- The inner membrane of mitochondria is rather complex in structure.
- It has many folds that form a layered structure called cristae, and this helps in increasing the surface area inside the organelle.
- The cristae and the proteins of the inner membrane aid in the production of ATP molecules.
- The inner mitochondrial membrane is strictly permeable only to oxygen and ATP molecules.
- A number of chemical reactions take place within the inner membrane of mitochondria.

### *Mitochondrial Matrix*

- The mitochondrial matrix is a viscous fluid that contains a mixture of enzymes and proteins.
- It also comprises ribosomes, inorganic ions, mitochondrial DNA, nucleotide cofactors, and organic molecules.
- The enzymes present in the matrix play an important role in the synthesis of ATP molecules.

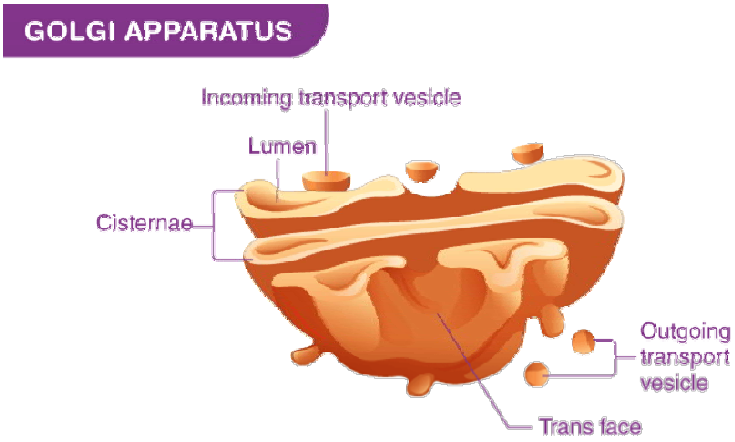
### *Functions of Mitochondria*

- The most important function of mitochondria is to produce energy through the process of oxidative phosphorylation.It is also involved in the following process:

1. Regulates the metabolic activity of the cell
2. Promotes the growth of new cells and cell multiplication
3. Helps in detoxifying ammonia in the liver cells
4. Plays an important role in apoptosis or programmed cell death
5. Responsible for building certain parts of the blood and various hormones like testosterone and oestrogen
6. Helps in maintaining an adequate concentration of calcium ions within the compartments of the cell
7. It is also involved in various cellular activities like cellular differentiation, cell signalling, cell senescence, controlling the cell cycle and also in cell growth.

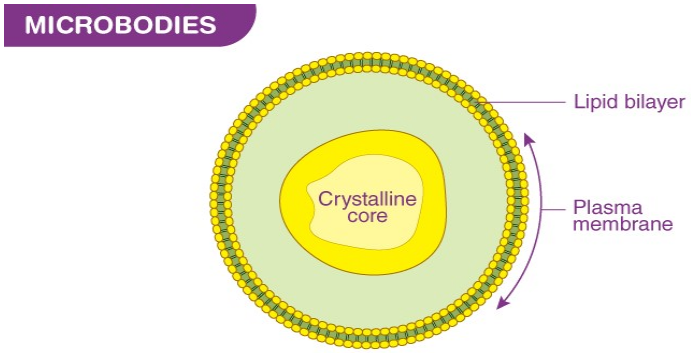
## 8. Golgi Apparatus

- Golgi Apparatus is also termed as Golgi Complex.
- It is a membrane-bound organelle, which is mainly composed of a series of flattened, stacked pouches called cisternae.
- This cell organelle is primarily responsible for transporting, modifying, and packaging proteins and lipids to targeted destinations.
- Golgi Apparatus is found within the cytoplasm of a cell and is present in both plant and animal cells.




## 9. Microbodies

- Microbodies are membrane-bound, minute, vesicular organelles, found in both plant and **animal cells.**
- They contain various enzymes and proteins and can be visualized only under the electron microscope.



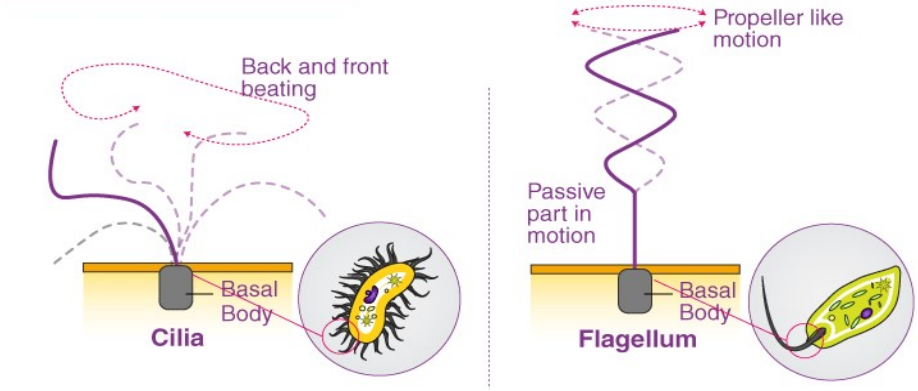

## 10. Cytoskeleton

- It is a continuous network of filamentous proteinaceous structures that run throughout the cytoplasm, from the nucleus to the plasma membrane.
- It is found in all living cells, notably in the eukaryotes.
- The cytoskeleton matrix is composed of different types of proteins that can divide rapidly or disassemble depending on the requirement of the cells.

- The primary functions include providing the shape and mechanical resistance to the cell against deformation, the contractile nature of the filaments helps in motility during cytokinesis.

## 11. Cilia and Flagella

- Cilia are hair-like projections, small structures, present outside the cell wall and work like oars to either move the cell or the extracellular fluid.
- Flagella are slightly bigger and are responsible for the cell movements. The eukaryotic flagellum structurally differs from its prokaryotic counterpart.
- The core of the cilium and flagellum is called an axoneme, which contains nine pairs of gradually arranged peripheralmicrotubules and a set of central microtubules running parallel to the axis.

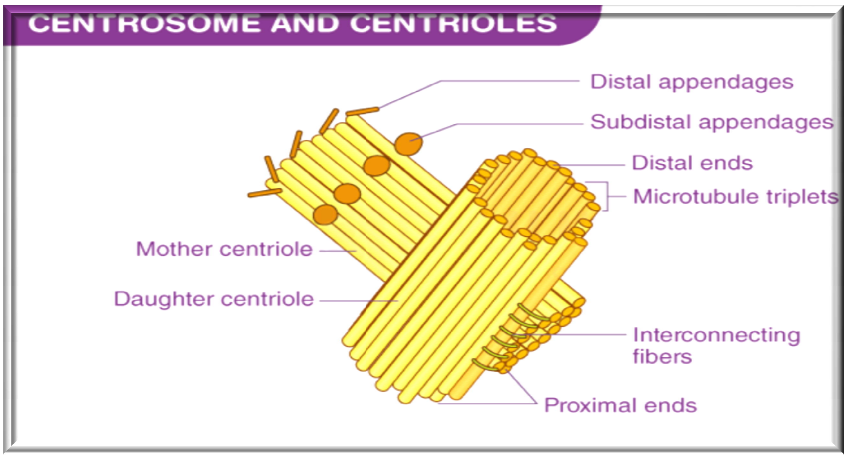



- The central tubules are interconnected by a bridge and are embedded by a central sheath.
- One of the peripheral microtubular pairs is also interconnected to the central sheath by a radial spoke.
- Hence there are a total of 9 radial spokes. The cilia and flagella emerge from centriole-like structures called basal bodies.

## 12. Centrosome and Centrioles

- The centrosome organelle is made up of two mutually perpendicular structures known as centrioles.
- Each centriole is composed of 9 equally spaced peripheral fibrils of tubulin protein, and the fibril is a set of interlinked triplets.

- The core part of the centriole is known as a hub and is proteinaceous.
- The hub connects the peripheral fibrils via radial spoke, which is made up of proteins.
- The centrioles from the basal bodies of the cilia and flagella give rise to spindle fibres during cell division.




## 13. Vacuoles

- Vacuoles are mostly defined as storage bubbles of irregular shapes which are found in cells.
- They are fluid-filled organelles enclosed by a membrane.
- The vacuole stores the food or a variety of nutrients that a cell might need to survive.
- In addition to this, it also stores waste products. The waste products are eventually thrown out by vacuoles.
- Thus, the rest of the cell is protected from contamination. The animal and plant cells have different size and number of vacuoles. Compared to the animals, plant cells have larger vacuoles.

*A Brief Summary on Cell Organelles*

| Cell Organelles | Structure | Functions |
|---|---|---|

| | | |
|---|---|---|
| Cell membrane | A double membrane composed of lipids and proteins. Present both in plant and animal cells. | Provides shape, protects the inner organelles of the cell and acts as a selectively permeable membrane. |
| Centrosomes | Composed of centrioles and found only in the animal cells. | It plays a major role in organizing the microtubule and cell division. |
| Chloroplasts | Present only in plant cells and contains a green-coloured pigment known as chlorophyll. | Sites of photosynthesis. |
| Cytoplasm | A jelly-like substance, which consists of water, dissolved nutrients and waste products of the cell. | Responsible for the cell's metabolic activities. |
| Endoplasmic Reticulum | A network of membranous tubules, present within the cytoplasm of a cell. | Forms the skeletal framework of the cell, involved in the detoxification, production of lipids and proteins. |
| Golgi apparatus | Membrane-bound, sac-like organelles, present within the cytoplasm of the eukaryotic cells. | It is mainly involved in secretion and intracellular transport. |
| Lysosomes | A tiny, circular-shaped, single membrane-bound organelles, filled with digestive enzymes. | Helps in the digestion and removes wastes and digests dead and damaged cells. Therefore, it is also called as the "suicidal bags". |
| Mitochondria | An oval-shaped, membrane-bound organelle, also called as the "Powerhouse of The Cell". | The main site of cellular respiration and also involved in storing energy in the form of ATP molecules. |
| Nucleus | The largest, double membrane-bound organelles, which contains all the cell's genetic information. | Controls the activity of the cell, helps in cell division and controls the hereditary characters. |
| Peroxisome | A membrane-bound cellular | Involved in the metabolism |

| | | |
|---|---|---|
| | organelle present in the cytoplasm, which contains the reducing enzyme. | of lipids and catabolism of long-chain fatty acids. |
| Plastids | Double membrane-bound organelles. There are 3 types of plastids:<br>1. **Leucoplast** –Colourless plastids.<br>2. **Chromoplast**–Blue, red, and yellow colour plastids.<br>3. **Chloroplast** – Green coloured plastids. | Helps in the process of photosynthesis and pollination, imparts colour to leaves, flowers, fruits and stores starch, proteins and fats. |
| Ribosomes | Non-membrane organelles, found floating freely in the cell's cytoplasm or embedded within the endoplasmic reticulum. | Involved in the synthesis of proteins. |
| Vacuoles | A membrane-bound, fluid-filled organelle found within the cytoplasm. | Provide shape and rigidity to the plant cell and help in digestion, excretion, and storage of substances. |

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# Microtomy

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## Introduction

- Microtome is an instrument with the help of which sections of tissues are cut and the process of cutting thin sections is known as Microtomy.
- The thickness of sections produced during microtomy may be between fractions of 50-100 nm, in ultramicrotomy, to several 100 microns.
- The common range is between 5-10m but both the maximum and minimum thickness is limited by the consistency of relation of the thickness of sections to the nature of tissues.
- These sections are stained using suitable staining techniques followed by observing them under the microscope.

### Types of microtomes

#### 1.) Rotary microtome

- The Rotary microtome is so-called because of a Rotary action of the hand wheel responsible for the cutting moment.
- The block holder is mounted on a steel carriage, which makes up and down in groves this type of instrument is the most ideal for routine and research work it is excellent for cutting serial sections.

#### Parts of the rotary microtomes

- Block holder
- Knife clamp screw
- Knife clamps
- Block adjustment
- Thickness gauge
- The angle of tilt adjustment

- Operating handle

## Working Principle

- Here the feed mechanism is activated by turning a wheel on one side of the machine.
- The knife is fixed with its edge fixed upwards and the object is moved against the knife rising and falling vertically.
- One rotation of the operating wheel produces a complete cycle downwards cutting stroke and an upward return stroke and activation of the advanced mechanism.
- It is often modified to cut ultrathin sections between 50Å – 200Å
- The wheel may be electrically operated or manually.
- In the former case the hands may be made free for tissue maintenance, makes it available for incorporation in automated cryostats.

## Advantages of the Rotary microtome

- Heavy and stable.
- Ideal for serial sections in large numbers.
- Paraffin-embedded tissues are cut by a rotary microtome.
- The knife holder is movable.
- The sections are cut are flat.
- It is useful for routine and research papers.

## 2.) Sliding or Base Sledge Microtome

- This is a large heavy instrument with a fixed knife beneath which the object moves mounted on a heavy sliding base containing the feed mechanism used primarily for cutting the sections of cellulose nitrate embedded tissues with an obliquely set knife.

## Parts of Base-sledge microtome

- Angular tilt adjustment
- Knife clamps
- Block holder
- Coarse feed adjustment
- Operating handle
- Thickness gauge
- Adjustment locking nut
- Block adjustment screw
- Split nut clasp

## Working Principle

- The blocks holder is mounted on a steel carriage which slides backward and forwards on groups against a fixed horizontal knife this microtome is heavy and very stable.
- The block is raised towards the knife at a predetermined thickness.

- This type of microtome is designed for cutting sections of very large a block of tissues for example whole brain, this microtome has become popular for routine use.

### Advantages of Base-sledge microtome

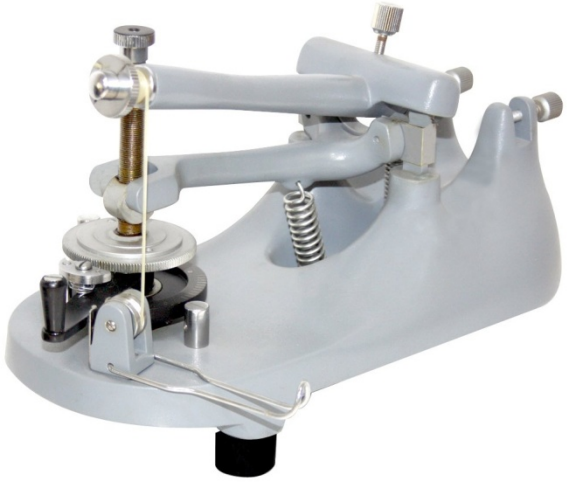
- It is useful for cutting extremely hard blocks and large sections.
- The microtome is heavy and stable.
- The knife used is sledge shaped which requires less honing.

### 3) Cambridge rocking microtome

- The instrument is so named because the arm has to move in a rocking motion while cutting the sections.
- The instrument was invented by Sir Horace Darwin in 1881 was developed by Cambridge company hence it is called the Cambridge rocking microtome.
- It is a simple machine in which the knife is held by means of microtome thread.
- The rocking microtome was designed primarily for cutting paraffin wax sections but in an emergency use frozen section by inserting a wooden block in which the tissue is frozen.

### Parts of the rocking microtomes

- Knife holder
- Block holder or chuck
- Upper arm
- Screw
- Lever
- Pawl
- Ratchet wheel
- Mil head microtome screw
- Sleeve
- Lower Arm
- Scale
- It cuts the sections between 1 to 20 microns.



### Working Principle

- The knife is fixed with the edge, while the object is moved against this knife circularly, producing a sharply curved surface to the block with each stroke the tissue holder automatically moves vertically towards the life.
- Cutting stroke is spring operated and is easy to handle. The microtome must be placed on a solid non-slippery surface to allow a better hold

### Advantages of Cambridge rocking microtomes

- The cost of a knife and microtome is low.
- Celloidin embedded tissues can be sectioned easily.

### 4) Freezing microtome

- This type has been designed for the production or preparation of frozen sections of fluid and non-fluid tissues usually without preliminary embedding.
- The object stage is connected to the cylinder of compressed carbon dioxide for the rapid cooling of the tissues and provisions are also made for the cooling of the knife.

### Part of freezing type microtome

- Knife clamps
- Operating handle

- Thickness gauge
- Stage
- Stage valve
- Coarse adjustment

## Working Principle

- The movement of the knife takes place horizontally across the surface of the tissues.
- Ribbon sections cannot be prepared using this microtome. All freezing microtomes have the feature of employing a non-movable tissue block and cooling system.

## Advantages of freezing microtome

- It is used for sections required for Rapid diagnosis
- It cuts non-dehydrated fresh tissue in a frozen state.
- The method is useful for Rapid histopathological diagnosis during operation
- This type of microtome is also used when lipids, enzymes, and neurological structures are to be demonstrated.
- Nowadays, the most commonly used type of microtome is a Rotary microtome which is easy to operate and ideal for routine use for diagnosis and research purposes.

## 5) Rotary microtome

### Working Principle

- It is used for slicing paraffin tissue sections of uniform thickness.
- This method is designed to cut 1-60 micron thick sections.
- A knob on the device (typically at the backside) is used to modify the thickness of the sections.
- A knife is constant inside the knife holder and clamped tightly.
- The tissue block is drawn throughout the knife-edge and it is mechanically advanced. The top and bottom of the block have to be parallel and horizontal and as a minimum 1mm of paraffin has to be present in all aspects beyond the tissue.
- The trimming of the edges of the block is usually completed with a single-sided razor blade and the block face is trimmed with the microtome knife.
- The technician decides the type of section to be made in line with the nature of tissue and instructions received from the pathologist.

- At some stage in section slicing, as the wheel of the microtome turns, sections are cut and slide on the knife. A ribbon of sections is produced.
- The ribbon of sections is transferred to warm water inside the tissue floatation bath to put off any wrinkles present in the section.
- The best quality section that is free from any scratches and cracks can be decided on from the tissue ribbons. The tissue ribbons are then taken on smooth glass slides with a respective identification number.
- The slides are pulled from the water and the preferred sections are positioned flat on the surface of glass slides. The slides with the sections are positioned on a rack in a hot air oven to dry.

## Cell Counting Methods

A key step in many experimental workflows involves the counting of cells.

Researchers often need to count cells prior to cell culture or before studying downstream processes and using analytical techniques that require an accurate and consistent number of input cells.

Cell counting can be performed either by manually using a hemocytometer, or by using an automated cell counter.

### Hemocytometer

For over 100 years the hemocytometer has been used by cell biologists to count cells.

It was first developed for the quantitation of blood cells but became a popular and effective tool for counting a variety of other cell types, particles, and even small organisms.

Currently, hemocytometers equipped with improved Neubauer grids are a mainstay of cell biology labs.

Cell counting using a hemocytometer suffers from a variety of shortcomings.

These shortcomings include, but are not limited to, a lack of statistical robustness at low sample concentration, poor counts due to device misuse, and subjectivity of counts among users.

In addition, cell counting using a haemocytometer is a time consuming and tedious operation.

## Automated Cell Counters

In recent years automated cell counting has become an attractive alternative to manual haemocytometers-based cell counting, offering more reliable results in a fraction of the time needed for manual counting.

Automated cell counters, such as the TC20™ automated cell counter, can provide a total count of mammalian cells and a live/dead ratio in a single step.

Because there is no bias in counting, automated cell counters yield more accurate and reproducible results.

Examples of processes that benefit from the speed and accuracy of automated cell counting include flow cytometer, toxicology studies, viral production, high content screening, and high content analysis.

## Importance of Cell Counting

### For maintaining cell cultures

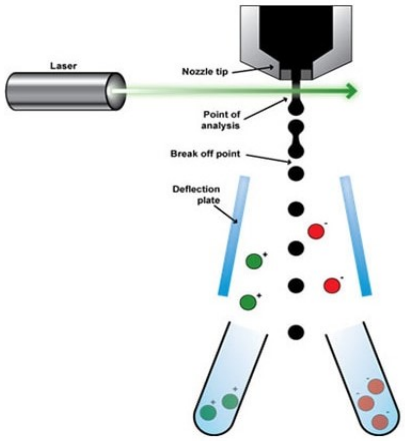
Splitting cells or preparing for the next passage (usually cells are diluted into a new culture flask with fresh media for optimal growth)

For preparing cells for transfection experiments

For preparing cells for downstream experiments that require accurate and consistent numbers of input cells, including qPCR

### Fluorescence-activated cell sorting

- Fluorescence-activated cell sorting (FACS) is a powerful flow cytometry technique that separates individual cells from a mixed population based on their physical and fluorescent properties.
- Cells are labeled with fluorescent markers and passed through a laser beam; detectors measure their size, internal complexity, and fluorescence to identify and physically sort specific cell types into separate containers for further analysis.




## Procedure

**1. Cell Labeling**:

Cells are stained with fluorescent antibodies that bind to specific cell surface markers.

**2. Fluid Stream**:

The labeled cells are then suspended in a liquid stream and passed one by one through a laser beam.

**3. Light Measurement**:

- **Light Scattering**: Detectors measure how much light is scattered in the forward and side directions.
- **Forward scatter (FSC)**: indicates the size of the cell.
- **Side scatter (SSC)**: provides information about the internal complexity or granularity of the cell.
- **Fluorescence**: The laser excites the fluorescent markers on the cells, and detectors measure the emitted light.

**Cell Sorting**:

- Based on the signals from the detectors, an electronic system identifies cells of interest.
- The stream is broken into droplets, and charged droplets containing the target cells are then deflected by an electrostatic system into a collection container.

### Applications of FACS

- **Research**:

Isolation of rare or specific cell types for transcriptomic analysis, studying cellular development, and investigating disease mechanisms.

- **Clinical**:

Diagnosis and treatment of blood disorders like leukemia and lymphoma, and for isolating tumor-infiltrating lymphocytes for cancer therapy.

- **Stem Cell Isolation**:

A widely used technique for separating stem cells from other cell populations.

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# Artificial intelligence and Biostatistics in Healthcare: Advances, real-world applications, and future perspectives

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## Abstract

Biostatistics helps people make fact-based decisions by studying biology, medicine, and public health using statistical tools. It covers how to design observational studies and experiments, how to gather data in a methodical manner, how to apply the appropriate statistical models, and how to interpret the findings. Testing hypotheses, estimating parameters, survival analysis, and assessing longitudinal data are a few of the primary topics. The field is widely used in epidemiological studies, clinical trials, environmental health, genetics, and health services research. In order to study complex biological systems, biostatistics has expanded recently by integrating cutting-edge techniques like machine learning, predictive modelling, and high-dimensional data analysis. It ensures that safety and efficacy are thoroughly tested, which is crucial for drug discovery and regulatory approval. By mapping diseases, monitoring them, and identifying risk factors, biostatistics aids in public health planning. By integrating patient-level data with predictive tools, biostatistics aids in the development of individualized treatment plans as precision medicine gains traction.

## Introduction

The historical development of biostatistics, which began with ancient epidemic findings and continues to advance through modern statistical innovations, is an intriguing example of the relationship between continuity and transformation. The field's roots can be found in ancient writings like the Hippocratic treatise "On Airs, Waters, and Places" (c. 400 BCE), which examined how the environment affects the spread of disease. This fundamental

concept served as the foundation for a methodical investigation of health and illness trends in populations. The ground-breaking work of pioneers like Bradford Hill, Ronald Fisher, and Karl Pearson gave rise to the contemporary era of biostatistics.These researchers developed fundamental statistical concepts that are now the cornerstone of contemporary bio statistical methodology, including hypothesis testing, experimental design, and randomized controlled trials **(Matthews, 2016)**.

Biostatistics, or biometry in technical contexts, is the application of statistical methods in biological and health sciences research. This broad field encompasses all phases of the research process, including data collection, presentation, analysis, and interpretation (Mishra and Khan, 2024). Its scope is broad and includes biological experiments, clinical studies, epidemiological research, and public health surveillance, among other areas. Applying mathematical formulas to biological data is only one aspect of the field. Instead, researchers can use the strong foundation that biostatistics provides for scientific inquiry to address complex questions through carefully thought-out experiments and rigorous statistical reasoning (Gore, 2024). This approach emphasizes how important good study design is as the foundation for trustworthy findings.

Biostatistics offers practical methods for selecting control groups, putting randomization schemes into practice, determining appropriate sample sizes, and minimizing bias in research studies (Pagano et al., 2022). These tools are crucial to the reliability and validity of research findings in the biological and health sciences. In recent years, biostatistical education has evolved to meet the demands of an increasingly data-driven research environment. Modern curricula place a strong emphasis on integrating traditional study design principles with the advanced computational skills needed to handle real-world health data. This includes instruction in data modification, cleaning, and quality assurance methods to equip biostatisticians to manage the intricacy of extensive health datasets (Sakarna et al., 2025). As the field advances, biostatistics continues to be at the forefront of advancing our understanding of health and illness, providing the methodological underpinnings for scientific healthcare and public health initiatives (Sullivan 2023).

## Applications of Artificial Intelligence in Biostatistics

Designing research, evaluating information, and interpreting findings in the life sciences and health sciences are the main objectives of biostatistics. AI encompasses various computational approaches—from neural networks and support vector machines to decision trees and clustering algorithms—that can

automate and enhance traditional statistical tasks, especially in processing complex, high-dimensional, and unstructured datasets **(Pose and Zelina 2023)**. AI can increase speed, flexibility, and accuracy in processing large databases, providing robust techniques for pattern recognition, predictive modeling, and data integration. Integration of AI with classical statistical methods enhances the analytics capabilities in biomedical research. The challenges to address the interface between medical statistics and AI concern population inference vs. prediction, generalizability, reproducibility and evidence interpretation, as well as the stability and statistical guarantees **(Dascălu *et al.,* 2025)** .AI algorithms provide robust and advanced techniques to maximize data analysis, recognize complex data patterns, and improve predictive analytics and modeling**(Jackson*et al.*,2018)**. While biostatistics usually follows a hypothesis-driven approach. Common AI tools used in biostats workflows are deep learning, random forests as well as support vector machines **(Ossowska *et al.*,2022).**

## Machine Learning and Deep Learning

AI encompasses multiple sophisticated technologies that complement traditional biostatistical approaches. High-dimensional biomedical data, such as imaging, genomics, and electronic health records, are thoroughly processed by deep learning algorithms, such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs). For classification and regression tasks in clinical settings, support vector machines, decision trees, and random forests offer accurate substitutes **(Dascălu *et al.,* 2025).**

## Natural Language Processing

The benefits of processing natural languages (NLP) have transformed research reporting and clinical documentation. In order to drastically cut down on time and effort spent on medical documentation, experts are using natural language processing (NLP) to automate the creation of clinical study reports. GPT-4 and other large language models (LLMs) exhibit exceptional clinical knowledge; they scored 96.0% on the MedQA benchmark, which is a 28.4 percentage point improvement since late 2022(**Maslej *et al.,* 2025).**

## Precision Medicine and Personalized Treatment

AI-powered genetic risk factor optimisation facilitates drug discovery, disease screening, patient stratification, and improved comprehension of disease mechanisms. By combining various data sources, such as symptoms of patients, medical history, aspects of lifestyle, and genetic information, AI-driven methods increase diagnostic accuracy. Personalised choices for

treatment is made possible by machine learning algorithms that can forecast therapeutic results and drug responses**(Serrano *et al.*,2024)**

## AI-Assisted Data Analysis

Biostatistical methodology has advanced significantly with the advent of artificial intelligence-based statistical evaluation tools. Although thorough verification is still necessary to avoid statistical error, large language models can help with code generation, literature synthesis, and report drafts. When compared to conventional methods, data interpreter agents built on LLMs perform better in real-life data evaluation tasks (**Min *et al.*,2024)**

## Real-World Evidence and Electronic Health Records

In healthcare contexts, real-world data (RWD) analysis employing AI techniques offers insights into the efficacy of therapy across a range of populations.Machine learning algorithms applied to electronic health records support causal effect estimation and individualized treatment recommendations. AI systems can analyze EHR text data to predict hospital length of stay and identify high-mortality-risk patients (**Ismail *et al.*, 2023)**

## Machine Learning in Healthcare

Machine learning (ML) is an old concept that has recently gained a lot of attention due to the explosion of data generation processes in healthcare.ML is defined as "the ability of a machine to mimic intelligent human behavior". An algorithm is trained to learn from data and then make decisions based on similar characteristics or variables from new data **(Alanazi., 2022).**

## Clinical Decision Support and Diagnostic Imaging

ML-driven decision support extends beyond imaging. Ensemble models combining clinical, laboratory, and demographic data have been used to predict sepsis onset up to 12 hours before clinical recognition, enabling timely intervention and reducing mortality by up to 20% in retrospective analyses **(Wang *et al.*, 2022).**

## Personalized Medicine and Genomics

ML facilitates the integration of high-dimensional "omics" datasets—genomics, transcriptomic, proteomics—to identify biomarkers and stratify patients for targeted therapies. Deep learning architectures such as auto encoders and graph neural networks extract latent features from multi-omics profiles, improving biomarker discovery rates by 35% compared to traditional methods. In protein structure prediction, ML algorithms accelerated the

identification of novel drug targets, contributing to a 208% increase in related publications in 2024 (CAGR 25%) **(Unger and Kather, 2024)**.

## Clinical Trials and Drug Development

ML augments clinical trial design and execution. Adaptive randomization protocols driven by ML optimize treatment assignments in real time, yielding up to 15% higher overall response rates compared to fixed randomization. Predictive models forecast patient enrolment, dropout rates, and trial duration, improving planning accuracy by 25% and reducing under-enrolment risks. AI-based eligibility screening in paediatric oncology trials demonstrated a 90% reduction in manual workload while maintaining 95% concordance with expert review **(Cho *et al.,* 2025).**

## Real-World Evidence and Population Health

Machine learning applied to real-world data (RWD) from EHRs, claims databases, and wearable sensors enables causal inference and treatment effectiveness studies outside controlled trial settings. Causal ML frameworks such as targeted maximum likelihood estimation (TMLE) estimate treatment effects with bias reductions up to 30% compared to regression-based methods. Predictive analytics on wearable device data facilitate early detection of chronic disease exacerbations, reducing hospitalization rates by 15% in heart failure cohorts **(Alhumaidi *et al.,*2025).**

## Privacy-Preserving and Federated Learning

Collaborative ML approaches such as federated learning address privacy and regulatory constraints by training models across multiple institutions without sharing raw patient data. In federated hospital networks, ML models achieved 95% of the performance of centralized models on diagnostic tasks while maintaining local data privacy. Differential privacy techniques further prevent patient re-identification by injecting noise into model updates, balancing privacy protection with model accuracy **(Horst *et al.,*2025).**

## Future Direction in The Integration of AI and Biostatistics

The convergence of artificial intelligence (AI) and biostatistics promises to revolutionize biomedical research by combining the interpretability and rigor of statistical inference with the flexibility and predictive power of AI. Explainable AI, federated learning, hybrid statistical–AI models, as well as autonomous machine learning pipelines, are examples of current developments

that are supported by strong validation platforms and ethical leadership (**Choudhury and Goel, 2025)**

## Explainable AI (XAI) for Clinical Adoption

Interpretation is crucial to establishing medical professionals' trust and adhering to regulatory requirements as deep learning models proliferate in the health care sector. By providing a clear understanding of model predictions, explainable AI techniques like attention-based map visualisations, local rules-based explanations, and SHAP (Shapley Additive Explanations) help close the gap between interpretability and accuracy **(Vani et al., 2025)**. A new framework called PersonalCareNet combines convolutional frameworks with SHAP to provide patient-specific and global explanations for critical care risk predictions. It achieves 97.9% accuracy while maintaining healthcare trust **(Vani et al., 2025)**.

