Frontiers in Nanopharmacy and Clinical Therapeutics

Dr. V. JAYASHREE
Dr. JAYA VASAVI G
Dr. VIJAYAKUMAR MURUGESAN
Dr. S. HEMALATHA

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Dr. V. JAYASHREE
Associate Professor, Department of Pharmacology
School of Pharmaceutical Sciences
Vels Institute of Science, Technology & Advanced Studies (VISTAS), Chennai, Tamil Nadu, India.

Dr. JAYA VASAVI G
Assistant Professor, Department of Pharmaceutics
School of Pharmaceutical Sciences
Vels Institute of Science, Technology & Advanced Studies (VISTAS), Chennai, Tamil Nadu, India.

Dr. VIJAYAKUMAR MURUGESAN
Department of Pharmaceutics, School of Pharmacy
JSS Academy of Higher Education and Research
Mauritius.

Dr. S. HEMALATHA
Professor and Head
Department of Pharmacy Practice
Karpagam Academy of Higher Education
Coimbatore, Tamil Nadu, India.

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PREFACE

The field of nanopharmacy and clinical therapeutics is undergoing a profound transformation, driven by the convergence of advanced materials science, molecular biology, and intelligent technological systems. *Frontiers in Nanopharmacy and Clinical Therapeutics* is conceived as a comprehensive volume that captures the evolving landscape of modern drug discovery, precision medicine, and emerging therapeutic strategies. The chapters in this book collectively reflect the shift from conventional, one-size-fits-all treatments toward highly targeted, data-driven, and patient-specific interventions.

A central theme of this volume is the integration of multidisciplinary approaches in modern drug discovery. The incorporation of nanoscale systems into pharmaceutical design has enabled enhanced drug delivery, improved bioavailability, and targeted therapeutic action with reduced adverse effects. Alongside this, advances in molecular diagnostics and computational biology are accelerating the identification of novel drug targets and biomarkers, thereby refining therapeutic precision.

The book also explores critical developments in disease-specific therapeutics. Topics such as viral pathogenesis, hypertension management, metabolic disorders, and rare genetic diseases are examined through the lens of cutting-edge research. The discussion on vaccine development and antiviral strategies highlights the importance of rapid and adaptive responses to infectious diseases. Similarly, emerging therapies in conditions like diabetic

nephropathy and Fabry disease underscore the growing role of regenerative medicine and enzyme-targeted interventions.

Precision oncology and personalized medicine form another cornerstone of this work, emphasizing the tailoring of treatment based on genetic, environmental, and lifestyle factors. The application of genome editing technologies, particularly CRISPR-based systems, demonstrates the potential to model diseases with high accuracy and develop gene-specific therapies. These advancements are complemented by studies utilizing model organisms, which provide valuable insights into disease mechanisms and therapeutic responses.

Innovative technological paradigms are also addressed, including the use of swarm robotics and high-throughput screening systems in pharmacovigilance. Such approaches signify a paradigm shift in how drug safety and efficacy are monitored, introducing automation, scalability, and real-time analysis into the pharmacological domain. Additionally, the book acknowledges the continued relevance of traditional medicine, examining the challenges and opportunities in integrating herbal and phytochemical therapies within modern pharmacovigilance frameworks.

The inclusion of emerging drug classes, such as novel oral therapeutics for chronic diseases, further illustrates the dynamic nature of pharmaceutical innovation. These developments highlight the importance of translational research in bridging laboratory discoveries with clinical applications.

This volume is intended for researchers, academicians, clinicians, and students seeking to understand the current frontiers and future

directions in nanopharmacy and clinical therapeutics. By presenting a cohesive narrative across diverse yet interconnected topics, the book aims to foster interdisciplinary collaboration and inspire continued innovation in the pursuit of effective and personalized healthcare solutions. We extend our sincere thanks to our publisher, Scientific Research Reports, Chennai, India, for their dedicated efforts in preparing this book and for ensuring the inclusion of enriched and high-quality technical content.

Wishes and Regards,

Dr. V. JAYASHREE
Associate Professor, Department of Pharmacology
School of Pharmaceutical Sciences
Vels Institute of Science, Technology & Advanced Studies (VISTAS),
Chennai, Tamil Nadu, India.

Dr. JAYA VASAVI G
Assistant Professor, Department of Pharmaceutics
School of Pharmaceutical Sciences
Vels Institute of Science, Technology & Advanced Studies (VISTAS),
Chennai, Tamil Nadu, India.

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Department of Pharmaceutics, School of Pharmacy
JSS Academy of Higher Education and Research
Mauritius.

Dr. S. HEMALATHA
Professor and Head
Department of Pharmacy Practice
Karpagam Academy of Higher Education
Coimbatore, Tamil Nadu, India.

CONTENTS


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Chapter 1

Integrated Approaches in Modern Drug Discovery

Lathiga D[a*], Deepika D[a], V.Jayashree[b]

[a]*Student, M.Pharm I Year, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai 600117*

[b]*Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai 600117*

** Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Modern drug discovery has transformed from a linear, single-discipline process into a highly collaborative and multidisciplinary enterprise that integrates advances in chemistry, biology, pharmacology, computational sciences, biotechnology, and clinical medicine. The increasing complexity of diseases such as cancer, neurodegenerative disorders, metabolic syndromes, and antimicrobial resistance demands a systems-level understanding of pathophysiology and therapeutic intervention. Traditional trial-and-error methods have largely been replaced by rational drug design, target-based screening, and data-driven strategies supported by technological innovations. A critical milestone in multidisciplinary drug discovery was the completion of the Human Genome Project, which enabled the identification of novel molecular targets through genomics and proteomics approaches. Advances in medicinal chemistry facilitate structure–activity relationship optimization, while molecular biology and systems pharmacology enhance target validation and mechanistic insights. Concurrently, computational

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tools and artificial intelligence platforms—such as those developed by DeepMind—have revolutionized protein structure prediction, virtual screening, molecular docking, and toxicity forecasting, significantly reducing time and cost in early-stage discovery.

Keywords: Multidisciplinary research, drug discovery, artificial intelligence, medicinal chemistry, pharmacology.

1. Introduction

The scientific process of finding and creating novel medicinal chemicals to treat illnesses is known as "drug discovery." In the past, natural product separation and random screening were the primary methods used in drug development. But as science and technology have advanced, the process of finding new drugs has grown more methodical and multidisciplinary. Chemistry, biology, pharmacology, and computer science are just a few of the scientific fields whose knowledge is integrated into modern drug discovery. Researchers can better understand disease mechanisms, find pharmacological targets, and create compounds with enhanced therapeutic potential with the aid of this multidisciplinary approach. Multidisciplinary approaches improve the success rate of finding viable medication candidates by fusing computational techniques, biological data analysis, and experimental research.

1.1. Medicinal Chemistry's Contribution

The design and synthesis of therapeutic compounds depend on medicinal chemistry. To improve therapeutic action, stability, and selectivity, scientists alter chemical structures. Researchers can better understand how chemical changes affect biological activity by using structure-activity relationship (SAR) investigations. Lead compounds can be adjusted to increase potency and decrease toxicity

through these investigations. Therefore, medicinal chemistry is essential to turning initial lead compounds into therapeutic medications that work.

1.2 Function of Genomics and Molecular Biology

Genomics and molecular biology offer important insights into the molecular and genetic causes of illnesses. Scientists can find genes and proteins involved in the development of disease through genomic investigations. New therapeutic targets can now be found thanks to technologies like gene editing, DNA sequencing, and gene expression analysis. These findings aid in the creation of focused treatments that target particular chemicals linked to disease.

1.3 Value of Bioinformatics

To examine complicated biological data, bioinformatics integrates biology, computer science, and statistics. It is crucial to the interpretation of proteomic and genomic data. Potential drug targets can be found, protein structures may be predicted, and drug-target interactions can be simulated with the aid of bioinformatics tools. Researchers can save time and money by evaluating thousands of chemicals using computational methodologies through virtual screening methods.

1.4 Drug response in body

Pharmacology is the study of how medications affect biological systems. It assesses the potential adverse effects, modes of action, and therapeutic outcomes of medication candidates. In pharmacological investigations, drug action is evaluated by laboratory trials with cells, tissues, and animal models. Pharmacokinetic characteristics like absorption, distribution, metabolism, and excretion are also investigated in these

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investigations. Determining the safety and efficacy of a medication candidate requires these kinds of investigations.

1.5 Drug Design via Computation

In contemporary drug discovery, computational drug design has emerged as a potent instrument. Quantitative structure-activity relationship (QSAR) models, molecular docking, and molecular dynamics simulations are examples of computer-based techniques that are frequently employed. These methods aid in the prediction of drug compounds' interactions with biological targets. To find viable medication candidates and optimize chemical structures, artificial intelligence and machine learning techniques are being utilized more and more. The time and expense associated with drug discovery are greatly decreased by computational methods.

2. Cutting-Edge Drug Discovery Technologies

The process of finding new drugs has been completely transformed by technological developments. Scientists can rapidly examine hundreds of chemical compounds for biological activity thanks to high-throughput screening. Detailed information on protein expression and metabolic processes implicated in illnesses is provided by proteomics and metabolomics. These tools aid in the discovery of biomarkers and possible therapeutic targets. Drug discovery is becoming quicker and more effective thanks to the application of artificial intelligence in the analysis of intricate biological datasets and the prediction of therapeutic results.

3. Drug Development

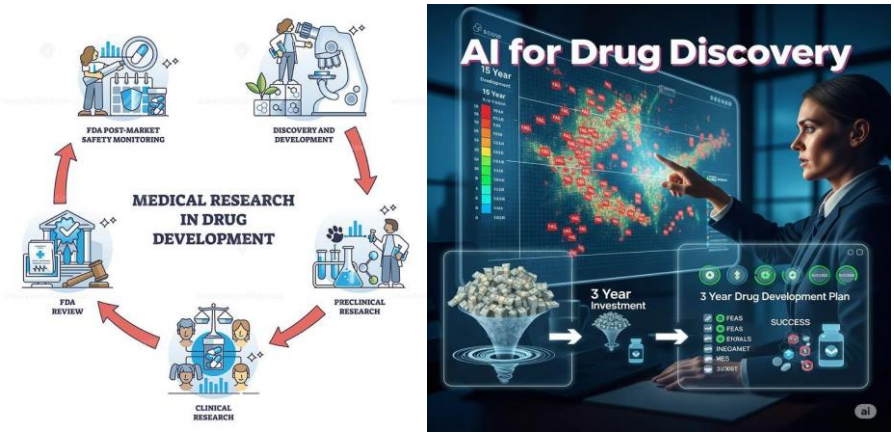

Figure 1: Drug discovery

3.1 Multidisciplinary Drug Discovery's Challenges

Drug discovery still confronts a number of obstacles, despite the many benefits of multidisciplinary approaches. The process is costly and time-consuming; it frequently takes years to generate a single medication. Safety or efficacy concerns cause many promising medication candidates to fail clinical trials. Integrating massive datasets produced by different disciplines presents another difficulty. To tackle these challenges, scientists from many disciplines must effectively collaborate.

4. Conclusion

In today's drug discovery, multidisciplinary techniques are crucial. The efficiency of drug creation has significantly increased thanks to the cooperation of chemists, biologists, pharmacologists, and computational scientists. The drug development process is still being improved by cutting-edge technologies including genomics, artificial intelligence, and high-throughput screening. Stronger interdisciplinary cooperation will be essential in the future to create safer and more potent medications.

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Chapter 2

Rabies Virus : Pathogenesis, Complications, Vaccine Development, and Therapeutic Approaches

Beevi Ayisha banu. J[a*], Ashifa.T.A[a], V.Jayashree[b]

[a]*B.Pharm Student, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai*

[b]*Associate Professor, Department of Pharmacology, School of Pharmaceutical Science, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

** Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Rabies is a fatal viral zoonotic disease caused by the rabies virus, which primarily affects the central nervous system of humans and other mammals. The virus is mainly transmitted through the bite or saliva of infected animals, particularly dogs. Rabies is a fatal viral disease that affects the central nervous system of humans and animals. It is caused by the rabies virus and is mainly transmitted through the bite or saliva of infected animals. After entering the body, the virus spreads through peripheral nerves to the brain, leading to severe neurological damage. The infection can cause complications such as encephalitis, paralysis, and respiratory failure. Since rabies is almost always fatal once clinical symptoms appear, early prevention is essential. Current preventive measures include effective vaccines and post-exposure prophylaxis. Therapeutic approaches mainly involve proper wound care, administration of rabies immunoglobulin, and vaccination. Continuous advancements in

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vaccine development and treatment strategies are important for controlling rabies and reducing its global impact.

Keywords: Rabies virus, Pathogenesis, Complications, Rabies vaccine, Therapeutic approaches.

1. Introduction

The family Rhabdoviridae consists of more than 100 single-stranded, negative-sense, nonsegmented viruses that infect a wide variety of hosts, including vertebrates, invertebrates, and plants. Human pathogens of medical importance are found in the genera Only the rabies virus, medically the most significant member of the genus *Lyssavirus.* The rabies virus causes acute infection of the central nervous system [1]. Rabies is a zoonotic disease caused by the rabies virus [13]. All rhabdoviruses encode five structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and an RNA-directed RNA polymerase (L) (Figure 1). The N protein encapsulates the RNA genome, forming a tightly wound N-RNA complex known as a ribonucleoprotein (RNP) [3]. The majority of lyssavirus species have been detected in various bat species and, as such, are speculated to have originated in bats [4]. This virus has been largely eliminated throughout Western Europe in both domestic and wild terrestrial carnivore species [4]. The major element of transcriptional regulation in nonsegmented negative-strand RNA viruses (*Mononegavirales*), which include the families *Filoviridae*, *Paramyxoviridae*, *Rhabdoviridae* and *Bornaviridae*, is the gene order [5]. To date, all rabies virus (RABV) studies in bats have been performed in wild-caught animals [6]. Rabies has the highest case fatality rate of any conventional infectious disease [8]. The rabies virus (RABV) is a highly neurotropic

pathogen that typically leads to mortality of infected animals and humans [10]. Rabies virus infection of dorsal root ganglia (DRG) was studied *in vitro* with cultured adult mouse DRG neurons [11].

The RABV transcription and replication strategy. The negative-sense genomic RNA (in orange) is the template for the L-P polymerase complex. A) During transcription, five 5′ end-capped (C) and polyadenylated (A) mRNAs (in green) encode the viral proteins. The polymerase complex disassociates from the template at each termination signal (STOP). The polymerase does not always re-engage successfully, leading to a negative transcription gradient from 3′ to 5′**.** B) During replication, the negative-sense genome is transcribed into a positive-sense antigenomic RNA intermediate (in green) by a more processive form of the viral polymerase. The anti-genome is then transcribed back into a negative-sense RNA to complete replication.

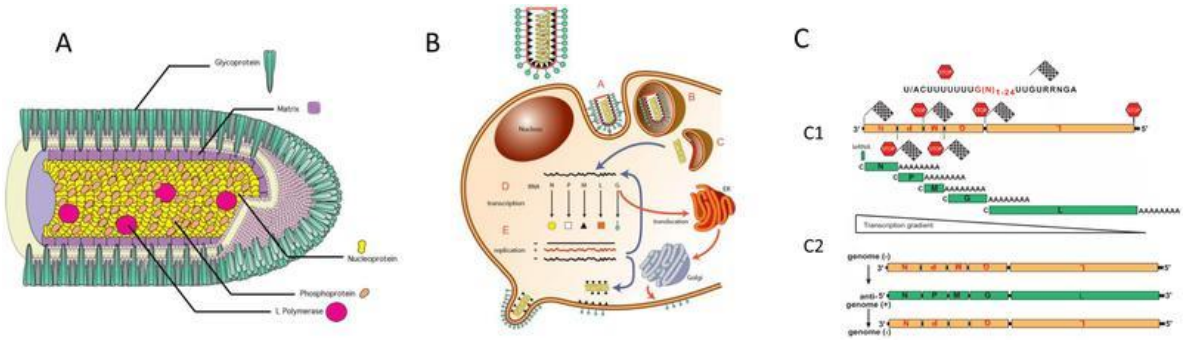

Figure 1: The RABV transcription and replication strategy

1.1 Pathogenesis

After inoculation, rabies virus may enter the peripheral nervous system directly and migrate to the brain or may replicate in muscle tissue, remaining sequestered at or near the entry site during incubation, prior to central nervous system invasion and replication. It then spreads centrifugally to numerous other organs. The case-fatality ratio approaches unity, but exact pathogenic mechanisms are

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not fully understood [1]. From a peripheral site of exposure, neurotropic pathogens such as RABV must enter the CNS to spread and cause disease. However, the mammalian CNS has several anatomical and biochemical barriers that separate it from the rest of the body. Among the most widely studied natural defense barriers is the blood-brain barrier (BBB), the highly selective permeability barrier of the neurovascular epithelium, made up of tight junctions between the epithelial cells [3].

1.2 Etiology

The RABV most likely came from a bat ancestor and evolved through multiple host-switching events in dogs, bats, and other animals. Seven main lineages of RABV exist worldwide, each with many variants associated with specific animals and geographies. The most widespread lineage occurs in dogs and wildlife species such as foxes, jackals, and skunks in Europe, Africa, the Americas, and Asia. Many bat-associated lineages in Latin America continue to cause rabies in humans and domestic livestock. Continued genetic diversification of RABV and other *lyssaviruses* raises concerns that the existing HRIG and rabies vaccines may cease to be effective for human rabies prevention [12].

1.3 Complications

- Seizures
- Fasciculations
- Psychosis
- Aphasia
- Autonomic instability
- Paralysis
- Coma
- Death [12].

2. Clinical Treatment

Treatment for clinical rabies caused by RABV and related *lyssaviruses* is largely supportive, focusing on minimizing patient suffering.

- Mouth care, provision of high-water-content foods, and intravenous fluids for hydrophobia
- Antipyretics, often administered rectally for fever
- Benzodiazepines for the management of agitation, anxiety, and seizures
- Anticholinergics for the management of hypersecretion and disordered swallowing
- Opioids for pain management [12]

3. Current Rabies Vaccines

3.1 Modified live vaccine (MLV)

Non-pathogenic in animals, ability to propagate high virus titers in cells, ability to induce protective immunity after administration, and thermal and genetic stability. To ensure the safety of candidate vaccines, most researchers modified the virus by serial passage in various cells. This technique has led to the development of attenuated live vaccines for controlling the infectious disease [14].

3.2 Inactivated rabies vaccine

Inactivated rabies vaccines require that high RABV titers be produced in tissues or cells. RABV can be grown in brain tissue, and nerve tissue vaccines (NTVs) consisting of inactivated rabies vaccine produced from RABV-infected brain tissue of sheep, goats, and mice were developed about 100 years ago and have been used in some Asian and African countries [14].

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3.3 Dna-Based Vaccines

One approach for developing new-generation rabies vaccines is to use a DNA-based or plasmid vaccine encoding the rabies glycoprotein gene. Advanced recombinant DNA technology has made it possible to generate a variety of DNA vaccines against infectious agents. DNA-based vaccines developed to induce a broad-spectrum immune response when delivered to the host have several advantages, such as action in the presence of maternal antibodies, strong stability, mass production, and cost effectiveness. DNA-based vaccines should provide efficient ways to induce a cell-mediated cytolytic $CD8^+$ T cell response, $CD4^+$ T cells, and VNA [14].

4. History

The study of rabies virus infection in bats can be challenging due to quarantine requirements, husbandry concerns, genetic differences among animals, and lack of medical history [6]. Worldwide, more than 70,000 people die of rabies every year in undeveloped and developing nations; 95% of all human rabies deaths are the result of infection with a canine rabies variant [6]. Although rabies has been the subject of large-scale public health interventions, chiefly through vaccination efforts, the disease continues to take the lives of about 40,000-70,000 people per year, roughly 40% of whom are children [3]. Rabies remains an important public health problem, with more than 95% of all human rabies cases caused by exposure to rabid dogs in areas where effective, inexpensive vaccines are unavailable. Rabies causes an estimated 55,000 human deaths globally each year, 23,750 of which occur in Africa. Moreover, 11 million people undergo rabies postexposure prophylaxis (PEP) worldwide each year. Rabies is a zoonotic disease, with dogs remaining the principal host in Asia, parts

of the Americas, and large parts of Africa, and rabid dogs are the cause of most human rabies. Between 30% and 60% of the victims of dog bites are children under the age of 15. Inappropriate dog vaccination programs, limited access to vaccination, and postexposure treatment of individuals that have been exposed to rabid dogs are major problems in developing countries [2]. Rabies is an ancient disease, and its history can be traced back more than 5000 years [9].

5. Differential Diagnosis

- Guillain–Barré syndrome
- Psychosis
- Seizures
- Poisoning with belladonna alkaloids
- Cerebral malaria
- Meningitis
- Acute encephalitis from any other infectious or noninfectious causes
- Poliomyelitis
- Poisoning
- Metabolic causes such as hypoglycemia and thiamine deficiency
- Cerebrovascular accident
- Creutzfeldt–Jakob disease
- Brain tumor
- Neurosyphilis
- Tetanus
- Autoimmune encephalitis [12]

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Chapter 3

Recent Advances in Hypertensive Therapy

Deepika D[a*], Shruthi P K[a], V.Jayashree[b*]

[a]*Student, M.Pharm I Year, School of Pharmaceutical Sciences,* Vels Institute of Science, Technology & Advanced Studies, Chennai

[b]*Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences,* Vels Institute of Science, Technology & Advanced Studies, Chennai

** Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

In addition to being a major risk factor for heart disease, stroke, and kidney problems, hypertension is a substantial worldwide health burden. Despite the fact that traditional antihypertensive medications, including diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers, successfully lower blood pressure, problems such as resistant hypertension, side effects, and poor patient adherence still exist. Novel pharmacological treatments such as enhanced mineralocorticoid receptor antagonists, direct renin inhibitors, and angiotensin receptor–neprilysin inhibitors are the focus of recent developments in hypertension medicine. Treatment results and compliance have improved with fixed-dose combo treatments. Additionally, pharmacogenomics-supported personalized medicine techniques and device-based therapies like renal denervation are showing promise as ways to maximize the control of hypertension and enhance long-term cardiovascular outcomes.

Keywords: Hypertension, Antihypertensive therapy, Resistant

hypertension, Fixed-dose combination, Renal denervation.

1. Introduction

One of the main causes for heart morbidity and mortality worldwide is hypertension, a chronic non-communicable disease. It dramatically raises the risk of heart failure, stroke, myocardial infarction, and chronic renal disease. Many patients still have suboptimal blood pressure control despite the availability of several antihypertensive medication classes, such as diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). This is because of resistant hypertension, adverse drug reactions, and poor therapy adherence.

The goals of recent developments in antihypertensive treatment have been to increase patient compliance, safety, and efficacy. Angiotensin receptor–neprilysin inhibitors (ARNIs), direct renin inhibitors, and tailored mineralocorticoid receptor antagonists are examples of novel pharmacological strategies that have shown encouraging clinical results, especially in high-risk groups and resistant hypertension. In order to improve adherence and accomplish quicker blood pressure management, fixed-dose combination treatments are also becoming more and more advised. Renal destruction and baroreceptor activation therapy are two new device-based therapies that are being investigated as potential alternatives for patients who do not respond well to medication. Additionally, chances to customize antihypertensive medication based on individual genetic profiles are presented by breakthroughs in pharmacogenomics and personalized medicine, potentially increasing therapeutic outcomes.

2. Pathophysiology of Hypertension

Multiple physiological systems are involved in the complicated and

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multifactorial condition known as hypertension.

2.1 Renin–Angiotensin–Aldosterone System (RAAS)

RAAS is essential for controlling fluid balance and blood pressure. Increased vasoconstriction and salt retention brought on by excessive RAAS activation raise blood pressure.

2.2 Sympathetic Nervous System Activation

Hypertension is a result of increased sympathetic activity, which also raises heart rate, increases cardiac output, and constricts blood vessels.