## Federated Learning for Privacy-Preserving Collaboration:

Large-scale AI models require diverse data from multiple institutions, yet privacy concerns often limit data sharing. Federated learning enables decentralized model training by sending algorithms to local servers rather than pooling patient data, maintaining compliance with HIPAA/GDPR while leveraging broad datasets **(Hawking 2025).** Recent reviews highlight successful federated trials for chest X-ray AI models, demonstrating robust performance gains without data leakage, and underscore the technology's role in expediting R&D by improving cross-site patient recruitment and monitoring

## Hybrid Statistical–AI Models

Hybrid models combine classical statistical techniques (e.g., Cox models, generalized linear models) with AI algorithms (e.g., neural networks, random forests) to harness both interpretability and predictive strength. Vidal et al. introduced hybrid systems that multiply the Cox hazard function by neural network outputs, yielding a unified hazard predictor and demonstrated a 15% accuracy improvement over standalone AI models in patient-outcome prediction. Such hybrids balance theoretical guarantees of inference with AI's capacity to model complex nonlinearities (**Vidal *et al.*,2025).**

## Automated Machine Learning (AutoML) Pipelines

Automation of ML workflows encompassing data ingestion, feature engineering, model selection, and hyper parameter tuning streamlines bio statistical analysis and reduces human error. Guideline frameworks integrate hypothesis specification, automated pre-processing, model fitting (e.g., random

forests, support vector machines), and interactive visualization for decision support, shifting routine tasks from analysts to automated platforms (**Dhillon *et al.*, 2022)**

### Real-World Evidence and Target Trial Emulation

Integration of AI-driven causal inference methods (e.g., propensity scores, marginal structural models) with bio statistical trial emulation enables robust analysis of electronic health records and registries. AI tools facilitate high-dimensional confounder adjustment and survival prediction, while statistical frameworks ensure unbiased effect estimation and variance quantification. The combined approach supports regulatory decision-making by delivering real-time insights on treatment effectiveness and safety in routine practice (**Dascălu *et al.*, 2025)**

### Data Mining and Pattern Recognition in Biostatistics

Data mining and pattern recognition have revolutionized biostatistics by transforming how researchers analyse complex biological and medical data. These computational techniques have made it possible for large biological databases to automatically reveal previously unnoticed patterns, relationships, and insights that would be challenging to find with only conventional methods of statistical analysis. In biostatistics, data mining combines techniques from machine learning, artificial intelligence, and statistical analysis to find significant trends in medical data, supporting rational selection and precision medicine **(Dhillon *et al.*, 2022).**

#### Traditional Statistical Pattern Recognition

Statistical pattern identification, which employs algorithms and mathematical models to identify patterns in large datasets, is the foundation of data mining in biostatistics. This approach's three primary principles—representation (identifying relationships in n-dimensional vector space), generalization (developing rules that apply to data that hasn't been seen), and evaluation (assessing system accuracy and efficiency) are used to gather features and patterns using prior data elements and statistical techniques (**Entezami *et al*., 2020).**

## Data Mining Techniques In Biostatistics

### Supervised Learning Methods

The classification technique is one of the most popular approaches for supervised learning in biostatistics. This method is very helpful in healthcare risk assessment, fraud detection, and diagnosis because it separates data into

pre-established categories or groups.Systems of classification are used in healthcare settings to identify treatment actions, classify the severity of illness, and predict the outcome of patients. For example, classification models are used by banks to evaluate the credit risk of loan applicants and by hospitals to forecast mortality among patients or intensive care unit admission needs**(Ono& Goto,2022).**

## Unsupervised Learning Approaches

Lack of predetermined groups, clustering algorithms are essential unsupervised learning tools for uncovering undetected trends in biological data. Clustering techniques aid in the identification of illness categories, the grouping of patients with similar characteristics, and the optimization of medications in healthcare applications. In order to help medical professionals with organising and making decisions, organisational clustering, for instance, has been effectively used to group patients based on the duration of stay (Wu et al., 2022). For extremely complex biological information, Principal Component Analysis (PCA) offers a crucial reduction of dimensionality.For improved visualisation and evaluation, PCA is frequently used to represent samples containing thousands of genes onto two or three dimensions. In studies of genomics, where datasets frequently contain tens of thousands of variables but relatively few samples, this technique proves especially useful. PCA preserves key data features while assisting in sample cluster identification, batch effect detection, and complexity of computation reduction**(Hassan et al., 2023)**

## Association Rule Mining

The application of association rules in healthcare data has become increasingly important for determining treatment relationships and disease coincidences. This approach identifies important connections between different diseases, symptoms, and treatments by looking at patterns in electronic health records. For example, association rule mining can demonstrate that patients with specific genetic markers are more likely to experience specific complications, enabling proactive treatment approaches (Kost et al., 2012). The effectiveness of association rules is measured by lift (importance of the relationship), confidence (rule reliability), and support (frequency of occurrence). In health care applications, these metrics are used to prioritize medically significant correlations and eliminate random interactions(**Narindrarangkura*et al.*,2023).**

## Advanced machine learning integration

### Deep Learning, Ensemble Methods, and Applications

Deep learning's advanced recognition of pattern abilities for intricate, diverse datasets has revolutionised healthcare information analysis. In the field of medical imaging, convex neural networks (CNNs) have outperformed conventional techniques in areas like disease identification, organ segmentation, and tumour detection. Manual feature engineering is no longer necessary, thanks to thesedeep learning architectures' abilities to automatically extract hierarchical features from unprocessed medical pictures (**Miotto *et al.*,2018).** The most widely used method for identifying complicated structures in biological data is neural pattern recognition. Artificial neural networks, which are based on the architecture of the human brain, are able to identify patterns in a variety of data types, such as text, images, and audio. They are crucial for uses such as drug discovery, genomic analysis, and personalised medicine because of their capacity to handle unknown data and process complicated interactions (**Miotto *et al.*,2018).**

Ensemble learning techniques exceed individual algorithms by combining predictions from various models. Ensemble techniques like bagging and boosting aid in biostatistics by lowering variance as well as bias while enhancing model stability. Successful ensemble implementation is demonstrated by Random Forest, which uses feature randomness and bagging to produce uncorrelated decision tree structures that together produce predictions that are more accurate **(Altman and Krzywinski 2017)**. By training several models on various bootstrap samples of the original dataset, bootstrap aggregation, also known as bagging, lowers variance in statistical learning techniques. In biostatistics, where datasets may be small or noisy, this method is especially helpful in enhancing model generalisation and validity **(Altman and Krzywinski 2017).**

### Public Health and Epidemiology in Biostatistics

A theoretical basis for using statistical techniques to analyse disease trends, evaluate the health of populations, and direct interventions is provided by public health and epidemiology. Biostatistics supplies the quantitative tools that underpin epidemiologic study designs, data analysis, and evidence-based decision making, forming the scientific basis of public health practice **(Schwaid 2017).**

### Epidemiological Surveillance: Descriptive and Analytical Approaches

Descriptive epidemiology characterizes health events by person, place, and time, establishing baseline measures such as incidence and prevalence. Bio statistical techniques summarize these data using rates, ratios, and age-standardized measures to allow comparisons across populations and over time **(Soucie 2012)**

Analytical epidemiology employs study designs to investigate causal associations:

1. **Cohort studies** estimate incidence and relative risk, using survival analysis (Kaplan–Meier curves, Cox models) to handle censored follow-up times.
2. **Case–control studies** compare exposure odds between affected and unaffected individuals, applying logistic regression for adjusted odds ratios.
3. **Cross-sectional studies** assess prevalence and associations at a single time point, analyzed via chi-square tests and prevalence ratios **(Schwaid ,2017).**

Biostatistics guides sample size determination, control of confounding through stratification or multivariable modeling, and inference via hypothesis testing with p-values and confidence intervals **(Fiveable 2024)**

## Applications in public health and epidemiology in biostatistics

### Disease Surveillance and Outbreak Investigation

Biostatistics serves as a critical tool for public health surveillance, enabling continuous monitoring of population health trends and disease patterns. Statistical methods help identify disease outbreaks, assess intervention effectiveness, and guide resource allocation decisions. During the COVID-19 pandemic, biostatistical techniques proved essential for understanding disease transmission patterns, evaluating prevention strategies, and informing public health policy (**Nsubuga *et al.*,2011).**Statistical techniques are used by public-health monitoring programs to gather, examine, and evaluate medical data from various sources. These systems make it possible to track disease trends, identify risk factors early, and assess public health initiatives. To examine intricate surveillance data, biostatisticians use hierarchical modelling techniques, time-series analysis, and spatial analysis(**El Allaki *et al.*,2012)**

### Population Health and Intervention Strategies

Comprehensive public health surveillance is made possible by biostatistics, which analyzes disease patterns, identifies risk factors, and evaluates the results of interventions. Health care professionals use

biostatistical techniques to manage epidemics, determine mortality rates, and create frameworks for disease prevention strategies. These analyses guide resource allocation and inform evidence-based public health policies for the maximum impact on population health (Gore, 2024). Biostatistical methods are used to assess the effectiveness of medical initiatives, such as immunization campaigns and post-surgery follow-up programs. By examining program impact data, healthcare administrators can quantify performance gains, identify successful interventions, and adjust strategies based on evidence-based insights. This method of thinking ensures that public health initiatives are both cost-effective and effective (**Yazeed Sakarna *et al.*,2025)**

## Environmental health and risk assessment

### Environmental Exposure Assessment

Probabilistic strategies are used to quantify the relationships between health outcomes and exposure to environmental factors, such as air pollution, water contamination, and other environmental hazards. Using advanced statistical methods, such as applying machine learning to extensive ecological databases, researchers can compute specific exposures across large populations and establish causality for particular public health interventions (**Yazeed Sakarna *et al.*, 2025)**

### Chemical Mixture Analysis

In cutting-edge ecological health studies, biostatistics is used to analyze complex chemical mixtures and their cumulative harmful health effects, despite the fact that real-world exposures involve multiple chemicals at once. These assessments inform regulations and direct preventive healthcare practices for environmental protection (**Yazeed Sakarna *et al.*, 2025)**

### Real-World Applications of Biostatistics

This field provides the foundation for evidence-based healthcare and public health practice by providing essential statistical methods and strategies for assessing complex biomedical data in order to improve patient outcomes and population wellness. Because of its applications in all facets of healthcare, from creating medications and clinical trials to monitoring patients' health and creating policies, it is a crucial field in modern medical research and practice **(Sullivan, 2023)**

### Clinical Trials and Therapeutic Evaluation

Statistics are essential to the creation, operation, and evaluation of clinical trials in order to ensure that investigation generates accurate and valid

findings for medical decision-making. Biostatisticians assist with endpoint definition, sampling procedures, sample size calculation, and study design optimization from the very beginning of planning to the final reporting. They ensure that clinical trials maintain the appropriate statistical power to detect meaningful treatment effects while minimizing bias and maximizing the validity of results. The application of biostatistical methods in clinical trials encompasses efficacy, safety, and outcome prediction.Modern scientific studies are increasingly employing adaptable designs, umbrella trial designs, and complex statistical methods that require specialized biostatistical expertise. These innovative methods enable more efficient medication development processes and improved patient outcomes through data-driven treatment optimization (**Estrada et al., 2020).**

## Real-World Evidence and Post-Market Surveillance

Real-world data (RWD) analysis has become increasingly important in biostatistics because it provides data on treatment safety and efficacy in a range of individual populations outside of controlled clinical trial settings. Biostatisticians employ sophisticated analytical techniques like multiple imputation methods, instrumental variable analysis, and propensity score matching to address confounding biases and missing data in real-world datasets (**Blonde et al., 2018).**

## Genomic Medicine and Biomarker Development

Biostatistics is now essential in precision medicine applications, where statistical analyses enable the customization of medical interventions based on individual patient characteristics. Predictive modeling and pattern recognition techniques can be used to identify genetic variations, biomarker expressions, and other factors that influence treatment response and disease susceptibility (Kosorok and Laber, 2019). Biostatistical techniques have revolutionized oncology's approach to cancer treatment through the development of targeted therapies and genomic profiling. Statistical models predict patient responses to immunotherapies and identify predictive biomarkers for tailored treatment selection. In a similar vein, statistically derived genetic risk scores for cardiovascular diseases help identify an individual's individual risk for the condition and guide preventative actions (**Kosorok and Laber 2019).**

## Treatment Regime Optimization

Identifying the optimal treatment plans that suggest actions based on each patient's particular characteristics is the aim of precision medicine statistical studies. These approaches include semi-parametric modeling, causal

inference, and machine learning techniques to support individualized treatment decisions. Biostatisticians develop clinical hypotheses for additional research and develop decision support systems for healthcare organizations through the use of rigorous statistical analysis (**Nilius *et al*., 2024).**

## Pharmacovigilance and drug safety

### Risk Detection and Benefit–Risk Assessment

Biostatistics provides crucial tools for pharmacovigilance, the science of detecting, assessing, and preventing adverse drug reactions. Statistical methods like disproportionality analysis, proportional reporting ratios, and reporting odds ratios can be used to identify potential safety signals in databases that are created on their own. Advanced data mining algorithms and machine learning techniques are used to identify new or unusual adverse drug reactions that might otherwise go unnoticed. **(Jeetu and Anusha, 2010)**. Statistics professionals compare the risks and benefits of medicinal products using quantitative frameworks and predictive algorithms.

In order to manage sparse data and update safety profiles as new information becomes available, these evaluations integrate data from various data sources using Bayesian hierarchical models and sophisticated statistical techniques. The integration of real-world evidence enhances safety evaluations by providing insights from diverse patient populations and extended follow-up periods (**Blonde *et al.*, 2018)**

## Conclusion

Biostatistics plays a pivotal role in advancing biomedical science and public health by providing robust quantitative tools for study design, data analysis, and interpretation. Its applications in clinical trials ensure reliable assessment of therapeutic efficacy and safety, while epidemiological methods facilitate understanding of disease etiology and population health trends. The integration of modern computational techniques such as machine learning, AI, and data mining—expands the scope of biostatistical analysis to complex, high-dimensional datasets and real-world evidence. As healthcare continues to generate massive and diverse data streams, biostatistics will remain essential for extracting actionable insights, optimizing clinical and public health strategies, and supporting precision medicine initiatives. Ongoing methodological innovation and interdisciplinary collaboration will be critical to address emerging challenges in data quality, model interpretability, and ethical use, ensuring that biostatistics continues to drive evidence-based improvements in human health.

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# A comparative study of human intelligence and artificial intelligence

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## Introduction

The rapid advancement of artificial intelligence technology has revolutionized the modern world by automating complex tasks and transforming industries. This evolution has sparked renewed interest and concern about the unique traits that distinguish human intelligence. Understanding these differences is crucial not only for technological development but also for addressing ethical, social and practical challenges in society. This chapter examines the core aspects of both forms of intelligence, highlighting their respective strengths, limitations and the implications for their coexistence.Human intelligence and artificial intelligence (AI) represent two fundamentally different approaches to cognitive processing, learning, and problem-solving, each with distinct strengths and limitations. Below is an in-depth comparison organized into relevant sections, with detailed insights and references throughout.

## Origin and Nature of these Intelligences

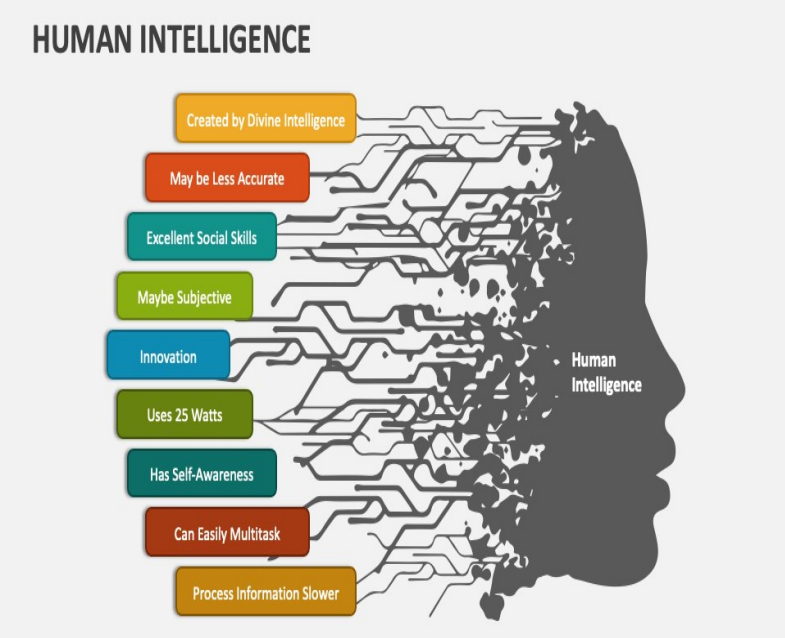
Human intelligence is a product of evolutionary biology, shaped by millions of years of adaptation and environmental challenges. It draws on complex cognitive abilities such as abstract thinking, emotional expression, intuition, and social interaction, linked intrinsically to consciousness and the biological structures of the brain.

Artificial intelligence, on the other hand, is a technological creation designed to mimic specific cognitive functions, such as learning, reasoning, and perception. AI is rooted in algorithms, computer code, and data, and lacks consciousness, emotions, or subjective experience.

- Human intelligence is naturally occurring and self-generated.
- AI is engineered, reliant on human input for design and improvement.

## Defining Human Intelligence

Human intelligence is a multifaceted construct comprising problem solving, reasoning, memory, creativity, emotional intelligence, social awareness and self consciousness. It is shaped by millions of years of evolution and influenced by inheritance, education, environment and culture.



## Key Features of Human Intelligence

### Problem solving and reasoning:

Human can interpret complex situations, make logical or creative decisions and adapt solutions to unique circumstances, across diverse domains such as mathematics, engineering and arts.

- Learning and Memory:

Human beings use experience to accumulate and recall knowledge. This allows a flexible response to new situations and the development of expertise over time.

- Imagination and Creativity:

The human mind generates novel ideas and artistic expression. Imagination enables people to see possibilities beyond immediate reality.

- Emotional Intelligence:

Human recognize, understand and manage emotions( their own and others).EQ is foundational to relationships, leaderships and collaborative environments.

- Social Consciousness:

Individuals manage relationships, collaborate and navigate complex social systems. Understanding nuanced social cues underpins the construction of civilizations.

- Self Awareness:

Consciousness enables self reflection, adaption and moral decision making. Human awareness is fundamentally subjective and incorporates meaning beyond data.

- Understanding Artificial Intelligence:

Artificial Intelligence refers to computer systems capable of performing tasks that typically require human cognition such as reasoning, learning, perception and decision making. AI is realizd through fields like machine learning (ML)natural language processing(NLP) and computer vision.

## Core Components of AI:

Machine Learning

ML algorithms analyze massive dataset to identify patterns

**Machine Learning:** ML algorithms analyze massive datasets to identify patterns and predict outcomes, improving performance with more data. ML applications have transformed industries like healthcare and finance

- Natural Language Processing

NLP allows machines to understand, interpret, and generate human language, enabling conversational agents and intelligent assistants.

Computer Vision AI systems interpret images and videos, powering applications from facial recognition to automated medical diagnostics.

- Automation:

AI driven tools automate repetitive, date intensive tasks revolutionizing supply chains, logistics, customer service, and more in the development changes.

## Strengths and Capabilities:

### Human Intelligence:

Empathy and Ethics: Human are integrate emotional understanding and moral reasoning into their decisions.

Context Awareness: People naturally consider social, cultural and ethical factors in realtime.

Creativity: Human beings produce art, invent technologies and think beyond rote rata envisioning the unseen.

Adaptability: People adapt rapidly to changing, ambiguous or unfamiliar situations, drawing on intuition and prior experience.

## Artificial Intelligence:

**Energy and Resource Intensive:** Large-scale AI training requires substantial computing power and electricity

**Dependence on Data:** The quality of AI depends on data fed into its algorithms. Biases or limitations in data propagate into outputs.

**Lack of Consousness:** AI lacks self awareness, subjective experience, genuine understanding and critical thinking.

**Lack of true comprehension:** AI cannot grasp common sense or context outside its programmed domain, making it prone to misinterpretations when facing novel inputs.

**Ethical and Societal Risks:** Algorithmic bias, lack of accountability, and potential misuse are significant concerns.

**Pattern Recognition:** AI excels at detecting subtle trends in huge datasets, including those

Speed and Scalability: AI analyzes data sets at speeds unmatched by humans, making it ideal for repititive, high volume tasks.

Consistency: AI can deliver highly consitent outputs, devoid of fatigue or destrction.

Availability: Machines can perform continuosly without rest,ideal for tasks requiring long hours or hazardous environments.

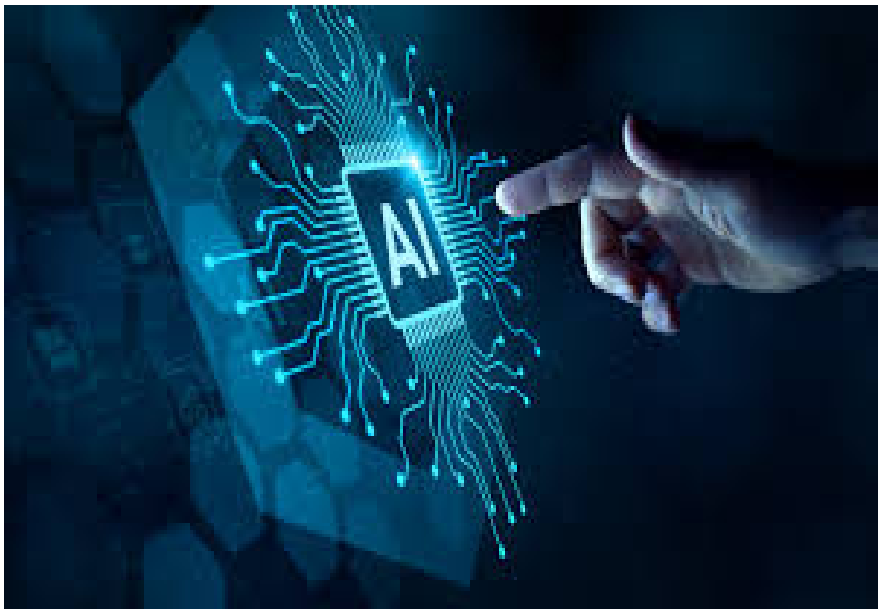
## Memory and Learning Process

Human intelligence learns through a blend of education, experience, and exposure, generalizing knowledge across diverse domains and adapting rapidly to novel situations. Memory in humans is intrinsically complex; it's context-rich and influenced by factors such as emotion, motivation, and environment.

AI learns by processing vast amounts of data and training algorithms, excelling at specific, repetitive tasks and achieving high performance through frequent training and feedback loops.

- Humans can learn from few examples and apply knowledge creatively.
- AI requires massive datasets and struggles to extrapolate skillfully across domains unless reprogrammed.

## Efficiency and Processing speed of the human Intelligence and AI




AI outperforms humans in sheer speed, endurance, and computational accuracy. Machines can process large volumes of information far beyond human capacity and operate continuously without fatigue.

Humans, while slower in processing, bring flexibility, creativity, and the ability to solve problems under uncertainty or ambiguity. Human processing is also subject to physical and psychological limits, such as the need for rest.

### Innovation and Creativity thinking differences

Creativity is a hallmark of human intelligence, expressed through the arts, scientific discovery, inventiveness, and imaginative thinking. Humans generate original ideas and innovate beyond learned patterns.

AI's creativity is limited to pattern recognition and recombination based on existing data. It can produce novel outputs within structured parameters but does not possess true imagination, intent, or the ability to think "outside the box".

- Humans excel at creating art, music, and literature.
- AI replicates styles or generates content based on data but lacks genuine innovation.

### Emotional awareness and Social Intelligence

Human intelligence is deeply intertwined with emotions, empathy, and social awareness. These abilities facilitate understanding nuance, forming relationships, interpreting nonverbal cues, and responding to complex emotional contexts.

In artificial intelligence, even advanced conversational models, cannot truly comprehend or experience emotions. At best, AI detects and reacts to emotional cues identified in data, but its understanding is superficial and devoid of intrinsic empathy.

### Ethics and decision making

Humans incorporate intuition, values, ethics, and social norms into decision-making, reflecting cultural and moral context. Decision processes are subjective, often influenced by non-logical factors.AI makes decisions based strictly on the programmed rules, accumulated data, and objective logic. It does not possess intrinsic morality or a conscience and can fail when faced with ethical dilemmas or ambiguous situations.

### Error Handling in Data and Adaptability of these Intelligences

Humans are remarkably adaptable, adjusting to new circumstances and rapidly learning from mistakes. Human intelligence thrives in uncertain, unpredictable environments and multitasks efficiently.

AI systems are highly specialized, excelling within their programmed domains but struggling with unforeseen scenarios and ambiguity. AI adapts slowly, often requiring reprogramming or retraining when conditions change.

- Humans show resilience and flexibility under cognitive stress.
- AI, though precise and consistent, is less robust in the face of unpredictable situations.

## Differences and similarities of AI & HI

| Feature | Artificial Intelligence (AI) | Human Intelligence (HI) |
|---|---|---|
| Learning | Data-driven and pattern recognition | Experience, intuition, creativity |
| Adaptability | Limited to training data, slow to generalize | Rapidly adapts to novel situations |
| Social Skills | Struggles with nuanced social cues | Intuitive, highly adaptive social engagement |
| Processing | Fast, algorithmic, scalable | Flexible, analog, context-dependent |
| Physical Limits | Can work 24/7, no fatigue | Requires rest, limited endurance |
| Adaptability | Limited to training data, slow to generalize | Rapidly adapts to novel situations |
| Emotional Ability | Lacks emotion, cannot empathize | Rich, empathetic, builds social bonds |
| Decision-Making | Objective, rule-based, speedy | Incorporates ethics, contextual, sometimes subjective |
| Creativity | Limited, based on recombination | High, includes invention and imagination |
| Physical Limits | Can work 24/7, no fatigue | Requires rest, limited endurance |

## Limitations in Physical Constraints

The human brain is limited by biological constraints energy consumption, need for rest, and varying capacity across individuals. AI, housed in computers and servers, can work around the clock and scale with computational resources, unconstrained by typical human limits.

## Language and Concept Understanding

Humans excel at interpreting context, recognizing irony, sarcasm, humor, and understanding the emotional undertones of language. Human communication integrates cultural background, intent, and deep social meaning.

AI processes syntactic and semantic elements of language rapidly and effectively. However, it still struggles with pragmatics fully grasping contextual subtleties and emotional depth remains a formidable challenge.

## Future challenges and Potential Complementary

While AI offers unmatched performance in computation, optimization, and repetitive tasks, human intelligence remains essential for creativity, ethical reasoning, emotional understanding, and holistic decision-making.

The future interplay between human and artificial intelligence is likely to be complementary. AI will automate routine functions and enhance efficiency, freeing humans to focus on domains requiring insight, judgment, and creative problem solving

## The Comparison Table of AI & HI

| S.No | Different Aspects | Human intelligence | Artificial Intelligence |
|---|---|---|---|
| **1** | Adaptability | Highly flexible, quick to learn | Specialized, slow to adapt |
| **2** | Learning Process | Experience, intuition, creativity | Data, feedback loops, structured training |
| **3** | Processing Speed | Slower, biologically constrained | Rapid, tireless |
| **4** | Nature | Biological, conscious, emotional | Digital, algorithm-driven, emotionless |
| **5** | Error Handling | Resilient, robust in ambiguity | Likely to fail in ambiguity or lack of data |

## Conclusion of Human Intelligence and Artificial Intelligence

Human intelligence and artificial intelligence are distinct but increasingly intertwined forces shaping modern society. While AI empowers humanity with efficiency, precision, and scalability, it cannot replace human attributes such as creativity, empathy, ethical judgment, and adaptability. The optimal path forward lies in leveraging the strengths of both, fostering collaboration where AI's computational prowess augments rather than replaces human intelligence.

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# Toxicological Effect of Nitrite on Protein level and Enzymatic Changes in Freshwater Fish Cirrhinus mrigala

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## Introduction

Persistent presence of pollutants like salts, heavy metals in aquatic ecosystems has reportedly caused metabolic stress in organisms even to extent of mortality in some cases. Agrahari *et al*. (2007) reported that analysis of biochemical parameters could help to identify target organs of toxicity as well as the general health status of animals. It may also provide an early warning signal in stressed organism. Biochemical parameters were often used when clinical diagnosis of fish physiology was applied to determine the effects of external stressors and toxic substances. According to Vutukuru (2003) biochemical and physiological methods of diagnosis constitute a promising approach to the problems of detecting the effects of toxic chemicals at the earliest possible stage. The biochemical profile changes the metabolism and biochemical processes of the organism, resulting from the effects of various pollutants, and they make it possible to study the mechanisms of the effects of the substances (Adedeji, 2010).

Biochemical mechanisms involved in cellular detoxification are particularly relevant in understanding the deleterious effects of environmental pollutants and useful biomarkers of exposure to aquatic pollutants. The use of biochemical methods offer promises in these areas viz, detection of states of stress, suggestion of modes of action and tentatively as tools to explain the metabolic basis for conventional fishery like growth. Measurement of plasma biochemical parameters is mostly used in clinical diagnosis of fish physiology to determine the general status of health. Plasma and serum reflect the physiologic state of an animal because they are the products of intermediate metabolism (Firat and Kargin, 2010). Fish physiologists make use of blood chemistry normal value indices for evaluation of fish stress responses, nutritional condition, reproductive state, tissue damage due to handling procedures and health status. Alteration of blood chemistry may be indicative of unsuitable environmental conditions (temperature, pH, oxygen concentration) or the presence of stressing factors, such as toxic chemicals. Blood metabolites have been used as an indicator to identify the physiological state of aquatic animals.

Biomarkers are essential to assess the environmental health and measure the interaction between a biological system and on environmental agent, which may be chemical, physical or biological. The induction of biomarkers is a good environmental tool to assess the exposure and the potential effects of aquatic organism. Moreover, biochemical and physiological biomarkers are frequently used for detecting on diagnosing sublethal effects in fish exposed to different toxic substances (Abou EI-Naga *et al*., 2005). Selection of the appropriate biological markers for monitoring effect / low dose response relationships is frequently controversial issue and it is evident that studies on the impact of metal and salts biochemical status of fish are limited (Almeida *et al*., 2001).

Proteins are one of the most important and complete groups of biological materials comprising the nitrogenous constituents of the body and performing different biological functions. Proteins are involved in major physiological events. Protein being involved in the architecture and physiology of the cell, they seem to occupy a key role in cell metabolism. Catabolism of proteins makes a major contribution to the total energy production in fish (Kortmaz *et al*., 2009). Whole body protein concentrations are influenced by a variety of environmental factors. Measurement of total protein provides an insight on the biological mechanism of metabolism under stressful conditions. The concentration of protein in the serum of fish has been used as an indicator of their general state of health.

Significant decrease in protein level was reported in *Ictalurus nebulosus* and *Heteropneustes fossilis* exposed to copper, *Penaeus japonicas* exposed to nitrite (Chen and Cheng, 1995), *Salvelinus fontinalis* exposed to aluminium, and in *Brycon cephalus* exposed to phenol, (Hori *et al*., 2006) observed a significant decline in plasma protein level during acute and sublethal manganese toxicity. Similar results have been reported in *Channa punctatus* during sublethal zinc and arsenic toxicities, in *Catla catla* exposed to arsenic (Kavitha *et al.,* 2010), in *Cyprinus carpio* exposed to chlorpyrifos, in *Labeo fimbriatus* exposed to endosulfan (Saravanan *et al.,* 2011), in *Cyprinus carpio* exposed to atrazine and in *Cyprinus carpio* exposed to lindane (Saravanan *et al.,* 2011). In contrast to above decrease in protein level significant increase in plasma protein level was recorded in *Pseudopleuronectes americanus* and in *Tilapia zilli* exposed to mercury and cadmium, in *Salvelinus fontinalis* and in white fish *Coregonus wartmanni* exposed to aluminium, in brook trout and in *Oreochromis niloticus* exposed to copper, Zhang *et al*. (2006) in *Lateolabraz japonicas* and in *Brycon cephalus* exposed to phosphorous and phenol, respectively.

Among the variety of biomarkers adopted in ecotoxicological investigations, there is notable interest in parameters related to enzymatic detoxification and activation. Enzyme assays can make important contributions to the diagnosis of disease because very small changes in the concentration of an enzyme activity can be easily measured. Christensen *et al*. (1982) observed that toxic chemical pollutants often affect the enzyme activities at least to some degrees and hence enzymes are used as logical candidates in biomonitoring. Pollution monitoring method using enzyme inducement or enzyme depression in fish has been proposed for studying polluted environments. Cell injury of certain organs leads to release of tissue-specific enzymes into the circulation. In toxicological studies, changes in concentration and enzymatic activities often directly reflect cell damage in specific organs.

Adenosine triphosphate (ATPase) is a group of enzymes that plays role in intracellular functions and is considered to be a sensitive indicator of toxicity. They hydrolyse adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and inorganic phosphate (P). In this process, the energy released becomes available for cation transport. ATPase, in various ion dependent forms, is an enzyme and responsible for the transport of ions through the membrane and thus regulates, among other cellular volume, osmotic pressure and membrane permeability. Detection of ATPase

inhibition could prove to be an important index for tolerable levels of a large group of environmental contaminants (Agrahari and Gopal, 2008).

In aquatic organisms particularly in fish gills, the enzyme is expressed abundantly in the tubular system of chloride cells and performs an integral role in the maintenance of ion balance in these animals. It has been suggested that the branchial $Na^+/K^+$ -ATPase is of central importance in ion regulation and cellular water balance by aquatic vertebrates and invertebrates, and directly related to their osmoregulation capacity. In fish gills, this enzyme is expressed abundantly in the maintenance of ion balance. Significant increase in gill $Na^+/K^+$ -ATPase activity was noted in *Oncorhynchus mykiss* exposed to zinc, in *Oncorhynchus tshawytscha* exposed to copper, in *Oncorhynchus mykiss* exposed to lead (Alves and Wood, 2006), in *American lobster, Homarus americanus* exposed to cadmium, in *Oncorhynchus mykiss* exposed to copper and in *Oncorhynchus mykiss* exposed to lead (Alves and Wood, 2006). However, gill $Na^+/K^+$ -ATPase activity was decreased in *Salmo gairdneri* exposed to aluminium, in *Salmo gairdneri* exposed to methyl mercury, in *Oncorhynchus mykiss* exposed to chromium in *Cyprinus carpio* exposed to copper (De Boeck *et al*., 2001) and in *Tilapia zillii* exposed to azoinphosmethyl.

Freshwater fish take up $NO_2^-$primarily across the gill. Nitrite accumulates in plasma, gill, liver, brain, spleen, muscle, etc., similar to the bio-accumulation of a pollutant and its effect in fish tissues and their immune system responses are very similar to those of the pollutant. Nitrite can actually be found in high concentrations in plasma of fish exposed to high nitrite levels. However, nitrite also accumulates in other tissues such as gill, liver, kidney, brain and muscle. Nitrite accumulation causing tissue damage has been reported in fish (Arillo *et al.,* 1984). Although an enormous amount of literature is available on nitrite effects on fish, information on the effects on biochemical profiles in fish and particularly in the Indian major carps is almost negligible. Hence the present investigation is aimed to assess the toxicity of nitrite in plasma glucose and glycogen, protein level and gill $Na^+/K^+$ -ATPase activity of an Indian major carp *Cirrhinus mrigala* in order to understand the mode of action, stress response and using of these parameters as suitable biomarkers for nitrite toxicity.

## Materials and Methods

### Estimation of Adinosine Triphosphate (Atpase) Sodium And Potassium Atpase

The specific activities of $Na^+/K^+$-ATPase were estimated following the method of Shiosaka *et al*. (1971).

### Principle

Adenosine triphosphate catalyses the conversion of ATP to ADP. During this conversion, one molecule of phosphorous is liberated.

### ATPase

Adenosine triphosphate  Adenosine diphosphate + Pi

The inorganic phosphorous liberated was assayed according to the method of Fiske and Subbarow (1925). In this method, the protein free filtrate is treated with acid molybdate solution and the phosphoric acid formed is reduced by the addition of 1-amino-2-naphtho l-4 sulphonic acid (ANSA) reagent to produce the blue colour. The intensity of the colour is proportional to the amount of phosphorous present.

### Reagents

1. **Tris-HCl buffer solution (0.1M; pH 7.5**) - 12.10 g of Tris hydroxyl methyl amino methane was dissolved in 80.00 ml of 1N HCl and made up to 1L with distilled water. The pH was adjusted to 7.5
2. **0.02M Adenosine triphosphate solution -** 11.023 mg of free ATP was dissolved in 1.00 ml of distilled water (W/V). This was prepared freshly for every use.
3. **Ammonium Molybdate solution -** 25.00 g of ammonium molybdate was dissolved in 100.00 ml (W/V) of distilled water. In 1L flask, 300.00 ml of 10 N concentrated sulphuric acid (83.10 ml of concentrated sulphuric acid of 36 N was made up to 300.00 ml with distilled water) was taken and ammonium molybdate was added and made up to 1L with distilled water.
4. **5% Trichloro acetic acid solution (TCA) -** 5.00 g of TCA was dissolved in 100.00 ml of distilled water (W/V).
5. **15% Sodium bisulphite solution -** 30 .00 g of sodium bisulphite solution was dissolved in 200.00 ml of distilled water (W/V). If the

prepared solution is turbid, it is allowed to stand for several days and filtered.

6. **20% Sodium sulphite solution -** 20.00 g of anhydrous sodium sulphite was dissolved in 100.00 ml of distilled water (W/V).
7. **ANSA Reagent (1-Amino-2-napthol-4-Sulphonic acid) -** 0.50 g of ANSA was dissolved in 195.00 ml of 15% sodium bisulphate solution in a dark brown bottle and 5.00 ml of 20 % sodium sulphite solution was added and mixed well. This was prepared freshly for every use.
8. **100 mM Sodium chloride solution -** 584.00 mg of NaCl was dissolved in 100.00 ml of distilled water (W/V).
9. **100 mM Potassium chloride solution -** 746.00 mg of KCl was dissolved in 100.00 ml of distilled water (W/V).

## Standard Preparation

0.315 g of pure monopotassium phosphate was dissolved in distilled water and transferred quantitatively to 1L volumetric flask. Then, 10.00 ml of 10 N sulphuric acids was added and diluted to the mark with distilled water and mixed well. This solution contains 0.40 mg of phosphorus in 5.00 ml.

## Procedure For Standard Graph Preparation

From the standard solution, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0 ml of the solution were taken in 10 test tubes, respectively, which correspond to their respective concentration of 8, 16, 24, 32, 40, 48, 56, 64, 72, and 80 µg of phosphorus. Distilled water was added to all the tubes and made up to 1 ml. Then, 1ml of ammonium molybdate and 0.4 ml of ANSA reagent were added to all the tubes. The appearance of the blue colour was read immediately against blank at 680 nm using UV Spectrophotometer and the respective O.D. values were noted.

For plotting the standard graph, the OD values were taken on the Y-axis and the concentration of phosphorus was plotted in X axis. Different concentrations and their respective OD values were plotted and points obtained were joined by a straight line (Fig. 1).

## Procedure For Enzyme Assay

Test tubes were taken and labeled as ‘Blank’ and ‘Test’ (T). To each tube, 0.3 ml of Tri-Hcl buffer (pH7.5), 0.1 ml of 0.02 M ATP, 0.1 ml of 100 mM NaCl and 0.1 ml of KCl (for $Na^+$, $K^+$ - ATPase) were added. Then, 0.1

ml of distilled water was added to 'Blank' and 'Test' tubes. Then 0.1 ml of tissue extract (gill) was added to the respective tubes. The contents of all tubes were mixed well and incubated in water bath at 37˚ C for 15 min. After the incubation period, the reaction was terminated with 2.00 ml of 5% TCA. Then all the tubes were kept at 4˚ for 30 min. and centrifuged for 5 min at 500 rpm. To the supernatant, 1 ml of ammonium molybdate and 0.4 ml of ANSA reagent were added and allowed to stand for 10 min at room temperature. The intensity of the blue colour developed was read at 680 nm against reagent blank using Spectrophotometer. Suitable standards were also run through each batch of assays. The enzyme activity was expressed in terms of micrograms of inorganic phosphorous formed per gram of tissue.

### Calculation Step 1

The O.D. values of both control and nitrite treated samples were marked on the Y axis of the standard graph and it was extrapolated to the corresponding phosphorous concentration on the X axis.

**Step 2**

The $Na^{+}$, $K^{+}$ - ATPase enzyme activity was calculated as per the following formula.

### For Gills

Total volume taken for homogenization

Activity =

Conc. of phosphorous X X

Volume taken for analysis

1000 1

4 X ---------- X expressed in µg/h/g tissue Weight of tissue taken 1000

## Results

Changes in the gill $Na^{+}/K^{+}$-ATPase activity of *Cirrhinus mrigala* exposed to sublethal concentration of nitrite showed a decreased activity when compared with the control group and registered a minimum percent decrease of 8.66 at the end of 7$^{th}$ day and a maximum percent decrease of 67.20 at the end of 35$^{th}$ day (Table 23 and Fig. 22). There were significant ($P < 0.05$) variation among the treatments ($F_{1, 40} = 375.02$; $P < 0.05$), periods ($F_{4, 40} = 29.75$; $P < 0.05$) and their interactions ($F_{4, 40} = 28.53$; $P < 0.05$).

Table 24 and Fig. 23 depict the data on plasma protein level of fish *Cirrhinus mrigala* exposed to sublethal concentration of nitrite for 35 days. During the above treatment period, plasma protein level in the nitrite exposed fish showed a declined trend throughout the study period showing a percent decrease of 0.85, 19.73, 38.29, 63.72 and 72.38 at the end of 7$^{th}$, 14$^{th}$, 21$^{st}$, 28$^{th}$ and 35$^{th}$ day respectively. There were significant ($P < 0.05$) variation among the treatments ($F_{1, 40} = 16177.06$; $P < 0.05$), periods ($F_{4, 40} = 1382.06$; $P < 0.05$) and their interactions ($F_{4, 40} = 1923.16$; $P < 0.05$).

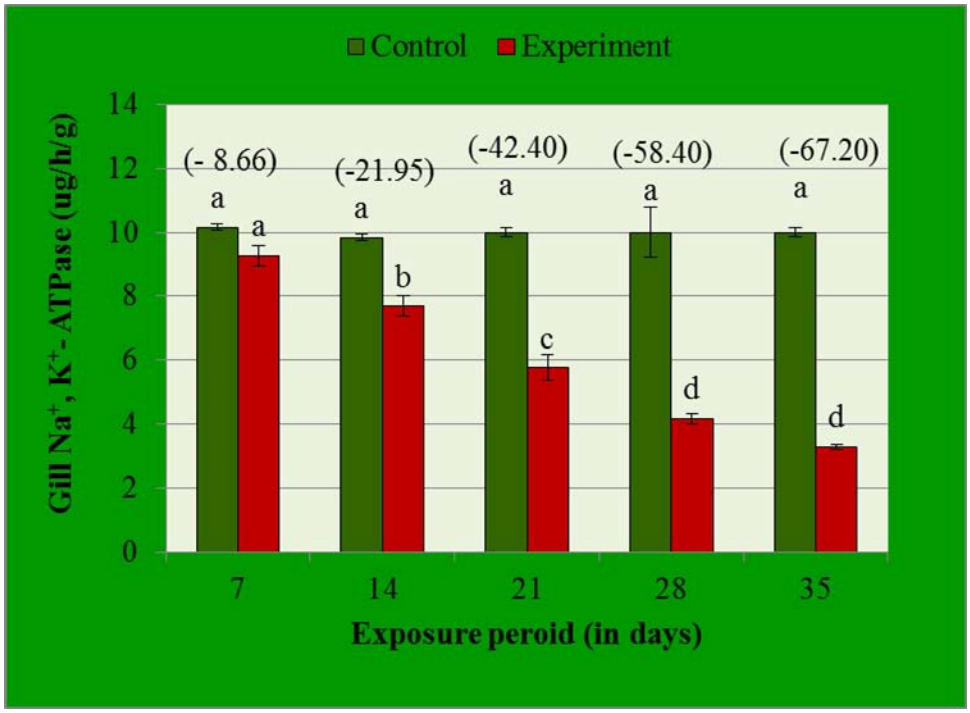


Fig. 22.

**Fig. 22.** Gill $Na^+/K^+$- ATPase activity of *Cirrhinus mrigala* exposed to sublethal concentration of nitrite for 35 days. Error bars indicate the standard error of the mean. Bars bearing same letter are significantly different according to DMRT ($P > 0.05$). The numericals in the parenthesis indicates percent change.

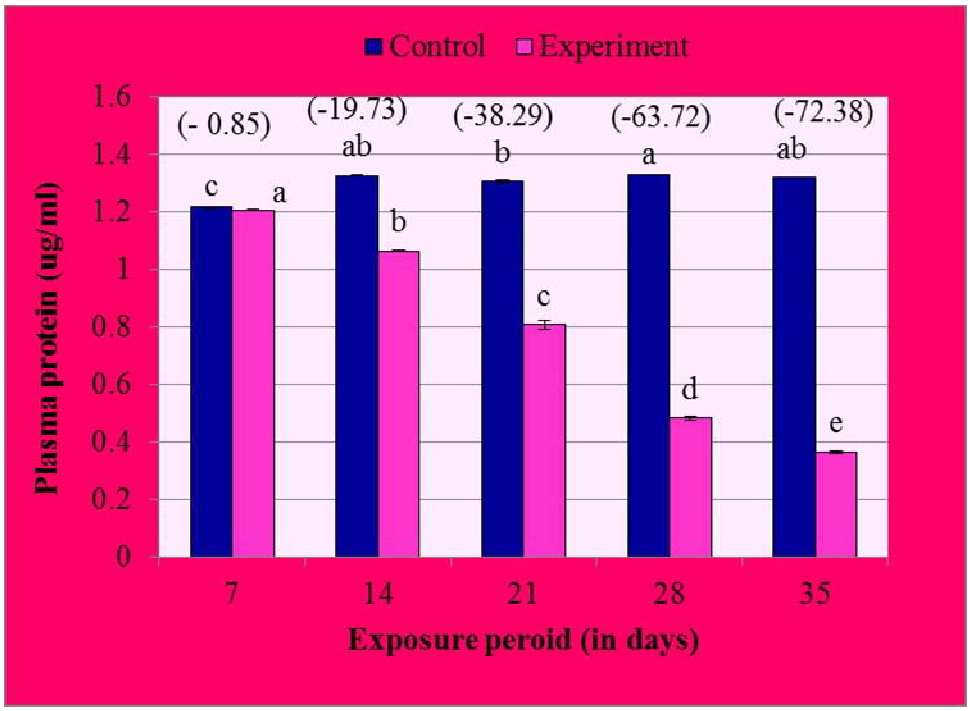


Fig. 23.

**Fig. 23.** Plasma protein level of *Cirrhinus mrigala* exposed to sublethal concentration nitrite for 35 days. Error bars indicate the standard error of the mean. Bars bearing same letter(s) are significantly different according to DMRT ($P > 0.05$). The numericals in the parenthesis indicates percent change.

## Discussion

Changes in physiological rates in response to chemical stress are manifestations of superimposed physiological effects across a variety of organizational levels from cellular to systemic. The biochemical and physiological mechanisms in an organism play an important role during stress conditions. In general the presence of toxicants in aquatic media exerts its effect at cellular or molecular level which results in significant changes in biochemical parameters (Kavitha *et al*., 2010). Protein and carbohydrates play a major role as energy precursors for fish under stress conditions. Changes in each of these blood components have been employed as useful general indicators of stress in teleosts.

Hyperglycaemia is typically associated with an increased metabolic rate, which is accelerated by both acute and chronic stress, because the stress response in fish is an energy demanding process observed that all types of stress elevated the secretion of catecholamine which in turn increased the breakdown of glycogen and elevated blood glucose level.

Fish under stress condition may also mobilize protein to meet energy demand to maintain increased physiological activity. Decrease in serum protein concentration and the albumin/globulin ratio in the blood indicates some liver dysfunction. When exposed to stressors, the gills become ‘‘leaky’’ to water and ions, often resulting in osmoregulatory imbalances. Thus the decline in serum total protein, albumin and globulin may also be due to a high degree of haemodilution under the stress of pollution. The significant decrease in plasma protein level in lindane treated fish during sublethal treatment might have caused from impaired protein synthesis due to liver disorder (Saravanan *et al.,* 2011). Further, excretion of proteins by kidney due to kidney disorder may also leads to depletion of protein in the blood. The significant decrease in serum protein concentration *Clarias gariepinus* exposed to nonylphenol and octylphenol may be an indication of protein catabolism, the process converting blood and structural protein and carbohydrate reserves to energy, to meet the higher energy demand during the prevailing stress caused by both NP and OP (Sathyanarayanan *et al*., 2011). The reduction of plasma protein of fish *Cyprinus carpio* exposed to acute atrazine treatment indicates the toxic effect of ATR on spleen, liver and kidney.

Das *et al.* (2004) reported that the higher energy demand might have triggered an increase in protein catabolism, a process in which both blood and structural protein are converted to energy, thereby reducing serum protein. They further reported that dilution of plasma volume after haemolysis and shrinkage of RBC could also cause a small reduction in protein percentage in serum and he suggested that reduced level of serum protein may be due to nephrosis or liver cirrhosis. Kidney damage causing increased renal excretion of blood protein may also have contributed to the depletion of serum protein in the fingerlings. However, the decrease of total protein in ATR treated fish *Oreochromis niloticus* and *Chrysichthyes auratus* was mainly due to globulin, explaining the toxic effects of ATR on the immune system of these fishes. The reduction of serum protein in the fish *Labeo rohita* at the higher deltamethrin concentrations are strong indicators not only of hepatic dysfunction, but also of immunosuppressive of the deltamethrin (Nayak *et al*., 2004).

The small and non-significant reductions in the serum protein in 1–2 mg/L nitrite exposures might have resulted from the protein catabolism and plasma dilution (Das, 2004). The reduction/failure of haemopoietic activity, implicated in higher nitrite concentrations (4– 10.4 mg/L), is a characteristic of kidney damage. The kidney damage in fingerlings exposed to higher nitrite concentrations (4–10.4 mg/L) might have caused an additional loss of blood protein through renal excretion causing the significant reduction of protein from serum. The 96 h of exposure of nitrite causing damage to kidney at 8– 10 mg/L has been observed by the authors in histopathological study. In the present study the observed decrease in plasma protein level during acute and sublethal treatment might have resulted from an increase in protein catabolism or impaired protein synthesis due to liver disorder or nephrosis.

Enzymes are used as indicators of pathological processes and they play an important role in toxicology and as indicators of stress. Gill $Na^+/K^+$-ATPase is intimately involved in electrolyte balance and the determination of ATPase activity would prove to be an important index for tolerable levels of a large group of environmental contaminants (Mathan *et al.,* 2010). Xenobiotics can alter $Na^+/K^+$-ATPase activity due to disruption of energy producing metallic pathways or interact directly with the enzyme. The off target movement of chemicals used in industry and agriculture get into natural water and cause significant tissue damage in fish. Gills are the primary target organ for toxic action and they represent the greatest area of the animal in contact with external environment. Toxic substances may causes damage to gill tissues, thereby reducing the oxygen consumption and disturbing the osmoregulatory functions of aquatic organisms (Wendelaar Bonga, 1997).

It seems likely that the increased gill $Na^+/K^+$-ATPase activity, at higher nitrite exposure concentrations, was a compensatory response to maintain serum Na levels at a constant level. Recently, Saravanan *et al.* (2011) reported that the significant increase in gill $Na^+/K^+$-ATPase activity in *Cyprinus carpio* exposed to the pharmaceutical drugs clofibric acid and diclofenac indicating the direct action of these drugs on ATPase function. The increase in gill $Na^+/K^+$-ATPase activity may be a compensation for a dysfunctional regulation of ionic levels or a process to restore electrolyte levels. In the present study also the significant increase in gill $Na^+/K^+$-ATPase activity during acute toxicity indicate the direct toxicity of nitrite on ATPase function or a compensatory response to maintain serum Na levels at

a constant level (in the present study the plasma Na levels was decreased both in acute and sublethal nitrite treatment).

Inhibition of gill $Na^+/K^+$-ATPase activity has been described in *O. mossambicus* , and shown to occur by covalent binding of copper to SH-groups and interaction with $Mg^{2+}$ binding sites, although there was an increase in the number of $Na^+/K^+$-ATPase rich chloride cells in *O. mossambicus* after 5–6 days of exposure to copper. The significant decrease of $Na^+/K^+$-ATPase activity during acute and sublethal treatment might have resulted from the direct toxicity of the cypermethrin on ATPase function (Suvetha *et al.,* 2010). One of the reasons for the decrease in the enzyme activity may be a disturbance in the essential sulphydryl groups). Gills $Na^+/K^+$-ATPase activity depression could also result from gill destruction, mainly of chlorine cells.

Nitrite acts as a protonophore, i.e., an uncoupler that increases the proton permeability of membranes by a shuttling mechanism. An uncoupler is an agent that stimulates basal electron transport, inhibits ATP synthesis, stimulates ATP hydrolysis and inhibits various exchange reactions catalysed by the ATP-ase. Nitrite intoxication in fresh water teleost cause osmoregulatory defects and decline in plasma $Na^+$. In sea bass nitrite exposure caused a significant reduction in gill $Na^+/K^+$-ATPase activity whereas elevated kidney $Na^+/K^+$-ATPase activity in sturgeon yearlings was implied as a key process for elimination of excess ions during recovery from nitrite exposure (Gisbert *et al.,* 2004).

Nitrite is absorbed across the gills along with water. Inhibition of enzyme in gill indicates disruption in its cellular and ionic regulation and salt uptake (Jensen, 2003). Nitrite exposed to gills exhibit rapid alterations that include detachments and lifting of epithelial linings from the surfaces of gill filament. This led to extensive hemorrhage from the gills. Thus quantity of blood flowing across the gills decreased substantially, leading to hyperplasia. Toxicants as chemicals alter the enzyme $Na^+/K^+$-ATPase activity due to disruption of energy (Watson and Beamish, 1980). In the present study, the decrease in gill $Na^+$, $K^+$,- ATPase activity during sublethal treatment indicates disruption in its cellular and ionic regulation and salt uptake. Gills $Na^+/K^+$-ATPase activity depression could also result from gill destruction, mainly of chlorine cells. Since the gills are primary target organ for toxic action of nitrite it affect the major target molecules the ion dependent ATPase, which lead the disturbances in ion homeostasis.

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# Sustainable Edible Films From Garlic Peel With Bioactive Potential and Food Packaging Applications

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## Introduction

The increasing demand for green and biodegradable packaging materials has encouraged scientists to explore alternative sources derived from food waste. With rising concerns about plastic waste and food safety, the food packaging industry is steadily shifting toward biodegradable films (Kumar *et al.,* 2022). In particular, nanotechnology-based approaches are being applied to enhance the functional properties of such films, including improved thermal stability and antimicrobial activity.

Garlic peel, an abundant agricultural by-product, has emerged as a promising raw material for edible film development. Incorporating garlic peel into packaging films offers a cost-effective and sustainable solution by reducing raw material costs while simultaneously addressing waste management challenges (Correia *et al.,* 2022). Studies suggest that films derived from garlic peel can potentially replace conventional plastic packaging, offering an environmentally friendly option with desirable functional characteristics (Chaudhary *et al.,* 2021). Moreover, the economic feasibility of large-scale production continues to attract research attention (Kumar *et al.,* 2022).

At the industrial level, biodegradable films can deliver fiscal benefits for companies transitioning away from synthetic plastics. Integrating garlic peel into packaging solutions also creates value-added opportunities for garlic processing industries, supporting circular economy practices (Medeiros dos Santos *et al.,* 2022). The physical and barrier properties of these films are strongly influenced by the fabrication method. For example, casting techniques allow uniform thickness and homogeneity, making them ideal for food packaging applications. In contrast, extrusion methods are better suited for large-scale production because they reduce processing time and costs (Fu *et al.,* 2022).

Garlic peel contains a wide range of bioactive compounds, including flavonoids, phenolic acids, and sulfur compounds such as allicin, which

contribute to its antimicrobial and antioxidant activity (Santos *et al.,* 2022). The polyphenolic constituents, in particular, provide strong free radical scavenging activity, making garlic peel-based films effective in extending the shelf life of perishable foods (Medeiros dos Santos *et al.,* 2022). Furthermore, extracts of garlic peel have demonstrated inhibitory effects against foodborne pathogens such as *Staphylococcus aureus* and *Listeria monocytogenes*, confirming its potential for active packaging applications (Correia *et al.,* 2022). One of the most significant deteriorating processes affecting a variety of fruits and vegetables is enzymatic browning, caused by the oxidation of phenolic molecules, also known as polyphenol oxidation (PPO). Phenols are catalyzed by polyphenol oxidase to ultimately produce polymeric pigment molecules (Karthika and Vijayakumar, 2022). Recent advances in edible film technology have also explored the integration of garlic peel extracts with other biopolymers such as chitosan and carrageenan to improve mechanical and functional properties (Fu *et al.,* 2022). Additionally, incorporating bioactive additives like clove oil further enhances antimicrobial and antioxidant activity, while also improving barrier performance through polymer–oil interactions (Tavassoli and Djomeh, 2011).

With increasing restrictions on single-use plastics and growing consumer demand for eco-friendly products, garlic peel-derived films represent a sustainable innovation in food packaging. They not only provide a means of upcycling agricultural waste but also align with global efforts toward cleaner, healthier, and more sustainable food systems. Therefore, the present study aimed to develop and characterize the physicochemical properties of edible films produced from garlic peel waste (Santos *et al.,* 2022).

## 2.1. Overview of Study

The global emphasis on food safety and environmentally sustainable packaging has driven extensive research into biodegradable edible films derived from natural resources. Traditional plastic packaging, due to its persistence in the environment and contribution to waste accumulation, is increasingly criticized. In contrast, edible films provide dual advantages: they are fully biodegradable and, in some cases, edible, while also serving as effective barriers to protect food products. The development of such films directly addresses challenges related to waste management, food preservation, and environmental protection (Correia *et al.,* 2022).

Among the various natural sources investigated, garlic peel has shown exceptional potential because of its rich bioactive profile, cost-effectiveness, and wide availability. Typically discarded during garlic processing, garlic peel

contributes significantly to agricultural waste, creating environmental concerns and missed economic opportunities. However, its high content of flavonoids, polyphenols, and sulfur compounds provides strong antimicrobial and antioxidant properties, making it a valuable material for edible film production (Medeiros *et al.,* 2022). These bioactive properties help suppress microbial growth and oxidative spoilage, thereby extending the shelf life of perishable foods.

Researchers are increasingly incorporating garlic peel into edible film formulations to create packaging materials that not only protect food but also add functional value. Current studies are investigating effective extraction methods for isolating garlic peel bioactives and strategies for their successful integration into film matrices (Fu *et al.,* 2022). Such films fall within the category of *active packaging*, a system designed not only to serve as a passive barrier but also to interact with the packaged food—either by releasing antimicrobial agents or by scavenging oxygen and moisture. Garlic peel is particularly suitable for this application, as its antioxidant and antimicrobial compounds provide natural food preservation benefits, reducing the need for synthetic preservatives (Kumar *et al.,* 2022).

This study therefore, focuses on characterizing and testing garlic peel-based films to demonstrate their functional superiority compared with conventional packaging. Beyond their protective role, these films exemplify the transformation of a low-value by-product into a high-performance biodegradable material. Such innovation aligns with circular economy principles, offering sustainable, waste-free alternatives with reduced environmental impact (Kumar *et al.,* 2022).

## 2.2. Worldwide Production

Garlic (*Allium sativum L.*) is cultivated worldwide, with China, India, Bangladesh, Egypt, and South Korea ranking among the top producers. China dominates global production, accounting for nearly 70% of the world's garlic supply, while India also plays a significant role in the international garlic industry (Medina-Juárez *et al.,* 2012).

The large-scale processing of garlic generates substantial amounts of waste, particularly garlic peel, which makes up approximately 25% of the total bulb weight (Lu *et al.,* 2011). At peak processing times, this fraction represents the most significant by-product, yet nearly 60% of it is discarded, with only a small portion composted (Kim *et al.,* 2013; Bhushan *et al.,* 2020). Such disposal practices not only contribute to waste management challenges but also result in the loss of valuable bioactive compounds.

Garlic peel is far from inert waste; it is a rich source of phenolic compounds, flavonoids, and sulfur-based molecules with strong antioxidant and antimicrobial activities (Sadh *et al.,* 2018). These functional attributes make it a promising material for incorporation into edible films and active packaging systems, where it can enhance shelf life and improve food safety. In addition to its technical benefits, garlic peel offers economic value as a low-cost raw material for producing functional biopolymer-based films.

Despite encouraging results from laboratory-scale research, questions remain regarding the scalability and affordability of garlic peel-based films. Some pilot studies—such as those involving school-level applications of bio-waste films—have shown positive outcomes, but comprehensive economic feasibility assessments are still lacking (Sadh *et al.,* 2018). Addressing these gaps could pave the way for integrating garlic peel into large-scale packaging innovations, thereby promoting sustainability and resource efficiency.

## 2.3. Nutritional Composition and Benefits

### 2.3.1 Nutritional Constituents

Although often discarded, garlic peel is nutritionally rich, with a high fiber content that contributes to the structural strength of edible films. Compounds such as methylcellulose aid in forming tight bonds within the film matrix, while minerals including calcium, potassium, and magnesium enhance the films' mechanical integrity. These nutrients not only support the film's structure but also help maintain the physical properties of packaged foods by preventing undesirable changes (Fu *et al.,* 2022).

### 2.3.2 Macronutrient Profile

Garlic peel contains limited amounts of proteins and carbohydrates; however, these compounds readily integrate into the film matrix during processing. Their participation in polymerization and matrix formation contributes to network strength, thereby improving the mechanical and barrier properties of the films (Kumar *et al.,* 2022).

### 2.3.3 Micronutrient Profile

In addition to macronutrients, garlic peel provides vitamins and trace minerals that further enhance both the nutritional and functional qualities of edible films. These micronutrients contribute to antioxidant defense

mechanisms, which help delay oxidative stress and prolong the shelf life of packaged foods (Medeiros *et al.,* 2022).

### 2.3.4 Functional Bioactive Compounds

Garlic peel is particularly valued for its bioactive compounds, including flavonoids, phenolic acids, and sulfur compounds such as allicin. These molecules exhibit strong antioxidant capacity, neutralizing free radicals and preventing lipid peroxidation in food systems (Ramanathan *et al.,* 2012). Their dual role in antimicrobial and antioxidant protection makes garlic peel an attractive candidate for active food packaging.

### 2.3.5 Health-Promoting Benefits

The combined action of fibers, macronutrients, micronutrients, and bioactive compounds in garlic peel provides multiple health-promoting benefits. Antioxidants reduce oxidative stress, while antimicrobial components inhibit spoilage and pathogenic microorganisms, enhancing food safety. Incorporating garlic peel into edible films therefore reduces reliance on synthetic preservatives and aligns with consumer demand for clean-label products (Fu *et al.,* 2022).

### 2.3.6 Synergistic Effects on Film Properties

The interaction of nutritional and bioactive components enhances the functional performance of garlic peel-based films. Fibers contribute to structural stability and water resistance, while bioactive compounds strengthen antioxidant and antimicrobial activity. These synergistic effects help maintain food quality and extend shelf life (Kumar *et al.,* 2022).

### 2.3.7 Impact on Food Preservation and Quality

Garlic peel-derived films directly influence food preservation by slowing lipid oxidation and inhibiting microbial growth. These protective effects improve product safety and sensory quality, making the films suitable for extending the freshness of high-fat and perishable foods (Medeiros *et al.,* 2022).

### 2.3.8 Economic and Environmental Benefits

Using garlic peel for edible film production addresses waste management challenges while contributing to a circular economy. Transforming this low-value by-product into a functional material not only reduces raw material costs but also decreases environmental pollution. Such innovations align with international sustainability goals aimed at minimizing synthetic packaging materials (Correia *et al.,* 2022).

## 2.4. Technologies Used for Developing Edible Film

The development of edible films using garlic peel as the main raw material showed efficiency, which is connected to several advanced physical and functional properties. The casting technique is the most common method, where a solution containing biopolymers (e.g., chitosan, gelatin, carrageenan) and garlic peel is set and then put into thin layers letting them dry for a while. This way allows the film to be as close as possible to the requested thickness and the homogeneity of it. It ensures the equal distribution of the garlic peel-derived bioactives, whose existence helps the film become useful, for instance, it can enhance its antimicrobial and antioxidant abilities (Correia *et al.,* 2022).
On the other hand, extrusion techniques come here for the mass production of these films, which are the most cost-effective, is also a way. Here, the film-forming mixture during production is processed at a controlled temperature and under pressure, which, as a result, increases the structural endurance and tensile strength of the final product (Chaudhary *et al.,* 2021).

Recent innovations, in turn, unveil a technique known as electrospinning, which generates ultrathin, nanofiber-based films. These films usually have a larger surface area than they do volume, thus they are better at the absorption and release of garlic peel-derived bioactive compounds to increase the antimicrobial ability and the moisture barrier function (Fu *et al.,* 2022).

Apart from the latter, the techniques of nanocomposite reinforcement and crosslinking are also in line of new developments in the manufacture of such films. These are being tested to see if they can act effectively to provide film flexibility, thermal stability, and mechanical strength, respectively. All these improvements are necessary so garlic peel-based edible films are able not only to be in compliance with packaging standards but also to be an agent in reducing food safety hazards and extending the product shelf life (Medeiros *et al.,* 2022; Kumar *et al.,* 2022).

Using solution-casting techniques, cornstarch-based edible and antibacterial films have been created, and their functionality has been improved by adding extracts from medicinal plants. To create new edible films with better qualities, it has been investigated to incorporate oils from aromatic and medicinal plants into sodium alginate films (Ali et al., 2023; Mahcene et al., 2020). The Ched-Chee's antioxidant potential (DPPH, ABTS, and FRAP activities), lipid (TBARS and free fatty acids), protein (total carbonyl content), oxidative stability, and microbial quality (microbial counts) all increased when the films containing *Caralluma fimbriata*nanoparticles (1.0–3.0%) were applied over the course of 90 days of storage (Lone *et al.,* 2025). According to Periyasami *et al.* (2025), the study demonstrates the viability of using *Caralluma fimbriata* in the production of functional beverages, providing a natural, health-conscious substitute for traditional drinks. Consequently, incorporating medicinal plants into edible films improves their functional qualities and satisfies consumer desire for environmentally friendly and health-promoting food packaging options. The topic of edible film technology could advance with more study and development in this area.

## Conclusion:

An agricultural by-product that is frequently thrown away, garlic peel shows great promise as a raw material for the creation of sustainable edible films. Packed with bioactive substances including phenolic acids, flavonoids, and sulfur-based components, it has antibacterial and antioxidant properties that are extremely beneficial for food preservation. Garlic peel is incorporated into biopolymer matrices to promote the idea of active and intelligent packaging while also improving the mechanical, thermal, and barrier qualities of films. The efficiency and range of applications of these films are further enhanced by emerging technologies such as electrospinning and nanocomposites. In addition to their practical uses, edible films made from garlic peels support circular economy principles by cutting production costs, decreasing agricultural waste, and providing environmentally benign substitutes for synthetic polymers. In order to turn these encouraging results into commercial realities, more study on large-scale processing, economic viability, and consumer acceptance is essential. In the end, films made from garlic peels are a feasible step toward environmentally friendly food packaging that supports the worldwide objectives of waste minimization, food safety, and environmental preservation.

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# Revolutionizing Biomedical Research: The Convergence of Generative AI and Quantum Technology

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## Abstract

The innovation in the field of Biomedical research by using quantum technologies and generative artificial intelligence (AI) which shows high potential in advancing research in Biomedical. It revolutionizing the analyzing process of big data problem of patient by computational methods, often struggle its large scale and complex information of biologic clinic [1]. Time of process and accurate output is the feature of Quantum technology with AI driven. It using the principles concept of quantum mechanics from Physics, known as Biophysics [2]. Its application in health sector by applying quantum machine deep learning through AI for drug discovery by quantum dots (QDs), genomic analysis, simulating Protein-Ligand interactions, Image analyzing [3]. Quantum technologies with generative AI transforming the healthcare industry fast with more accurate data which helps to treat diseases like Cancer, Alzheimer's, diabetic retinopathy, tumors and rare disorders [4][5][6]. Quantum technology AI driven predict the future possibilities of a given data of each individual genomic data. GANs and VAE OF DGMs predict phenotypes disease. Personalized Diagnonsis regarding genetic profile by quantum technologies with generative AI driven which gives real-time analysis of patient data. Biomed Parse model design for Medical Image Analysis [7].

**Keywords**: Biomedical, Big Data Technologies, Generative AI, Quantum Technologies, Fluorescene Imaging.

# 1. Introduction

Health is fundamental basic needs for all living creatures and it is essential to do some advance Health research. Biomedical is that field in which global health gets improved. Recent study shows that number of research publication increased and they are striving to form cost effective medical research capacity by advanced technologies collab with Generative AI and Quantum Technologies in the field of Biomedical research [8]. Physics contain high potential in the field of Medicine, which leads an Innovation. Innovation to how the big data of patient diagnosisand can be translated into clinical solutions, known as Big Data Technology [9]. Modern biophysical techniques used to enhance the Global Health by its recent Generative AI Quantum technologies. This tool has a great potential to revolutionize practice in medial from diagnosis to therapy [10]. In India; ABHA (Ayushman Bharat Health Account) ID one of the new app. launched bythe Government of India (on 27th September, 2021) to maintain the account of all the medications and history of patients in one place for future references [11].

# 2. Quantum Technology

Quantum technology is a new generation of technology which is based on the principle of quantummechanics. In Quantum technology superposition, quantum tunnelling, entanglement, interference etc. are perform computation, quantum dots, quantum cryptography, quantum materials science, quantum simulation, communication and Quantum sensing task, which are beyond the classical technologies [12].

## 2.1 Quantum Technology in Biomedical Research

Quantum technology is widely used in biomedical field recently, offering unprecedented opportunities for breakthroughs in healthcare and medicine. Quantum Computing enables simulations of complex molecular interactions, accelerating drug discovery and development. For instance, IBM and Cleveland Clinic have partnered to dedicate a quantum computer to biomedical research. Quantum Sensing offers ultra-sensitive detection for biomolecules, imaging tissues, and monitoring physiological parameters. Technologies like optically pumped magnetometers (OPMs) [13] and nitrogen-vacancy (NV) centers in nanodiamonds show promise [14]. Medical Imaging used quantum-enhanced MRI systems exploit quantum coherence and entanglement for improved sensitivity and sharper scans. Personalized Medicine use quantum algorithms can analyze genomic and clinical data to predict treatment responses and tailor therapies. Disease Detection use

quantum sensing technologies aid early detection of diseases, potentially improving diagnosis and treatment outcomes. Quantum Dot CMOS Image Sensor: CSEM and QDI Systems developed an image sensor directly converting X-rays into electronic signals using QDs on a CMOS platform, enabling compact, low-cost, and scalable wide-spectrum imaging. Quantum-Dot Cellular Automata (QCA): QCA offers advantages like low power dissipation, faster switching speed, and extremely low circuit area for designing nano-scale image processing circuits [2].

Applications of quantum computing and quantum machine learning in:

### 2.11.Simulating Protein-Ligand Interactions[2]:

Accurate simulations for drug discovery and design. Accelerated Simulations by Quantum computing can simulate complex molecular interactions up to 100 million times faster than classical supercomputers, enabling rapid exploration of protein-ligand binding. For improved accuracy, Quantum algorithms lime QAOA and VQE offer more precise calculations of molecular electronic ground states, enhancing understanding of binding affinities. Combining classical and quantum computing (NISQ devices) known as Hybrid Approaches, shows promise for calculating protein-ligand interaction energies, as demonstrated with BACE1 inhibitors. Quantum computing used in drug design aids in identifying promising drug candidates by efficiently calculating molecular stability, binding affinity, and toxicity [15].

### 2.12. Genomic Analysis[2]:

Quantum-accelerated sequence alignment and variant detection. Quantum Computing for Genomic Data Analysis algorithms like Grover's search can rapidly comb through vast genomic databases, identifying subtle gene variants influencing treatment responses. Quantum Machine Learning (QML) models are being explored for binary classification of genome sequence data, enhancing pattern recognition and prediction capabilities. Quantum neural network (QNNs) has shown promise in identifying genetic biomarkers, such as those associated with CTLA4 activation pathways. Quantum computing can analyze complex genomic and clinical data to predict patient responses to therapies, tailoring treatments to individual genetic profiles [16].

### 2.13.Medical Imaging[2]:

### Quantum-inspired image reconstruction and analysis.

In medical imaging, DNA Modification. In recent time Quantum Dot Circuit (QDC) used in medical imaging. QDC enhance the processing of X-

Ray, MRI, CT scan. Quantum dots are revolutionizing medical imaging with their unique optical properties, enabling unprecedented diagnostic capabilities. In Fluorescene Imaging, QDs exhibit size-tunable fluorescence emission, high photostability, and brightness, making them ideal for visualizing cellular structures and processes. In Multi-modal imaging, QDs can be used in various imaging modalities, including fluorescence imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT). In Targeted imaging, QDs can be functionalized with targeting moieties like peptides or antibodies to selectively blind to disease-associated biomarkers. QDs helps in multi-color imaging enable to simultaneous detection of multiple targets with high sensitivity and specificity. Configurable architecture is allowed to the implementing of image processing, which is advance like reduction of noise and also used for morphological operation. QDC are also crucial for detecting Vascular Anomalies type disease (like tumors etc.). QDC are suitable for medical devices because of its efficient energy and also its compact nature. In overall study shows that QDC technology revolutionizing the Biomedical field and enhance the image processing operators [16].

## 3. Generative AI

Generative AI has emerged as a new rise in research because this AI model performs the experiment in a stimulation and gives the data by his decisions making power as soon as possible, it does the multiple scale examining of the subject. Generative AI is a fascinating field of artificial intelligence that focuses on creating new content like text, images, audio and even code by learning patterns from existing data. It's like having a super creative assistant that can produce original outputs often indistinguishable from human-created content [17]. Some tools like Gemini use large language models (LLMs), ChatGPT, Chatbots, DALL-E, Midjourney, GitHub. Generative AI holds immense potential for innovation, offering tools that can augment human capabilities and open new avenues for creative expression and problem-solving [18].

### 3.1. Generative AI in Biomedical Research

Generative AI typically involves training deep learning models on vast datasets, allowing them to learn patterns and generate new content based on prompts or inputs. Techniques include Generative Adversarial Networks (GANs), Variational Autoencoders (VAEs), and transformer models like GPT. Generative AI is transforming industries like healthcare, marketing, and software development, enhancing productivity and creativity [19]. Predictions

suggest significant growth, with Gartner forecasting that by 2027, nearly 30% of new applications will be automatically generated by AI [20]. Generative AI is transforming the pharmaceutical industry, enabling faster, more precise therapies for complex diseases like cancer, Alzheimer's, and rare disorders. Its potential is vast, with predictions suggesting significant growth in AI spending in pharamaceuticals [4].

### 3.11. Drug Discovery[2]:

Generative AI is revolutionizing drug discovery in the medical field, bringing unprecedented speed, efficiency, and innovation to the process. In De Novo Drug Design creates entirely new molecules from scratch, tailored to specific disease targets, such as lung cancer or rare genetic disorders like Duchenne muscular dystrophy. AI algorithms design novel molecular structures with desired properties, predicting interactions and optimizing efficacy. It rapidly screens potential drug candidates, simulating interactions with target proteins [21]. AI identifies new uses for existing drugs, like using a multiple sclerosis drug for amyotrophic lateral sclerosis (ALS). It customizes treatments based on individual genetic profiles, improving efficacy and reducing side effects [22]. As a new drug is discovered, its data use in stimulations for analyzing by Artificial Intelligence (AI). Silico Stimulations is such example of Generative AI in Biomedical Research [23]. Generating novel molecular structures and predicting binding affinity. Some examples, Rentosertib is developed by Insilico Medicine, this is the first drug where both target and compound were discovered using generative AI, receiving official naming from the USAN Council. Insilico Medicine used AI to design a drug candidate for idiopathic pulmonary fibrosis in under 50 days. Mount Sinai's AI Small Molecule Drug Discovery Center is a harnesses generative AI for designing novel drug-like molecules and predicting drug-target interactions [24].

### 3.12.Genomics[2]:

Generating genomic sequences and predicting gene function. Genomic Data Analysis where Generative AI accelerates analysis of vast genomic datasets, identifying patterns and correlations that might elude human researchers. On the basis of genetic profiles AI models predict disease, enabling early intervention and preventive strategies and by this data it personalized treatment plans. AI-driven platforms like Exscientia and NVIDIA's generative AI cloud services expedite drug discovery by analyzing patient tissue and molecular dynamics. Generative AI creates realistic, privacy-preserving synthetic patient data, addressing data scarcity and privacy concerns

in healthcare. Deep Generative Models (DGMs) is like Generative Adversarial Networks (GANs) and Variational Autoencoders (VAEs) generate synthetic genomic data and predict disease phenotypes [4].