2.3 Endothelial Dysfunction

By generating vasodilators like nitric oxide, the endothelium contributes significantly to the control of vascular tone. Vasoconstriction is encouraged, and nitric oxide generation is decreased by endothelial dysfunction.

2.4 Inflammation and Oxidative Stress

Chronic inflammation and oxidative stress have been linked to vascular damage and elevated blood pressure, according to recent research.

2.5 Genetic and Environmental Factors

Major causes of hypertension include genetic susceptibility, excessive salt consumption, obesity, sedentary lifestyles, and stress.

3. Conventional Antihypertensive Therapy

The mainstay of managing hypertension is still conventional antihypertensive medications. Among the main drug classes are:

Diuretics

These drugs promote sodium and water excretion, thereby reducing

blood volume and blood pressure. Examples include hydrochlorothiazide and furosemide.

ACE inhibitors

Angiotensin-converting enzyme inhibitors cause vasodilation and lower blood pressure by preventing angiotensin I from being converted to angiotensin II. Lisinopril and enalapril are two examples.

Angiotensin receptor blockers (ARBs)

ARBs prevent angiotensin II from acting on its receptors. Valsartan and losartan are two examples.

Calcium channel blockers

These medications cause vasodilation by preventing calcium from entering vascular smooth muscle cells. Nifedipine and amlodipine are two examples.

Beta-blockers

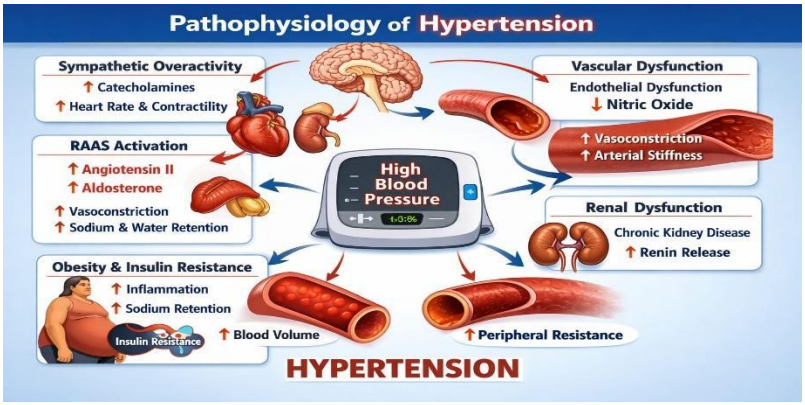

Figure 1: Pathophysiology of Hypertension

Beta-blockers decrease blood pressure by decreasing cardiac output and pulse rate. Propranolol and atenolol are two examples. For the best blood pressure control, combination treatment with two or more medications is frequently necessary.

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4. SGLT2 Inhibitors in Hypertension

A relatively recent family of medications called sodium-glucose cotransporter-2 (SGLT2) inhibitors was first created to treat type 2 diabetes. Recent research, however, has shown that these medications also have positive effects on the kidneys and heart. Dapagliflozin, empagliflozin, and canagliflozin are a few examples of SGLT2 inhibitors. Through a number of processes, including osmotic diuresis, natriuresis, and enhanced endothelial function, these medications lower blood pressure. SGLT2 inhibitors lower cardiovascular events and enhance results among individuals with hypertension and cardiac failure, according to clinical trials like the DAPA-HF and EMPEROR-Reduced investigations.

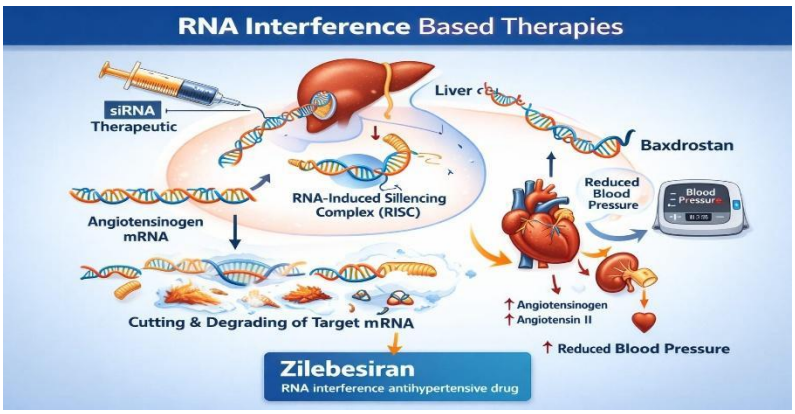

Figure 2: RNA Interferences

5. Non-Steroidal Mineralocorticoid Receptor Antagonists

The treatment of hypertension has traditionally involved the use of mineralocorticoid receptor antagonists. However, adverse effects, including hyperkalemia and hormonal imbalances, are linked to conventional medications like spironolactone. A new non-steroidal mineralocorticoid receptor antagonist with better selectivity and fewer side effects are finerenone. Finerenone lowers cardiovascular and renal problems in people with diabetes and hypertension, according

to clinical trials like the FIDELIO-DKD research.

6. Aldosterone Synthase Inhibitors

Aldosterone is crucial for controlling blood pressure and salt retention. Resistant hypertension is linked to excessive aldosterone production. Aldosterone synthesis is decreased by the selective aldosterone synthase inhibitor baxdrostat. Baxdrostat dramatically reduces blood pressure in patients with treatment-resistant hypertension, according to recent clinical studies. A potential strategy for treating individuals who don't react well to traditional treatments is this new class of medications.

7. RNA Interference-Based Therapies

One new therapeutic approach that can specifically silence genes linked to illness is RNA interference (RNAi) technology. Zilebesiran is one of the most promising RNA-based medications for hypertension. The gene that produces angiotensinogen, a crucial part of the RAAS pathway, is the target of zilebesiran, a small interfering RNA. This medication successfully decreases blood pressure by lowering angiotensinogen levels. Zilebesiran may be a long-acting treatment for hypertension since clinical research has shown that a single injection can lower blood pressure steadily for several months.

8. Device-Based Therapies

For individuals with resistant hypertension, device-based therapies are becoming more popular.

Renal Denervation

A catheter-based technique called renal denervation damages the sympathetic nerves in the renal arteries. This process decreases blood pressure by decreasing sympathetic activity. Renal denervation

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dramatically lowers blood pressure in individuals with resistant hypertension, according to recent clinical trials.

Baroreceptor Activation Therapy

Baroreceptors in the carotid sinus are electrically stimulated during this treatment. Reflex processes that lower blood pressure are triggered when these receptors are activated.

9. Precision Medicine in Hypertension:

The goal of precision medicine is to customize medical care based on a patient's genetic profile, way of life, and surroundings. Numerous genetic variations linked to hypertension have been found because of advancements in genomics. These findings might aid in the creation of individualized treatment plans. Wearable blood pressure monitors, smartphone apps, and telemedicine platforms are examples of digital health technology that are enhancing patient monitoring and treatment compliance.

10. Future Perspectives

Future studies in the treatment of hypertension will concentrate on finding novel pharmacological targets and creating cutting-edge therapeutic approaches. Long-acting injectable medications, microbiome-targeted therapeutics, and gene-based medicines may be crucial to the treatment of hypertension in the future. Predicting illness risk and improving treatment strategies may potentially be aided by artificial intelligence and big data analytics. To enhance treatment results and lessen the impact of hypertension worldwide, further research and clinical trials are necessary.

11. Conclusion

Patients now have a far wider range of treatment choices because of recent developments in hypertension management. SGLT2 inhibitors,

finerenone, and aldosterone synthase inhibitors are examples of novel pharmaceuticals that have demonstrated encouraging outcomes in lowering cardiovascular problems and enhancing blood pressure control. Patients with resistant hypertension have fresh hope thanks to RNA interference-based treatments and device-based interventions such as renal denervation. In the future, managing hypertension may be significantly enhanced by the combination of digital health technology and precision medicine.

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Chapter 4

Precision Oncology and Personalized Medicine

Shruthi P K[a*], Lathiga D[a], V.Jayashree[b*]

[a]*Student, M.Pharm I Year, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai 600117*

[b]*Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai 600117*

**Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Precision oncology and personalized medicine mark a transformative shift in modern cancer therapy. Unlike traditional approaches that rely on generalized strategies, precision oncology accounts for tumor heterogeneity and genetic variability to optimize treatment outcomes. By integrating genomic profiling, biomarker discovery, and advanced computational methods, clinicians can tailor therapies to individual patients. Technologies such as next-generation sequencing, liquid biopsy, and multi-omics analysis enable identification of molecular drivers of tumor development and progression. Targeted therapies (e.g., EGFR inhibitors) and immunotherapies (e.g., PD-1 checkpoint blockade) have improved efficacy and reduced toxicity compared with conventional chemotherapy. Artificial intelligence and machine learning further enhance clinical decision-making by deciphering complex genomic datasets. Despite these advances, clinical, economic, and computational barriers—including tumor heterogeneity, high costs of testing, and challenges in data interpretation—limit widespread adoption. Continued research,

integration of emerging technologies, and expansion of biomarker-driven clinical trials will strengthen the role of precision oncology, ultimately advancing more effective, less toxic, and patient-centered cancer care.

Keywords: Precision oncology, personalized medicine, genomic profiling, biomarkers, next-generation sequencing.

1. Introduction

Cancer is a complicated and diverse disease that affects people in different ways because of genetic, molecular, and environmental factors. Chemotherapy and radiation are two common cancer treatments that often use a "one-size-fits-all" approach. This can cause different responses to treatment and serious side effects. Recent progress in genomics, molecular biology, and bioinformatics has changed cancer research and treatment forever. This has led to the idea of precision oncology, which is a key part of personalized medicine. Precision oncology is the process of customizing cancer diagnosis, prevention, and treatment plans to fit the unique genetic and molecular traits of a patient and their tumor. By looking at changes in the genome, patterns of gene expression, and molecular biomarkers, doctors can find specific targets that make tumors grow and spread. This makes it possible to choose targeted therapies or immunotherapies that work better and are less harmful than standard treatments.

2. Concept of precision oncology

Precision oncology refers to the customization of cancer therapy using genomic and molecular information of individual patients. Identification of oncogenic mutations allows clinicians to select therapies targeting specific signaling pathways responsible for tumor

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progression. This strategy enhances therapeutic efficacy while minimizing unnecessary toxicity treatment plans that work better and have fewer side effects, giving patients a better chance of beating their cancer while still having a good quality of life.

3. Personalized medicine in oncology

Personalized medicine involves tailoring medical treatment to the individual characteristics of each patient. In oncology, this includes analyzing a patient's genetic profile, environmental exposures, lifestyle factors, and disease characteristics to determine the most appropriate therapy. Pharmacogenomics plays an important role in personalized medicine. It studies how genetic variations affect drug metabolism, efficacy, and toxicity. By identifying genetic markers that influence drug response, clinicians can optimize treatment strategies and reduce adverse drug reactions. Personalized medicine also enables early disease detection and preventive strategies through genetic screening and risk assessment programs.

4. Genomic Technologies in precision oncology

Genomic technologies have changed the way cancer is studied and treated. Researchers can look at genetic changes linked to cancer using methods like next-generation sequencing (NGS), whole genome sequencing (WGS), and whole exome sequencing (WES). Next-generation sequencing (NGS) makes it possible to quickly sequence large pieces of DNA, which makes it possible to find mutations, gene amplifications, and chromosomal rearrangements. RNA sequencing aids in the assessment of gene expression patterns and the identification of aberrant signaling pathways implicated in tumor progression. These technologies give us important information about

how cancer works on a molecular level and help us make targeted therapies that work better.

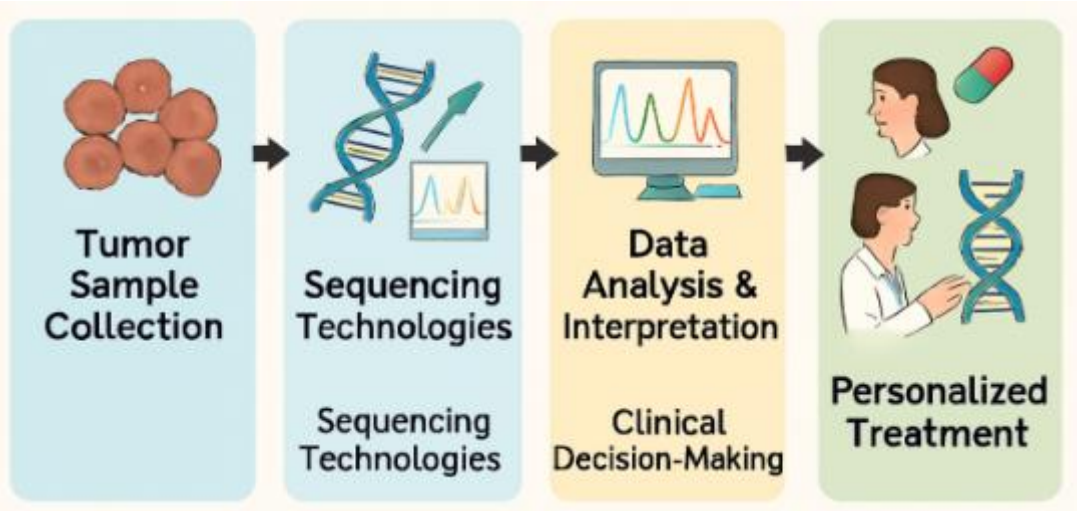

Figure 1: Genomic technologies in precision oncology

4. Biomarkers in Precision Oncology

Biomarkers are measurable biological signs that give important clues about how a disease is developing or how well a treatment is working. In precision oncology, they play a key role in diagnosing cancer, predicting how the disease might progress, and choosing the best treatment options. Diagnostic biomarkers help catch cancer early, while prognostic biomarkers give insights into how the disease might advance and what the chances of survival are. Predictive biomarkers can show whether a patient is likely to benefit from a particular therapy. Some well-known examples include HER2 in breast cancer, EGFR mutations in lung cancer, and PD-L1 levels, which help guide decisions about immunotherapy treatments. These biomarkers help doctors tailor treatments more precisely to each patient's unique cancer.

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5. Drug therapy

Targeted therapy is a vital part of precision oncology focused on attacking the specific molecules that drive cancer growth and survival. These treatments include small molecule inhibitors, like tyrosine kinase inhibitors, which block faulty signals inside cancer cells that promote their growth. Another type, monoclonal antibodies, attaches to specific proteins on the surface of cancer cells to stop them from growing. Compared to traditional chemotherapy, targeted therapies are usually more precise and tend to cause fewer side effects throughout the body. Still, one of the biggest challenges is that cancer cells can sometimes develop resistance to these drugs, making treatment less effective over time.

Table 1: Targeted therapy and traditional chemotherapy

Aspect	Targeted Therapy (Precision Oncology)	Traditional Chemotherapy
Treatment Principle	Based on molecular and genetic characteristics of the tumor	Based on general tumor type and stage
Target	Specific genes, proteins, or signaling pathways involved in cancer	Rapidly dividing cells in the body
Selectivity	Highly selective toward cancer cells with specific mutations	Non-selective; affects both cancer and healthy cells
Mechanism of Action	Inhibits specific molecular pathways that promote tumor growth	Interferes with DNA synthesis or cell division
Personalization	Personalized treatment based on genomic profiling	Standard treatment for most patients with the same cancer type
Diagnostic Requirement	Requires biomarker testing or genomic analysis	Usually does not require genetic testing

Aspect	Targeted Therapy (Precision Oncology)	Traditional Chemotherapy
Effect on Normal Cells	Minimal damage to normal cells	Significant damage to normal rapidly dividing cells
Side Effects	Generally milder and more manageable	Often severe (hair loss, nausea, bone marrow suppression)
Examples of Drugs	Imatinib, Trastuzumab, Erlotinib	Cisplatin, doxorubicin, and Cyclophosphamide
Resistance Development	Resistance may develop due to mutation changes	Resistance can also occur but through broader mechanisms
Treatment Outcome	Higher effectiveness in patients with specific targets	Effective in many cancers but less precise
Role in Modern Oncology	Core component of precision and personalized medicine	Conventional cornerstone of cancer treatment

6. Immunotherapy and Precision Oncology

Immunotherapy is an innovative approach that stimulates the body's immune system to recognize and destroy cancer cells. Precision medicine helps identify patients who are most likely to benefit from immunotherapy through biomarker analysis. Immune checkpoint inhibitors such as PD-1, PD-L1, and CTLA-4 inhibitors enhance immune responses against tumors. Another promising approach is CAR-T cell therapy, where a patient's immune cells are genetically modified to attack cancer cells. These therapies have shown remarkable success in the treatment of several cancers, including melanoma and lung cancer.

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7. Molecular Pro-Lifting

Molecular profiling is the detailed examination of the genetic and molecular changes in a tumor. This process helps doctors find specific mutations that can be targeted with tailored treatments. To do this, they use techniques like DNA sequencing, RNA sequencing, and proteomic analysis, which study different aspects of the tumor's biology. The information gathered allows doctors to categorize tumors based on their unique genetic features and create personalized treatment plans designed to be more effective for each patient.

8. Liquid biopsy

Patient Sample Collection (Blood / Body Fluid)

↓

Sample Processing (Plasma or Serum Separation)

↓

Isolation of Biomarkers (ctDNA, Circulating Tumor Cells, Exosomes)

↓

DNA / RNA Extraction

↓

Molecular Analysis (PCR, qPCR, Next Generation Sequencing, Digital PCR)

↓

Data Analysis & Interpretation

↓

Clinical Application (Early Cancer Detection, Prognosis, Therapy Monitoring, Drug Response)

Liquid biopsy is a new and promising diagnostic method that detects fragments of tumor DNA and other cancer-related markers in a simple blood sample. Unlike traditional biopsies that require taking tissue directly from the tumor, liquid biopsies are minimally invasive

and can be done repeatedly, making it easier to keep track of how the disease is progressing. This approach is valuable for spotting early genetic changes in cancer, monitoring how well treatments are working, and uncovering how cancer cells might be developing resistance to drugs.

9. Tumor heterogeneity and drug resistance

Tumor heterogeneity refers to the presence of genetically diverse cancer cell populations within a single tumor. This diversity can lead to different responses to therapy and contribute to drug resistance. Cancer cells may develop resistance through secondary mutations, activation of alternative pathways, or changes in the tumor microenvironment. Understanding these mechanisms is important for designing effective combination therapies.

10. Challenges and limitations

Despite its potential, precision oncology faces several challenges, including high costs of genomic testing, limited access to advanced technologies, and the complexity of analyzing genomic data. Tumor heterogeneity and development of resistance also complicate treatment strategies. Ethical concerns regarding genetic data privacy and regulatory considerations must also be addressed to ensure responsible implementation of personalized medicine

11. Future Perspectives

The future of precision oncology lies in integrating multi-omics data, including genomics, proteomics, metabolomics, and transcriptomics. Emerging technologies such as liquid biopsy, single-cell sequencing, and CRISPR-based gene editing are expected to further enhance personalized cancer therapy. Additionally, global collaborative research initiatives and advancements in computational biology will

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accelerate the development of new targeted treatments. Precision oncology is expected to transform cancer care by enabling earlier diagnosis, more accurate prognostic predictions, and highly individualized treatment strategies.

12. Conclusion

Precision oncology and personalized medicine have transformed the landscape of cancer treatment by enabling individualized therapeutic strategies based on molecular characteristics of tumors. The integration of genomic technologies, biomarker discovery, targeted therapy, and immunotherapy has improved treatment efficacy and reduced toxicity. Although challenges remain, ongoing technological advancements and collaborative research efforts will continue to expand the potential of precision oncology, ultimately improving survival rates and quality of life for cancer patients worldwide

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Chapter 5

Swarm Robotics for High-Throughput Pharmacovigilance Screening

Tasnim Naina Mohammed[a*], V Jayashree[b*]

[a]*Student of B.Pharmacy, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai*

[b]*Associate Professor, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai*

**Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Traditional pharmacovigilance systems have several limitations, such as polypharmacy, misinformation, underreporting, scalability, and reporting bias. These challenges can be addressed using High-Throughput Screening (HTS) systems and artificial intelligence. But this system is centralized, which poses some challenges. To overcome those challenges, swarm-based pharmacovigilance through HTS is proposed, a decentralized multi-agent system that coordinates many simple robots to complete the task as quickly as possible. The architecture of swarm robotics contains five components. They are data ingestion, swarm agent layer, coordination and communication layer, AI analytics layer, and decision support layer. This system has advantages such as improved scalability, minimized detection time, prediction accuracy, and improved transparency that increases regulatory trust. Validation metrics such as sensitivity and specificity showed increased performance when external validation was done. Swarm-based pharmacovigilance shows a paradigm shift toward decentralized, adaptive, and intelligent pharmacovigilance.

Keywords: Decentralized system, paradigm shift, improved transparency, external validation.

1. Introduction

According to the WHO, pharmacovigilance is "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any drug-related problems" [1]. Detection means identifying ADRs through continuous reporting, systems, and observation of clinical symptoms and comparing them with healthcare databases [1]. Assessment means evaluating adverse drug reactions/events in terms of their causality, severity, and frequency [1]. Understanding is knowing the drug-drug interaction for the ADR, knowing its mechanism, and knowing the risk factors involved [1]. Prevention is applying risk minimization strategies, following safer prescribing guidelines, and using a clinical decision support system [1]. Pharmacovigilance is mapped out as a structural monitoring system for post-marketing use of drugs, and it's a mechanism that helps to figure out the adverse drug reactions in real-world clinical settings [1].

Pharmacovigilance is a modern risk-benefit evaluation process throughout the drug's lifecycle [2]. Pharmacovigilance is important for implementing risk minimization strategies and continuous monitoring of drug safety profiles and helps in identifying serious ADRs that may not be assessed during clinical trials [1,2]. It also helps in identifying drug-drug interactions and helps in reducing long-term toxicity [1, 2]. Pharmacovigilance helps in clinical decision-making through clinical decision support tools, predictive models that help in identifying ADR risk, and the incorporation of the pharmacovigilance findings into Electronic Health Systems (EHR) [1,

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2]. Traditional pharmacovigilance systems have challenges, with few being advanced at present. Underreporting is one of the serious concerns in the traditional system; many ADRs are not reported by healthcare professionals and patients, especially mild or expected reactions, which are not well-reported. Reporting bias may happen, which twists the signal detection and may lead to overestimation or underestimation of certain risks [2]. Incomplete information about the ADR is also a major drawback in traditional systems, like incomplete medication histories and missing information about the frequency of the reported drug [1,2].

Polypharmacy is also a challenge because it is difficult to identify which drug caused that ADR and difficult to assess drug-drug interactions at the initial stage [1]. To overcome the challenges, high-throughput screening has taken the world by storm. It helps the processing of individual case safety reports (ICSRs) in massive numbers. It also helps in expanding Electronic Health Record (EHR) databases [3, 4]. It makes the automation of case processing, duplicate detection, classifying seriousness, and casualty indicators using AI. Machine learning helps in signal detection by analyzing pattern recognition, predicting risk, and improving sensitivity. It also helps in the quick identification of rare adverse events of a drug [4].

Using HTS systems develops validation frameworks [3]. So, the manual workload will be reduced, signal detection will be faster, and rare disease challenges will be when using HTS systems [3, 4]. Swarm robotics is a decentralized multi-agent system that works collectively with the help of AI for the distribution of data screening and decision-making systems. These techniques improve efficacy [5]. From the traditional system of pharmacovigilance to AI to collective agent systems is a processing step for swarm robotics in the future [6].

Swarm Robotics helps in analyzing complex datasets in a very short period. AI models learn from datasets, and swarm robotics will self-organize when new data comes without centralized control [5, 6].