### 3.13. Image Analysis[2]:

Synthesizing medical images for date augmentation and anomaly detection. In Image Synthesis generative models likeGANs and diffusion models create synthetic medical images (MRI, CT, X-ray, ultrasound)that mimic real-world data, augmenting datasets and preserving patient privacy. Image enhancement and reconstruction where generative AI denoises and reconstructs medical images, improving diagnostic utility and reducing radiation exposure. In Image Segmentation, AI algorithms automatically segment images into regions of interest, helping doctors identify tumors, lesions, or abnormalities more accurately. It detects diseases like diabetic retinopathy, breast cancer, and age-related macular degeneration with high accuracy [4][5][6].

## 4. Convergence of Generative AI and Quantum Technology

As the humans have evolved, their problems also. In the last few decade the humans suffering from diseases (most are deadly diseases) that have increased in a compounding rate. So now we need to speed up our efficiency of medication and its accuracy too. That's the point where Generative AI and Quantum Engineering enter in the research of Biology called as Biophysics [2]. Because these stimulations perform multiple scale examining of big data provided that we provide and in response to it alot of information regarding the possible outcomes is provided to us by it. And these results are just next to accurate (that too as a quickest response). And to deal with all this complex data, big data technology has emerged which has its root from AI and Quantum level computing of data.When Quantum Dots circuit integrated with the medical imaging processing algorithms based on Generative AI.Quantum Dots circuit has decision making accuracy that’s why they help in early detection of disease, improving the automated screening accuracy and they also planning for personalized treatment [12]. This synergy is transforming how we identify, design, and test new medications, making the process faster, cheaper, and more precise [16].

Exploring the potential of combining these technologies for:

### 4.1. Accelerated Drug Discovery:

Quantum-accelerated generative models for novel molecule generation. AI and quantum computing can reduce drug discovery timelines from years to mere weeks or months, significantly lowering expenditures [25]. Quantum algorithms like Variational Quantum Eigensolver (VQE) accurately model molecular systems, predicting interactions and efficacy. Researchers have successfully used AI and quantum computing to design molecules targeting previously "undruggable" cancer proteins like KRAS [26].

### 4.2. Personalized Medicine:

Quantum-enabled genomic analysis and AI-driven treatment planning. Quantum computing and AI analyze individual patient data, including genetic profiles, to create personalized treatment plans. AI Quantum computing facilitates real-time analysis of patient data, allowing for adaptive treatment adjustments [27].

### 4.3. Medical Image Analysis:

Quantum-inspired generative models for image synthesis and analysis. A groundbreaking biomedical foundation model "BiomedParse" developed by researchers at Microsoft Research and other institutions can jointly perform image segmentation, object detection, and recognition across nine major imaging modalities. This model outperforms traditional methods, enabling scalable and precise analysis of complex biomedical images. Photon-Counting CT (PCCT), research has shown that PCCT scans of the lung provide better image quality while using significantly less radiation dose compared to conventional CT scans [28].

## 5.Potential Benefits

- Faster Drug Discovery: Quantum computing optimizes and accelerates identification of potential drugs, reducing time and cost.
- Targeted Therapies: Enhanced simulation accuracy enables design of more effective, targeted drugs.
- Complex Disease Research: Quantum computing facilitates research into complex or neglected diseases.
- Accelerated Discovery:Faster and more accurate discovery of novel therapeutics and diagnostics.
- Improved Personalization: Tailored treatments and disease prevention strategies.

- Enhanced Understanding: Deeper insights into complex biological systems and disease mechanisms.
- Improved Diagnostic Accuracy: Enhanced image quality and synthetic data augmentation boost detection capabilities.
- Reduced Healthcare Costs: Streamlined analysis and personalized treatments can increase access to care.
- Education and Training: Synthetic images help medical students practice diagnosis in safe environments.
- Efficiency and Scalability: AI-driven tools like BiomedParse are streamlining medical image analysis, saving time and reducing errors [1][2][12][16][28].

## 6. Challenges

- Technical Limitations: Current quantum hardware faces issues like qubit stability and error correction.
- Toxicity: Potential toxicity of QDs is a concern; research focuses on biocompatibility and safety.
- Clearance: Efficient clearance of QDs from the body is crucial for medical applications.
- Regulatory Approval: Limited clinical trials and approvals highlight the need for further development and testing.
- Data Security: Quantum computing poses risks to encryption; quantum-secure methods are being developed.
- Workforce Development: Growing need for professionals fluent in quantum tech and life sciences [1][2].

## 7.Future aspects

- Quantum Hardware Development: Advancements in qubit stability and error correction are crucial.
- Integration with Classical Methods: Hybrid approaches will likely play a significant role.
- Talent and Collaboration: Cross-functional collaboration and attracting quantum expertise are key to success.

- Precision Medicine: Generative AI is transforming precision medicine by enabling tailored treatments based on individual genetic and clinical profiles.
- Research Acceleration: AI-driven genomics research accelerates discoveries, improves diagnostic accuracy, and fosters personalized therapies [1][2].

## 8. Initiatives and Collaborations

- NCATS Qu-BIT Program: Supports development of quantum sensing and computing for biomedical applications, with awards for innovative proposals [1].
- Pasqal and Qubit Pharmaceuticals: Collaborating on hybrid quantum-classical approaches for protein hydration analysis and ligand-protein binding [29].
- IBM Quantum: Exploring quantum systems for identifying promising drug candidates [30].
- QuPharm: Consortium pooling expertise on quantum computing applications in pharma [31].
- IBM Quantum System One: Dedicated quantum computer for biomedical research at Cleveland Clinic, part of a partnership for accelerated medical discoveries [32].
- Research Partnerships: Collaborations between academia, industry (like IBM, Google, D-Wave), and healthcare institutions drive quantum advancements in genomics and medicine [1][32].

## Conclusion

It holds transformative potential for biomedicalresearch, driving innovations in diagnostics, treatments, and healthcare delivery. Quantum Technologies with generative AI driven represents a significant potential it shows in Biomedical research as compared to Classical Mechanics. Capabilities like computational, genomic analyzing, drug discovery and image modification.

Biological simulations enhance protein-ligand interaction, molecular dynamics models, sequencing of genomic analysis image analyzing with higher accuracy and reduced computational costs. Interdisciplinary of Quantum AI collaboration medical innovations are ethical, reliable, and scalable. Despite of so many challenges, the future of Quantum AI leads to Globalization of

digitization efforts. It is the adoption of hybrid quantum from classical frameworks.

Initiative collaboration of quantum physicists AI researchers, medical practitioners and bioinformations establish global standardizing quantum AI protocols algorithm validation, environment friendly AI driven model and global regulatory frameworks will lead to the Innovation gaining profit and public trust.

Current situation challenges we face but despite of its Quantum technologies with generative AI driven models holds promising to bring Revolutionizing Biomedical Research in the future with doing initiative collaboration[1].

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# Neurobiotechnology: From Neurons to Behavior

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## Abstract

The human brain controls everything we think, feel and do. It is composed of billions of neurons that communicate using electrical and chemical signals.Neurobiotechnology is the field that applies advanced tools to study how neurons work, how they influence behavior, emotions, learning and psychological health. By combining Biology, technology and psychology, scientists can now explore how brain activity shapes our daily lives, treat neurological disorders and even grow simplified versions of the brain in the laboratory called organoids. This chapter explores how neurons communicate, how brain networks are linked to behavior and how new technologies are transforming research and treatment all in ways that are easy to understand and closely related to everyday experiences.

**Keywords:** Neurobiotechnology, neurons, brain function, neural communication, behavior, emotions, learning, neurological disorders, brain organoids, biotechnology, psychology

## Introduction

Have you ever wondered why you feel nervous before a presentation or happy when you achieve a goal? The answer lies in the brain - the body's command Centre. It constantly sends signals to control how you move, what you feel and even how you learn new skills. Why understanding the brain is essential and relation between thoughts, emotions and action.The human brain is a remarkably complex organ, responsible for controlling everything from basic physiological functions to higher cognitive process such as memory, learning, emotions, and decision making. At the heart of this complexity are billions of neurons- specialized cells that transmit information through electrical and chemical signals. In recent decades, biotechnology has emerged as a powerful tool for exploring the links between brain activity and behavior.. While classical neuroscience focused on anatomy, physiology and psychology, biotechnology extends this understanding by providing molecular, genetic and

engineering tools that allow researcher to observe the brains in unexpected ways. The convergence of these disciplines has given rise to neurobiotechnology. So, this is the field dedicated to uncovering how molecular and cellular mechanism within the nervous system generate behavioraloutcomes. Neurobiotechnology is and emerging field that helps to study and enhance our nervous system. It integrates molecular biology, nanotechnology, and computational tools. This aims to decrease the complexity of the brain and develop new innovative strategies for the treatment of neurological disorders. The nervous system is one of the highly integrated part of the human body, which is difficult to repair once damaged. The new technologies combining advanced biosensors, stem cell technologies for research and clinical applications In recent decade, remarkable process has been made in the field of neurobiotechnology, such as brain-computer interfaces. And therapies using stem cells.. This neurobiotechnology can transform healthcare, and helps to understand the most complex system in the human body - the human brain.

## 1. Neurons: The Communication network of the brain:

Neurons are Special cells in our brain and nervous system that acts like messenger. We can say that neurons are like the brain's telephone wire. They use electrical and chemical signals to send messages, connect with each other and form network that control everything we do.

Structure of neurons consist of dendrites, cell boys, axon, synapse.

### 1.1 How neurons communicate:

- **Electrical signals (actionpotential) :** Neurons uses tiny electric impulses to send messages quickly along the axon.
- **Chemical signals (neurotransmitters ) :** At the synapse, the electrical signal is turned into chemical one.

Neurotransmitters cross the gap and pass the message to the next neuron.

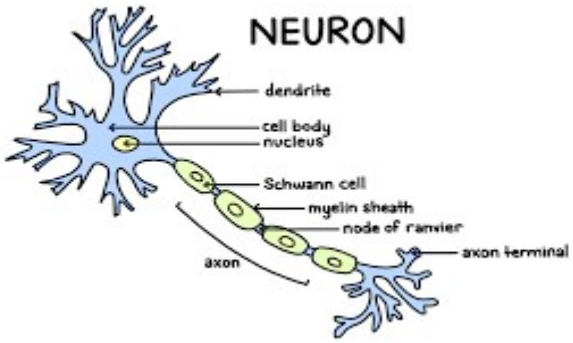


**Fig 01: Neuron**

### 1.2 Neurons as a network :

➢ The human brains has about 86 billion neurons, each connected to thousands of others. Together forming a huge network allow us to learn, remember, make decision and control our behavior..

### 1.3 Its importance in Health and disease

➢ If neurons or their connection are damaged brain communication is disturbed.

➢ This can lead to disease like Alzheimer's, Parkinson's, epilepsy or depression. So, its important studying neurons is important studying neurons is important for both neuroscience and biotechnology.

➢ Neurotransmitters like dopamine, serotonin, and acetylcholine play key role in mood, learning and motivation.

## 2. Mini case study: Neurons and concentration

A 21-year-old student preparing for exams struggles with poor focus and headaches. Excess caffeine and lack of sleep reduced neurotransmitter balance, causing neuronal communication.

Key learning:

➢ Neurons rely on balanced and healthy neurotransmitter activity for proper function.

➢ sleep plays a crucial role in synaptic plasticity and memory.

➢ External factors such as caffeine or stress can directly influence neuronal

communication and brain performance.

So, Neurons depend on healthy neurotransmitter activity and synaptic plasticity, which are strongly influenced by lifestyle.

## 3 The Psychology connections: Brain meets mind

The brain is the biological organ made of neurons and networks, and the mind is the collection of thoughts, emotions, memories and consciousness that emerges from brain activity.

The human brain is the foundation of our mental life and it carries our hopes, fears, dreams, and struggles. Every experience we have, whether joyful or painful, is processed and stored in the mind, shaping how we respond to the world around us.

Psychology gives us the tools to understand the inner experiences and explores how we interpret situations.

### 3.1 The science behind it

Neurons do not work in isolation; they form intricate networks, connecting with thousands of other neurons. Behavior arises from the integration of signals across different brain regions. For instance, the hippocampus regulates memory, the amygdala controls emotional responses, and the prefrontal cortex influences decision-making.

- **Cognition - Thinking patterns**

The mind interprets information, forms beliefs, and solves problems. Cognitive psychology studies how our thoughts influence emotions and actions.

Example: Negative thought patterns can lead to anxiety, and reframing situations can build confidence.

- **Emotions**

The heart of our experience emotions are powerful forces within the mind that shape our behavior. Neurobiology shows how brain areas like the amygdala process fear and pleasure while hormones like oxytocin influence trust and bonding.

- **Memory: Holding our past**

Our past experiences, stored in the mind, influence how we react today. Psychology helps us uncover how we react today. Psychology helps us uncover how memories are formed and how trauma can leave lasting marks. Therapies

like - cognitive behavioral therapy gently reshape harmful patterns.

- **Consciousness - The Awareness of the self mind**

Mind awareness allows us to reflect, question and grow. psychology explores how mindfulness and meditation practices strengthen self-awareness, helping individuals cultivate compassion and inner peace.

## 4 Understanding brain disorders

Brain disorders are a heterogeneous group of conditions that affect the structure or function of the central and peripheral nervous systems and that profoundly influence cognition, emotion, sensation, and behavior.

Globally, neurological condition - from migraine and stroke to neurodegenerative disease like Alzheimer's and Parkinson's represent a leading cause of disability and death and are increasing in burden as of aging and changing lifestyles. These brain disorders are most challenging health issues worldwide as of epilepsy, depression, and traumatic brain injury not only reducing quality of life also creating heavy social and burden but now, neurobiotechnology- a combining field, offers advanced methods for diagnosis, treatment and prevention.

### 4.1 Clinical phenotypes of disorders

- **Neurodevelopmental disorders:**autism spectrum disorders, intellectual disability ( synaptogenesis )
- **Neurodegenerative disorders:**Alzheimer's disease, Parkinson's disease, Huntington's disease ( In this, progressive loss of specific neuronal population, protein aggregation.
- **Neuropsychiatric disorders:** major depressive disease, schizophrenia
- **Cerebrovascular and trauma-related:** Stroke, traumatic brain injuries.
- **Neuroinjections and epilepsies:** Multiple sclerosis and hyperexcitable networks.

## 5. Brain disorders

- **Depression:** A negative affective state, ranging from unhappiness an discontent to an extreme feeling of sadness, cognitive and social changes and despondency that interferes with daily life.
- **Schizophrenia:** A psychotic disorder characterized by disturbances in thinking ( cognition) emotional responsiveness and behavior with age of onset between teens and mind. It shows symptoms as delusions, hallucination,

disorganised speech, can-tonic behavior or negative symptoms ( eg: lack of emotional responsibilities , extreme apathy )

- **Post traumatic stress disorder:** A disorder may result when individual lives through or witness an event that they believe that there is a threat to life and safety and experiences fear, terrier or helplessness. Re-experiencing trauma in painful flashbacks, dreams or diminished responsiveness.

- **Bipolar disorder:** Any of a group of disorders which shows symptoms of mania and depression alternating. In DSM-IV, DSM - S and DSM - S - TR, group includes bipolar disorders, mania or bipolarII hypomania or cyclothymic disorder. Its a disorder associated with episodes of mood swings ranging from depressive lows to highs . In major depressive disorder, suicide includes.

- **Traumatic brain injury and stroke:** TBI - External force ( eg : accident, fall) leads to bleeding, swelling or oxygen loss in the brain.Stroke - Internal cause ( blocked or bust blood vessel ) cuts off blood supply. Both disrupt neuronal communication, leading to major, cognitive and behavioral problems. TBI can increase stroke risk later due to vascular damage and inflammation.

- **Alzheimer's disease -** A progressive neurodegenerative disorder marked by memory loss, cognitive decline and personality changes. It shows disorientation, confusion, and difficulty in speaking.

- **Parkinson's disease -** A movement and major disorder caused by the loss of dopamine-producing neurons in the substantial. It leads to tremors, stiffness, slow movement and balance problems.

Likewise, different disorders occur, which include key mechanisms such as protein misfolding, neurotransmitter imbalance, and neuroinflammation.

### 5.1 Mini case study

A person had Parkinson's disease with tremors and rigidity, treated with levodopa. Over time, he developed hallucinations and delusions like schizophrenia.

This occurred because dopamine loss in motor pathways causes Parkinson's, while dopamine excess in limbic areas leads to psychosis. The doctor reduced the levodopa added quetiapine, balancing both conditions.

Conclusion: this case study shows how different brain circuits react to dopamine imbalances - too little - Parkinson's, too much — schizophrenia like symptoms.

## 6. Neurobiotechnology :

Neurobiotechnology applies biological technologies to study and interact with the nervous system, creating tools and treatment for neurological disorders and enhancing their brain functions. This is a multidisciplinary field, which combines bioengineering, neuroscience, and biotechnology. It encompasses areas like brain computer interfaces, optogenetics, neuroprosthetiics and stem cell therapies.

Its goals includes advancing treatments for conditions like Parkinson's and epilepsy, developing new drug delivery methods for the brain. Neurobiotechnology translates neuronal mechanisms into diagnostics, therapies, AI systems, and education tools, directly linking neurons to behavior in medicine, technology and daily life.

This emerging field of neurobiotechnology hasbeen revolutionized by offering innovative tools and technologies to explore the brain's inner workings.Technologies such as functional magnetic resonances (FMRI), electroencephalography (EEG) and optogenetics have enabled researchers to observe neural activity in real time. Neural interfaces and BCIs are developed to assist individuals with motor impairments, while artificial intelligence and machine learning algorithms are helping decode patterns of neural signals to better underrated the cognitive functions and neurological disorders.

These advancements in neurobiotechnology are not only expanding the frontiers of research but are also transforming clinical care, enabling early diagnosis, personalized treatments and improved therapeutic interventions.

## 7. Tools of Neurobiotechnology :

The tools of neurobiotechnology ranging from imaging methods like FMRI and EEg to cutting edge interventions like optogentics and gene editing. They enable researchers and clinical to explore how neurons control thoughts, emotions and actions - improving diagnostics, therapies and brain - computer interactions.

Lets explore how chemical changes in brain alter behavior:

1. Neuroimaging tools : These help correlate neural activity with behavioural tools.

- FMRI ( functionalMRI ) : shows which brain regions are active during specific behaviors or cognitive tasks. Captures brain activity by monitoring blood flow.

- PET ( Position Emission Tomography ) : Tracks neurotransmitter systems involved in rewards or learning.
- EEG ( Electroencephalography) : links Brian waves to attention, sleep and decisions making.

2. Neurophysiological tools : these allow direct manipulation or observation of neurons influencing behavior.

- Optogentics : It is a technique that uses light to control neurons. Scientists genetically modify specific neurons to be sensitive to light, then use fibre optics or LED's to turn on or off. This helps study brain circuits, understand behavior and develop treatments for disorders like Parkinson's and epilepsy. It controls behavior our like fears, movement, or rewarded seeking by selectively activating or inhibits neurons.
- Chemogentics : Involved in emotions, memory and movement. Used in research and potential therapies and neurodegenerative disease.
- Micro electrodes : used to record signals from individual neurons.

3. Molecular and genetic tools : used for probing, modifying or understanding molecular pathways in neurons.

- CRISPR /. Cas9 gene editing ( clustered regularly interspaced short ) palindromic repeats. ) : It is a gene editing tool that changes DNA in neurons or precisely alter DNAS sequences. It can correct genetic mutations that causes neurological disorders like Alzheimers's or Huntington's disease. Specific genes influence neurons functions and behavior like learning or addiction. It enables development of gene therapies to treat brain disease by repairing and modifying neural genes.
- Viral vectors : deliver genes that affect neurotransmitter systems, altering behavior like anxiety or learning. ( eg : lentivirus )
- Biomarkers : molecular indicators of neural functions or disease.
- RNA interference ( RNAi) : Silences specific genes to study their functions

4. Calcium imaging at cellular level : Tracks neuron firing during tasks such as learning or motor coordination.

5. Neuropharmacology Tools :

- Drug Interventions - Target specific brain regions , influence neurotransmitter systems , Affecting Mood, cognition and Motor behavior.
- Neurotransmitter assays - Quantify neurotransmitter like Dopamine ,

Serotonin.

6. Stem cells :

Stem cells are unspecialized cells that can develop into different types of cells, including neurons. In neurobiotechnology,

- They are a tool used to create neurons for research or therapy.
- Help study brain development ,repair ,damaged neurons and treat diseases like Parkinson's or spinal cord injuries.
- These stem cells are used to grow brain organoids and test drugs for understanding how neurons affect behavior
- Examples of stem cells : Induced pluripotent stem cells {ipcs}

These are widely used to create patient specific neurons for research on Alzheimers or Autism. This helps in understanding how Genetic differences influence brain function and behavior.. These are somatic cells such as skin or blood cells that have been reprogrammed to an embryonic like state.

## 8. Technologies and applications of neurobiotechnology :

1. Brain Computer Interfaces ( BCIs ):

- Decoding neural signals to allow people to control external devices.
- Helps restore movement in patients with spinal cord injuries or stroke related paralysis.

2. Neuromodulation techniques :

- Deep brain stimulations ( DBs ) or TMS is used to alter neuronal circuits.
- Helps regulate abnormal neural pattern that cause tremors, depression, or compulsive behavior. It control system implanted to treat movement disorders.

3. Neuroprostheics : Helps restore lost functions ( like hearing or vision ) demonstrating how neural signals drive perception and action.

4. Wearable neurofeedback devices : Uses real - time brain activity monitoring to train individuals to change patterns associated with anxiety, ADHD or stress.

5. Disease modeling :

- Used to replicate conditions like microphelyautism, epilepsy and Alzheimer's diseases.

- Allow researchers to understand how genetic mutation or injection ( like Zika virus ) affect neural growth and function.

6. AI - driven behavioral diagnostics : Software that analyses neural patterns to assess mental health.

7. Mental Health interventions : Understanding neurotransmitter through biotechnology helps create targeted drug therapies and behavioral interventions for anxiety, mood disorders and addiction.

## 9. Brain organoids: Mini Brain for research

Brain organoids are 3D, miniaturized models of the human brain, grown from stem cells in the laboratory. These stem cells are capable of becoming any type of cell. Under controlled conditions, they form small clusters that mimic some brain structures. They are created in a special nutrient solution. These clusters develop into structures similar to Brian tissue. Though they are less complex than a real brain. Its expansion in the year 2013, as a whole by Jurgen Knoblich's lab using induced stem cells.

### Importance:

- Provide human specific models for studying brain development and diseases.
- Helps uncover how neurons form connect and function, linking cellular changes to potential behavioral outcomes.
- Used for drug testing, disease modeling and personalized medicine.
- Offering more accurate insights without relying on animal models.
- This mini brain helps in studying brain disease conditions like Alzheimer's, autism or epilepsy can be modelled in the lab to treat new treatments and explore brain development. These brain organoides are critical tool in neurobiotechnology, bridging the gap between neurons and behaviour by advancing therapeutic research.

## 10. Mini cases study :

**Background**: Zika virus outbreaks ( 2015-2016 ) were linked to newborn microcephaly. Animal models failed to fully capture human-specific effects, making brain organoids a vital tool.

**Case Description:** In 2016, Alyson R.Muotri and colleagues used human brain organoids to study Zika infection. They observed that the virus preferentially infected neural progenitor cells, causing cell death and impaired proliferation.

Infected organoids were significantly smaller, mimicking the microcephaly phenotype observed in affected infants.

**Key findings:**

- Zika virus targeted neural progenitors, reducing neurogenesis.
- Viral infections triggered apoptosis and disrupted cortical development.
- Organoides served as a rapid- response model for an emerging infectious disease.

### 11 . Future Directions in Neurobiotechnology

1. Personalized therapies: Tailored gene editing, neuromodulation, and drug design.
2. AI integration: Machine learning for brain signals decoding and disease prediction.
3. Next- gen BCIs: Wireless, durable, and with sensory feedback
4. Regenerative tools: Stem cells, organoides, and neural tissue engineering.
5. Neuroethics: Safeguarding mental privacy and cognitive rights.

## Conclusion

Neurobiotechnology, from neurons to behavior, represents a frontier where biology, psychology, and technology converge, By decoding how individual neurons connect into circuits and how those circuits give rise to thought and behavior, the field is transforming broth science and society. The integration of molecular tools, organoids models, brain- computer interfaces, and AI is no longer limited to explaining the brain but is beginning to redefine mental health, cognition, and human potential. This study is not only about advancing neuroscience, it is about merging biology with psychology. This shows that the mind is not only the part of the brain but its the expansion of the mind networks. The future of neurobiotechnology is to heal the brain when it fails and light up the mind in its full capacity.

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# MicroRNA: A Revolutionary Tool for Biological Sciences

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## Abstract

MicroRNAs (miRNAs) are small, non-coding RNA molecules that play a pivotal role in post-transcriptional gene regulation across diverse biological systems. Since their discovery, miRNAs have revolutionized molecular biology by unveiling new dimensions of gene expression control, cellular differentiation, development, and disease mechanisms. Their ability to fine-tune gene networks makes them powerful biomarkers for diagnosis, prognosis, and therapeutic interventions in various diseases, including cancer, cardiovascular, and neurodegenerative disorders. Moreover, miRNA-based technologies have opened promising avenues in plant biotechnology, environmental monitoring, and synthetic biology. The recent advancements in miRNA profiling, bioinformatics, and delivery systems have further enhanced their potential as diagnostic and therapeutic tools. This review highlights the fundamental biology of miRNAs, their mechanisms of action, and their transformative applications across biological and biomedical sciences, underscoring their significance as revolutionary regulators and tools for modern biological research.

**Keywords**: microRNA, gene regulation, biomarkers, molecular diagnostics, therapeutics, gene silencing, biotechnology, bioinformatics

## 1. Introduction

Micro-RNA (miRNA) is a ribonucleotide which have approximately 18-24 nucleotides in length, are small non-coding RNA, that negatively regulates gene expression via inhibiting mRNA translation or promoting RNA deadenylation, leading to its subsequent degradation. The interaction between miRNA and their mRNA targets involves base pairing of 6-8 nucleotide sequences.(Venneri)

Victor Ambros and Gary Ruvkun independently discovered miRNA in the early 1990s, for which they have been awarded Nobel Prize in 2024 in Physiology or Medicine. Their exploration and examination in Caenorhabditis elegans revealed a non-traditional approach by which small RNA (particularly miRNA) regulates gene expression, which advanced the understanding of cellular development and functions. (Victor Ambrost Rosalind C. Lee, 1993).

miRNA has significant value in the field of molecular biology and cellular function. Under certain conditions, miRNA can also activate translation or regulate the process of transcription. The interaction of miRNA with their target genes is delicate and dynamic, dependent on several factors like sub-cellular location of miRNA, the abundance of miRNA and target mRNA and the affinity of miRNA-mRNA interaction. Extracellular miRNA functions as a chemical messenger to mediate cell-cell communication.

## 2. Biogenesis of miRNA

The intronic or extronic regions of non-coding genes contain miRNA coding sequences. Most miRNAs are transcribed as independent transcriptional units, while others, which are present in clustered form, are transcribed as single polycistronic units.

The synthesis of miRNA is a multistep process. miRNA genes are transcribed in the nucleus, as long primary miRNA (pre-miRNA) by RNA Polymerase II and are processed into approximately 60-70 nucleotide miRNA precursor (pre-miRNA) by RNase III Endonuclease Drosha. In the cytoplasm, the pre-miRNA is exported by Exportin 5 and further processed into the mature two-stranded duplex (miRNA-miRNA*) by Dicer RNase III Endonuclease. Argonaute protein (Ago protein) then loads the miRNA complex. The Guide strand (as only one of two strands of miRNA binds to the protein) is retained in the Ago protein and forms the stable RNA-induced silencing complex. The Ago-miRNA complex binds to 3’ Untranslated regions (3’UTRs) of the targeted mRNA and consequently induces the translational repression or degradation. (Venneri)

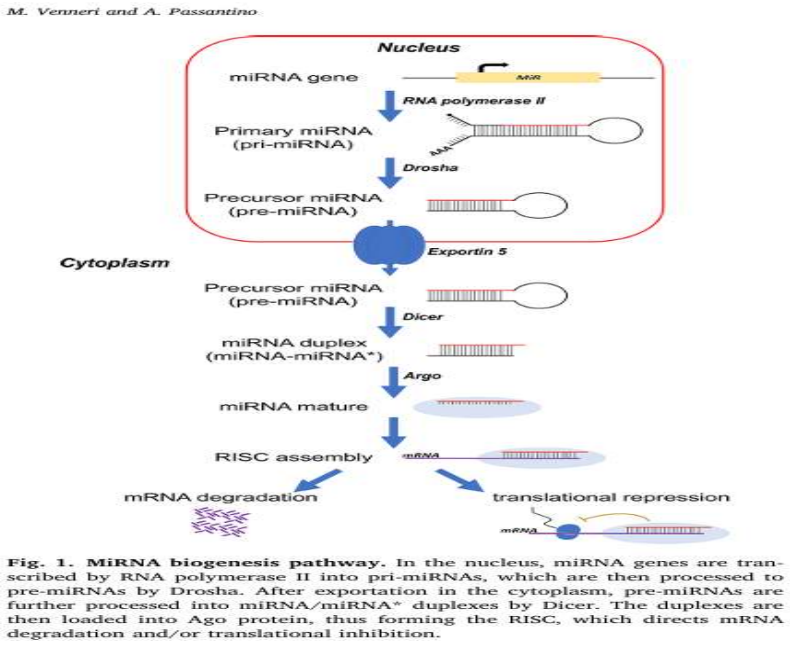


Fig 01: miRNA Biogenesis Pathway

## 3. Applications of miRNA

1. In cancer diagnosis- Several findings suggest that there is correlation between miRNA expression and tumor-related metabolism like tumor growth, metastasis and tumor invasion.

i. Tumor-suppressor miRNA (TS-miRs)- which inhibit cancer cell growth eventually leading to cell death.

ii. Oncogenic miRNA (onco-miRs)- which promote proliferation and survival of cancer cells.

iii. Expression profile of miRNA can provide us a detailed classification, prognostication and diagnosis of various cancer types.(Zhang B, 2007)

2. In cardio-vascular diseases- Processes like angiogenesis, inflammation and cardiac-remodeling which are the crucial model for development and regulation of cardio-vascular diseases are also impacted by miRNA. For

example, miRNA 208a is specifically expressed in cardiac tissue and has been shown to promote cardiac hypertrophy in animal cells.(Romaine SPR, 2015).

3. In response to Environmental hazard- Various environmental hazards including radiation, air pollutants, heavy metals, pesticides and pathogens are influenced by miRNA. Cellular stress and response and contributing to the onset and progression of diseases such as cancer, cardiovascular and neurodegenerative conditions.(S.S. Shetty, Sept. 2023).

4. In neurodegenerative disease- miRNA plays a vital role in the normal functioning of CNS and their dysregulation can alter the functioning, leading to several neurodegenerative diseases, like loss of memory and progressive loss of function of neurons. For instance, research was conducted on miR-124 on the regulation and differentiation in Alzheimer's disease and miR-133b in Parkinson disease. (S. Ju´ zwik CA, 2019).

5. In metabolic disorders- The disturbance and dysregulation in the functioning of miRNA can create or alter the metabolic diseases like Obesity, Type-2 Diabetes etc. For example, miR-122 is a liver specific miRNA for lipid metabolism have been affected by NAFLD.(Fern´andez-Hernando C, 2013).

6. Ininflammatory and auto-immune disease- The autoimmunity and inflammation in the body is also regulated by miRNAs via, affecting differentiation, maturation and functions of various immune cells. Several studies have shown that the decreased production of key enzyme like Dosha and Dicer required for the regulation of miRNA, has reduced expression in lupus erythematosus patients.

7. As Biomarkers- miRNA through modern scientific interventions have the capability as attractive non-invasive biomarker candidates for accurate diagnosis and prognostication in disease progression.

8. In Crop improvement – The miRNA has been explored by scientist to study their biogenesis, functional attributes and potential application in crop quality, with the techniques such as gene silencing, ZFN, HIGS and CRISPR Cas 9.(Tang J, 2017)

## 4. Emerging trends in miRNA

Since the discovery of miRNA, new doors are opened for exerting regulatory effects on gene expression, various physiological and pathological events. Because miRNA is involved in mRNA stability, transcription, and translation, they are indispensable in molecular biology. However, our understanding of

miRNA in transcription is limited; it opens a new venture for further research and exploration.

miRNA is also being used widely in advanced therapeutics like 3D matrices and inhalation, diagnostic and prognostic biomarkers for diseases such as cancer and infectious disease, the study of epigenetic modifications and its role in metabolic diseases and miRNA-microbiome interactions. (Atiyabanu N. Saiyed, 2022)

## 5. Conclusion

It is now widely agreed upon the fact that miRNA is not only a possible biomarker for disease but also plays a vital role in intercellular communication. To explore the possible benefits of miRNA, there is a need for careful analysis and consideration of experimental techniques when attempting to understand the miRNA activities**.**

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# Stem Cell Technology in Regenerative Medicine

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## Abstract

Stem cell technology has emerged as a pillar in the field of Regenerative medicine, which offers transformative solutions to repairing, replacing and restoring damaged tissues and organs. This chapter focuses on the basics of sources and classifications of stem cells, also aims to provide basic information on advances in isolation, culture system, bioreactor, gene editing (CRISPR Cas9) and organoid technologies, which expanded therapeutic applications. Clinical progress has been illustrated through trials in the field of neurological disorders, cardiovascular repair, musculoskeletal injuries, skin and wound healing, and organ regeneration, among these, haematopoietic transplants leading as remarkable success. Ethical, legal and regulatory concerns – including consent, genetic privacy and tumorgenicity – highlight the complexity faced by clinical translations. Despite having challenges in this field like immune rejection, genomic instability and high production cost, revolution in biomaterial, gene editing and personalized therapies, gives direction towards a future where stem cell-based treatments may overcome limitations of conventional medicine. This chapter emphasises both remarkable success, promise and persistent hurdles, in Stem cell technology, envisioning a future where precision-engineered therapies revolutionize healthcare by addressing conditions once considered untreatable.

**Keywords**: Stem cell technology, regenerative medicine, induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), clinical trials, gene editing, organoids, tissue engineering

## Introduction

Regenerative remedy makes a speciality of remodeling and rejuvenating human cells, tissues, or organs to restore their everyday functions. This entails repairing damaged tissues, consisting of regenerating new bone, by activating the body's herbal repair strategies. In instances of insufficient self-repair, laboratory-grown organs may be transplanted, minimizing rejection

dangers as cells are derived from the patient's very own tissues, addressing organ donation shortages. Key techniques encompass stem cell injections (mobile therapy), the usage of biologically active debris to beautify regenerative potential (immunomodulation therapy), and tissue engineering through in vitro increase. modern advances regularly involve biological cellular cures, with future ability for embryonic stem cellular use, despite the fact that reintegration of structural components stays tough. A philosophical divide exists among biomaterials scientists pursuing nanotechnology and people focused on cellular answers, aiming for an incorporated approach combining both fields. most important medical conditions like coronary heart failure and diabetes lack powerful cell-based treatments, highlighting possibilities for breakthroughs in regenerative skills. a hit techniques would possibly contain disruptive technologies replacing many conventional medicinal drugs, together with stem cellular-derived β-islet cells probably negating the need for insulin in diabetes. additionally, the developing courting between gene therapy and regenerative remedy via techniques like cell reprogramming emphasizes the mixing of genetics and cellular strategies, regardless of regulatory hurdles.

## 1. Background

Between 1995 and 1998, Michael D. West, PhD, oversaw a collaboration between Geron and academics James Thomson and John Gearhart, which resulted inside the first isolation of human embryonic stem cells (ESCs). In March 2000, West, at the side of Dr. Antony Atala and others, founded the peer-reviewed magazine *Biomed The magazine of Regenerative medication* to speak about regenerative medicinal drug topics including stem mobile therapy and tissue engineering. The Society for Regenerative remedy become formed to unite professionals on this field.

In June 2008, a crew led by Professor Paolo Macchiarini on the Barcelona sanatorium medical institution done the primary tissue-engineered trachea transplant. They cultivated human stem cells from a patient's bone marrow into cartilage cells and used a decellularized trachea received from a deceased donor. This transplant efficiently changed the affected person's trachea, which confirmed signs of vascularization a month after surgery. In 2009, the SENS foundation was hooked up, aiming to apply regenerative medicinal drug in age-related conditions. Macchiarini completed a extra effective trachea transplant using the patient's very own cells in 2012.

On September 12, 2014, in Kobe, Japan, retinal pigment epithelium cells derived from precipitated pluripotent stem (iPS) cells were transplanted right into a lady stricken by age-related macular degeneration. however, by

means of 2016, Macchiarini had been expelled from Karolinska university due to incorrect research findings.

The evolution of studies from the late nineteenth century to the cutting-edge traits in ESCs and iPSCs marks a brand new technology in medical development. Stem cellular therapy shows promising results in treating many sicknesses, consisting of cancer and neurodegenerative sicknesses, but demanding situations inclusive of immune rejection and tumor formation remain. Ongoing advances in biotechnology, medical checking out, and gene enhancing are critical to overcoming those obstacles. future strategies emphasize customized regenerative treatment alternatives, potentially replacing modern-day pharmaceutical pills and offering wish for lots clinical situations.

## 2. Basics of Stem Cell

Stem cells have the wonderful capacity to repair damaged cells and might become any type of cell. Modern-day studies endorse that stem cell therapy options can also treat conditions like paralysis and Alzheimer's disease. Stem cells can be categorized into numerous types:

1. Embryonic stem cells: these cells, derived from fertilized eggs, are totipotent (able to differentiating into all cellular kinds), pluripotent (from early embryos, capable of remodeling into any cell type), multipotent (constrained to precise cell types, such as hematopoietic stem cells), oligopotent (capable of differentiating into some cell sorts, which consist of grownup lymphoid cells), and unipotent (producing simplest one type, consisting of muscle stem cells).

2. Human stem cells: Derived from absolutely advanced organs and tissues, human stem cells help restore and update broken tissue of their area. Hematopoietic stem cells in bone marrow are within the fundamental used in transplantation for particular cancers.

3. Introduced on pluripotent stem cells (iPSCs): Created in laboratories by way of the usage of reprogramming tissue-particular cells into embryonic-like cells, iPSCs retain houses just like embryonic stem cells, serving as crucial gear for analyzing improvement, sickness progression, and drug attempting out.

4. Mesenchymal stem cells: Originating from the connective tissue surrounding organs (stroma), those stromal cells can differentiate into bone, fats, and cartilage. One among a type mesenchymal stem cells derived from super human tissues are used to treat severa illnesses, and their houses variety depending at the tissue of starting area.

## 2.1 Sources of Stem cells

Mesenchymal and hematopoietic stem cells are extensively distributed in bone marrow. Resembling fat, muscle, bone, and cartilage, mesenchymal stem cells are found in adipose tissue. The most popular source for allogeneic stem cell therapy (using cells from a different person) is umbilical cord stem cells, whereas both of these sources are frequently used for autologous stem cell therapy (using cells from the same patient). A multitude of sources, such as the following, can provide stem cells.

### 2.1.1 Bone Marrow

Stem cells are essential for replacing broken cells attributable to herbal tactics. Hematopoietic stem cells (HSC) in bone tissue give upward thrust to myeloid and lymphoid lineage cells, which are quick-lived but important for blood and immune function. Those stem cells undergo asymmetric division, generating same progenitor cells that differentiate into various cellular sorts, prompted with the aid of their microenvironment and growth factors. Traditionally, bone infusion has been the primary technique for stem mobile collection due to its better yield; it may offer as much as 18 instances greater cells than blood progenitor cell harvesting, although it includes an invasive, painful surgical operation with associated dangers. Studies indicates that cytokine therapy before blood progenitor mobile harvesting enhances stem cellular yield in the bloodstream, making it extra clinically possible. A double randomized observe showed that blood progenitor mobile collection led to significantly extra usable stem cells and patients tolerated the system better than bone infusion. As a end result, supplemental blood progenitor cellular collection is turning into increasingly more desired due to its lower invasiveness and headaches.

### 2.1.2 Amniotic Cells

Traditionally, embryonic stem cells (ESCs) and precipitated pluripotent stem cells (iPSCs) had been the primary pluripotent stem cell types. despite advances, medical challenges persist, drastically low survival charges and tumorigenicity. current studies has remoted multi-potential stem cells from amniotic fluid and placental membranes, diagnosed as human amnio-derived stem cells (hADSCs), which consist of amniotic epithelial cells and mesenchymal cells, showcasing numerous useful houses. these cells emerge in the course of the second one week of being pregnant, with amniotic epithelial stem cells (hAESCs) developing from the epiblast and amniotic mesenchymal stem cells (hAMSCs) from the hypoblast, prior to gastrulation, ensuing in their multipotent nature. historically, multipotency and immune-compatibility had

been visible as exclusive, with multipotency connected to ESCs and immune-compatibility to mesenchymal stem cells. however, latest research have established that each development is present in hADSCs.

### 2.1.3 Adipose Tissue

Bone-derived stem cells (BMSCs) face challenges like harvesting strategies and occasional yield, prompting exploration of alternative mesenchymal stem cellular (MSC) sources, substantially mortal adipose tissue. Enzymatic digestion of adipose tissue yields a heterogeneous group of cell precursors called stromal vascular fraction (SVF), inside which adipose-derived stem cells (ADSCs) are located. ADSCs normally cluster with MSCs, expressing several usual CD markers. They showcase multipotency, differentiating into numerous mesodermal-derived cells, which includes osteoblasts and chondroblasts, and also can turn into insulin-secreting cells in vitro. Harvesting ADSCs is less difficult than BMSCs, as white adipose tissue (WAT) offers plentiful sources, primarily located subcutaneously in humans. ADSCs constitute a better percent of the SVF as compared to the minuscule amounts of stem cells in bone tissue, facilitating easier retrieval. moreover, ADSCs have low expression of MHC II and co-stimulatory molecules, improving their immunosuppressive skills. They secrete a range of beneficial elements and may be reprogrammed into induced pluripotent stem (iPS) cells, including to their usefulness in transplantation.

### 2.1.4 Umbilical Cord

Wire stem cells may be harvested from diverse assets, such as twine blood, umbilical wire perivascular and endothelial cells, chorion, and amnion. when you consider that 1988, cord blood has been desired for its low-danger extraction method and supply of hematopoietic stem cells. With a global beginning fee exceeding one hundred million annually, cord blood affords ample possibilities for stem cell sourcing. The extraction procedure entails accumulating blood into sterile anti-coagulant bags, followed by means of cryopreservation in liquid nitrogen. A key benefit of umbilical cord stem cells is their immaturity, leading to reduced transplant rejection and lower host-versus-graft mortality charges. those stem cells can differentiate into various cellular types, demonstrating decrease variability in comparison to person-derived sources. CD34-effective cells from twine blood exhibit more desirable hematopoietic ability. research suggest that children with hematological problems receiving cord blood from healthy donors display comparable or progressed survival costs as compared to those receiving bone marrow transplants. cord blood stem cells can differentiate into hematopoietic,

mesenchymal, and embryonic lineages, able to self-renewal. Ongoing research explores their packages in cardiomyogenic and neurological treatment plans, offering an ethically favorable opportunity to embryonic stem cells in regenerative medicine.

### 2.1.5 Placental Tissue

Placental tissue includes stem and epithelial cells that could separate into multitudinous towel types, which includes adipogenic, myogenic, hepatogenic, osteogenic, cardiac, endothelial, pancreatic, pulmonary, and neural towel. particular lineages arise from precise placental regions, which include hematopoietic cells from the chorion, allantois, and thralldom sac, and mesenchymal lineages from the chorion and amnion. mortal fetal placental cells are distributed into amniotic epithelial cells, amniotic mesenchymal stromal cells, chorionic mesenchymal stromal cells, and chorionic trophoblast cells. mortal amniotic epithelial cells( hAECs), deduced from the amnion, can induce whim-whams cells and are being explored for the treatment of affections along with Parkinson's, a couple of sclerosis, and spinal line accidents. in addition they show off functions which include ammonia processing and albumin manufacturing.

## 3. Stem cell Technology and tools

### 3.1 Research on stem cells using new isolation and culture technologies

Traditional culture styles generally involve reprogramming pluripotent cells to pluripotency by periodic passages under adherent culture conditions on fused cells or extracellular matrix assemblies. Stem cells using these methods are susceptible to contamination by pathogens; these methods involve separation of fused cells from the desired cell type which increases cost and is prone to variability. In recent times, several new separation and culture techniques have been developed to realize the broad operational possibilities of stem cells in disease mechanisms and their treatment, including the Suspense technology and the SB431542 asset separation system.

### 3.1.1 Suspense technology

Induced pluripotent stem cells (iPSCs) are gaining more attention due to their therapeutic advantages in the creation of high-quality disease models, derivation of individual-specific iPSC lines, tailoring of drug action, and as a source of cells for regenerative medicine. Zandstra’s group has developed a method to obtain reliable multipotent stem cells in a continuous adhesion- and matrix-free suspension culture system, which has the potential to accelerate and regulate iPSCs exploration. Gene expression analysis showed high

correlation between the two processes, including reprogramming in suspension culture and regular disciple culture, with respect to specific reprogramming genes.

### 3.1.2 SB431542 Asset Isolation System

Mesenchymal stem cells (MSCs) are person stem cells derived specifically from bone marrow stromal cells and are under full-size research for his or her healing makes use of in cardiac, renal, neural, and bone ailments, in addition to in infectious sicknesses and hematopoietic co-transplantation. they're generally harvested from person bone marrow or adipose tissue, even though those resources necessitate invasive techniques and yield low frequencies of MSCs (0.001% from bone marrow and zero.05% from fats). Gillot's paper outlines a traditional method for separating fetal MSCs from first-trimester bone marrow. In contrast, Fisk's institution advanced a novel, faster gadget to achieve MSCs (around 10 days) from embryonic stem cells (ESCs) or prompted pluripotent stem cells (iPSCs) using the described medium MTSR1 and Matrigel, eliminating the need for fused cells. Their new approach concerned particular situations for MSC isolation, enhancing velocity and probable scientific implications for osteoporosis patients. additionally, numerous researchers have superior stem cellular separation and way of life techniques to improve disorder treatment efficacy. research have shown that the chromatin shape of stem cells plays a vital position in their separation and capability applications in regenerative medicine and most cancers remedy, similarly demonstrating the significance of MSCs in medical therapies.

## 3.2. Stem cell cultivation in scaffolds bioreactor system

Advancements in stem cellular biology have progressed due to new lifestyle environments, biomaterials, and bioreactors that mimic neighborhood tissue characteristics. The significance of inductive cues in 3-dimensional tissue configurations has been identified, at the side of challenges posed through easier strategies like mesenchymal stem mobile pellets and neurospheres, which have barriers in size, population control, biophysical cues, and the lack of extracellular matrix. at some stage in the Nineties, the idea emerged that 3-D human tissue replacements could be created in vitro the usage of scaffolding substances as biodegradable templates, coupled with bioreactor structures to beautify environmental manage and provide biochemical cues. This "biomimetic paradigm" aimed to duplicate in vivo developmental occasions in vitro. As tissues increase, cells come upon diverse dynamic alerts, which includes multiple cell sorts, extracellular matrix additives, and physical elements. in view that then, numerous biomaterial

scaffolds and in vitro systems were developed to imitate this dynamic environment, assisting cell increase and tissue maturation. innovations in biomaterials allow for creating 3-D scaffolds with precise structural houses, mechanical developments, and degradation charges, using diverse herbal and synthetic materials to enhance the cell microenvironment and direct cell function efficiently.

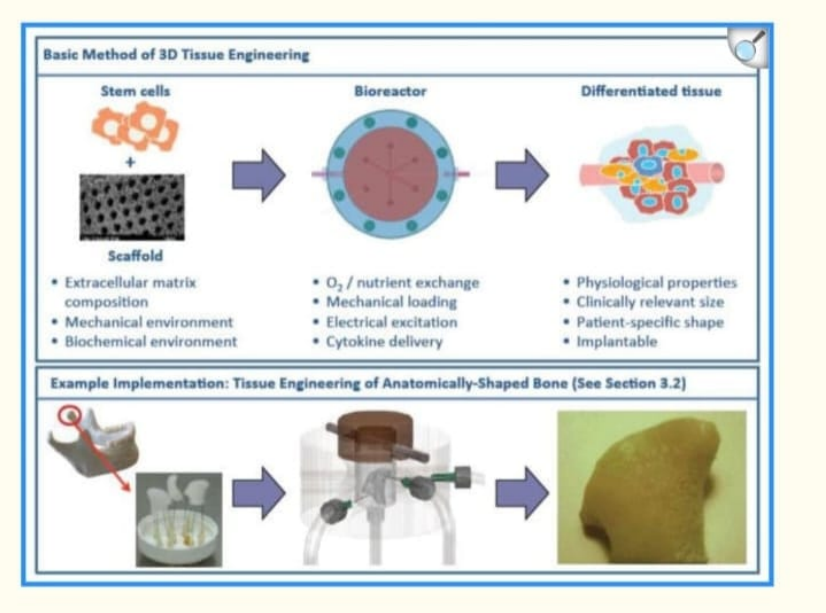


Fig 01: Basic Methods of Tissue Engineering

### 3.3 Gene editing and CRISPR Cas-9

Gene enhancing has emerged as a vital tool in molecular biology, in particular with the appearance of CRISPR-Cas9, which allows particular modifications of DNA to correct genetic problems and explore their underlying causes. in the beginning part of a bacterial immune device, CRISPR has been adapted for gene enhancing due to its performance, price-effectiveness, and versatility. The gadget utilizes a guide RNA to direct the Cas9 enzyme to particular DNA sequences to create double-strand breaks, enabling precise genetic changes or mutations via cellular repair strategies.

In comparison to older techniques like ZFNs and TALENs, CRISPR-Cas9 gives great benefits, including ease of use and the capacity to target multiple genes concurrently. but, it isn't with out downsides, such as capacity immune responses to Cas9 and the danger of off-goal mutations, together with challenges in attaining excessive performance of homology-directed restore.

Improvements in CRISPR generation have brought about the improvement of excessive-fidelity versions and opportunity techniques like base editing, which allows unmarried-nucleotide modifications with out growing double-strand breaks, improving safety and accuracy. packages of CRISPR-Cas9 in research include modeling genetic sicknesses, identifying pharmacological objectives, and growing remedies for situations like sickle cell anemia and Duchenne muscular dystrophy, with promising effects in scientific trials.In spite of its transformative potential, CRISPR-Cas9 raises good sized ethical issues, especially concerning germline editing and the possibility of misuse. considerably, the arguable case of unregulated germline modifying through He Jiankui emphasised the pressing want for stringent moral pointers and oversight on this vicinity.

Looking ahead, studies will cognizance on expanding the variety of treatable genetic problems, improving delivery mechanisms, and enhancing specificity in gene modifying. The synergy among CRISPR generation and triggered pluripotent stem cells (iPSCs) holds promise for personalized regenerative medicinal drug. To completely understand CRISPR's healing ability at the same time as ensuring moral integrity, collaboration amongst scientists, clinicians, and policymakers is essential as the sphere progresses. while many demanding situations remain, successful developments in CRISPR technology should provide full-size improvements in treating previously incurable genetic conditions, fostering desire for lots sufferers.

### 3.4 Organoids and disease modeling

iPSCs have enhanced regenerative medication and disease modeling abilties, however their capacity is fully realized in three-dimensional (three-D) cultures, particularly organoids. Organoids are multicellular, self-organizing systems derived from stem cells, facilitating a physiologically applicable platform for investigating drug responses, sickness development, and tissue formation. with the aid of developing affected person-unique organoids from iPSCs, researchers can extra appropriately mimic human organ complexity in vitro, main to groundbreaking insights into quite a number sicknesses, along with cancer and neurodegenerative disorders.

Organoids had been first correctly evolved from adult stem cells for intestinal systems in the early 2010s, leading to the introduction of fashions for diverse organs which include the mind, liver, kidney, and pancreas. those models serve as advanced systems for analyzing sicknesses, such as infectious sicknesses, most cancers, and neurological problems. additionally, organoids derived from sufferers permit tailored testing of treatments and exploration of

genetic abnormalities. as an example, mind organoids have revealed how Zika virus contamination influences neural improvement, while intestinal organoids have enabled studies on the consequences of CFTR modulators related to cystic fibrosis.

Organoids represent a essential tool in toxicity screening, drug development, and sickness modeling. Pharmaceutical groups are more and more using organoid-based structures in preference to traditional cell strains or animal fashions to evaluate drug responses, including nephrotoxicity and hepatotoxicity predictions. improvements in single-mobile sequencing and multi-omics technology in addition enhance organoid-based totally studies, taking into account special exploration of disorder mechanisms. This has confirmed powerful in diverse molecular studies, together with investigating host-pathogen interactions for the duration of SARS-CoV-2 infection and coming across new resistance mechanisms in colorectal most cancers organoids, riding hobby in organoid transplantation for regenerative treatment plans in situations like liver failure and retinal degeneration.

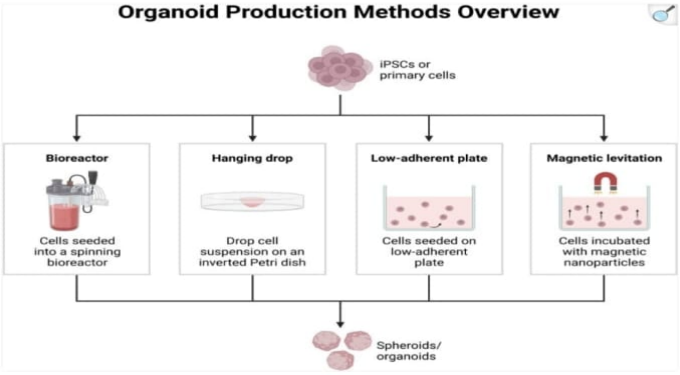


Fig 02: Organoid Production

## 4. Applications of Stem Cells in Regenerative Medicines

### 4.1 Neurological disorders (Parkinson's, spinal twine harm, strokes):

Parkinson's ailment is a revolutionary neurological situation characterized by the loss of dopamine-producing mind cells, often because of genetic, getting older, and environmental elements. signs and symptoms consist of tremors, stiffness, sluggish moves, cognitive modifications, and sleep disturbances. Regenerative remedy objectives to update lost dopamine production via dopaminergic neurons, with preclinical research showing promise in differentiating embryonic and caused pluripotent stem cells into dopamine-producing cells. Mesenchymal and neural stem cells exhibit

paracrine consequences, reducing neuroinflammation and assisting neuron survival. In instances of stroke, stem cells can mitigate infarct length, sell angiogenesis, and help healing in motor and cognitive functions. For spinal wire accidents, stem cells can differentiate into neurons and glial cells, improving neural connections and decreasing scar tissue formation, with intrathecal administration showing safety and partial practical development.

### 4.2 Cardiovascular repair (myocardial infarction, heart failure):

Cardiovascular sicknesses are leading causes of mortality globally, necessitating alternatives to donor dependency. Regenerative remedy using stem cells, specifically mesenchymal and cardiac progenitor cells, indicates ability in treating myocardial infarction and coronary heart failure by differentiating into cardiomyocyte-like cells, promoting angiogenesis, and reducing fibrosis. scientific research indicate enhancements in cardiac function and reduced infarct sizes publish-MI, despite the fact that risks of graft failure and arrhythmias persist.

### 4.3 Musculoskeletal regeneration (cartilage, bone, tendon):

Stem cell applications in musculoskeletal regeneration consciousness on cartilage, bone, and tendon restore. MSCs can differentiate into chondrocytes to aid cartilage restore whilst mixtures with biomaterials improve consequences. For bone regeneration, stem cells with osteoinductive factors decorate new formation, whilst tendon-derived stem cells display promise in restoring tendon integrity.

### 4.4 Skin and wound healing (burns, diabetic ulcers):

Stem cells, together with epidermal and MSCs, considerably aid skin and wound restore with the aid of differentiating into essential cell sorts and secreting growth elements. medical studies spotlight greater restoration in diabetic ulcers and burns when the usage of MSCs and epidermal grafts.

### 4.5 Organ regeneration (liver, kidney, lungs):

Stem cells preserve promise for organ regeneration, specially inside the liver, kidney, and lungs. They useful resource in liver feature development, kidney protection towards damage, and lung alveolar damage repair, although medical programs are nonetheless growing.

### 4.6 Hematopoietic Stem Cells in blood most cancers and immune illnesses:

HSCT is extensively used for treating blood cancers and immune issues, with autologous and allogeneic stem cells changing diseased structures.

improvements like omidubicel enhance recuperation in blood most cancers patients. in spite of risks like graft-as opposed to-host disorder, HSCT remains vital in regenerative medication.

## 5. Clinical trials and Translational Progress

Within the past decades, stem mobile scientific trials developed from protection-focused research to substantial randomized trials assessing efficacy for various conditions. Initial trials utilized Embryonic Stem Cells (ESC) for retinal diseases, with great reports indicating protection and mild vision improvements for age-related macular degeneration and Stargardt ailment. Subsequent trials with Mesenchymal Stem Cells (MSCs) centered ischemic heart disease, osteoarthritis, spinal wire injury, stroke, liver disorder, and chronic wounds, following section 1 protection studies into large efficacy trials and meta-analyses. Hematopoietic stem cell transplantation (HSCT) has long been a popular care method in hematology, ongoing research maintains to refine donor sources and graft manipulation. Progressive cord blood products like omidubicel these days won phase III approval, enhancing neutrophil restoration submit-transplant. Big trials consisting of TRANSEURO for Parkinson's sickness and AST-OPC1 for spinal cord accidents are actually underway, showcasing the medical application of stem cell advancements. Tremendous achievements consist of HSCT remodeling treatment for leukemias and congenital immune disorders and the FDA's 2023 approval of omidubicel, setting up new production standards for mobile treatment plans. These landmark trials now not best confirmed the efficacy of stem cellular treatments however additionally set regulatory frameworks for future principal apprehensive gadget programs.

## 6. Ethical, legal and Regulatory Issues

The improvement of stem cell-based totally treatments carries the potential for each restorative solutions and treatments, however it's miles fraught with ethical dilemmas. issues embody the want for knowledgeable consent, mainly highlighted by means of the case of HeLa cells derived from Henrietta Lacks with out consent, which magnifies the necessity of explicit consent in obtaining substances for studies. ethical practices for collecting stem cells contain considerations for residing donors and cadavers, whilst privateness worries stand up from sharing genetic information in research, in addition complex with the aid of ability consequences from genome sequencing. This emphasizes the significance of informed consent, specifically in research related to sensitive data, making sure recognize for members in biomedical studies.

Scientific conditions for clinical testing include reliable production of cellular types appropriate for treatment and rigorous safety trying out prior to human software. The complexity of stem mobile-derived products makes preclinical tests difficult, requiring modeling systems that replicate human body structure. despite the fact that animal testing stays not unusual, innovative methods inclusive of disorder modeling the use of stem-cellular strains or advanced "organ-on-chip" technologies provide promising options. these systems ought to enact patient-precise models potentially decreasing reliance on animal studies even as facilitating greater efficient medical reconnaissance.

Stem cellular tourism represents a burgeoning area where individuals are seeking for experimental treatments, typically in growing nations. Given the experimental nature of many treatments, public cognizance and know-how of the associated risks stay critical. Empirical studies recommend that healthy people might also nonetheless don't forget stem cellular tourism underneath distressing situations, indicating a need for moral considerations surrounding scientific tourism.The invention and medical use of recent stem cellular interventions gift regulatory challenges. some advise for pathways allowing critically ill patients get admission to unproven therapies outdoor conventional scientific trials under unique situations. This consists of the usage of FDA’s compassionate use rules and permitting clinicians to offer progressive remedies whilst ensuring negative events are recorded centrally for protection tracking.

## 7. Future Prospectives and Emerging trends:

Stem-mobile treatment holds wonderful ability to revolutionize medicinal drug thru new technology and research improvements. A key location is its integration into precision medicinal drug, paving the manner for personalised remedies primarily based on genetic profiles, improving therapeutic outcomes and minimizing aspect outcomes. research on immune modulation, addressing troubles like immune rejection, and the use of engineered stem cells targets to enhance treatment compatibility. additionally, gene-modifying gear like CRISPR-Cas9 will ensure the protection and precision of these healing procedures, allowing targeted corrections of genetic problems at the mobile stage. The aggregate of stem cells with advanced biomaterials gives possibilities for developing useful tissues and organs, permitting full-size improvements in tissue engineering and regenerative remedy.

Future advantages of stem cell research encompass disorder modeling, which enables recognize mechanisms and increase remedies for conditions like Alzheimer’s, diabetes, and kidney sickness the usage of patient-derived

precipitated pluripotent stem cells (iPSCs). furthermore, stem cells ought to lead to lab-grown organs, decreasing reliance on donors. innovations on the intersection of stem cells and gene modifying offer new remedy avenues for hereditary disorders.

Stem cells also gift a promising road for autoimmune illnesses, including those associated with AIDS, by means of selling immune regeneration and presenting wish for situations like kind 1 diabetes and rheumatoid arthritis. Regenerative medication objectives to restore or update broken tissues and organs, potentially remodeling therapies for heart disorder, Parkinson's, and spinal twine injuries. ultimately, iPSCs allow the advent of personalised therapeutic cells, substantially decreasing immune rejection dangers and bearing in mind tailor-made treatments for diverse medical situations, highlighting the multidimensional future of stem-cell therapy.

## 8. Challenges and Limitations

Immune rejection poses considerable challenges for graft survival in cell and organ transplantation. Allogenic cells, considered foreign by a recipient's immune machine, cause immune responses via recognition of human leukocyte antigens (HLA). This consequences in inflammation and destruction of grafts, diminishing their therapeutic benefits. Autologous cells can behave similarly if they accumulate mutations or strain-precipitated changes, exacerbating issues in publish-damage environments characterised with the aid of hypoxia and high cytokine ranges. To tackle those troubles, techniques which includes transient immunosuppression, cautious HLA matching, and innovative shipping strategies (e.g., hydrogels) are employed. rising technology include growing hypoimmunogenic cells with knocked out HLA genes aimed at sustaining grafts with minimal immunosuppression.

Tumorigenesis is a important difficulty for regenerative medication, specially with pluripotent stem cells potentially main to teratomas due to incompletely differentiated cells. Genomic instability from reprogramming or way of life strategies can pose oncogenic risks requiring stringent safety measures. This consists of purification tactics, genomic quality manipulate, and sturdy tracking to limit dangers from transplantations.

Production cellular treatment plans at a scientific scale is complex, reliant on severa elements which include the health of donors and subculture conditions, with even minor changes affecting cellular viability. Transitioning from research to GMP-compliant bioreactors entails big engineering and quality manipulate. cost and accessibility troubles arise as developing and

turning in these treatment plans is expensive, especially for autologous treatments. Efforts to beautify affordability consciousness on scaling allogeneic merchandise, automating procedures, and enhancing yields, however extensive cost discounts are essential for broader access, particularly in decrease-profits regions.

## Conclusion

Stem cell technology has installed itself as a transformative pressure in regenerative drug, with the eventuality to repair towel function and form harm that became formerly taken into consideration unrecoverable. The defining traits of stem cells — their functionality to tone- renew and separate into technical mobile kinds — cause them to important in growing curatives for ordinary, degenerative, and existence- putting conditions. Unlike conventional treatments that target symptom operation, stem cell- grounded interventions aim to regenerate purposeful apkins, providing in addition long lasting and restorative troubles.

In recent times, progress in information stem cellular biology has extended their scientific eventuality. Embryonic stem cells, convinced pluripotent stem cells, and person stem cells each hold particular benefits for exceptional operations, from repairing spinal cord accidents to regenerating cardiac towel and treating autoimmune diseases. Reciprocal advances in towel engineering, 3-d bioprinting, biomaterials, and gene enhancing technology have farther extended the restatement of stem cell exploration into remedial realities. Those inventions are gradationally moving regenerative drug from experimental procedures to realistic, affected person-unique treatments.Nevertheless, demanding situations persist. Moral organisations concerning embryonic stem cells, pitfalls of vulnerable rejection, tumorigenicity, excessive costs, and strict nonsupervisory fabric preserve to restrict extensive clinical operation. Prostrating those walls calls for strong clinical trials, interdisciplinary collaboration, and precisely designed moral and safety norms.

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# Botanical Brilliance: Bioactive Compounds Transforming Skincare

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## Abstract

The extracellular matrix, also in the dermal and epidermal layers of the skin, degrades with age, resulting in changes to the physical characteristics of the skin as well as visual indicators on its surface. Time causes chronological aging, but environmental factors can also cause premature aging. Visible signs of premature aging include irregular dryness, dark/light discoloration, sallowness, severe atrophy, telangiectasia, premalignant lesions, looseness, leathery appearance, and deep wrinkles. Many synthetic skincare cosmetics are available on the market to address early signs of aging. The most frequent side effects of these products are phototoxic and photoallergic responses, irritating contact dermatitis, and allergic contact dermatitis. Following scientific confirmation, the utilization of natural compounds originating from ancient times is anticipated in current developments in anti-aging research.The current era of treating aging skin has become more intrusive in terms of technology; however, herbal products, including botanicals, are still relevant, and combining them with the molecular techniques discussed in this overview will help to maintain the desired anti-aging benefits and maximize results.It would be beneficial to investigate the scientific validity of using herbs as an anti-wrinkle action using a variety of models. To uncover effective leads from natural resources useful in the treatment of skin wrinkling, the plants from traditional and other sources need to be evaluated according to the combined techniques of exploitation and exploration.Medicinal herbs are still a valuable resource for finding new drug leads today, as they have demonstrated in the past as a source of compounds with therapeutic promise. The pharmaceutical industry has spent the last several decades primarily using libraries of synthetic chemicals as a source for new therapeutic discoveries. They exhibit strong compatibility with well-established screening high-throughput (HTS) platforms and are relatively simple to create and restock. Though it is considered to be difficult, drug development from natural sources is gaining attention from

scientists due to a trend of fewer new medications being released into the market.Although highly integrated interdisciplinary approaches are necessary due to the inherent complexity associated with natural product-based drug discovery, it is evident from reviewed scientific advances, recent technological advancements, and research trends that natural products will continue to be a major source of new drugs in the future.

**Keywords:** Plant extracts, Phytochemicals, Antioxidants, Anti-inflammatory, Anti-aging, Natural ingredients, Green cosmetics

## Introduction

Being the biggest living organ in the body, the skin shields the internal organs from external threats by preventing dangerous chemicals and bacteria fr om entering the body, eliminating sunlight, and preserving homeostasis(C,&Fis cher,2018,).An uppermost layer of skin called the stratum corneum is adiverse, selectively permeable epidermal layer that stays sufficiently wet to operate yet offers defense against environmental harm and dryness(NilforoushzaMAdarrint aj et al., 2018,).

Skin hydration decreases and transepidermal water loss increases when skin ba rrier function is compromised, which often presents as altered stratum corneum integrity.Cosmetics containing active ingredients with drug-like qualities are referred to as "cosmeceuticals".Medication-based cosmetics prevent degenerative skin disorders and have positive local benefits(Yosipovitch,G.etal .,2019,). By providing the minerals needed for improved appearance, they enhance appearance by supplying nutrients for health care. (Thi et al., 2021)

A material that is created or discovered in nature and is directly sourced from plants or animal products is referred to as ``natural”. (Ciddi, 2012, )Natural components can be found in plants, fruits, flowers, leaves, minerals, water, and the earth. The effectiveness of natural substances in skin care products depends on both their in vivo and in vitro performance as well as the kind of dermatological base that they are combined with.Since plants have long been utilized medicinally, new products incorporating natural oils and herbs are probably going to keep appearing on the market in the years to come. Prior to utilizing artificial compounds with comparable characteristics,All cosmetics were derived primarily from plants. Researchers are still interested in natural plant compounds (Fowler JF Jr et al., 2010) (Thi et al., 2021, )

Bioactive compounds, harvested from a plenty of plant components employing diverse extraction techniques, are increasingly coveted for their innate naturalness and perceived safety. Industries spanning cosmetics, food, agriculture, and pharmaceuticals clamour for these compounds owing to their multifaceted health advantages (J. Azmir et al., 2013,). With properties encompassing antibacterial, antimicrobial, anti-inflammatory, anti-aging, and anti-cancer effects, they stand as potent promoters of both human and animal well-being.

In the cosmetics realm, bioactive compounds are considered for their ability to revitalize and rejuvenate skin, offering a holistic approach to skincare. In the food industry, they are harnessed for their antioxidant properties, enhancing the nutritional profile and extending shelf life. In agriculture, these compounds exhibit pesticidal and growth-promoting attributes, fostering sustainable farming practices. Moreover, in pharmaceuticals, they serve as promising candidates for novel drug discovery, addressing a myriad of health concerns.Amidst an increase in awareness of the importance of natural remedies and sustainable practices, bioactive compounds emerge as light of hope. Their versatility, coupled with their eco-friendly origins, positions them at the forefront of modern innovation, promising a brighter, healthier future for both humans and the environment (Aimee &Waśkiewicz, 2020, )

## Exploring The Renaissance Of Plant-Derived Bioactive Compounds In Modern Skincare Trends

When it comes to plant-based medicine development, the random screening approach chooses plant extracts, enhanced fractions, or isolated molecules based only on availability. This technique is especially promising in areas with significant endemism and biodiversity, as the richness of the source organisms is typically reflected in the chemical diversity of natural products. Researchers hope to find unanticipated bioactivities that might not have been predicted based on current understanding by selecting test materials at random. Although random screening has inherent limits, it also has the potential to yield unexpected results. This method's pharmacological assays usually have low- to medium-throughput capacities, which means that the testing procedure might be labor- and resource-intensive. Moreover, the number of bioassays in which initial test samples—such as extracts or isolated compounds—can be assessed is frequently constrained by their limited availability. It is challenging to thoroughly investigate the bioactivity of each sample due to this limitation.Additionally, knowledge-based approaches may involve the

utilization of computational methods, such as virtual screening or molecular docking, to predict the potential bioactivity of compounds before experimental testing.In conclusion, while random screening serves as a valuable initial exploration method in plant-based drug discovery, its limitations necessitate the adoption of complementary knowledge-based strategies to enhance efficiency and maximize the identification of bioactive compounds

In conclusion, while random screening serves as a valuable initial exploration method in plant-based drug discovery, its limitations necessitate the adoption of complementary knowledge-based strategies to enhance efficiency and maximize the identification of bioactive compounds. By integrating existing knowledge, computational tools, and targeted experimental techniques, researchers can overcome the challenges associated with random screening and advance the discovery of novel pharmacologically active plant compounds. (Atanasov et al., 2015, )

## Antioxidants In Skincare: A Comprehensive Guide

Antioxidants are chemicals that are essential for shielding our cells from the damaging effects of free radicals. These extremely reactive molecules, known as free radicals, can induce oxidative stress, which can harm cells and perhaps be a factor in a number of health problems, including inflammation, aging, and chronic illnesses like cancer and heart disease.

Free radicals are neutralized by antioxidants, stopping them from damaging our cells. They accomplish this by giving the free radicals an electron, which stabilizes them and lessens their harmful effects. Many foods contain antioxidants, but fruits, vegetables, nuts, and seeds are particularly high in them. Antioxidants that are well-known include selenium, beta-carotene, vitamin C, and vitamin E.