1.1 Pharmacovigilance and High-Throughput Screening

Pharmacovigilance is the process of detecting, assessing, understanding, and preventing adverse drug reactions after clinical trials when the drug is available in the market [1,2]. Pharmacovigilance ensures drug safety, especially when it comes to patients having polypharmacy or having a rare disease condition [1, 2]. The role of pharmacovigilance includes case processing, where reporting of adverse events and case validation takes place using the Individual Case Safety Report (ICSR) [3,4]. It also involves signal validation, signal detection, and prioritization in which risk-benefit impact is evaluated. Risk assessment and regulatory actions, like withdrawing the marketed drug if needed, are carried out [3-5]. When using machine learning, a large volume of datasets can be analyzed for detecting patterns that may be missed when using the traditional manual system [3,4]. High-throughput screening is a rapid and parallel testing of large numbers of compounds for identifying their biological and chemical activity [3]. It helps in processing structured and unstructured data and helps with drug discovery [3,4]. Traditionally, sources for pharmacovigilance data are taken from continuous reporting systems, clinical trial safety data, and literature reports, and AI in pharmacovigilance uses sources from Electronic Health Records (EHRs), patient registries, social media, digital platforms, and real-world evidence (RWE) [5,6].

1.2 Swarm Robotics

Swarm robotics is a field of multi-robot systems that use natural

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swarms, such as ants and fish, in which large numbers of simple robots are used to perform complex tasks with decentralized control [7,8]. As it is a decentralized control, decision-making is distributed across all agents, and there is no leader robot [7]. It enables adaptive collective behavior [8]. Self-organization operates through mechanisms of positive and negative feedback and randomness for exploration [7,8]. Emergence is the complex global pattern that arises from simple local rules. They solve complex problems collectively rather than individually [7,8]. System performance improves as the number of agents increases, and the architecture does not require redesign [7,8].

Figure 1: Swarm robotics in pharmacovigilance with the HTS system

Swarm robotics works with the mechanism of collective decision-making, task allocation, exploration, and resource localization [7,8]. Swarm robotics systems have homogenous or semi-homogenous robots, simple onboard processing, communication range, and autonomous operation [7]. Advantages include decentralized intelligence, high adaptability, scalability, and minimum infrastructure needs [7,8]. Hazardous tasks can be done with swarm robotics, with which humans can be saved [9]. And automated quality control for the drug products [9].

2. Swarm-Based Pharmacovigilance Architecture

Traditional centralized pharmacovigilance systems are difficult for

scalability, latency, and data heterogeneity. Because it needs to analyze large-volume datasets for detecting the pattern [12,13]. It is also slow in handling high-dimensional structured and unstructured datasets [12]. Machine learning models such as Random Forest and Bayesian networks work well with ADR detection, but centralized AI systems have challenges when combining with structured data through distributed healthcare information [14]. Swarm intelligence, which is observed from natural systems that collectively work with decentralized coordination, fault tolerance, and emergent problem solving [10, 11]. So, with the help of robotics and AI, parallel tasks can be conducted, and adjustments may be made, and this helps in building a consensus [10,11].

3. Proposed Architecture

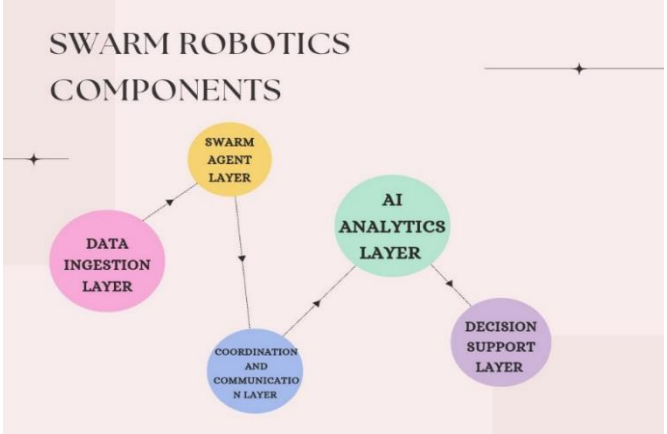

Figure 2: Swarm Robotics Components

The swarm robotics system, which is currently in a research state, contains five layers. It includes a data ingestion layer, a Swarm agent layer, a coordination and communication layer, an AI analytics layer, and a decision support and visualization layer, which are derived from distributed automation systems and swarm intelligence healthcare frameworks [9-11]. The data ingestion layer merges all the pharmacovigilance data sources from electronic health records (EHR), spontaneous adverse drug reaction reporting systems,

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insurance claim databases, and clinical reports processed with the help of NLP [14]. The swarm agent layer locates multiple computational agents. Every agent processes a large dataset, applies local ADR detection models, and maintains the local statistical estimations [10,11]. The communication layer communicates through local interaction rules such as weighted consensus building, signal transmitting, and confidence score sharing [10]. As it is a decentralized interaction, it minimizes the dependency on a single computational tool and alerts when similar duplicates are detected by multiple agents [10]. An AI analytics layer combines with multiple models, such as machine learning classifiers, applied to structured RWD to improve classification accuracy [14]. Bayesian models quantify causal relationships between drug exposure and adverse events [13,15]. The final layer, which is the decision support layer that generates signal prioritization scores and risk stratification dashboards [12,13].

4. Algorithm Modeling

Swarm-based pharmacovigilance systems have multi-level algorithmic modeling. Initially, The local agent detection model,

$$P(\text{ADE} \mid \text{Drug, Features}) = \text{Bayesian posterior probability}$$

$$Ci = \text{probability score x model reliability weight [13-15]}$$

Second, a swarm consensus algorithm where agents exchange their Ci values with nearby agents

$$C_{global} = \Sigma w_i C_i / \Sigma w_i \text{ [10]}$$

Third, the adaptive learning mechanism is built with historical accuracy, agreement, and a low false positive rate [11]. And finally, the fault-tolerance mechanism redistributes the workload if an agent

fails due to an error [10,11].

4.1 Performance Advantage

It has advantages like scalability, where parallel processing follows linear scalability [9]. It minimizes the detection time compared to sequential disproportionality methods [12]. Improvement in the accuracy of prediction, especially when using Bayesian models, which reduces the false signals [14,15]. This allows transparency in decision-making, which allows the users to trust [16].

Table 1: Properties of centralized and decentralized systems for pharmacovigilance

S.No	Properties	Centralized	Decentralized
1.	Fault tolerance	Decreased	Increased
2.	ADR detection	Slow	High
3.	Adaptability	slow	High
4.	Scalability	Average	Good

4.2 Application

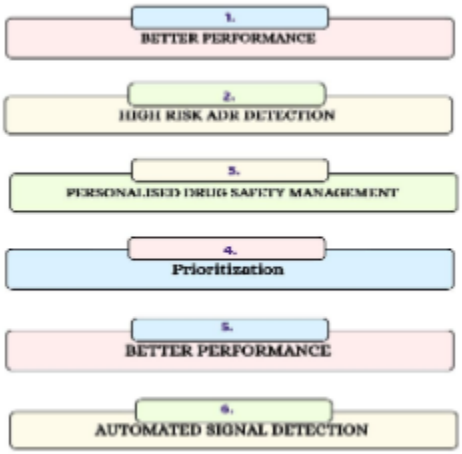

Figure 3: Applications

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This advanced pharmacovigilance system helps in predicting adverse drug reactions [18]. Most studies show varied sensitivity and specificity by validation, but show better performance, which ensures that ML plays a major role in high-risk ADR detection [18].

Classification tasks with Random Forest are the most used ML for structured real-world data, which is increasingly used, but a small number of models are tested in clinical environments [17]. It helps with ADR detection from both the structured and unstructured data and supports personalized drug safety management [19]. It assists in prioritization and signal management using ML models, and NLP would automate the signal detection and validation [20].

5. Validation and Benchmarking Metrics

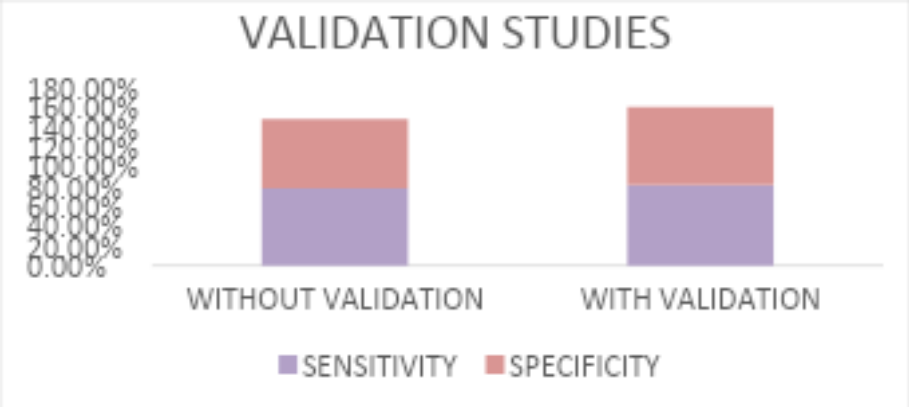

Figure 4: Studies confirming the need for validation

Common benchmarking metrics are sensitivity and specificity. Pooled sensitivity for models without external validation was found by 78.1% and specificity of 70.6%. But with validation, sensitivity is 81.5%, and specificity is 79.5%. This shows the performance of ADR prediction [18]. Only a few ADR prediction models have analyzed independent clinical datasets that are needed for ensuring generalizability and practical utility [18].

6. Challenges

Only 23% of studies implemented external validation, which shows that models may not be fit for specific datasets and may not generalize well to other clinical settings [18]. Lack of standardized data models is one major concern that may affect the data quality and processing [17]. About 16% of studies were tested in clinical settings, which is a serious concern in implementing for practice due to technical, regulatory, and trust issues [17].

7. Future Directions

Implementing standardized preprocessing protocols for structured RWD for consistent model training and consistent results, along with a pharmacovigilance system [17]. Developing AI methods that support interpretability and causal reasoning is a key future direction, enabling models not just to predict but to explain why certain ADRs are flagged, improving regulatory trust and clinical uptake. This aligns with broader gaps identified in the field [17]. Broader clinical validation and trials, enabling multicenter studies and validation to demonstrate real clinical statistics [18]. At present, structured EHR data can be analyzed, but in the future, it needs to introduce models that could analyze the unstructured data, such as images and genomics [17].

8. Conclusion

Pharmacovigilance plays a vital role after the post-marketing approval of the marketed drugs to detect, assess, understand, and prevent the ADR. But the centralized system of pharmacovigilance has limitations of data heterogeneity, underreporting, scalability, and delayed signal detection. High-throughput screening combined with AI improves these challenges and makes it an automated system. But using a

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decentralized system, it is even easier, faster, and more accurate than the centralized system. So, swarm robotics is introduced with a fault-tolerance paradigm that improves distributed data screening and collective decision-making. Although challenges remain, including limited external validation and standardization issues, swarm-based pharmacovigilance systems show a hopeful future direction for intelligent, high-throughput, and clinically applicable drug safety monitoring.

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Chapter 6

MECP2 Gene Dysfunction and Emerging Molecular Therapeutics Strategies in Rett Syndrome

Ashifa.T.A[a], Beevi Ayisha Banu.J[a], V.Jayashree[b*]

[a] *B.Pharm Student, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

[b]*Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

** Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Rett Syndrome is a rare X-linked neurodevelopmental disorder that primarily affects females and is mainly caused by mutations in the MECP2 gene. The disorder results in neurological regression, loss of speech and motor skills, seizures, and cognitive impairment. The MECP2 gene plays a crucial role in regulating gene expression and maintaining normal neuronal function. However, recent advances in molecular biology have introduced new therapeutic approaches such as AAV-mediated gene therapy, CRISPR-based gene editing, RNA editing, and MECP2 reactivation strategies. These emerging therapies aim to restore normal gene function and may provide promising disease-modifying treatments for Rett syndrome in the future. This chapter explores the molecular mechanisms of MECP2 dysfunction and highlights current and emerging therapeutic strategies with potential to transform the management of Rett syndrome.

Keywords: Rett Syndrome; MECP2 Gene Mutation;

Neurodevelopmental Disorder; Neuronal Dysfunction; Gene Therapy;

1. Introduction

Rett Syndrome is a rare X-linked dominant neurodevelopmental disorder that primarily affects females and is characterized by severe cognitive and motor impairments. The disorder typically appears after a period of apparently normal early development, followed by progressive neurological regression, loss of acquired speech, impaired motor coordination, and stereotypic hand movements [1]. Rett syndrome is considered one of the most common genetic causes of severe intellectual disability in girls.