Food, drink, cosmetics, medications, and even the food industry all use antioxidants. They have to be used as stabilizers, active compounds, and health supplements. Both natural and synthetic antioxidants are utilized in cosmetic products. Propyl gallate, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and other synthetic antioxidants are extensively utilized due to their low production costs. On the other hand, studies indicate that consuming synthetic antioxidants in excess may be harmful to your health. The market is dominated by synthetic antioxidants, although demand for natural antioxidants has grown recently and is predicted to rise further. The increased customer preference for natural and organic products, which have fewer additives and possibly fewer adverse effects, can be used to explain this trend. (Thi et al., 2021, )

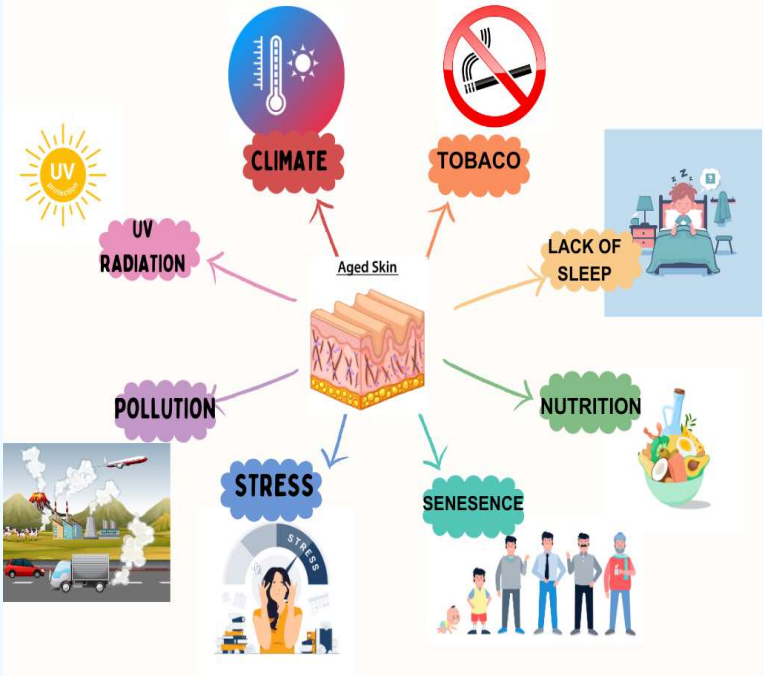


**Fig. 01: driving factors for skin aging.**

**Table 01: Natural antioxidant**

| S. No | Source | Antioxidant | Potential Activity |
|---|---|---|---|
| 1. | Apple | Phenolic compounds | Inhibitors of sulfotransferases, influence epigenetic processes and heritable changes not encoded in the DNA sequence, DNA protection against UV radiation |
| 2. | Baccharis species | Phenolic compounds | Inhibit reactive oxygen and nitrogen species (RONS), inhibit carrageenan-induced edema |
| 3. | Basil leaves | Phenolic compounds | Antiacne, antiaging, remove dead skin cells |

| | | | |
|---|---|---|---|
| 4. | Blueberry pomace | Phenolic compounds | Enhance polyphenol oxidase activity and potent antioxidants |
| 5. | Cape gooseberry | Phenolic compounds and carotenoids | Anticoagulant, antispasmodic |
| 6. | Carrot | Carotenoids, anthocyanins | Protection from UV-induced lipid peroxidation, in treatment of erythropoietic protoporphyria |
| 7. | Chestnut | Polyphenols | Moisturizer, in treatment of oxidative stress-mediated diseases and photoaging |
| 8. | Coffee leaves | Chlorophylls and carotenoids | antioxidant, and |
| 9. | Feijoa | Phenolic compounds | antioxidant, and |
| 10. | Ginkgo biloba leaves | Flavonoids | Prevent UVB-induced photoaging, anti-inflammatory, antioxidant, and blood microcirculation |
| 11. | Grape | Anthocyanins and phenolic compounds | Protection from UV radiation, antioxidants and antiaging, depigmenting, anti-inflammatory, wound healing |
| 12. | Mango | Carotenoids | Wound healing, prevent skin aging, antioxidant |
| 13. | Pineapple | Polyphenols | Antimalarial, antinociceptive, and anti-inflammatory activities, improve skin barrier function |

| | | | |
|---|---|---|---|
| 14. | Strawberry | Anthocyanins and phenolic compounds | Antimicrobial, antioxidant, anti-aging |
| 15. | Sweet potato | Polyphenols and anthocyanins | Antioxidant, wound healing, serve as natural, safe and effective colorants, antimicrobial, antifungal |
| 16. | Tomato | Flavonoids and lycopene | Antioxidant, protection from cell damage, provide protection against UV rays, wound repair |
| 17. | Banana | Phenolic compounds and flavonoids | Provide UV protection, antimicrobial, wound healing |
| 18. | Turmeric | Phenolic compounds | Anti-inflammatory, antioxidant, treatment of psoriasis |

## Vitamins: Enhancing Skin Health Naturally

Vitamin and antioxidant absorption and assimilation are essential for human health; these are obtained mostly from diet and, to a lesser degree, via the use of artificial supplements. For general health, keeping these nutrients in balance is essential. The biggest organ in the body and the first line of protection against the outside world, our skin is always up against dangerous free radicals that come from our surroundings. Reactive oxygen species (ROS) are produced by environmental contaminants and UV light, among other things. Because they have one unpaired electron, free radicals are extremely reactive and can harm nearby chemicals and tissues. Free radical activity significantly damages DNA and biomembranes, two of the many biological components impacted. It is believed that topically applied vitamin and antioxidant cosmetics provide defense against free radical damage and may even help heal it. Some vitamins can benefit skin by helping to lessen pigmentation and bruises, boosting collagen synthesis, fine-tuning keratinization, and reducing inflammation.

## Vitamin A

Vitamin A was the first vitamin to receive approval from the Food and Drug Administration as a skincare ingredient with anti-aging benefits, specifically targeting wrinkles and enhancing skin appearance. It belongs to the retinoid family, which includes substances similar to retinol in their biological effects. These substances are measured in retinol equivalents for standardization due to their varied biological activities. Vitamin A and its derivatives are highly effective in combating aging signs, regulating cell processes such as apoptosis, differentiation, and proliferation.

Retinoids, including vitamin A, play a crucial role in promoting keratinocyte proliferation, strengthening the epidermis' protective function, reducing water loss through the skin, preventing collagen breakdown, and inhibiting certain enzyme activities. They achieve these effects by binding to nuclear receptors like retinoid acid receptors and retinoid X receptors with high affinity. Vitamin A and its precursor, beta-carotene, are commonly found in cosmetic products, with beta-carotene being abundant in vegetables like carrots and tomatoes, while vitamin A is primarily sourced from animal products like egg yolk and liver.

Beta-carotene, a potent antioxidant, helps protect against DNA damage caused by reactive oxygen species like singlet oxygen, particularly in response to UV radiation. Studies have shown its photoprotective effects on the skin, alongside vitamin A. However, due to beta-carotene's instability, other forms of vitamin A are often preferred in cosmetic formulations.

Retinol, a fat-soluble form of vitamin A, penetrates the skin layers, influencing cellular processes, receptor binding, and growth factor secretion. It promotes epidermal cell turnover, strengthens skin barriers, reduces water loss, protects collagen, and regulates melanin distribution, contributing to even skin tone. Retinoids also play a role in regulating sebum production and preventing acne formation by inhibiting enzymes involved in lipid synthesis and sebocyte activity. Overall, retinoids, particularly retinol, are widely recognized as effective anti-aging and skincare agents.

**Table 02: Example of vitamin a and its derivatives**

| S. No. | Vitamin A and Its Derivatives | Application |
|---|---|---|
| 1. | Retinol | Used in dyspigmentation, dryness, and anti-wrinkle treatment |
| 2. | Retinoic acid | Used in treatment of psoriasis, chronic inflammation of hair |
| 3. | Retinyl acetate and palmitate | Stabilizes properties in wrinkle treatment and acts as antioxidant |
| 4. | Retinaldehyde | It works as stabilizer in treatment of wrinkle |
| 5. | Naphthalenecarboxylic acid | Reduces inflammation, acne, and excessive keratosis |
| 6. | Tazarotene | Used in treatment of psoriasis and acne, works as photoprotection from sunlight |

## Vitamin B

Vitamin B, a water-soluble nutrient, is abundant in a variety of foods, especially whole grains and green leafy vegetables. Panthenol, also known as vitamin B5 in its alcohol form, has long been utilized in hair care products due to its humectant properties, which enhance hair moisture and elasticity. In cosmetics, panthenol serves as an effective moisturizer by drawing water into the outer skin layer (stratum corneum) and softening the skin.

Another member of the vitamin B family is niacinamide, synthesized in the body through nicotinic acid conversion. Niacinamide plays key roles in cellular energy metabolism, DNA synthesis regulation, and transcription processes, leading to diverse biological effects observed in laboratory and clinical studies. Notably, niacinamide acts as a potent inhibitor of nuclear poly (ADP-ribose) polymerase-1 (PARP-1), crucial for regulating NF-B-mediated

transcription that influences the expression of adhesion molecules and pro-inflammatory mediators, thereby contributing to its anti-inflammatory effects.

The anti-inflammatory properties of niacinamide primarily stem from its ability to inhibit leukocyte chemotaxis, lysosomal enzyme release, and lymphocyte transformation rather than acting directly as a vasodilator. It also modulates melanosome transfer from melanocytes to keratinocytes, distinguishing it from other skin-lightening agents like arbutin and kojic acid that target tyrosinase. Furthermore, niacinamide provides photoprotective benefits by inhibiting photocarcinogenesis and shielding against UV-induced immunosuppression, making it a versatile and valuable ingredient in skincare products.

## Vitamin C

Vitamin C, also known as ascorbic acid (AA), is a hydrophilic compound that exists in two states: ascorbic acid or ascorbate (its reduced form) and dehydroascorbic acid (its oxidized form), which is a product of AA's two-electron oxidation process. Its antioxidant properties stem from its ability to neutralize oxidative stress through electron transfer or donation mechanisms. Beyond replenishing other antioxidants like alpha-tocopherol, vitamin C helps reduce levels of unstable oxygen, nitrogen, and sulfur radicals.

Research on human plasma has highlighted vitamin C's role in preventing lipid peroxidation caused by peroxide radicals. Additionally, it aids in the absorption of iron, calcium, and folic acid, preventing allergic reactions. A decrease in intracellular vitamin C levels can lead to immunosuppression. Vitamin C is vital for immunoglobulin synthesis, interferon production, and the regulation of interleukin-18, a factor linked to malignant tumors.

When applied topically, vitamin C can counteract reactive oxygen species (ROS) triggered by solar radiation, smoke, and pollutants. Its efficacy extends to treating conditions like hyperpigmentation, melasma, and sunspots by inhibiting tyrosinase, an enzyme crucial in melanin production. Furthermore, vitamin C supports keratinocyte differentiation and enhances the cohesion between the dermal and epidermal layers.

## Vitamins E and K

Vitamin E, a fat-soluble nutrient abundant in foods like soy, nuts, whole-wheat flour, and oils, offers significant health benefits for the eyes and cardiovascular system by combating lipid peroxidation. When applied topically, vitamin E brings several skin-related advantages, primarily due to its potent antioxidant properties. It's often referred to as a "protector" because of its ability to effectively neutralize free radicals, especially lipid peroxyl radicals, resulting in reduced UV-induced skin inflammation and swelling, along with improvements in skin aging symptoms such as wrinkles and skin tumor development.

Extensive research has focused on tocopherol and its acetyl ester form, tocopherol acetate, highlighting their ability to penetrate the skin's surface. Additionally, phytonadione (vitamin K), essential for liver clotting factor production, is mainly derived from green leafy vegetables and intestinal bacteria. In clinical settings, vitamin K is used to reverse prothrombin deficiency caused by coumadin use. Topical vitamin K shows promise in addressing and preventing age-related vascular issues by speeding up bruise healing and reducing future bruising, thanks to its ability to remove blood from the skin, complemented by retinol's effects on photoaging concerns.

## The Role of Phytochemicals and Phytonutrients In Skin health

Phytochemicals and phytonutrients, the naturally occurring compounds found in plants, have garnered significant attention in the realm of skin health due to their remarkable therapeutic properties. These plant-derived compounds possess a wide array of biological activities, including anti-inflammatory, antioxidant, and antimicrobial effects, making them potential allies in the quest for maintaining healthy skin.

Studies have reported the existence of approximately 25,000 different phytonutrients, belonging to diverse classes such as polyphenols, phenolic acids, flavonoids, diarylalkanoids, carotenoids, and alkaloids (Hamuel, 2012). These compounds are known to exhibit a multitude of health benefits, including the potential to safeguard skin from various dermatological concerns.(Sharma et al., 2019) Flavonoids, in particular, have been extensively studied for their preventive activities against skin cancer, as well as their capacity to promote wound healing and anti-inflammatory effects.(Asaduzzaman & Asao, 2018) Anthocyanins, a subclass of flavonoids,

have been found to possess potent antioxidant properties and may contribute to the overall skin health.

Furthermore, the consumption of fruits, vegetables, nuts, beans, tea, and whole grains has been linked to a reduced risk of skin cancer, likely due to the abundance of phytonutrients present in these food sources. Topical application of antioxidant and anti-inflammatory agents derived from phytochemicals has also demonstrated protective effects against chronic skin damage induced by ultraviolet radiation.(Evans & Johnson, 2010)

## Medicinal Plants With Anti-Aging Properties

Herbal cosmetics are becoming more and more well-liked outside of Asia, as people all around the world realize how much they can improve the aging of their skin. In order to shed light on the possibilities of natural remedies in contemporary skincare practices, this article will examine the wide variety of medicinal plants and their ingredients renowned for their ability to prevent skin aging.

**Table 03: List Of Anti-Aging Plants And Their Mechanism Of Action**

| S. no. | Name of the plants and family | Part used | Possible mechanism of action | reference |
|---|---|---|---|---|
| 1 | Centella asiatica L. Urban. (Umbelliferae) | Whole plant | Improvement of the clinical score for deep and superficial wrinkles, suppleness, firmness, roughness and skin hydration<br>Induce type-I collagen synthesis | Haftek et al. (2008) |
| 2 | Aesculus hippocastanum L. (Hippocastanaceae) | leaves | Generate contraction forces | Fujimura et al. (2006) |

| | | | | |
|---|---|---|---|---|
| **3** | Calendula officinalis L. (Asteraceae) | flower | Control the activity/secretion of MMP-2 and MMP-9 | Yris et al. (2010) |
| **4** | Citrus sinensis L. (Rutaceae) | fruit | NF-B and AP-1 translocation and procaspase-3 cleavage | Cimino et al. (2007) |
| **5** | Piper betel L. (Piperaceae) | Leaves | Protect photosensitization-mediated lipid peroxidation (LPO) | Mula et al. (2008) |
| **6** | Zingiber officinale L. (Zingiberaceae) | Rhizomes | Inhibits fibroblast derived elastase | Tsukahara et al. (2006) |
| **7** | Theobroma cacao L. (Sterculiaceae) | Bean | Down regulation of hydroxyproline and pepsin-resistant hydroxyproline content | Mitani et al. (2007) |
| **8** | Camellia japonica L. (Theaceae) | Oil | Induce type-1 procollagen synthesis and inhibit MMP-1 activity | Jung et al. (2007) |
| **9** | Glycine max L. Merr. (Fabaceae) | Seeds | Inhibit melanosome phagocytosis Prevented the activation of caspase-3 pathway | Tsoyi et al. (2008) |
| **10** | Vitis vinifera L. (Vitaceae) | Shoot | Antioxidant and free radical scavenging capacity | Cornacchione et al. (2007) |

## Conclusion

The growing demand for safer, sustainable, and effective skincare solutions has reinforced the significance of plant-derived bioactive compounds in modern cosmetology. Evidence from both traditional practices and contemporary research highlights that antioxidants, vitamins, phytochemicals, and medicinal plant extract not only mitigate visible signs of aging but also strengthen skin health at the molecular level. Unlike many synthetic formulations that may trigger adverse effects, botanical ingredients offer multifunctional benefits ranging from anti-inflammatory and antimicrobial action to collagen stimulation and photoprotection.

As biotechnology, biofermentation, and computational approaches advance, the integration of these natural compounds into skincare will become more precise, targeted, and efficient. Future research should emphasize validating the therapeutic mechanisms of botanicals through robust in vitro, in vivo, and clinical studies. By combining traditional knowledge with cutting-edge scientific tools, botanicals can continue to provide innovative and eco-friendly alternatives, ultimately shaping the future of clean beauty and green cosmetics

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# The agro-industrial biorefinery transforming waste biomass into high-value nutraceuticals and functional ingredients for a circular economy

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## Abstract

For generations, the global rise in food production has resulted in an enormous buildup of agro-industrial waste, a byproduct now recognized as a critical global challenge. This excess biomass is produced wherever farming and processing industries operate worldwide. Crucially, this residual material is now understood to be far more than mere waste; it is an untapped resource, rich in bioactive molecules and complex structural polymers with significant intrinsic value. In alignment with the principles of the Circular Economy, waste valorization offers a potent solution, effectively tackling both severe environmental pollution and the problem of dwindling resources. Consequently, interest in exploring and maximizing the utility of industrial waste streams for producing valuable commodities has soared in recent decades. It is essential, however, that we provide robust scientific proof to validate the logical and sustainable methods used to convert these low-cost byproducts into beneficial, commercially viable products. Valorization techniques, such as biorefinery and eco-friendly extraction, provide a proven, scalable route, having successfully transformed residues into high-demand nutraceuticals, functional food additives, and advanced biomaterials for years. This sustainable approach holds vast potential for becoming a reliable source

of raw materials and new income streams for the chemical and pharmaceutical sectors. This chapter provides an in-depth examination of the current technological advancements, economic viability, and diverse therapeutic uses achieved through the valorization of common agro-industrial waste materials. Specifically, we review the general applications and medicinal properties of the numerous components successfully recovered from these waste streams.

**Keywords** - Agro-industrial waste, waste valorization, Circular Economy, bioactive molecules, biorefinery.

## Introduction

The sheer scale of global food waste has escalated into a critical environmental and economic dilemma, with the industrial and household discarding of fruit peels contributing significantly to this problem. The routine disposal of these agricultural byproducts in landfills results in substantial releases of potent greenhouse gases, such as methane, thereby intensifying climate change and representing a profound waste of the resources (water, energy, labor) invested in cultivation **(FAO, 2019)**. Recognizing this liability as an opportunity demands a shift in perspective, acknowledging the underutilized potential of fruit peels as valuable bioresources—essentially concentrated packets of biological complexity waiting to be recovered. The core objective of valorization (transforming a low-value waste into a high-value material) is therefore twofold: to achieve environmental mitigation by drastically reducing landfill volume and pollution, and to foster a circular economy by maximizing resource use and generating new, diversified revenue streams **(Gupta et al., 2020)**. The significance of this approach lies in providing sustainable, natural alternatives for industrial ingredients, fulfilling the growing consumer demand for "clean label" products across the food, cosmetic, and pharmaceutical sectors. This potential is rooted in the remarkably rich fruit peel composition, which serves as a natural treasure trove of functional components: Natural Bioactives,the antioxidant heavy hittersprimarily Polyphenols (Flavonoids and Phenolic Acids), and concentrated Vitamins (like Vitamin C), are sought after for their potential anti-inflammatory and cardioprotective effects **(Sharma et al., 2021)**. Fibers, the structural backbone, include Pectin, a key gelling agent and prebiotic, and Cellulose/Hemicellulose, which provide essential dietary fiber and serve as raw materials for biorefining. Pigments, such as Anthocyanins (red/purple) and Carotenoids (yellow/orange), are natural colorants valued for their strong antioxidant properties and as clean-label alternatives to synthetic dyes, thus justifying the comprehensive recovery of this agricultural surplus **(Kaur & Mondal, 2020)**.

## Sources and Composition

### Varieties of fruit peel waste

The vast fruit processing and fresh consumption industries worldwide are the primary generators of fruit peel waste, with major contributors being citrus (oranges, lemons), banana, mango, pomegranate, apple, and pineapple, often accounting for 10% to 40% of the total fruit weight, which represents a massive, yet overlooked, reservoir of bioresources **(Kaur & Mondal, 2020)**.

### Nutritional composition of fruit peels

The nutritional and biochemical profile of fruit peels is notably richer and more complex than the corresponding fruit pulp, underscoring their immense potential for valorization. For instance, the peels are highly concentrated in fibers, which includes complex structural components like cellulose and hemicellulose, alongside functional polysaccharides such as pectins (particularly high in citrus and apple peels), which serve as essential gelling agents and dietary fibers**(Sharma et al., 2021)**. Furthermore, the peel's defensive role in the plant results in a high concentration of antioxidant-rich phenolic compounds (like phenolic acids and tannins), of which flavonoids (e.g., naringin in citrus, mangiferin in mango) and vibrant coloring carotenoids (giving orange and yellow hues) are especially important for their demonstrated anti-inflammatory and free-radical-scavenging properties. Many fruit peels, especially citrus, also house significant amounts of essential oils in their outer layers (flavedo), primarily composed of terpenes, which are valued for their aroma, flavor, and antimicrobial activity **(Gupta et al., 2020)**.

### Influence of fruit variety, maturity, and processing method on composition

Critically, this composition is not static; it is significantly influenced by external factors, as the fruit variety dictates the baseline genetic capacity for compound production (e.g., different grapefruit cultivars exhibit variable levels of total phenolic content), the stage of maturity affects the concentration of compounds (e.g., pectin content and molecular weight typically decrease as fruit ripens due to enzyme activity, while some phenolic compounds may increase), and the processing method (e.g., drying temperature, cutting, or juicing techniques) can substantially impact the final yield and quality of the extracted bioactives due to the thermal degradation or enzymatic breakdown of sensitive compounds like phenolics and vitamins **(Dias et al., 2020).**

# Environmental Impact of Fruit Peel Waste Disposal

## Landfill accumulation and greenhouse gas emissions

The pervasive issue of fruit peel waste disposal presents a critical environmental challenge, driven primarily by the high volume of organic matter that, under conventional waste management systems, ends up contributing to landfill accumulation and significant greenhouse gas emissions. When fruit peels and other food waste decompose in the anaerobic conditions of a landfill, they generate methane, a potent greenhouse gas with a global warming potential far greater than carbon dioxide, thus exacerbating global warming and climate change **(Meherishi et al., 2019; Velenturf& Pelling, 2023)**. This accumulation also contributes to leachate generation, a toxic liquid that can contaminate groundwater and soil, and consumes increasingly limited landfill space **(Kumbhar et al., 2024)**.

## Challenges in conventional waste management systems

The challenges in conventional waste management systems are multifaceted; these systems are often inefficient, characterized by poor collection, a lack of source segregation, and insufficient infrastructure to handle the high moisture content and rapid biodegradability of fruit waste **(Kumbhar et al., 2024; Williams, 2017).**Furthermore, traditional disposal methods like uncontrolled dumping or even some composting processes can lead to the release of malodorous volatile organic compounds (VOCs), creating air pollution and nuisance issues for nearby communities **(Cheng et al., 2021)**. Consequently, there is an urgent need for sustainable and circular approaches to fruit waste handling that fundamentally shift away from the linear "take-make-waste" model. The circular economy offers a transformative framework, emphasizing the elimination of waste and pollution by design, the circulation of products and materials at their highest value, and the regeneration of natural systems (Ellen MacArthur Foundation, n.d.). For fruit peels, this means moving beyond disposal toward valorization, which involves treating them as a valuable secondary resource rich in compounds like polyphenols, fibers, and essential oils that can be extracted for use in the food, cosmetic, pharmaceutical, and bioenergy industries**(Tiwari et al., 2020).**

## Need for sustainable and circular approaches to fruit waste handling

Implementing sustainable strategies such as anaerobic digestion to produce biogas (renewable energy), composting to create nutrient-rich soil amendments, or converting peels into biochar to sequester carbon and improve soil fertility not only mitigates landfill emissions but also closes nutrient and

energy loops, promoting environmental and economic sustainability **(Tiwari et al., 2020; Velenturf& Pelling, 2023)**.

## Techniques And Strategies For Fruit Peel Valorization

### Physical and mechanical processing

The journey from discarded fruit peel waste to valuable resources is a testament to innovation, relying on a suite of sophisticated valorization techniques and strategies that unlock the inherent worth of these by-products. The initial step, Physical and Mechanical Processing, is crucial for preparing the peels for subsequent, more intensive treatments. This involves fundamental methods like drying to reduce high moisture content, which is key for stability and efficient transport, followed by milling, grinding, and size reduction to increase the surface area. This pre-treatment is not merely preparation; it actively enhances the subsequent extraction or conversion rates by breaking down the tough cellular matrix of the peels **(Anand et al., 2021)**.

### Biotechnological Approaches

Following this, Biotechnological Approaches offer an environmentally sound path for transforming complex organic material. Fermentation, utilizing yeasts or bacteria, can convert sugars in the peels into valuable products like bioethanol, organic acids, or probiotic-rich functional foods (Bibi et al., 2023). Enzymatic hydrolysis employs targeted enzymes to break down specific components, such as pectin or cellulose, making sugars and other compounds readily available for further processing or extraction **(Goyal et al., 2022)**. Meanwhile, Microbial valorization uses microorganisms to produce high-value products like single-cell protein or biopigments directly from the peel substrate **(Anand et al., 2021)**.

### Chemical and Green Extraction Methods

To directly isolate and harness the potent health-promoting compounds, Chemical and Green Extraction Methods are employed. Traditional solvent extraction is widely used, though it often requires optimization to minimize the use of harsh chemicals. More modern, sustainable, or "green" methods are becoming prevalent. Ultrasound-assisted extraction (UAE) uses acoustic energy to enhance solvent penetration, significantly reducing both processing time and solvent consumption **(Bibi et al., 2023)**. Microwave-assisted extraction (MAE) employs electromagnetic energy to rapidly heat the solvent and sample, leading to faster and more efficient compound release. Perhaps the most environmentally benign technique is Supercritical extraction, which uses carbon dioxide under high pressure and temperature to selectively extract non-

polar compounds, leaving no toxic solvent residue and thus producing food-grade ingredients **(Goyal et al., 2022)**.

### Integrated Biorefinery Concept

The ultimate goal of these diverse strategies is achieved through the Integrated Biorefinery Concept. This is not a single technique but a holistic approach, akin to a petroleum refinery but using biomass, where multi-product recovery is maximized. The biorefinery systematically utilizes the peel to sequentially recover every fraction: first, high-value bioactive compounds (like antioxidants and pigments) via green extraction; then, the remaining material is used to produce bioenergy (such as biogas or bioethanol) or is transformed into biopolymers (like pectin or cellulose-based films) for sustainable packaging **(Anand et al., 2021)**. This integrated model is essential for achieving true waste circularity, boosting economic viability, and minimizing the environmental footprint of the fruit processing industry.

## High-Value Products From Fruit Peel Waste

### Functional Food Ingredients and Nutraceuticals

The drive toward a circular economy has transformed discarded fruit peels from environmental burdens into a **goldmine of high-value products**, capitalizing on their rich and complex biochemical composition. This valorization unlocks a wide array of commercially attractive applications, beginning with **Functional Food Ingredients and Nutraceuticals**. Fruit peels are concentrated sources of **polyphenols** (potent antioxidants like flavonoids and phenolic acids), which are extracted for their protective health benefits against chronic diseases (Goyal et al., 2022). They are also excellent sources of **dietary fiber**, often including both soluble components like pectin and insoluble fiber, which can be incorporated into food products to enhance satiety and gut health (Anand et al., 2021). Furthermore, natural **pigments** like carotenoids and anthocyanins can be recovered for use as vibrant, healthy food colorants, replacing synthetic and often harmful alternatives (Bibi et al., 2023).

### Natural preservatives and antimicrobial agent

Moving beyond nutrition, these extracts are powerful Natural Preservatives and Antimicrobial Agents. The inherent antibacterial and antifungal properties of certain peel extracts—derived from their high concentration of essential oils and phenolic compounds—make them ideal for food shelf-life extension, where they can be applied as a natural surface coating or incorporated directly into the food matrix to inhibit spoilage microorganisms **(Tiwari et al., 2020)**.

### Biofuels and Bioenergy Production

The less-utilized residues remaining after high-value extraction are efficiently channelled into Biofuels and Bioenergy Production. The carbohydrate-rich biomass is an ideal substrate for bioethanol production via fermentation, while the overall organic load is perfect for biogas generation (methane) through anaerobic digestion (Anand et al., 2021). Alternatively, pyrolysis of the residues yields biochar, a stable, carbon-rich material used for soil enhancement and long-term carbon sequestration **(Goyal et al., 2022)**.

### Bioplastics and Edible Films

In a compelling example of sustainable packaging, the pectin and cellulose from the peels are refined into materials for Bioplastics and Edible Films. Pectin-based films serve as eco-friendly bioplastic alternatives and innovative, edible food coatings that reduce the need for conventional plastic packaging, offering protection against moisture and microbial contamination **(Bibi et al., 2023).**

### Cosmetics and Pharmaceutical Applications

Finally, the high-purity extracts find their way into Cosmetics and Pharmaceutical Applications. Their robust antioxidant and anti-aging properties make them sought-after ingredients for high-end skin care formulations, combating oxidative stress and promoting skin elasticity, while their bioactive compounds are continually being researched for their potential in various medicinal formulations due to their anti-inflammatory and therapeutic effects **(Tiwari et al., 2020).**

## Economic and Environmental Benefits

### Reducing food industry waste disposal costs

The shift to valorizing fruit peel waste represents a powerful convergence of Economic and Environmental Benefits, fundamentally reshaping the financial landscape and sustainability profile of the food industry. One of the most immediate financial gains is Reducing food industry waste disposal costs; by diverting high-volume organic waste from landfills, companies avoid escalating tipping fees and the logistical expenses associated with disposal, transforming a liability into a resource **(Anand et al., 2021).**

### Promoting circular economy and sustainable production models

This transition is the very essence of promoting circular economy and sustainable production models, where waste is not the end-point but a valuable

input for a new product cycle, minimizing resource depletion and lowering the carbon footprint associated with processing and disposal **(Bibi et al., 2023).**

### Contribution to rural and agro-based industries

This valorization also provides a significant Contribution to rural and agro-based industries. New value chains are created around the collection, pre-processing, and extraction of peel compounds, generating income and employment opportunities in farming communities and supporting the development of small- and medium-sized enterprises (SMEs) focused on high-value bioproducts **(Goyal et al., 2022).**

### Market potential and commercialization opportunities

Crucially, the Market potential and commercialization opportunities for these fruit peel-derived products, such as natural antioxidants, dietary fiber, flavorings, and biodegradable materials, are substantial and rapidly expanding. The global market for natural food extracts and clean-label ingredients is experiencing robust growth, driven by increasing consumer demand for healthy, sustainable, and transparently sourced products, with some citrus peel extract markets alone projected to reach billions of dollars, offering profitable commercialization avenues that ensure the long-term economic viability of the entire valorization process **(Fact.MR, 2025).**

## Future Perspectives

### Emerging green technologies for waste valorization

The future of fruit peel valorization is marked by a transformative shift toward efficiency, sustainability, and technological integration, promising to realize the vision of a truly circular food economy. This revolution is powered by Emerging green technologies for waste valorization, which move beyond conventional methods to enhance yields and reduce environmental impact. Techniques like Pulsed Electric Field (PEF) extraction and Natural Deep Eutectic Solvents (NaDES) extraction are gaining prominence for their ability to selectively and efficiently recover high-value bioactive compounds with minimal energy consumption and zero toxic residues, making the entire process greener and more scalable **(Goyal et al., 2022)**.

### Integration of artificial intelligence and data analytics for waste optimization

Simultaneously, the integration of Artificial intelligence (AI) and data analytics for waste optimization is poised to revolutionize the operational landscape of fruit processing. AI algorithms can analyze real-time data across

the supply chain—from fruit quality at harvest to processing parameters—to predict the optimal time for valorization, identify the most valuable compounds to extract, and fine-tune biorefinery conditions, thereby maximizing resource utilization and drastically reducing residual waste **(Bibi et al., 2023)**.

### Potential for zero-waste fruit processing industries

This data-driven precision brings closer the Potential for zero-waste fruit processing industries, where every fraction of the fruit, including the peel, seeds, and pomace, is systematically channelled into co-produced productsfrom nutraceuticals and bioplastics to bioenergytransforming processing plants into integrated, profitable biorefineries **(Anand et al., 2021).**

### Policy support and global initiatives promoting sustainable food systems

Achieving this global transformation requires robust Policy support and global initiatives promoting sustainable food systems. International frameworks, such as the UN Sustainable Development Goals **(SDG 12.3 to halve food waste by 2030)**, drive national governments and multinational corporations to invest in valorization infrastructure and create economic incentives. Policy measures, including tax breaks for circular businesses and mandated waste-to-value schemes, are essential to accelerating the adoption of these innovative technologies and ensuring the successful transition to a sustainable, resource-efficient global food system **(Tiwari et al., 2020).**

## Conclusion

The potential of fruit peel valorization is immense, representing a critical pivot point for the global food industry from a linear "take-make-dispose" model to a resilient, circular bioeconomy. The core strength of this field lies in its triple benefit: it significantly advances sustainability by diverting vast volumes of nutrient-rich waste from landfills, reducing both pollution and greenhouse gas emissions; it champions innovation through the deployment of cutting-edge green extraction technologies and the transformative integration of AI and data analytics for process optimization; and it promises substantial economic feasibility by converting low-value by-products into premium, marketable ingredients (Caldeira et al., 2020). The key potential is the recovery of valuable compounds like pectin, dietary fiber, essential oils, and potent antioxidants, which are often found in higher concentrations in the peel than in the edible pulp. Looking ahead, the future vision involves effortlessly transforming fruit peel waste into high-value bioproducts for food, health, and industry, where centralized, digitized biorefineries efficiently process diverse fruit wastes to co-produce next-

generation ingredients: functional food additives for enhancing nutritional profiles, novel feedstuffs for reducing livestock emissions, sustainable bioplastics for eco-friendly packaging, and pharmaceutical precursors for health and wellness applications (Yaashikaa et al., 2022). This comprehensive approach not only tackles the waste challenge but creates new revenue streams, establishing fruit processing as a zero-waste operation and proving that environmental responsibility can be a powerful engine for economic growth (Ubando et al., 2021).

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# Harnessing artificial intelligence in life sciences: Revolutionizing research and pedagogy in the digital era.

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## 1. Introduction

In an era where biological research and scientific education are rapidly evolving, the integration of Artificial Intelligence (AI) into the teaching of Life science marks a significant move. This chapter acts as a scholarly review and guide for educators, curriculum designers and researchers who are working at the node of biology teaching and technological innovation.

## 2. Usage and Importance of AI in Teaching Life Sciences:

### 2.1.Usage of Artificial Intelligence (AI) :

In the context of Life sciences teaching, AI tools are being set up in numerous modalities:

•**Virtual laboratories and simulations:** AI-driven platforms allow students to simulate biological experiments (e.g., cell division, ecological interactions, genetics) which may be too expensive, dangerous, or impractical in real-life settings. One review records the use of 3D modelling and visualisation as core AI affordances in biology instruction.

•**Adaptive learning systems and personalised feedback:** Systems that record student responses, misconceptions and progress and then modify content or prompts accordingly. For instance, systematic reviews show that AI tools are used in science education to create quizzes, assess work and predict student performance.

•**Automation of assessment and analysis:** AI is used to score open-ended biological explanations, to analyse student reasoning about natural selection, and to provide teachers with diagnostic data.

**•Teacher support and content generation:** Educators use AI for generating teaching materials, designing tasks, producing visualisations, and even planning lessons. The systematic review found that many science teachers welcomed such supports.

**•Multimodal and immersive learning:** The advent of multimodal large-language and vision-enabled AI models enables interactive biology lessons where students can engage with images, animations and text in real time.

**•Data-driven insights & analytics:** AI tools collect and analyse large amounts of learning-data (student responses, engagement metrics) and help educators identify patterns, at-risk learners, and opportunities for intervention.

**•Bridging access and inclusion:** Some studies highlight how AI can offer inclusive learning experiences – e.g., with language translation, support, or adaptive difficulty – which is particularly relevant in diverse or under-resourced settings.

## 2.2 Importance: Why AI is Significant:

The importance of integrating AI into Life Sciences teaching arises from both the changing nature of biological sciences and the evolving demands of 21st-century education:

**•Complexity of biology content:** Biology increasingly involves dynamic, interlinked systems (genomics, systems biology, ecology). Traditional teaching (textbooks, lectures) may struggle to render these in a way that increases deep conceptual understanding. AI-driven simulators and visualisations can help make abstract processes noticeable.

**•Individual differences in learners:** In large classrooms, students vary widely in prior knowledge, learning pace, language proficiency and engagement. AI

tools that personalise support and feedback can help reduce gaps and provide better distinguished learning.

•**Motivation and engagement:** The traditional "chalk-and-talk" model in biology may limit student interest, particularly if they struggle to visualise micro-processes (e.g., molecular biology, cell signalling). AI tools (with gamification, interactivity, immediate feedback) can improve interest and empower more active learning.

•**Teacher workload and scalability:** Preparing differentiated materials, supports and assessments for diverse learners is time-intensive. AI can help automate repetitive tasks (grading, generating questions, tracking progress), freeing teachers to focus on higher-order pedagogy (discussion, inquiry, mentoring).

•**Alignment with future research and workforce:** Biological research increasingly uses AI (bioinformatics, computational modelling, machine learning in genomics). By integrating AI into biology teaching, students begin to improve fluency with AI-mediated scientific practices—not just content knowledge.

•**Equity and access potential:** In resource-limited or remote contexts, AI-enabled tools offer the potential to deliver high-quality simulation-based learning even where lab infrastructure is weak, thereby potentially promoting access and inclusion.

•**Data-informed instruction:** Beyond just delivering content, AI-systems enable the capture, analysis and reflection on learning data — thereby enabling dynamic, responsive instruction rather than static lesson plans.

Thus, from both pedagogical and practical perspectives, AI in biology/science/Life Sciences teaching is not simply a novelty—it supports deeper learning, more efficient teaching, and alignment with contemporary scientific practice.

## 3. Merits (Benefits) of Using AI in Science & Biology Teaching:

Here we outline key advantages of AI integration, supported by recent research.

### 3.1 Deeper conceptual understanding

AI-enabled visualisations and simulations allow learners to explore biological systems dynamically (e.g., gene expression, ecological food webs, cellular processes). This cultivates richer mental models, promotes conceptual change, and may reduce misconceptions. The systematic review found that AI tools improved understanding of complex concepts.

### 3.2 Personalisation and differentiation

AI can adjust to each student's pace and profile: offering remediation for those who struggle, extension tasks for advanced learners, and tailored supports (scaffolds, hints). For example, the Islamabad study found improved outcomes when AI-tools were used in biology at secondary level.

### 3.3 Improved engagement and motivation

Interactive AI tools provide immediate feedback, visual appeal, active tasks and real-time scaffolding—all of which contribute to higher student engagement. Teachers in the global review indicated positive attitudes toward AI when it enhanced student motivation.

### 3.4 Efficient assessment and feedback

Instead of manual grading of open-ended biology responses, AI tools (like those described in the Oxford Academic chapter) can automatically score student explanations and provide diagnostic feedback. This enables more frequent formative assessment and timely interventions.

### 3.5 Teacher-support and workload reduction

AI can assist teachers by generating question banks, creating scaffolded tasks, tracking student progress and alerting teachers to issues. This gives teachers more bandwidth for interactive, inquiry-based pedagogy rather than administrative tasks.

### 3.6 Data-driven pedagogy

With analytics from AI-systems, educators can identify common misconceptions, monitor progress trends, personalise groupings and refine teaching design. The systematic review emphasizes this capability.

### 3.7 Agent of equity (potentially)

When implemented thoughtfully, AI can help provide high-quality resources to learners in under-resourced settings, adapt to individual needs, and support inclusive instruction (for example, via translation or adaptive scaffolding). The biology teaching-effectiveness study noted inclusion as a value. eurasia-science.org

### 3.8 Future-readiness and alignment with research

Since many biological research domains now use AI (bioinformatics, systems biology, genomic data analysis), students exposed to AI in teaching gain relevant skills and mindsets. This alignment bridges teaching and emerging bioresearch practices.

## 4.Demerits (Limitations, Risks and Challenges) of Using AI:

While the advantages are substantial, a balanced view requires acknowledging the limitations, risks and caveats.

### 4.1 Accuracy, reliability and domain specificity issues

AI tools often rely on training data and algorithms developed in generic contexts. They may make errors, misinterpret domain-specific reasoning, or lack nuance in biological conceptualisation. The review noted AI's struggle with understanding complex subject matter in science teaching.

### 4.2 Over-reliance, reduced student effort and shallow learning

If students come to rely on AI tools for question generation, answers or simulations without critically engaging, there is a risk of superficial learning. Reliance on automation may diminish deep processing, critical thinking, or self-regulated learning.

### 4.3 Teacher readiness, digital literacy and training gaps

Many teachers may not be adequately trained in AI tools, lack confidence, or resist change. The survey of AI in education highlights teacher resistance, low digital literacy, infrastructure issues and trust concerns.

### 4.4 Ethical, equity and data-privacy concerns

•Bias in AI algorithms and data sets can perpetuate inequity (e.g., differential adaptation for certain students).

•Student data privacy, consent and security are significant concerns.

•Unequal access to devices, high-speed internet or quality AI tools can widen the digital divide rather than narrow it.

•Academic integrity issues: AI might enable plagiarism, shortcutting, or misuse of generated solutions.

### 4.5 Cost, infrastructure and maintenance burden

Introducing AI-enabled tools (software licences, hardware, network infrastructure) can be costly. Ongoing maintenance, updates and teacher professional development impose additional demands—especially in resource-constrained settings.

### 4.6 Appropriateness and pedagogical fit

A “one-size-fits-all” AI tool may not align well with local curriculum, cultural context, grade level or specific biology topics. The adaptability and contextual relevance of AI tools were flagged as key concerns.

### 4.7 Changing role of the teacher and depersonalisation risk:

If AI is seen as replacing rather than supporting teachers, there is a risk that the relational, mentoring, and socio-emotional aspects of teaching may be diminished. The human-centre of teaching must remain intact.

### 4.8 Potential for shallow visuals or simulation misuse:

While simulations are powerful, there is danger if they are used superficially (just to “see” without engage) or if they become substitutes for

real inquiry and hands-on tasks. Over-visualisation without reflection may reduce transfer of learning.

## 5. Recent Teaching Trends in Science & Biology with AI (In the Bioresearch Context)

As the title of this book suggests ("Emerging Trends in Bioresearch"), it is pertinent to highlight how AI in biology teaching is evolving, especially as it connects to research trends and pedagogy.

### 5.1 Shift towards multimodal AI and immersive experiences

Recent literature describes the rise of multimodal large language models (MLLMs) that process text, visuals, audio (e.g., combining a diagram of a cell with a student query). Such models are beginning to enable biology teaching that is richer, more interactive and less text-bound.

### 5.2 Data-driven teacher decision making

More biology and science educators are using dashboards and analytics from AI systems to inform instruction: identifying misconceptions (e.g., in genetics), grouping students, adapting scaffolding, rather than teaching "blindly". The systematic review highlights this trend.

### 5.3 Focus on access, equity and inclusion in under-resourced contexts

Studies from diverse geographies (including secondary-level biology in Islamabad) show that AI tools improved student outcomes when properly implemented and access barriers addressed.

### 5.4 Teacher professional development in AI literacy

Given that AI tools are proliferating, there is increased emphasis on training teachers not just to use them, but to critically engage with them (understand their assumptions, limitations, bias) and integrate them into pedagogy. For example, the research on AI in science education identifies teacher self-efficacy, attitudes and the need for training as crucial.

### 5.5 Integration of AI into bioresearch-linked pedagogy

Biology teaching is increasingly becoming research-informed: for example, AI tools used in protein-structure prediction, genomics, ecological modelling are being introduced into higher-level biology teaching so that students can see how the science field is evolving. This helps bridge teaching and emerging bioresearch practice.

### 5.6 Ethical, critical and metacognitive dimensions

There is growing recognition that beyond just "using AI", students and teachers must engage in AI literacy: understanding how AI works, its limitations, how to evaluate AI-generated outputs, and the role of ethics in AI in biology (e.g., data usage, bias, research integrity). The systematic reviews emphasise the ethical dimension.

## 6. Strategic Recommendations for Integrating AI in Biology & Science Teaching:

Based on the merits, demerits and trends, here are recommended strategies for effective integration of AI in biology/science teaching contexts:

### 1. Define clear pedagogical aims first

Begin with learning goals (e.g., understanding gene regulation, ecosystem modelling). Then evaluate how an AI-tool supports those goals (simulation, scaffold, feedback) rather than using AI for its own sake.

### 2. Maintain teacher-led facilitation and human-centre

The teacher remains central: facilitating inquiry, prompting reflection, interpreting data, guiding discussion. AI is a partner, not a replacement.

### 3. Select tools thoughtfully, assess domain fit

Check whether an AI tool's content aligns with biology curriculum, grade level, language, and the teacher's pedagogy. Consider pilot testing with students.

### 4.Ensure student-AI literacy and critical use

Teach students how AI tools work, what limitations they have, how to critically evaluate AI-outputs, avoid over-dependence and maintain effortful thinking.

### 5. Promote blended learning and hands-on inquiry

Combine AI simulations with real-world investigation, laboratory work, fieldwork or hands-on activities so students ground learning in concrete experience.

### 6. Plan for access, equity and infrastructure

Provide devices, connectivity, ensure that all learners have access. Consider low-bandwidth or offline AI options. Monitor whether some students are excluded.

### 7. Implement data privacy, ethics and integrity protocols

Use AI tools that protect student data, obtain consent, avoid bias. Establish guidelines for academic integrity in AI-supported assignments.

### 8. Provide teacher professional development

Offer training not just on "how to use the tool" but on integrating AI into pedagogy, interpreting analytics, evaluating outputs, and adapting teaching.

### 9. Monitor and evaluate impact continuously

Collect both quantitative (student performance, engagement metrics) and qualitative (student/teacher perceptions, use cases) feedback. Iteratively refine your approach.

### 10. Stay current with emerging bioresearch practices

Embed activities that connect biology teaching to new AI-enabled bioresearch (e.g., genomics, bio-modelling, AI in ecology) so students appreciate the link between what they learn and real research frontiers.

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# A Comprehensive Review on Biostatistics in Health Science

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## Abstract

Biostatistics underpins contemporary scientific and pharmaceutical inquiry by providing rigorously defined methods for designing studies, collecting data, and drawing defensible inferences from empirical observations. Core descriptive summaries—measures of central tendency (mean, median) and dispersion (standard deviation, range, confidence intervals, and standard error)—enable researchers to characterize datasets efficiently and transparently, distinguishing between sample variability and the precision of estimated parameters.Complementing these summaries, hypothesis testing offers a disciplined inferential framework for appraising evidence under uncertainty by translating research questions into null and alternative hypotheses and evaluating sample data to support population-level conclusions. Statistics are integral to medical and pharmaceutical sciences, underpinning theory development, study design, and the collection, analysis, and interpretation of data. As clinical and experimental studies grow more complex, rigorous statistical methods are indispensable for achieving reproducible and dependable findings. Conversely, misapplication or incomplete understanding of statistical procedures can undermine the validity and credibility of research conclusions. This review affirms biostatistics as a cornerstone of scientific inquiry, detailing core analytical techniques while highlighting recurrent mistakes and practical safeguards, thereby underscoring its indispensable role in propelling evidence-based medicine and experimental pharmacology forward.

**Keywords**: Statistics, Clinical trials, Diagnosis, Population, Standard Deviation.

# Introduction

Statistics is essentially a way to reason about variable data. This article explains basic biostatistical concepts and how to apply them to help postgraduate medical and allied science students analyze and comprehend their study data as well as critically assess published literature. These days, developing these skills is an essential part of their graduate studies. It has been noted that most postgraduate students have an innate fear of biostatistics and would prefer to avoid it, with the exception of learning a few facts to help them pass their postgraduate exam. There is little self-motivation to study and apply statistics effectively (Altman et al. 1994).

## Drug Development & Clinical Trials

Biostatistics serves as the backbone of modern clinical research, ensuring that findings are both scientifically valid and clinically meaningful. It provides the framework for designing trials, analyzing data, and drawing reliable conclusions that guide medical decision-making. Randomization plays a crucial role in eliminating selection bias by ensuring that patients are allocated to treatment or control groups purely by chance, making the groups comparable at baseline and enhancing internal validity of the trial (Schulz & Grimes et al., 2002). Similarly, blinding—whether single or double—further enhances credibility by preventing conscious or unconscious bias from participants and researchers from influencing trial outcomes, thereby strengthening the objectivity of observed effects (Karanicolas et al., 2010).A well-designed clinical trial also depends on rigorous sample size determination, which involves statistical power analysis to ensure the study has adequate participants to detect a genuine effect if one exists. This principle prevents underpowered studies that may miss clinically important findings and avoids unnecessarily large trials that waste resources (Chow et al., 2017). Once the trial is underway, hypothesis testing forms the core of data analysis. Techniques such as t-tests, ANOVA, regression models, and non-parametric methods are employed to compare outcomes between intervention and placebo groups, allowing researchers to evaluate the statistical significance and strength of observed differences (Altman et al., 1990).

Beyond comparison of outcomes, survival analysis is essential in clinical research, particularly for chronic or life-threatening conditions such as cancer or cardiovascular disease. Methods such as Kaplan–Meier survival curves estimate the probability of survival over time, while Cox proportional hazards models quantify treatment impact on risk, accounting for censoring and time-to-event data (Bland et al., 2004). Finally, interim analysis provides

an ethical safeguard in ongoing trials. By allowing early monitoring of results, it ensures that a study can be stopped prematurely if the treatment proves exceptionally beneficial or unexpectedly harmful, thereby optimizing participant safety while maintaining scientific rigor (Proschan et al., 2006).Overall, the integration of randomization, blinding, appropriate sample size planning, hypothesis testing, survival techniques, and interim analyses illustrates the foundational role of biostatistics in clinical research. These statistical pillars not only strengthen the credibility of evidence but also guide regulatory decisions and patient care, making biostatistics indispensable to the advancement of modern medicine.

## Genomic and Personalized Medicine

Advanced multivariate techniques like clustering and principal component analysis (PCA) facilitate the classification of patients into genetically distinct subgroups, assisting stratification for tailored interventions. Predictive modeling, particularly in pharmacogenomics, leverages genetic data to forecast individual drug responses, optimizing therapeutic efficacy and minimizing adverse effects. Genome-wide association studies (GWAS) represent a hallmark approach for discovering single nucleotide polymorphisms (SNPs) associated with disease susceptibility, offering a comprehensive view of genetic influences on health outcomes (Hardy et al., 2009).These biostatistical methods collectively contribute to the transformation of healthcare by facilitating personalized treatment approaches that consider individual genetic variability. Despite rapid technological advancements, challenges remain, including the need for robust statistical frameworks to handle large-scale data, interpret complex interactions, and ensure equitable application across diverse populations. Continued innovation in biostatistics is vital to fully realize the promise of genomics in precision medicine (Kanyanaet al., 2024).

The prediction of disease risk is an important component of personalized medicine, which encompasses early disease detection, prevention, and interventions. The polygenic risk score (PRS) has become the benchmark for quantifying genetic liability when predicting disease risk. PRS utilizes single-nucleotide polymorphisms (SNPs) with genetic risks elucidated by genome-wide association studies (GWASs) that are calculated as weighted sum scores of the SNPs with genetic risks, using their effect sizes from GWASs as their weights. PRS utility has been investigated in several common diseases, such as cancer, coronary artery disease, obesity, and diabetes, as well as in various non-disease traits, such as clinical biomarkers. These investigations

substantiated that PRS can recognize a high-risk sub-group of these disorders, thereby providing both a predictive biomarker and insight into modifiable risk factors that impact health outcomes. However, implementation of PRS into clinical use has several limitations, including biased sensitivity for the ethnicity of PRS calculation, as well as geography, even within the same ethnic populations. Furthermore, it remains unknown which PRS calculation method will ultimately serve as the most accurate predicting method from the numerous methods produced to date. Ultimately, while even more robustness and generalizability will be needed for eventual clinical use, PRS will represent a potent approach towards therapeutic interventions and lifestyle adaptations in common heterogeneous diseases. In this way, PRS could ultimately transform population health at some point in the future (Konuma et al.,2021).

## Medical Diagnosis and Screening

Biostatistics plays a pivotal role in evaluating the accuracy of diagnostic and screening tests, ensuring reliable assessment and comparison of their performance (Inacio et al.,2020) Core measures such as sensitivity (true positive rate) and specificity (true negative rate) determine a test's ability to correctly classify diseased and non-diseased individuals, typically validated against a gold standard (Altman et al., 1994a). Beyond these, predictive values—positive predictive value (PPV) and negative predictive value (NPV)—provide practical insights into the real-world reliability of test results, which are highly dependent on disease prevalence (Altman et al.,1994b). Receiver Operating Characteristic (ROC) curves further strengthen diagnostic evaluation by plotting sensitivity against (1–specificity) across thresholds, with the area under the curve (AUC) summarizing overall discriminative power (Hanley & McNeil, 1982). Additionally, Bayesian methods integrate pre-test probabilities with likelihood ratios derived from sensitivity and specificity, allowing clinicians to update disease probability as new diagnostic information emerges. Collectively, these statistical methods enhance diagnostic research, refine screening strategies, and support evidence-based decision-making, ultimately improving clinical practice and patient outcomes (Bossuyt et al., 2015).

## Hospital and Healthcare Research

Biostatistics is fundamental to healthcare and hospital research, enhancing quality, efficiency, and data-driven decision-making across clinical and operational domains (Friedman et al., 2015). Descriptive statistics are essential for summarizing patient demographics, hospital stay durations, and treatment outcomes, forming the basis for advanced analyses that help

institutions track trends and deliver tailored care (Vittinghoff et al., 2012). Monitoring quality indicators, such as mortality rates, readmissions, and infection rates, through rigorous statistical evaluation supports continuous quality-improvement programs, enabling hospitals to benchmark performance, identify areas for intervention, and maintain patient safety (Sorian et al., 2006). Regression models are widely applied to identify and quantify factors influencing recovery time, treatment efficacy, and adverse outcomes, allowing adjustment for confounders, predictive tool development, and effective risk stratification (Vittinghoff et al., 2012). In addition, cost-effectiveness analysis (CEA) informs resource allocation by comparing benefits and costs of interventions, helping healthcare systems optimize population health outcomes (Adamiak et al., 2006). Comprehensive health economics models, built on robust statistical frameworks, further guide policymakers in distributing resources efficiently, evaluating intervention impacts, and promoting equitable healthcare delivery (Gold et al., 2013). Collectively, these biostatistical tools enable hospitals and healthcare systems to make informed, evidence-based decisions, improving operational performance.

## Toxicology and Pharmacology

Statistical models and methodologies play a critical role in assessing drug safety and effectiveness in toxicology and pharmacology, facilitating quantitative evaluation throughout drug development and post-marketing surveillance (Noguchiet al., 2019).

## Therapeutic Index Calculation

Therapeutic index (TI), defined as the ratio of toxic dose (e.g., LD50) to effective dose (ED50), quantifies the safety margin of a drug. A higher TI signifies a larger gap between efficacious and harmful doses, implying increased safety and wider clinical use. Calculating TI informs regulatory decisions and dosage guidelines to balance benefit-risk ratios (Godfrey et al., 1982).

## Repeated Measures ANOVA

Repeated measures ANOVA is applied to compare drug effects across multiple doses and time points within the same subjects. This method accommodates intra-subject correlation and enhances power to detect significant changes over time or dose variations, supporting comprehensive pharmacodynamic and pharmacokinetic analyses (Maxwell et al., 2017).

## Evidence-Based Medicine (EBM):

Biostatistics provides a structured framework essential for Evidence-Based Medicine (EBM), enabling clinicians to integrate the best available research with their clinical expertise and patient values for informed decision-making (Patole et al., 2021). Systematic reviews methodically collect and critically evaluate all relevant studies addressing a clinical question, minimizing bias and maximizing evidence reliability (Ahn et al., 2018). Meta-analyses statistically combine data from these studies, enhancing statistical power and providing precise pooled effect sizes (Egger et al., 1998). The results are often visualized through forest plots, which display individual study outcomes alongside the combined estimate, facilitating easy interpretation (Egger et al., 1998). To assess consistency among studies, heterogeneity tests such as $I^2$ statistics and the Q-test quantify variability, guiding the choice of meta-analytic models (Ahn et al., 2018). Confidence intervals and effect sizes provide essential information on the precision and magnitude of treatment effects, supporting the clinical relevance of findings (Ahn et al., 2018). Collectively, these biostatistical tools ensure that EBM decisions are grounded in high-quality data synthesis and rigorous statistical evaluation, ultimately improving patient care outcomes.

## Statistical Foundations of Sample Size in Clinical and Biomedical Research

### Hypothesis Testing and Significance Levels

In statistical analysis, **hypothesis testing** forms the foundation for making valid inferences from research data. The **null hypothesis ($H_0$)** assumes that no real effect or association exists, thereby contradicting the researcher's expectations. For example, in a clinical trial, the null hypothesis may state that a new drug is no more effective than the standard treatment. In contrast, the **alternative hypothesis ($H_1$)** proposes that a genuine difference or effect does exist. Alternative hypotheses can be **directional** (predicting the direction of the effect) or **non-directional** (indicating only the presence of a difference) (Sadiq, I.Z et al.,2025)To test these hypotheses, researchers rely on the concept of **statistical significance**, which is assessed through the **p-value**. The p-value indicates the probability of obtaining the observed results, or more extreme ones, under the assumption that the null hypothesis is true. If the p-value is less than or equal to the pre-defined **significance level (α)**—commonly set at 0.05, 0.01, or 0.1—the result is considered statistically significant, providing evidence to reject the null hypothesis. Conversely, a p-value greater than 0.05 is considered nonsignificant, suggesting that the observed findings could be

explained by random variation (Bland JM et al.,1996 ;Fisher RAet al.,1992).Thus, **hypothesis testing and significance levels** together form a systematic framework for determining whether research findings in biomedical, clinical, and biological sciences reflect true effects or are merely products of chance.Assessing Disease Prevalence in CommunitiesPrevalence refers to the proportion of individuals within a population who are affected by a particular disease or possess a specific characteristic, either at a given point in time or across a defined period (Dicker RC et al.,2006). In epidemiology, it is distinct from incidence, as prevalence includes both past and current cases existing in the population at the time of measurement, whereas incidence only considers newly diagnosed cases (Bond, B. R et al.,2004). **Point prevalence** describes the proportion of individuals with a disease or condition at a single, specific time point, while **period prevalence** captures the proportion of individuals who experienced the disease or condition at any time during a specified interval (Dicker RC et al.,2006).

$$\text{Prevalence of disease} = \frac{\text{All new and pre-existing cases in a given period}}{\text{Population during the same period}} \times 10^n$$

$$\text{Prevalence of attribute} = \frac{\text{Persons having the particular attribute in a given period}}{\text{Population during the same period}} \times 10^n$$

Here, $10^n$ is a multiplying factor (e.g., $10^2$, $10^3$, $10^5$, etc.) used to express the prevalence per 100, 1,000, 100,000 population, depending on the context of the study.

## Standard Deviation (SD) in the Population

The **standard deviation (SD)** is a fundamental statistical measure that quantifies the degree of dispersion or variability in a dataset. It reflects how much the individual data points deviate from the mean (expected value). A **small SD** indicates that values are clustered closely around the mean, suggesting consistency within the dataset, while a **large SD** indicates a wider spread of data points, representing greater variability (Bland JM et al.,2996).

Mathematically, the population standard deviation is expressed as:

$$\sigma = \sqrt{\frac{\sum(x_i - \mu)^2}{N}}$$

Where:

- σ = population standard deviation
- $x_i$ = each individual data point
- μ = population mean
- N = total number of observations

A standard deviation approaching **zero** signifies that data points lie very close to the mean, reflecting minimal variability. In contrast, a higher standard deviation indicates that the data values are more widely dispersed, either above or below the mean (Lee DK et al.,2015).In health sciences, the standard deviation (SD) plays a vital role in interpreting data and ensuring research reliability. In **clinical trials**, SD is used to describe the variability in patient responses to treatments, which helps determine whether the observed differences between treatment and control groups are clinically meaningful (Chow, S. C et al.,2017). In **epidemiology**, SD is applied to assess variability in health indicators such as blood pressure, body mass index (BMI), and cholesterol levels across populations, thereby supporting risk stratification (Friis, R. H et al.,2020). In the field of **public health research**, SD is essential for calculating confidence intervals, which indicate the precision and reliability of estimates like prevalence and incidence rates (Bond, B. R et al.,2004). Overall, SD is not only a measure of variability but also a fundamental statistical tool that enhances decision-making, data interpretation, and the credibility of biomedical and clinical research findings.

## Descriptive Statistics

Before any inference is attempted, descriptive statistics provide summary measures of central tendency and variability that characterize a dataset (Larson, M et al.,2006 ; Vetter, T et al.,2017; Neely, J. G et al.,2002). The arithmetic mean,

$$\bar{X} = \frac{\sum_{i=1}^{n} X_i}{n},$$

Defined represents the average value of a sample and is commonly used to report health indicators such as mean blood pressure or cholesterol levels.This serves as the basis for both clinical and epidemiological study. When describing sample variability, the standard error of the mean (SEM) can be misleading because it understates between-subject variation (Vetter, T et al.,2017; Nagele, P et al.,2003). In clinical reporting, the mean is usually paired with the standard deviation to convey dispersion, while the SEM should be saved for inferential purposes. In cardiovascular and other clinical research, where descriptive summaries and graphical displays precede hypothesis testing or modeling, the mean should be applied carefully, especially for continuous variables that are common (e.g., blood pressure, laboratory chemistries) ( Larson, M et al.,2006 ; Gliner, J et al.,2000 ; Meaney, E et al.,2000).

## Survival Analysis:

Survival analysis is a dedicated subfield of biostatistics for modeling time-to-event outcomes, where interest centers on the elapsed time until an event such as death, relapse, or graft failure—occurs. In contrast to conventional regression methods, survival techniques are explicitly built to handle censoring, which arises when participants do not experience the event before follow-up ends or are lost to follow-up, ensuring unbiased estimation of survival functions and hazard relationships (Klein, J. P et al.,2006).One of the most frequently employed techniques in survival analysis is the Kaplan–Meier estimator—a non-parametric method that constructs the survival function directly from observed time-to-event data while accommodating right-censoring. It is formally defined as:

$$\hat{S}(t) = \prod_{t_i \le t} \left(1 - \frac{d_i}{n_i}\right)$$

where *di* denotes the number of events observed at time *ti,* and *ni* is the number of participants at risk immediately before ti*ti*. The Kaplan–Meier curve provides a stepwise estimate of the survival function, enabling clear visual comparison of time-to-event experiences across treatment groups (e.g., via survival probabilities and median survival), and is routinely applied in clinical research reporting (Collett D et al.,2023) In oncology trials, for example, Kaplan–Meier plots are used to display differences in survival between chemotherapy and immunotherapy arms, often complemented by log-rank tests and hazard ratios for inference (SEDGWICK, P et al.,2014 ; PALAZZO, M et al.,2007).

To statistically compare survival experiences between groups, the log-rank test is the most commonly applied nonparametric procedure. It evaluates the null hypothesis that the survival functions are identical across groups over the entire follow-up period, giving equal weight to event-time differences throughout the study horizon. The log-rank test statistic is typically expressed as:

$$Z = \frac{\sum_{i=1}^{m} (O_i - E_i)}{\sqrt{\sum_{i=1}^{m} V_i}}$$

where Vi is the variance, Oi is the actual number of events in group i, and Ei is the expected number of events. In randomized clinical trials, it is especially helpful to ascertain whether there are substantial differences in survival between the treatment and control arms (Bland JM et al., 2004).

## Conclusion

The foundation of contemporary health sciences is biostatistics, which provides the methodological rigor required for planning, evaluating, and interpreting research in the fields of public health and biomedicine. From genomics and clinical trials to diagnostics, toxicology, and epidemiology, statistical principles guarantee that results are both clinically relevant and scientifically sound in a variety of fields. Effective use of biostatistical methods improves study reproducibility, supports evidence-based decision-making, and boosts trust in research findings. Furthermore, the accuracy and dependability of medical knowledge are continuously improved by the incorporation of sophisticated statistical tools like regression modeling, survival analysis, and meta-analytic techniques.As health care becomes more dependent on data, biostatistics will require more than just the ability to perform calculations; biostatistics will assess and assist with translating difficult data into useful information that helps patients, public health, and medical science. Because of this, a background in basic biostatistics or common statistical methods will be critical for any health science professional engaged in discoveries and/or health care delivery that hold firmly to scientific high standards and provide evidence based quality health care.

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## Ethics Statement

Not applicable

## Conflict of Interest

The authors did not have any conflict of interest to disclose.

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# Cytokines

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## Abstract

Cytokines are small, soluble proteins secreted by immune and non-immune cells that play a critical role in regulating inflammation, immunity, cell growth, and tissue repair. They act as intercellular messengers, binding to specific receptors and triggering signaling pathways that influence innate and adaptive immune responses. Cytokines include interleukins, interferons, tumor necrosis factors, chemokines, and colony-stimulating factors, each performing distinct but often overlapping functions. Dysregulation of cytokine production is associated with various pathological conditions such as autoimmune diseases, chronic inflammatory disorders, infectious diseases, and cancer. Understanding cytokine biology is essential for developing targeted therapies, including monoclonal antibodies, cytokine inhibitors, and recombinant cytokines. This review provides an overview of cytokine classification, mechanisms of action, and their clinical significance in health and disease.

**Keywords:** Cytokines, Interleukins, Interferons, Chemokines, Immune Response, Inflammation, Cell Signaling, Immunoregulation, Autoimmune Diseases, Therapeutic Targets.

## Introduction

Cytokines are small proteins that act as messengers in the immune system, signaling between cells to control inflammation, immunity, and blood cell production, essentially acting as the "hormones" of the immune system, with key types including interleukins, interferons, and chemokines. Produced by immune cells (like T cells, macrophages) and others, they bind to cell receptors to stimulate or suppress immune responses, promoting cell growth, movement to infection sites, and differentiation, vital for fighting pathogens but also involved in disease when dysregulated. Cytokines are a broad and loose category of small proteins

important in cell signalling. Cytokines are produced by a broad range of cells, including immune cells, as well as endothelial cells, fibroblasts, and various types of connective tissue cells. A single cytokine may be produced by more than one type of cell. Cytokines are molecules, glycoproteins in nature which are primarily responsible for cell to cell signaling responses. They play vital role in developing an effector immune response.

## General properties

1. They are a class of regulatory proteins with low molecular weight mostly acting locally.
2. Cytokines are synthesized by gene transcription and their mRNAs are short lived in response to immune reaction and are not preformed.
3. They are secreted by the activated lymphocytes mostly $T_H$cells termed as lymphokines and monocytes/ macrophages termed as monokines in response to stimuli. Interleukins are cytokines that act as mediators between leukocytes.
4. Cytokines bind to specific receptors on target cells leading to downstream signaling responses leading to altered gene expression of the target cells.
5. The cytokine and its receptor share very high affinity thus only picomolar (pM) amounts of cytokine lead to signaling responses.
6. They can be (i) autocrine in which they bind to receptors on the same cell of their production, (ii) paracrine, in which they bind to receptors on target cells close to the cell producing it, or (iii) endocrine in which it binds to receptors on distantly located cells from its cell of production in its responses.
7. They exhibit pleiotropy in which a single cytokine has different biological effects on different cells, redundancy whereby two or more cytokines promote similar responses, synergy in which the altogether effect of two /more cytokines is greater than added effect of each cytokine and antagonistic properties whereby the effect of one cytokine is inhibited by the effect of the other cytokine.
8. They initiate physiological responses like: development of cellular and humoral immune response, inflammatory response, regulation of hematopoeisis, wound healing, cellular proliferation and differentiation. Combating an infection they enhance phagocytosis, production of nitric oxide (NO) and reactive oxygen inter mediates (ROI), regulate expression of class I and class II MHC molecule.
9. Cytokines produced from $T_H$ cells can influence the activity of other cells like B cells. T cells, NK cells, hematopoietic stem cells etc.

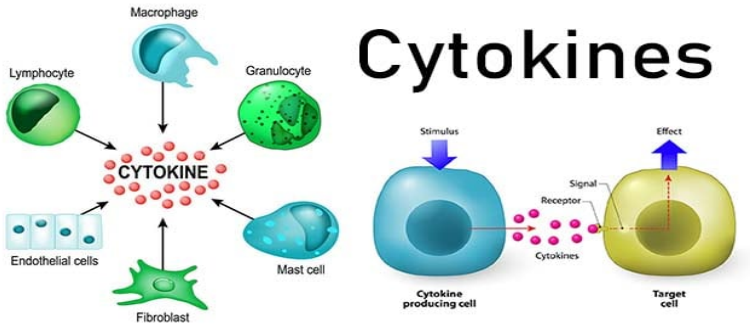



**Table 1: Cytokines vs Growth Factors and Hormones**

| Features | Similarities | Differences |
|---|---|---|
| Cytokines vs. Growth Factors | Functional in picomolar concentration | Growth factors are constitutive in expression while cytokines show regulatory responses. |
| Cytokines vs. Hormones | Functional in picomolar concentration | (i) Hormones are produced by endocrine organs while cytokines are produced by different cell types<br>(ii) Hormones are mostly endocrine in function while cytokines are mostly paracrine/autocrine in function. |

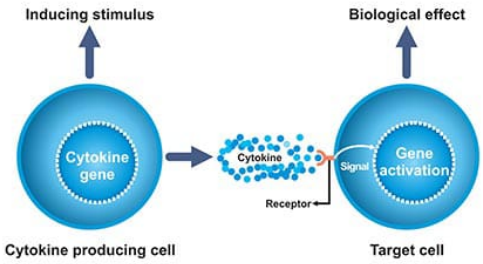
## General structure of cytokines

1. Glycoproteins in nature with less than 30kDa mol wt.
2. Despite diversity in amino acid sequence in cytokines, most cytokines resemble structural similarities with hematopoietins family of proteins.
3. They have mostly α helices connected by loops.
4. They show similar 4 α helical region in which the first and second helix and second and fourth helix are parallel to each other interconnected by loops.

## General Functions

1. They bind to their receptors and function as biological messenger.

2. They function by activating or inhibiting proliferation or differentiation of cells and thereby regulate immune responses.
3. Binding of the cytokine to its receptors lead to signaling events which lead to secretion of other molecules leading to activation or inhibition of immune response.




## Different classes of cytokines and their effects

There are three major classes of cytokines grouped according to their function:

### (A) Mediators of innate immunity

Including TNF-α, IL-1, IL-10, 11-12, type 1 interferons (IFN-α and IFN-β), IFN-γ. and chemokines.

1. **TNF-α** Produced by activated macrophages is response to gram negative bacterial Lipopolysaccharide (LPS). Acts as an important inflammation. to mediator of acute Has cytotoxic effects. Mediates recruitment of neutrophils and infection sites by macrophages stimulating endothelial cells to produce adhesion molecules and chemokines.
2. **IL-1 (IL-1 α, IL-1 β):** It is inflammatory cytokine release by activated macrophages, dendritic cells, endothelial cells. It is similar in effect to TNF-α and helps to activate T cells. Promotes clonal expansion, Induces fever & synthesis of acute phase proteins
3. **IL-10** Symthesised by activated macrophages and $T_H2$ cells. Mostly act as an inhibitory cytokine by inhibiting production of IFN-γ by $T_Hl$ cells. This enables $T_H2$ type of immune response. Inhibits cytokine production by activated macrophages and expression of class II MHC and co-stimulatory molecules.

4. **IL-12**Symthesised by activated macrophages and dendritic cells. Stimulates the production of IFN-y and induces the differentiation of TH cells to Tal cells. Enhances differentiation of CTLs and cytolytic functions of Te and NK cells.
5. **Type I interferons** including IFN-a and IFN-ß are produced by many cell types. They to inhibit viral replication in infected cells, influence expression of class 1 MHC molecules on APC. They also activate NK cells.
6. **INF-γ**: Produced primarily by $T_H$l cells, followed by Te and NK cells. It has numerous functions in both the innate and adaptive immune systems. It inhibits viral replication, increases expression of Class I and Class II MHC molecule. Mediates intermediate steps in delayed type hypersentivity reaction.
7. **Chemokines:** Chemokines are chemotactic cytokines produced by many kinds of leukocytes and other cell types. They represent a large family of molecules that function to recruit leukocytes to sites of infection and play a role in lymphocyte trafficking.