The disorder is mainly caused by mutations in the MECP2 (methyl-CpG-binding protein 2) gene located on the X chromosome. The MECP2 gene encodes a protein that plays an essential role in epigenetic regulation of gene expression and neuronal development. Dysfunction of this gene disrupts transcriptional regulation and neuronal communication, ultimately leading to the neurological symptoms observed in affected individuals [2,3].

Recent advances in molecular genetics and neuroscience have significantly improved the understanding of the mechanisms underlying MECP2 dysfunction. These discoveries have also contributed to the development of emerging therapeutic approaches such as gene therapy, genome editing, and epigenetic reactivation strategies aimed at restoring normal MECP2 function [6,8]. This chapter focuses on the molecular mechanisms of MECP2 gene dysfunction and highlights current and emerging therapeutic strategies for the management of Rett syndrome.

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1.1 Etiology

Rett syndrome (RTT) is a severe neurological disorder caused by mutations in the X-linked gene MECP2 (methyl-CpG-binding protein 2)[2]

MeCP2 selectively binds CpG dinucleotides in the mammalian genome and mediates transcriptional repression through interaction with histone deacetylase and the corepressor SIN3A[3].

2. Structure and Functions of MECP2 Gene:

The MECP2 (methyl-CpG binding protein 2) gene encodes the MeCP2 protein, an important epigenetic regulator involved in neuronal development and gene expression. The MeCP2 protein acts as a transcriptional regulator by binding to methylated cytosine residues in DNA. This interaction allows the protein to influence chromatin structure and regulate the expression of multiple genes involved in neuronal development and synaptic function. The protein mainly functions as a transcriptional repressor by recruiting histone deacetylase complexes, leading to chromatin condensation and suppression of gene transcription.

Structurally, the MeCP2 protein contains several functional domains, including the N-terminal domain (NTD), methyl-CpG binding domain (MBD), intervening domain (ID), transcriptional repression domain (TRD), and C-terminal domain (CTD). Among these domains, the MBD domain is responsible for binding methylated DNA, while the TRD domain interacts with co-repressor complexes that regulate chromatin organization and gene transcription. These domains work together to maintain neuronal gene regulation and chromatin stability.

Because MeCP2 regulates large networks of neuronal genes, proper levels of the protein are essential for normal neurological function. Both deficiency and overexpression of the MECP2 gene can lead to neurological disorders such as Rett Syndrome, highlighting its critical role in brain development and epigenetic regulatio[4].

The structural domains of the MeCP2 protein are illustrated in Figure 1, highlighting the major functional regions involved in transcriptional regulation.

Figure 1: Structural organization of the MeCP2 protein

3. Molecular Pathophysiology

MeCP2 is a basic nuclear protein that is highly expressed in the brain. Its amino acid sequence is conserved in vertebrate evolution, being 95% identical between humans and mice. Functional studies have identified a DNA-binding domain (MBD) as the major determinant of chromosome binding through its affinity for short sequences in the genome that contain 5-methylcytosine (mC)[2].

Transfection studies showed that MeCP2 can repress gene transcription when it binds to promoter regions through the GAL4 binding domain. This repression is partly mediated through interaction with histone deacetylase (HDAC) complexes. These findings suggest that MeCP2 acts as a transcriptional regulator targeting genes via DNA methylation. However, later studies indicate that its effect on gene expression is relatively subtle[5].

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3.1 Emerging Therapeutic Strategies

Recent advances in molecular and genetic research have opened promising avenues for developing targeted therapies aimed at correcting the underlying genetic defects associated with Rett syndrome. Since mutations in the MECP2 gene are the primary cause of the disorder, many emerging therapeutic strategies focus on restoring normal MECP2 function in affected neurons.

One of the most promising approaches is adeno-associated virus (AAV)-mediated gene therapy. This strategy involves delivering a functional copy of the MECP2 gene into neurons using viral vectors. Preclinical studies have shown that introducing a normal MECP2 gene can partially restore neuronal function and improve neurological symptoms in experimental models. However, precise regulation of MECP2 expression is essential because both insufficient and excessive levels of the protein can lead to neurological abnormalities[6,7].

Another innovation involves CRISPR-Cas9 gene editing technology, which enables precise modification of disease-causing mutations within the genome. By targeting specific mutations in the MECP2 gene, CRISPR-based systems have demonstrated the ability to repair genetic defects at the DNA level in cellular models. Eventhough, this technology is still in early stages of development for neurological disorders, it offers a promising strategy for correcting the root cause of the disease[7].

Another promising therapeutic strategy involves epigenetic reactivation strategies, that aim to activate the functional MECP2 gene present on the inactive X chromosome. Since females possess two X chromosomes, one copy of the MECP2 gene remains inactive.

Reactivating this silent gene could potentially restore normal levels of MeCP2 protein in neurons and improve neurological function[8].

4. Clinical Features of Rett Syndrome:

The clinical manifestations of Rett Syndrome usually appear between 6 and 18 months of age following a period of apparently normal development. Patients commonly exhibit developmental regression, loss of acquired speech, repetitive hand movements, and impaired motor coordination.

Symptoms such as:

- Sleep disturbance,
- Seizures,
- Breathing irregularities,
- Hand stereotypies,
- Hand function,
- Constipation,
- Use of gastrostomy,
- Communication skills,
- Anthropometry, and
- Bruxism [3,9,10].

4.1 Diagnosis of Rett Syndrome

Diagnosis of Rett Syndrome is primarily based on clinical evaluation and confirmation of mutations in the MECP2 gene through molecular genetic testing. Physicians evaluate developmental history and neurological symptoms such as loss of speech, stereotypic hand movements, and impaired motor coordination. Additional diagnostic investigations including

- electroencaephalography (EEG)
- neurological examination

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- and brain imaging

may also be used to assess associated neurological abnormalities and exclude other neurodevelopmental disorders [9].

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Chapter 7

Stem Cell Therapy in the Treatment of Diabetic Nephropathy

N Dhanush[a], V.Jayashree[b*]

[a]*B.Pharm Student, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

[b]**Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

**Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Diabetic nephropathy (DN) is one of the most serious complications of diabetes mellitus and a leading cause of end-stage renal disease (ESRD) worldwide. Current therapeutic strategies mainly focus on controlling blood glucose levels and slowing disease progression, but they are often unable to completely prevent renal damage. In recent years, stem cell–based therapy has emerged as a promising approach for the treatment of DN. Among the different types of stem cells, mesenchymal stem or stromal cells (MSCs) have gained considerable attention due to their regenerative potential, immunomodulatory properties, and ability to promote tissue repair. Several preclinical studies and early-phase clinical trials have demonstrated that MSC therapy may improve renal function, reduce inflammation, and inhibit fibrosis in diabetic kidneys. The therapeutic effects of MSCs are mainly attributed to their paracrine signaling, anti-inflammatory activity, and capacity to enhance cellular regeneration. This chapter reviews the recent advances in MSC-based therapy for diabetic

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nephropathy, highlighting the underlying mechanisms involved in renal protection and repair. In addition, the potential benefits, limitations, and possible risks associated with MSC therapy are discussed. Understanding these mechanisms may contribute to the development of novel therapeutic strategies and drug targets for the effective management of diabetic nephropathy.

Keywords: Diabetic nephropathy, Diabetes mellitus, End-stage renal disease, Stem cell therapy, Mesenchymal stem cells.

1. Introduction

Diabetic Nephropathy (DN) is a major microvascular complication of Diabetes Mellitus (DM) and a leading cause of End-Stage Renal Disease (ESRD) worldwide [1]. Persistent hyperglycemia in diabetes can damage several organs, particularly the kidneys, leading to progressive renal dysfunction [2]. Despite advances in glycemic control and the use of therapies targeting the Renin–Angiotensin–Aldosterone System (RAAS), current treatments mainly slow disease progression rather than completely preventing kidney failure [1]. Therefore, the development of new therapeutic strategies is essential. In recent years, regenerative medicine has emerged as a promising approach for the treatment of DN. Among these strategies, Mesenchymal Stem Cells (MSCs) have gained significant attention due to their ability to promote tissue repair, modulate immune responses, and secrete bioactive factors that support regeneration [3]. Preclinical studies and early clinical trials suggest that MSC-based therapy may help reduce renal inflammation, fibrosis, and structural damage, thereby offering a potential therapeutic option for slowing the progression of DN [4].

2. Diabetic Nephropathy

Diabetic Nephropathy (DN) is one of the most serious microvascular

complications of diabetes mellitus and a leading cause of End-Stage Renal Disease worldwide [1]. It develops due to long-term hyperglycemia, which progressively damages the renal microvasculature and glomerular structure [2]. The early clinical manifestation of DN is Microalbuminuria, followed by structural and functional alterations such as glomerular hypertrophy, thickening of the glomerular basement membrane, mesangial expansion, and renal fibrosis [2]. As the disease progresses, these pathological changes lead to glomerulosclerosis and gradual loss of kidney function. Current treatment strategies mainly focus on controlling blood glucose levels and inhibiting the Renin–Angiotensin–Aldosterone System using drugs such as ACE inhibitors and angiotensin receptor blockers [1]. However, these therapies primarily slow disease progression rather than completely reversing kidney damage. Therefore, novel therapeutic approaches, particularly regenerative medicine and stem cell therapy, are being explored as potential strategies to restore renal structure and function in DN [4].

3. Mesenchymal Stem Cells in Regenerative Medicine

Mesenchymal Stem Cells (MSCs) have become a major focus in regenerative medicine due to their therapeutic potential in treating various diseases [3]. First identified in the late 1960s in mesodermal tissues, MSCs are multipotent stromal cells capable of self-renewal and differentiation into multiple cell lineages [5]. They can be isolated from several tissues such as bone marrow, adipose tissue, umbilical cord blood, and amniotic fluid. MSCs possess several advantages for cell-based therapy, including easy isolation, rapid expansion in vitro, low immunogenicity, and the ability to migrate toward sites of tissue injury [3]. In addition, MSCs exert strong therapeutic effects through the secretion of bioactive molecules such as cytokines, growth

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factors, and extracellular vesicles including exosomes, which promote tissue repair and regeneration [6]. Due to these properties, MSCs have been widely investigated in preclinical and clinical studies for the treatment of various disorders, including neurodegenerative diseases, cardiovascular diseases, and organ failure [3]. These promising characteristics highlight the potential of MSC-based therapy as an emerging strategy in regenerative medicine.

4. Overview of MSC Therapy in Diabetic Nephropathy

Diabetic Nephropathy (DN) is one of the most serious complications of Diabetes Mellitus, and it is a major cause of End-Stage Renal Disease (ESRD) worldwide [1]. DN develops as a result of chronic hyperglycemia, leading to progressive kidney damage characterized by microalbuminuria, glomerular hypertrophy, mesangial expansion, and thickening of the glomerular basement membrane [2]. Current therapeutic approaches mainly focus on controlling blood glucose levels and regulating the Renin–Angiotensin–Aldosterone System (RAAS) using ACE inhibitors, angiotensin receptor blockers, and other antihyperglycemic agents [1]. However, these treatments only slow disease progression and do not completely prevent renal failure.

In recent years, regenerative medicine has emerged as a promising strategy for DN treatment. Among the various approaches, Mesenchymal Stem Cells (MSCs) have attracted significant attention due to their regenerative, immunomodulatory, and anti-inflammatory properties [3]. MSCs can migrate to injured tissues, secrete growth factors and cytokines, and promote tissue repair through paracrine signaling and extracellular vesicles such as exosomes [6]. Preclinical and early clinical studies suggest that MSC-based therapy may reducerenal inflammation, fibrosis, and oxidative stress, thereby

improving kidney function and slowing DN progression [4].

5. Mechanism of MSC Therapy in Treating DKD

Mesenchymal cells play a prominent role in treating Diabetic Kidney Disease (DKD) through strong immunomodulatory and anti-inflammatory effects [7]. They regulate the immune environment of the kidney through direct interaction with immune cells and secreting various cytokines. This decreases renal inflammation by suppressing pro -inflammatory cytokines such as IL-1β, IL-6, and TNF-α and decreasing infiltration of immune cells like dendritic cells, $CD8^+$ T cells, and macrophages [7]. MSC therapy also inhibits monocyte chemoattractant protein-1 (MCP-1), thereby limiting macrophage accumulation in kidney tissues.