### (B) Mediators of adaptive immunity

Cytokines that play a major role in the adaptive immune system include: IL-2, IL-4, IL-5, TGF-β, IL-10 and IFN-γ

1. **IL-2** :Interleukin 2 is produced by $T_H$ cells. It induces growth and proliferation of T cells. Promotes growth and activation of B cells and NK cells and monocytes IL-2 acts functions autocrine in a manner on Icells.
2. **IL-4**: Produced by mast cells. macrophages and $T_H2$ cells Stimulates the TH2 cell development from naïve $T_H2$ cells and it promotes the growth of differentiated $T_H2$ cells resulting in an antibody response, It also stimulates Ig class switching to the IgE isotype.
3. **IL-5:** Interleukin 5 is produced by $T_H2$ cells and it functions to promote the growth and differentiation of B cells and eosinophiles. It also activates mature eosinophiles. Also called as eosinophil differentiation factor (EDF).

### (C) Hematopoiesis Stimulators

They stimulate They differentiation of hematopoietic cells. GMCSF stimulates HSC differentiation, MCSF promotes differentiation of progenitors into monocytes and macrophages and GCSF promotes production of PMNs.

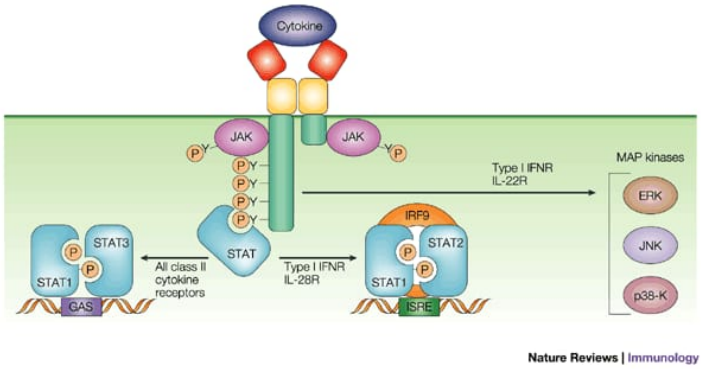



**Table 2: Different types of growth factors**

| Factor | Producers | Primary activity |
|---|---|---|
| PDGF | platelets, endothetial cells, placenta | promotes proliferation of connective tissue, glial and smooth muscle cells |
| EGF | submaxillary gland, Brunners gland | promotes proliferation of mesenchymal, glial and epithelial cells |
| TGF-α | transformed cells | may be important for normal wound healing |
| FGF | most leucocytes | promotes proliferation of many cells;inhibits some stem cells; induces mesoderm to form in early embryos |
| NGF | mast cells, eosinophils, bone marrowW stromal cells keratinocytes | promotes neurite outgrowth and neural cells survival |
| Erythropoietin | kidney cells | promotes proliferation and differtiation of erythrocytes |
| TGF-β | Activated $T_H1$ cells and NK cells | anti-inflammatory (suppresses cytokine production and class II MHC expression), promotes wound healing, inhibits macrophages and lymphocyte proliferation |

## Conclusion

Cytokines are essential signaling molecules that orchestrate immune responses by regulating inflammation, cell growth, differentiation, and communication between immune cells. They act through highly specific receptors and signaling pathways—such as JAK-STAT and NF-κB—to control the magnitude and nature of immune activation. While cytokines are indispensable for host defense, dysregulation can lead to pathological inflammation, autoimmune diseases, or severe systemic responses such as cytokine storms. Advances in cytokine biology have led to major therapeutic breakthroughs, including biologic inhibitors (e.g., anti-TNF, anti-IL-6) and recombinant cytokine therapies. As research continues, cytokines remain central targets for treating immune-mediated diseases, infectious conditions, and cancer.

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# Microbial diversity of air

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## Abstract

Air serves as a dynamic medium that supports a diverse range of microorganisms originating from soil, water, plants, animals and human activities. The microbial diversity of air primarily includes bacteria, fungi, viruses, and spores that are disseminated through natural processes such as wind, evaporation, and aerosolization, as well as anthropogenic sources. These airborne microbes play significant roles in ecological balance, biogeochemical cycles, and atmospheric processes, while also influencing human, animal, and plant health. Factors such as temperature, humidity, UV radiation, and particulate matter shape the composition and survival of airborne microbial communities. Advances in molecular techniques, including metagenomics and high-throughput sequencing, have enhanced the understanding of the microbial load, diversity, and distribution patterns in indoor and outdoor air environments. This knowledge is essential for monitoring air quality, controlling infectious disease transmission, and assessing environmental and occupational health risks.

**Keywords:** Airborne microorganisms, microbial diversity, aerobiology, bacteria, fungi, viruses, bioaerosols, air quality, metagenomics, environmental microbiology.

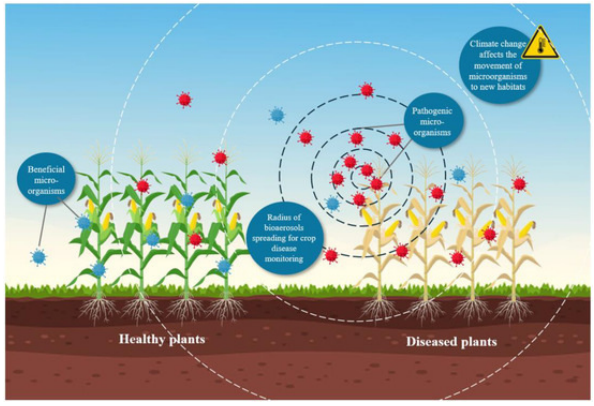
## Introduction

Study of microbial diversity of air or acromicrobiology has recently become a hot topic due to widespread air pollution by viable particles and its health effects. In addition to qualitative and quantitative examination of air it also includes the study of aerosolization, aerial transmission and deposition of biological materials. From pathological point of view, many scientists have defined acromicrobiology more specifically as the study of diseases that may be transmitted via the respiratory route. Despite the variations in definition, this relatively new field of environmental science is becoming increasingly

important in many aspects of diverse scientific fields as public health, environmental science, industrial engineering, agricultural engineering, biological warfare and space exploration. Though metabolically less important, the acrially borne microbes act as the source of infection of already colonized as well as virgin habitats. Many microbes are released as spores or viable cells to air from their habitat and travel thousands of kilometers to infect fresh habitat. The microbial succession of a habitat is determined by its interaction with the aerial microflora. Some microbial processes are required to be paused by a brief period of dormancy of cells or spores, when launched from a habitat to air. Thus air acts as a medium for exchange of microbes among the habitats and aeromicrobial diversity is an amalgamation of the microbial diversity of terrestrial and aquatic habitats.

## Characteristics of the atmosphere with viable particles

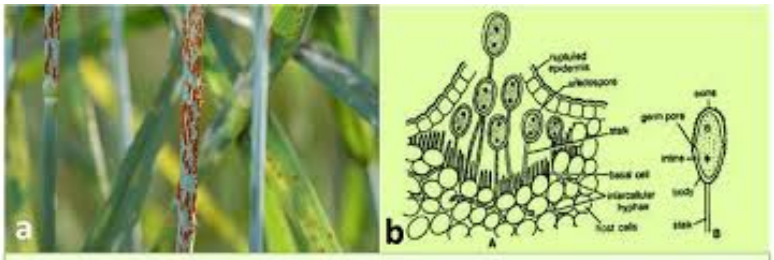
The atmospheric layers and the airflow pattern are the important forces in determining the distribution and dynamics of viable particles in air. The aeromicrobiological pathway (AMP) involves the path and pattern of movement of microbial particles in air and thereby its nature involves the atmosphere. The layer of most interest and significance in aeromicrobiology is the boundary layer, which extends up to 0.1 km from the earth's surface. It should be noted, however, that airborne transport of microorganisms is by no means limited to this layer and it is not uncommon to have microorganisms associated with layers of the troposphere above the turbulent boundary layer. However, it is the surface boundary layer that is largely responsible for the transport of particles over both short and long distances. The boundary layer consists of three parts: the laminar boundary layer, the turbulent boundary layer and the local eddy layer.



The laminar boundary layer is a layer of still air associated with the earth and all projecting surfaces, whether solid or liquid. This layer can be anywhere from 1 µm to several meters thick, depending on weather conditions. Still conditions cause the thickness of this layer to increase and windy conditions minimize it to a very thin layer that remains in close association with surfaces. The turbulent boundary layer is the layer that is considered to be always in motion and responsible for horizontal transport phenomena (wind dispersion), which occur whenever microorganism-associated particles are launched either indoors or outdoors. In the lower levels of the turbulent layer, the linear flow of air is interrupted by surface projections and their associated laminar boundary layers. This interaction results in the formation of friction against the airflow. This friction, which is apparent in the form of local areas of "swirling" turbulence, determines the rate of movement of the particles. The local eddy layer is the actual zone of interaction between the still laminar boundary layer of surface projections and the turbulent boundary layer.

## Atmospheric dispersal of microbes

The dispersal of microbes in air begins with the discharge of the microbial cells. Spores or particle loaded with viable particles (aerosol) to the atmosphere. It is followed by the subsequent transport via diffusion and dispersion of these particles and finally their deposition on any surface. An example of this pathway is that of liquid aerosols containing the influenza virus launched into the air through cough, sneeze, or even through talking. These virus associated aerosols are dispersed by a cough or sneeze, transported through the air, inhaled and deposited in the lungs of a nearby person, where they may begin a new infection. Traditionally, the deposition of viable microorganisms and the resultant infection are given the most attention, but all three processes (launching, transport and deposition) are of equal importance in understanding the aerobiological pathway. While a microbial particle (hypha, cell or spore) germinate and grow, when deposited on a compatible surface, gaining the metabolic efficiency, it perishes on coming in contact with an incompatible surface. For example, when a uredospore of *Puccinia gramini* falls on a wheat leaf, it germinates and causes secondary infection. On the other hand, if it falls on a rice leaf, it fails to germinate and establish the infection.

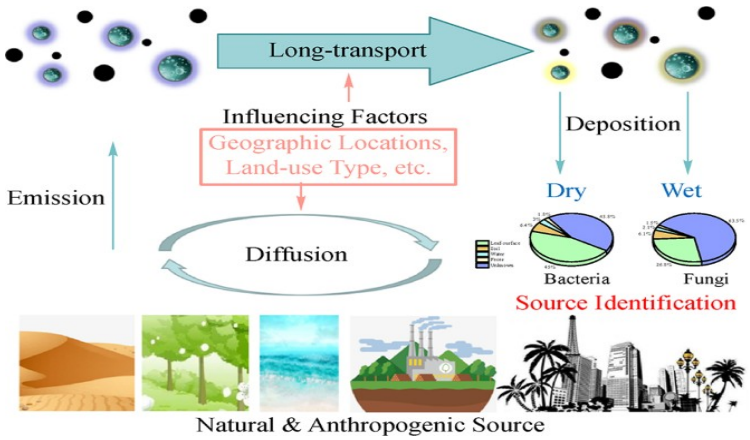



a) 'Red rust' in wheat caused by b) uredosorus and uredospores

## The bioaerosols

The bioaerosols are the atmospheric particles, mists or dusts of um range, associated with metabolically active and/or inactive viable particles. Bioaerosols vary considerably in size and composition depends on a variety of factors including the type of microorganism or toxin, the types of particles they are associated with such as mist or dust and the gases in which the bioaerosol is suspended. Bioaerosols, in general, range from 0.02 to 100 µm in diameter and are classified on the basis of their size. The smaller particles <0.1 µm in diameter are considered to be in the nuclei mode, those ranging from 0.1 to 2 µm are in the accumulation mode and larger particles are considered to be in the coarse mode. which undergo rapid sedimentation. The particles in nuclei or accumulation mode are considered to be fine particles and have the capacity to move long distances. These particles have also a long residence time in the environment the particles is coarse mode are considered coarse particles as they settle within few meters to few kilometers from the source.

The composition of bioaerosols can be liquid or solid or a mixture of the two and should be thought of as microorganisms associated with airborne particles or as particles containing microorganisms. This is because it is rare to have microorganisms (or toxins) that are not associated with other airborne particles such as dust or mist. This information is derived from particle size analysis experiments, which indicate that the average diameter of airborne bacterial particles is greater than 5 µm. By comparison, the average size of a soil borne bacterium, 0.3 to 1 µm, is less than one fifth this size. Similar particle size analysis experiments show the same to be true for aerosolized microorganisms of other groups (fungi, algae and viruses).




## Microbial diversity of air

There is significant difference of microbial diversity and density of indoor and outdoor air. The quality of bioaerosols also differs with the regional atmospheric conditions and cultural practices. In the outdoor environment, the expanse of space and the presence of air turbulence are two controlling factors in the movement of bioaerosols. While in the outdoor conditions the bioaerosol concentration fluctuates considerably in different parts of the day and is influenced by the rate of launching and air turbulence, the fluctuation is marginal in the indoor conditions. Environmental factors such as UV radiation, temperature and relative humidity modify the effects of bioaerosols by limiting the amount of time aerosolized microorganisms will remain viable. Such limitations are, however, not observed under indoor conditions. The microbial diversity and processes of some of the outdoor and indoor conditions are given here.)

## The outdoor bioaerosls

**Agriculture:** The air of agricultural areas contains the microbes related to the crops of the region. Contamination of crops and animals via bioaerosols has a huge economic impact worldwide. It shows the diversity of airborne microorganisms that infect plants. As the earth's population increases, the need for a larger, more stable supply of food becomes increasingly important. Rice and wheat are the two major staple crops that are paramount to world food security. Major pathogens of such crops are the wheat rust fungi, rice smut fungi and disease-causing bacterial pathogens. These spore-forming fungi cause some of the most devastating diseases of wheat and other grains. Spores of wheat rust and rice and sugarcane smut are capable of spreading hundreds of kilometers through the atmosphere. The airborne spread of rust disease has

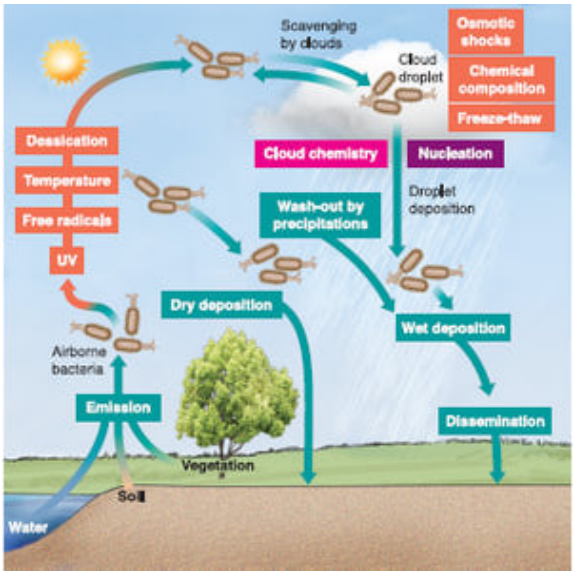
been shown to follow a predictable trend, depending upon the cultivation of wheat in the region. A rust-infected plant produces thousands of spores, which are released into the air by either natural atmospheric disturbance or mechanical disturbance during the harvesting process. Once airborne, these spores are capable of long-distance dispersal, which can cause downwind deposition onto other susceptible wheat plants.

## The indoor bioaerosols

The home and workplace are environments in which airborne microorganisms create major public health concerns. In comparison with the outdoor environment, indoor environments have limited circulation of external air and much less UV relative humidity, which are generally in the ranges that allow extended microbial radiation exposure. Indoor environments also have controlled temperature and survival. Thus, these conditions are suitable for the accumulation and survival of microorganisms within many enclosed environments, including office buildings, hospitals, laboratories and even spacecraft. The residence time of the bioaerosols in the indoor conditions is, however, short due to poor turbulent conditions.

In a residential building many factors such as the presence and/or efficiency of air filtering devices, the design and operation of the air circulation systems, the health and hygiene of the occupants, the amount of clean outdoor air circulated through the building, the type of lighting used, the ambient temperature in the building and the relative humidity can influence bioaerosols and therefore the hygienic conditions of the building. Some pathogens are uniquely adapted for survival and transmission in the indoor environment. For example, the gram-negative *bacilli Legionella spp*. are ubiquitous in the environment. They are found in association with lakes, ponds and streams and have even been found in deep terrestrial subsurface environments. *Legionella pneumophilia*, the causative agent of both Legionnaires disease and Pontiac fever, has however good growth and dispersal in poorly maintained cooling tower, which provide optimal conditions for its proliferation. On aerosolization this pathogen spreads into the buildings connected to the cooling systems. Stagnant water and temperatures in the range of 35-46°C are factors that can lead to the rapid multiplication of background levels of Legionella *spp.* The pathogen can also grow intracellularly within other microbes including amoebae, cyanobacteria and protozoa. Even on the surface of any airborne particle or water droplet the pathogen can increase its number and launch the cells and spores to air.

## Microbial survival in air




## The control of bioaerosol

Biocidal control represents an added treatment that can be used to eradicate all airborne microorganisms, ensuring they are no longer viable and capable of causing infection. Many eradication methods are available, for example, superheating, super-dehydration, ozonation and UV irradiation. The most commonly used of these methods is ultraviolet germicidal radiation (UVGI). The latter has been shown to be able to control many types of pathogens, although some microbes show various levels of resistance. Isolation (enclosure of an environment through the use of positive or negative pressurized air gradients and airtight seals) also is used as a control mechanism for reducing the airborne microbes. It is often used to protect other people in the hospital from the pathogens *(e.g. Mycobacterium tuberculosis)* present inside the isolation area. Air from these rooms is exhausted into the atmosphere after passing through a HEPA filter and biocidal control chamber. A negative pressure isolation chamber allows fresh and filtered air into the room keeping the particle concentration of the room under control. On the other hand, positive-pressure isolation chambers work on the opposite principle by forcing air out of the room, thus protecting the occupants of the room from outside contamination.

## Conclusion

In comparison to their role in water and soil, the microbes in air are metabolically Jess important. But air acts as a medium for microbes to spend a brief period of inactive state and also help the microbial cells and spores to move long distances and to infect new habitats. The AMB pathway is thus important in microbially communicating one habitat with the other. This chapter has covered several areas that can be affected by the AMB pathway. There are, however, several environmental problems associated with the AMB pathway. For example, it has been suggested that airborne bacteria and fungi are causative agents in the formation of calcium oxalate films on stone monuments. The formation of this film is caused by metabolic transformations of proteins and lipids associated with the stone. These calcium oxalate films are extensive, yellow-brown in colour and resist disinfection and they diminish the beauty of the monuments. In subterranean environments, cultural relics such as tombs, prehistoric caves and underground churches are subject to biodeterioration caused by contamination with airborne microorganisms. Deposition of airborne microorganisms are also responsible for degradation of papers, parchment, leather and adhesives in libraries. This becomes an especially important cause of degradation especially if the relative humidity in the library rises above 65%. Many of these decomposers are not yet fully studied. The determination of the total microbial diversity of air is now needed to control a number of plant and animal diseases and to make the use of these microbes in human welfare.

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# Current Understanding of Biomarkers and Genetic Contributors in Alzheimer's Disease Pathogenesis

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## Introduction

### Neurodegeneration

It describes a process of losing structure or function in tissues or organs. Therefore, any degenerative disease that primarily affects neurons is referred to be neurodegeneration in the strict sense of the word. In reality, neurodegenerative illnesses are a main category of neurological conditions for damage subgroup of neurons in specific functional anatomic & physiology systems. They develop for unclear causes and worsen with time(Przedborski et al., 2003).

### Alzheimer disease (AD)

Missense mutations for the genes producing β-amyloid, presenilin 1 (PSEN1), and presenilin 2 (PSEN2**),** precursor proteinlocatedin family forms. The sporadic forms believed to be source by a complicated interplay between several predisposing genes, including variant APOE, the α2-macrogobulin gene and possibly the tau protein gene, as well as additional variables like environmental contributions and chance(O, 2021).

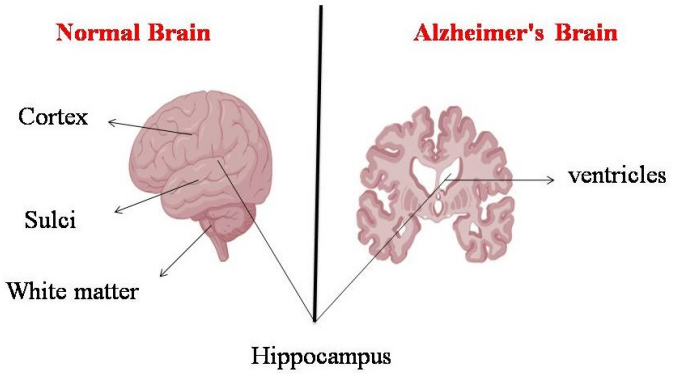


**Fig 1 Normal Brain Vs Alzheimer's Brain**

## Biomarkers

Biomarkers measurable indicators of biological processes are essential for therapeutic monitoring, early diagnosis, differential diagnosis, and disease progression prediction. From conventional imaging and cerebrospinal fluid (CSF) markers to blood-based proteins, genetic risk indicators, inflammatory mediators, and increasingly metabolomic biomarkers that reveal dynamic biochemical changes in real time, biomarker research in AD(R et al., 2022).

## Alzheimer's disease biomarkers

### Amyloid Biomarkers

Core Pathological Biomarkers Amyloid-β (Aβ) & tau buildup, through signs of neurodegeneration, are biological indicators of Alzheimer's disease.Although it only presently no diagnosesfor Alzheimer's disease (AD), it is widely acknowledged that a less invasive blood biomarker for preclinical screening would be essential for subsequent treatment. Cerebrospinal fluid (CSF) biomarkers are intrusive diagnostic techniques for AD, whereas positron emission tomography (PET) scanning is costly. ascertain of amyloid-β (Aβ) secondary structural modification in human blood.This alteration, which is utilized as a corresponds with CSF AD biomarkers and amyloid PET blood amyloid biomarker for prodromal AD, imaging in the cross sectional(S et al., 2002).

### Tau Biomarkers

Together with the combined data from basic clinical work-up, genetic screening, and brain imaging, the most one biochemical marker, CSF total tau (t-tau) protein, performs well enough to play a part in the clinical diagnostic settings of individuals with dementia. When separating early or incipient AD from age-associated cognitive decline, depression, and some secondary dementias, these CSF indicators are especially helpful. However, more precise and targeted markers are required to distinguish AD from other main dementia illnesses. Quantification of tau phosphorylation at particular places in CSF appears to improve early identification, differential diagnosis, and disease progression tracking in AD, according to preliminary data(Da, 2002).

### Neurodegeneration Biomarkers

The progressive loss of neural tissues is the hallmark of a broad spectrumof central nervous system disorders known as neurodegenerative

diseases. Because the central nervous system's neurons mechanism cannot repair unaccompanied following cell apoptosis or damage, there are no treatments for these illnesses. Numerous recent studies suggest that current developments may aid in neuroregeneration or neuronal cell replacement stem cell research.In order to establish the diagnosis at an earlier stage, enormous efforts associated in current years to uncover the neuropathological, biochemical, and genetic biomarkers of the disorders. In essence, biomarkers are biological molecules it utilized to detect the development or existence of a certain illness. For example, For Alzheimer's disease (AD) for instance, to help pinpoint the precise source of a dementia. Biomarkers are required differentiate between one illness from another with dementia for normal aging(Da, 2002).

## Genetic Biomarkers of Alzheimer's Disease

### A) One of the main genetic risk factors for sporadic AD

### 1) APOE (Apolipoprotein E)

Together with age and midlife hypercholesterolemia, the most significant genetic risk factor for late onset sporadic Alzheimer's disease (AD) is the presence of the Ψ4 allele in apolipoprotein E (ApoE). The important significant lipid transporter between cells in the central nervous system (CNS) is ApoE4, which associated with to the synthesis, fibrilization, and accumulation of amyloid β (Aβ), the aggregation and hyperphosphorylation of tau, the metabolism of brain cholesterol, and neurodegeneration. One indicator of the amount of Aβ plaque pathway in brain is less cerebrospinal fluid (CSF) Aβ1-42. A neurofibrillary tangle stage and load are correlated with high CSF p-tau& t-tau concentrations, which also indicate the severity of the illness process and axonal and neuronal damage and injury.Apolipoprotein E (apoE) is a protein involved in lipid transport has been linked to nerve damage repair. The collection of samples from CSF at lumbar puncture,analyses of apoE in CSF are used new enzyme linked immunosorbent assay (ELISA).Therefore, measuring apoE in cerebrospinal fluid (CSF) may be useful for researching various types of brain injury as well as for identifying continuing brain regenerating processes(H. C et al., 2000).

### B) Causative Genes for Familial (Early-Onset) AD

Mutations in these genes are deterministic**,** meaning carriers will almost certainly develop AD (usually before age 60).

### 2) APP (Amyloid Precursor Protein)

It is typified by the develope of β-amyloid peptide (Aβ) in the brain through cleaved and hyperphosphorylated versions of the microtubule-associated protein tau. The key stage in the development of AD appears to be the physiological production of the neurotoxic Aβ peptide from successive amyloid precursor protein (APP) proteolysis, according to genetic, biochemical, and behavioral evidence. A number of sequential proteases, including the intramembranous γ-secretase complex, quickly and intricately metabolize APP, a single-pass transmembrane protein that is abundantly expressed in the brain. These proteases also regulate other important regulatory molecules. It's unclear Aβ builds up in older people's brains, but it might be related to altered APP metabolism or Aβ clearance(Rj & Pc, 2011).

### 3) PSEN1 (Presenilin 1)

It has been established that presenilin-1 (PSEN1) is a significant contributing factor to early detection Alzheimer's disease (EOAD). PSEN1, a component of γ-secretase, can impact notch signaling,calcium metabolism, β-cadherin processing and amyloid precursor protein (APP) cleavage. WNF, GxGD, and PALP motifs are among the motifs and residues found in PSEN1 that may be important for γ-secretase processes. Although PSEN1 has more than 300 known variants, the clinical manifestations associated with these mutations may vary. Therefore, the age at which the disease manifests and the clinical characteristics of PSEN1 mutations may be significantly influenced by genetic modifiers. The function of PSEN1 in γ-secretase, the clinical manifestations associated with its mutations, and potential important protein residues(Bagaria et al., 2022).

### 4) PSEN2 (Presenilin 2)

One of the three proteins that, when mutated, results in cases of prematurefamilial Alzheimer disease (FAD) is PSEN2 (presenilin 2). PSEN2 has several γ-secretase-independent roles in several cell signaling pathways, including the regulation of intracellular Ca2+ homeostasis, in addition to its well-known position within the γ-secretase complex (the enzyme ultimately accountable for Aβ peptide production).The PSEN2 protein, a fundamental part of the γ-secretase complex, is also participated in numerous physiological processes linked to γ-secretase, such as autophagy, Notch signaling, innate immunity, and mitochondrial function. All of these physiological processes

have been linked to the advancement of AD, suggesting that PSEN2 is specifically involved in the pathophysiology of AD(F. C et al., 2019).

### C) Genetic Risk Factors Identified by GWAS

These variants modestly increase AD risk and influence inflammation, lipid metabolism, synaptic function, and endocytosis.

### 5) TREM2 (Triggering Receptor Expressed on Myeloid Cells 2)

Microglia show an innate immune receptor TREM2 exclusively. Alzheimer's dementia (AD) and other neurodegenerative illnesses have been linked to coding variants in TREM2. TREM2's genetic abnormalities linked to a number of neurological diseases have sparked interest in the protein. Nasu-Hakola disease (NHD) has been linked to homozygous missense variants of TREM2, such as Y38C or T66 M. The R47H mutation in TREM2 is one of the strongest single allele genetic risk factors for AD, with an odds ratio comparable to apolipoprotein E (APOE) ε4 allele. Following thorough examination of TREM2 polymorphisms, the R62H, D87N, and T96 K alterations in TREM2 were also involved to AD. Nevertheless, it is still unclear how exactly TREM2 mutations affect AD etiology(Zhong et al., 2018).

### 6) CLU (Clusterin)

A glycosylated protein with several biological roles, clusterin has garnered a lot of study interest. It is intimately related to the organism's physiological and pathological conditions. The degree of Clusterin expression in AD patients' brain tissue is directly correlated with the development of the disease. One of the most important processes in the development of AD is the deposition and production of β-amyloid, it is facilitated by clusterin. Through processes like reducing inflammation, cell death, and the removal of harmful proteins, clusterin may have an impact on the pathophysiology of AD(Yu & Tan, 2012)

### 7) PICALM (Phosphatidylinositol Binding Clathrin Assembly Protein)

The PICALM (Phosphatidylinositol binding clathrin-assembly protein) gene has been found to be the fundamental genetic susceptibility locus by genome-wide association studies (GWAS). Clathrin-adaptor protein PICALM is essential for autophagy and clathrin-mediated endocytosis. Numerous in vitro

and in vivo research have attempted to clarify the underlying mechanism by which PICALM regulates AD risk since the effects of genetic variations of PICALM as AD-susceptibility loci have been verified by independent genetic investigations in multiple diverse cohorts.The present understanding of PICALM's physiological roles, genetic variations, post-translational changes, and connection to the pathophysiology of AD(Ando et al., 2022).

### 8) CR1 (Complement Receptor 1)

At locus 1q32, CR1 is sited in a genomic cluster of complement-related proteins on chromosome1. Due to genomic duplications and deletions, the gene is found in four co-dominant alleles of varying sizes. The extracellular domain, transmembrane region, signal peptide, and cytoplasmic domain are the four primary structural domains of the CR1 protein. GWAS's discovery of CR1 strongly suggests that complement has a part in the pathophysiology of AD. Interpretatinghow well the CR1 mutations interact with other risk loci to affect AD risk and the specific function of complement in AD is now crucial. Co-localization studies have shown that C3b binding to E-CR1 is necessary for the clearance of circulating Aβ1–42(Hardy et al., 2023).

### 9) SORL1 (Sortilin-Related Receptor)

Replicated genetic studies have shown that heterogeneity**,**in the SORL1 gene, also known as LR11, is associated with Alzheimer's disease (AD). SORL1 is a type I transmembrane protein belonging to both the low-density lipoprotein receptor (LDLR) and vacuolar protein sorting 10 (VPS10) domain receptor families.It is made up of multiple different domains. The AD brain was discovered to have a lower level of SORL1, which was positively linked with the deposition of β-amyloid (Aβ). SORL1 limits the distribution of the precursor to endocytic compartments that promote amyloidogenic breakdown by interacting with different bundles of cytosolic adaptors for the anterograde and retrograde transit of APP between the trans-Golgi network (TGN) and early endosomes(Lee et al., 2008).

### 10) ABCA7

The central nervous system ATP-binding cassette (ABC) reporter family controls the equilibrium of cholesterol and phospholipids in peripheral tissues.ABCA7 shares 54% sequence similarity with ABCA1 and is a member of the A subfamily of ABC transporters. Although ABCA7 is expressed in

many different tissues and organs, including the brain, ABCA7 gene variations have been found to be susceptibility loci for late-onset Alzheimer's disease (AD) in recent genome-wide association studies (GWAS). Using both vitro and vivo models, there is growing evidence that ABCA7 impairment aggravates Aβ pathogenesis, which is consistent with human genetic investigations. ABCA7 is implicated in the microglial Aβ clearance pathway in addition to mediating phagocytic activity in macrophages. Additionally, ABCA7 absence causes an increase in Aβ synthesis, perhaps via promoting APP processing and/or endocytosis. When considered collectively, the available data indicates that ABCA7 dysfunctionalmay contribute to AD-related symptoms via a variety of mechanisms. In order to investigate AD pathogenesis, a deeper comprehension of ABCA7's role beyond lipid metabolism in both healthy and pathological settings is becoming more crucial(Aikawa et al., 2018).

### D) Other Genetic Biomarkers Associated with AD Risk

These genes provide additional risk but typically with smaller effects.

### 11) BIN1 (Bridging Integrator 1)

The main notable risk locus for late-onset Alzheimer's disease (LOAD) has recently been found to be the bridging integrator 1 (BIN1) gene, sometimes referred to as amphiphysin 2. Although additional impacted cellular processes, including as endocytosis/trafficking, inflammation, calcium homeostasis, and apoptosis, are reviewed, emerging evidence indicate that BIN1 predominantly influences AD risk by modifying tau pathology. We examine evidence that points to potential DNA methylation of the BIN1 promoter since epigenetic changes to have an influencein the pathophysiology of AD. Lastly, targeting BIN1 may offer new avenues for AD treatment given its possible roles in AD etiology(Gao et al., 2021).

### 12) CD33

Cluster of differentiation 33 (CD33) has been found to be a strong gene location, merged indicatewith AD in recent genomic research. CD33 is a type I transmembrane protein that is a member of the sialic acid-binding immunoglobulin-like lectins. It mediates cell-cell interactions and prevents immune cells from performing their normal tasks. CD33 is mostly expressed on microglial cells in brain. It discovered that the AD brain had higher levels of CD33, which were positively connected with the amount of amyloid plaque and

the severity of the illness. More significantly, CD33 caused the brain to develop amyloid plaques by impairing microglia-mediated Aβ clearance(Jiang et al., 2014).

### 13) MS4A Cluster (Membrane-Spanning 4-Domains Family)

Recent genome-wide association studies (GWAS) ha**ve** Modifications Associatewithin the membrane-spanning 4-domains subfamily A (MS4A) gene cluster to Alzheimer's disease (AD). Members of the MS4A family, which are cell membrane proteins, have been shown to be involved in the control of calcium signaling, which has been extensively studied in relation to AD and neurodegeneration. Additionally, despite the limited characterization of the MS4A family members, group members of this cluster including MS4A1, MS4A2, and MS4A4B have already been found to have a significant role in immunity, suggesting that the MS4A gene cluster may be involved in the pathophysiology of AD(Brown et al., 2013).

### 14) FERMT2

FERMT2, also called kindlin-2, is a member of the kindlin protein family, which also contains kindlin-1 and kindlin-3.Integrin activation and integrin-mediated cell-extracellular matrix (ECM) contact are mediated by the expressed integrin-interacting protein kindlin-2. In certain AD cases, just one β3-integrin co-activator, FERMT2, was found to be significantly correlated with variations in cerebrospinal fluid Aβ peptide levels. APP metabolism regulation is a neuronal function that may be a major regulator of axon guidance. Axonal development, synaptic connections, and long-term potentiation are all impacted by FERMT2 under-expression in an APP-dependent manner. APP's metabolism is directly impacted by FERMT2.The rs7143400-T allele, located in the 3'UTR of FERMT2 and linked to a higher risk of AD, caused a down-regulation of FERMT2 expression by binding miR-4504, among other mechanisms(Eysert et al., 2021).

### 15) INPP5D

One of the AD-associated SNPs, rs35349669, accounts for 3.8% of the total genetic risk for AD.is the important prevalent AD-risk mutation, INPP5D is a gene that is gaining prominence in AD-genetics research. Little is known about how SHIP-1 influences neurobiology or the pathophysiology of neurodegenerative diseases, despite the fact that INPP5D expression is nearly

exclusively limited to microglia in the brain. SHIP-1 is widely expressed by the majority of hematopoietically generated innate and adaptive immune cells outside of the brain, where it suppresses immunological responses like the creation of reactive oxygen species, phagocytosis, and proinflammatory cytokines. The severe multi-organ inflammatory illness that develops in mice after SHIP-1 deletion from hematopoietically-derived immune cells best illustrates the crucial role of SHIP-1 as a brake on immunological responses in the periphery(Chu et al., 2023).

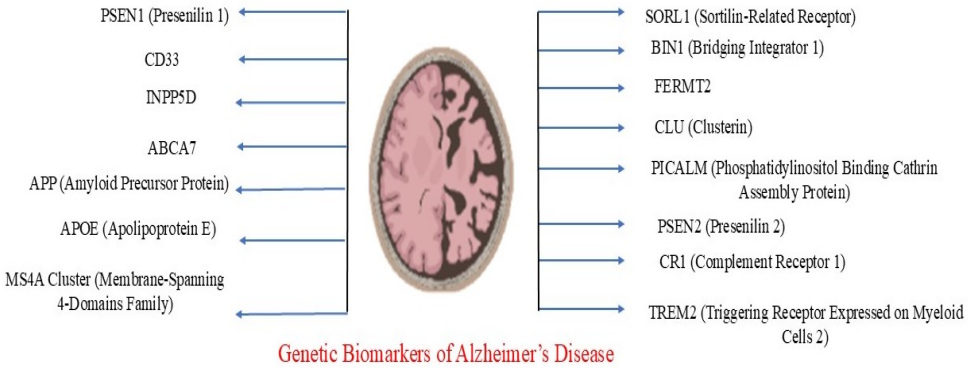


**Fig 2 Genetic Biomarkers of Alzheimer's Disease**

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