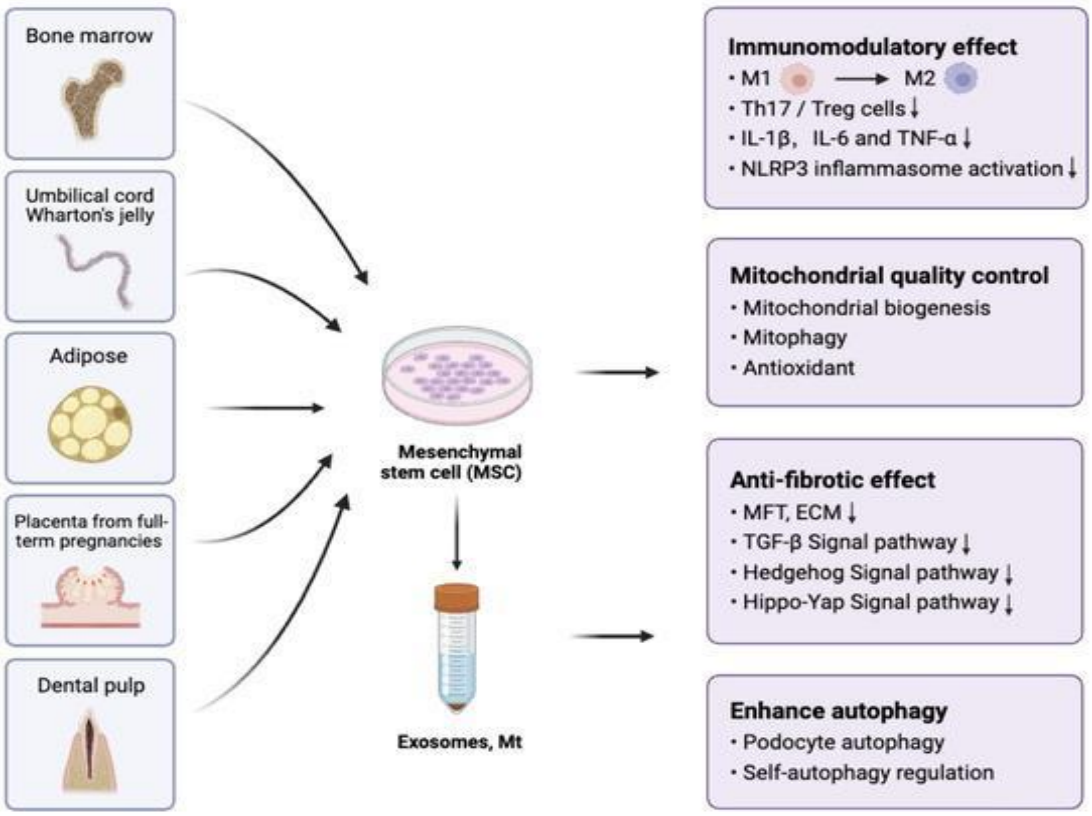

Figure 1: The therapeutic effects of MSCs and their derivatives from different sources in the treatment of DKD

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MSCs also help shift macrophages toward the anti-inflammatory M2 phenotype, which plays an important role in limiting tissue damage and promoting repair [8]. In addition to local effects in the kidney, MSCs influence systemic immune responses by lowering circulating inflammatory cytokines and restoring the balance between Th17 and Treg cells, which is often disturbed in DKD. Furthermore, MSCs and their released exosomes can suppress inflammatory signaling pathways such as Toll-Like Receptor Signaling and the NLRP3 Inflammasome [6], helping to protect kidney cells from further damage.

6. Mitochondrial Quality Control

Mitochondrial quality control plays an important role in maintaining normal cellular function by regulating processes such as mitochondrial DNA repair, mitochondrial fusion and fission, mitophagy, and mitochondrial biogenesis [9]. In Diabetic Kidney Disease (DKD), mitochondrial number and activity are often reduced, which contributes to kidney cell damage [9].

Mesenchymal Stem Cells (MSCs) can help restore mitochondrial function in damaged kidney cells. Studies have shown that MSCs are able to transfer mitochondria to injured cells through structures such as tunneling nanotubes or other cellular communication pathways [10]. This transfer improves cellular energy production, reduces oxidative stress, and limits apoptosis in kidney cells. MSCs also stimulate mitochondrial biogenesis and mitophagy, which help maintain mitochondrial balance and remove damaged mitochondria.

In addition, MSC therapy can improve the function of important kidney cells including tubular epithelial cells, glomerular endothelial cells, and podocytes by regulating mitochondrial signaling pathways.

Overall, MSCs support kidney repair in DKD by improving mitochondrial health and activating protective cellular mechanisms.

7. Antifibrotic Effect of MSC Therapy

Fibrosis and epithelial–mesenchymal transition are major pathological features of Diabetic Kidney Disease (DKD) [1]. These changes lead to excessive accumulation of extracellular matrix proteins in kidney tissue, resulting in glomerulosclerosis and reduced kidney filtration. Persistent hyperglycemia, cytokines, and advanced glycation end products stimulate myofibroblast formation and promote fibrotic changes in the kidney. Because the degree of fibrosis is closely associated with disease severity, preventing or reducing fibrosis is important for slowing the progression of DKD toward End-Stage Renal Disease (ESRD).

Mesenchymal Stem Cells (MSCs) and their secreted vesicles have been shown to reduce renal fibrosis by limiting extracellular matrix production and enhancing its breakdown. MSC therapy can suppress fibrotic signaling pathways and decrease the expression of proteins that promote matrix accumulation. In addition, MSC-derived factors can inhibit epithelial–mesenchymal transition and reduce collagen and fibronectin deposition in kidney tissue [8]. Since inflammation contributes to fibrosis, the anti-inflammatory actions of MSCs also indirectly help prevent fibrotic progression. Overall, MSC-based therapies may protect kidney structure and function by controlling fibrotic processes in DKD.

8. Conclusion

Mesenchymal Stem Cells (MSCs) have emerged as a promising therapeutic approach for the treatment of Diabetic Kidney Disease (DKD) due to their ability to regulate multiple biological processes

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involved in disease progression. Evidence from experimental studies shows that MSCs can reduce inflammation, limit fibrosis, improve mitochondrial function, and enhance cellular repair mechanisms such as autophagy. These effects are mainly achieved through the release of bioactive factors, exosomes, and the regulation of several important signaling pathways.

MSCs also help restore the balance of immune responses, reduce the accumulation of extracellular matrix proteins, and protect kidney cells from damage caused by chronic hyperglycemia. In addition, their ability to support mitochondrial quality control and activate protective cellular pathways contributes to improved kidney cell survival and function.

Although the current findings are encouraging, further research and large-scale clinical trials are required to better understand the safety, long-term effectiveness, and optimal application of MSC-based therapies. Overall, MSC therapy represents a potential regenerative strategy that may help slow the progression of DKD and improve future treatment options for patients.

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Chapter 8

Pharmacovigilance in Herbal and Traditional Medicines: Challenges and Future Perspectives

S.Dharshini[a], V.Jayashree[b*]

[a]*Student of B. Pharmacy, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai*

[b]**Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai*

* *Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

In recent years, the use of traditional and herbal medicines has gradually increased worldwide. Many people believe that natural products are safe; however, scientific reports indicate that herbal medicines can also cause harmful effects, side effects, toxicity, and interactions with other drugs. For this reason, pharmacovigilance plays an important role in ensuring and monitoring their safety. Herbal medicines are natural-based medicinal products obtained from plants, including roots, leaves, bark, seeds, or extracts, and are widely used in traditional systems. Most of these products are available without prescription and are frequently used for self-medication. In many cases, patients may use these products without consulting healthcare professionals or combine them with modern medications. Herbal products may produce adverse drug reactions such as liver damage, kidney problems, allergic reactions, and bleeding problems. Major concerns include wrongly identified plants, variation in product quality, contamination, and adulterated drugs.

Improving awareness among healthcare professionals and the public can help strengthen safety monitoring.

Keywords: Pharmacovigilance; Herbal and traditional medicines; Adverse drug reactions; Drug interactions; Quality control; Safety monitoring.

1. Introduction

Herbal and traditional medicines have been used for many centuries for the control and treatment of various diseases. These medicines are mainly obtained from natural sources such as roots, leaves, and plant extracts. Many people around the world depend on herbal medicines for healthcare, especially in developing countries where modern medical services may be limited [1,3]. Traditional medicine systems such as Ayurveda, Unani, and Chinese medicine play an important role in healthcare by using such medicinal products [3,4].

In the modern era, the use and popularity of herbal medicines have increased worldwide. Many people choose herbal products because they are considered natural and less harmful than synthetic drugs. However, this assumption is not always true, as herbal medicines can also produce side effects, toxicity, and drug–drug interactions [1,2]. The increasing use of herbal medicines without proper medical supervision has raised concerns about their safety, quality, and efficacy [2,4].

Pharmacovigilance refers to the science related to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) associated with medicinal products. With the increasing use of herbal and traditional medicines, safety monitoring has become essential for public health [1,2].

This chapter discusses the role of pharmacovigilance in herbal and

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traditional medicines, the challenges in monitoring their safety, and possible ways to improve these practices in the future.

2. Overview of Herbal and Traditional Medicines

Traditional medicine systems use plants, including roots, leaves, bark, and seeds, either alone or in combination [3,4,18]. Widely known systems include Ayurveda, Unani, Siddha, and Chinese traditional medicine, each with distinct diagnostic and treatment methods [3,18].

Medicinal plants contain bioactive compounds responsible for therapeutic effects, applied in single or multi-herb preparations. Product quality can vary with geographic origin, cultivation, and preparation techniques [3,4].

Table 1: Major Traditional Medicine Systems and their Characteristics

Traditional system	**Origin/Region**	**Key features**	**Examples**
Ayurveda	India	Based on balance of body energies [doshas]	Turmeric, Ashwagandha, Neem
Traditional Chinese medicine	China	Uses herbal formulations, acupuncture, and holistic diagnosis	Ginseng, Ginger, Licorice
Unani medicine	Middle East and South Asia	Derived from the theory of four humors	Senna, Aloes
Siddha medicine	South India	Include herbal, mineral, and spiritual healing	Amla, Pepper
Kampo medicine	Japan	Japanese form of Chinese herbal medicine	Licorice, Ginger

Global demand for herbal products, supplements, and functional foods has steadily increased. Many choose herbal medicines for their natural origin [4,8]. Authorities like WHO emphasize the importance

of standardization, safety monitoring, and integration into national healthcare systems [18].

3. Need of Pharmacovigilance in Herbal and Traditional Medicines

The increasing global use of herbal and traditional medicines has raised safety concerns. Though perceived as gentle, they can cause adverse effects, interactions, or toxicity if used improperly [1,2,12]. Pharmacovigilance monitors medicines to identify, evaluate, and prevent harmful effects. Key reasons for applying it to herbal products include:

- Uncontrolled use: Self-medication and combination with prescription drugs may be harmful [1].
- Polyherbal formulations: Complex preparations make it difficult to identify the ingredient causing adverse effects [12].
- Quality variation: Differences in cultivation, processing, and storage can lead to contamination or adulteration [12].
- Safety misconceptions: Belief that “natural = safe” may cause users to ignore risks [2].

An effective pharmacovigilance system enables healthcare authorities to detect harmful practices and take action, improving public health [1,12]. The need of pharmacovigilance in herbal and traditional medicines shown in Figure 1.

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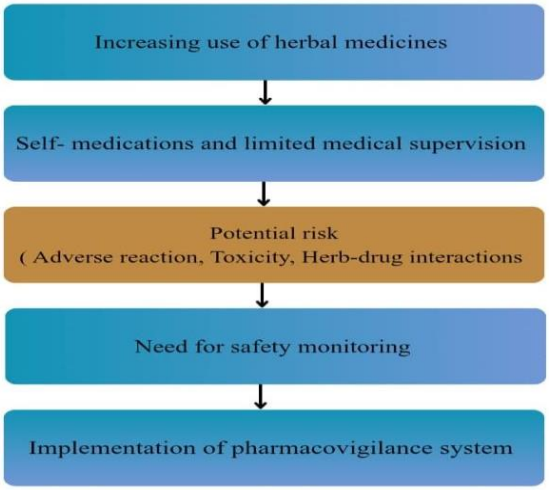

Figure 1: Need for pharmacovigilance in herbal and traditional medicines

4. Adverse Drug Reaction and Safety Concerns

People often use herbal and traditional medicines because they are natural and seem safe. But just because something is natural doesn't mean it is completely risk-free. Taking the wrong dose, using them without advice, or mixing them with other medicines can sometimes cause side effects [5,6].

One big problem is drug interactions. Herbs can change the way our body handles other medicines, which might make them less effective or cause extra side effects. For example, St. John's Wort can lower the effect of some prescription drugs [5,8].

Liver problems are another concern. Some herbs, such as kava, can damage the liver if taken in high doses or for a long period [7].

Some people may also experience allergic reactions, ranging from mild skin rashes to more serious immune problems, depending on the person and the herbs used [11,17].

Sometimes the issues aren't the herbs themselves but come from poor quality or contamination. Some products may have heavy metals,

pesticides, microbes, or even synthetic drugs, which can be harmful [11].

In short, while herbal medicines have benefits, they aren't completely safe. Using them carefully, following proper guidance, and monitoring for side effects is very important [5–8,11,17]. To explain the types of adverse reactions reported with herbal medicines, Table 2 outline the common examples, their effect with source reference.

Table 2: Example of ADR associate with herbal medicines

Herbal Medicine	**Adverse Effect**	**Description**
St. Jhon's wort	Drug interactions	Reduce efficacy of some medicines [5,8]
Kava	Hepatoxicity	Liver toxicity reported with prolonged use [7]
Ginkgo biloba	Bleeding risk	May rise bleeding with anticoagulants [6]
Various herbal products	Allergic reactions	Hypersensitivity reactions occur [11]

This table shows the different safety concerns related with herbal medicines, highlighting the need for systematic pharmacovigilance. In addition to the examples shown in Table 1, adverse reaction from herbal medicines can generally classified into several categories as illustrate in Figure 2.

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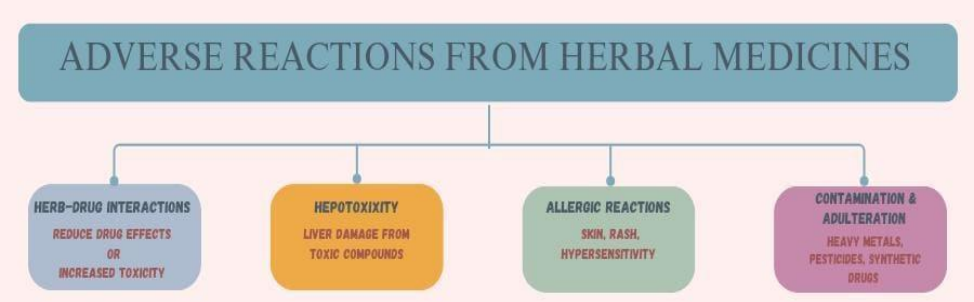

Figure 2: Types of ADRs from herbal medicines

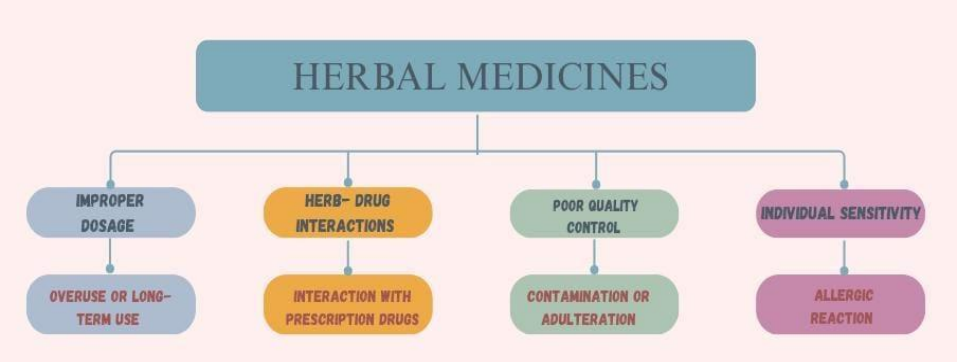

Figure 3: Factors Leading to Herbal Medicine ADRs

5. Challenges in Herbal and Traditional Medicine Pharmacovigilance

Monitoring the safety of herbal medicines is not easy. Many people don't report side effects, and healthcare professionals sometimes overlook them [9].

Herbal products can vary a lot in quality because of differences in plant types, origin, or preparation methods. Multi-herb mixtures make it even harder to know which ingredient caused a problem [10,13].

Lack of research and weak regulations in some countries make safety monitoring even more difficult [9,13].

In short, better reporting systems, clear standards, and more awareness among healthcare professionals and users are needed to make herbal medicine use safer.

Table 3: Major Challenges in Pharmacovigilance of Herbal and Traditional Medicines

Challenge	Description
Underreporting of ADRs	Many side effects from herbal and traditional medicines are not reported
Lack of standardization	The ingredients maybe different in each product
Poly-ingredient products	Traditional medicines often contain many herbs, so it is hard to know which one caused the side effects

6. Current Pharmacovigilance Programs and Startegies

Keeping herbal and traditional medicines safe needs strong monitoring systems. Many programs around the world track side effects (ADRs) to help protect people who use these medicines.

6.1 WHO Guidelines for Herbal Medicine and Safety Monitoring

WHO guidelines recommend adding herbal medicines to national monitoring systems, using standard forms to report side effects, training healthcare workers to spot problems, and keeping track of interactions and quality issues [20].

6.2 National Pharmacovigilance Systems

Many countries monitor herbal medicines alongside conventional drugs:

- India: Pharmacovigilance Program covers Ayurveda, Siddha, and Unani medicines.
- China: ADR Monitoring System includes Traditional Chinese Medicine.
- European Union: Herbal products are monitored with conventional medicines [15,16,20].

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6.3 Modern Strategies for Monitoring

Modern methods use technology to detect safety issues. Data mining identifies unusual ADR patterns [15,16], electronic reporting allows online submission of ADRs, and integration with digital health records helps with active monitoring and early detection [16].

Figure 4 shows the pharmacovigilance reporting process used in modern monitoring systems. It explains how adverse drug reactions are reported, analyzed, and evaluated for medicine safety.

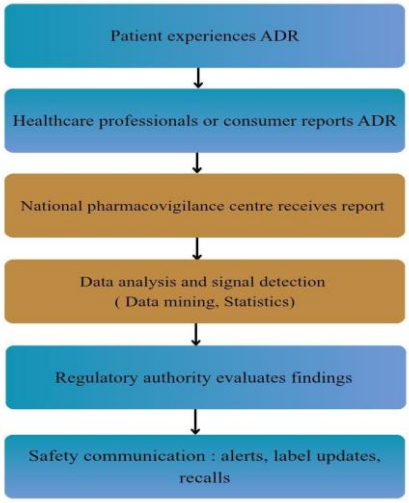

Figure 4: harmacovigilance Reporting Process

7. Future Perspectives and Conclusion

Herbal and traditional medicines are really helpful, but they aren't completely risk-free. People often think natural means safe, but side effects, interactions, or contamination can still happen [5,6]. Because of this, it's really important for healthcare workers and users to be aware and report any problems quickly [8].

One big challenge is that herbal products can be very different in quality, and not all countries have strong rules to check them. Better reporting systems, clearer regulations, and proper quality standards can make these medicines much safer [9,10,13].

In the future, more research is needed to standardize herbal products and understand possible side effects. Using digital tools, like online reporting or linking with health records, can help catch problems early [15,16,20]. It's also important for people to use herbs carefully and talk to doctors if they are taking other medicines [11,17].

In short, herbal medicines can give a lot of benefits, but we need to be careful. Using them properly, keeping track of side effects, and improving safety systems will help people enjoy their benefits without risking harm [5–8,11,17,20].

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Chapter 9

Impact of New Oral Glp-1 Drugs on Diabetes Treatment

Dharshini. M[a], V Jayashree[b*]

[a]*Student of B. Pharmacy, School of Pharmaceutical Sciences,* Vels Institutes of Science, Technology & Advanced Studies, Chennai

[b*]*Associate Professor, School of Pharmaceutical Sciences,* Vels Institutes of Science, Technology & Advanced Studies, Chennai

** Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Type 2 diabetes mellitus is a chronic metabolic disorder recognized by insulin resistance and progressive β-cell impairment, leading to prolonged hyperglycemia and increased risk of cardiovascular and metabolic complications, the incretin system mainly, GLP-1 and GIP which plays an important role in regulating postprandial blood glucose levels.GLP-1RAs are therapeutically effective antidiabetic agents that improve glucose-dependent insulin secretion, suppress release of glucagon, delays gastric emptying and promotes satiety, thereby improve glycemic control and assisting weight reduction. Traditionally, these therapies are available only in injectable form, which sometimes affect patient treatment compliance. The development of oral GLP-1 receptor agonists, such as oral semaglutide, represents a major advancement in diabetes treatment. This formulation uses the absorption enhancer that is (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate) to improve absorption in GIT. Advancing oral GLP-1 receptor agonists on small molecules are being studied and may make treatment of diabetes easier, more effective

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and help patients take their medicines regularly.

Keywords: GLP-1 Receptor Agonists, Oral semaglutide, Incretin system, Glycemic control, Antidiabetic Therapy.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a very common long term metabolic disorder and it is identified by decreased insulin sensitivity and gradually worsening beta cell dysfunction. It is closely associated with increased disease burden, elevated mortality rates and adverse clinical outcomes. If unmanaged, persistent hyperglycemia can lead to hyperlipidemia, oxidative stress, meta inflammation and endothelial dysfunction, all of these promotes atherogenesis and lipid formation inside arterial walls [1]. It can be controlled by glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) and it is a super useful medicine to control obesity. Its role is to enhance insulin secretion, reduces the glucagon level and slows gastric emptying and also supports weight loss. It not only control diabetes but also controls risk of heart disease.GLP-1&GIP hormones controls the post meal blood sugar level, reduces appetite and maintain energy balance. Traditional Injectable medicine is difficult for patients to follow so oral semaglutide has been developed and shows the same benefits with higher rate of medication adherence [2,3].

2. Physiology of Glp-1 and Incretin System

The incretin system means involving food-responsive hormones that are released after the intake of food, which helps to maintain the body's blood glucose level. This process involves stimulation of insulin release from the pancreas and in some cases, it releases glucagon secretion. The excellent and beautiful incretin system contains various elements of biology, such as GLP-1 and glucose-

dependent insulinotropic polypeptide (GIP), as well as the principles, for instance, post-meal glucose control and energy balance [3-5]. The incretin system uses GLP-1 hormone for delayed gastric emptying and decreases small intestine motility; therefore, it slows absorption of nutrients and controls the post meal glucose spike. The system utilizes GLP-1 and reduces the risk of lipid metabolism, antiinflammation and cardiac protection. However, the gastrointestinal tract contains slightly rougher side effects such as nausea, vomiting, and early fullness [5]. Numerous beneficial effects shapes metabolism process where GLP-1 acts on the brain and GIP acts on insulin secretion in a glucose dependent manner [4].

An major idea related to the incretin system is “incretin effect” which shows the larger insulin response which is seen after oral glucose administration compared to intravenous for instance similar blood glucose levels[3].This mainly occurs due to the release of incretin hormones only when the glucose is consumed orally[3-4].the communication between the intestine and pancreas that maintains secretion of insulin is known as “enteroinsular axis”(entero-instestine,insular-pancreas)which plays an crucial in glucose homeostasis[4-5].

A proper understanding of GLP-1 biology has result in development of modern therapeutic agents such as GLP-1receptor agonists (Eg; semaglutide) and dual agonists (Eg; Tirzepatide). Therefore, in patients with type 2 diabetes and obesity these agents can help to manage body weight, lowers blood glucose levels and even improves cardiovascular health [3-5].

3. Mechanism of Action of Oral Glp-1

Oral GLP-1 receptor agonists act by copying the effect of body’s

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natural glucagon like peptide-1(GLP-1).The GLP-1hormone is secreted by intestinal L-cells due to nutrient intake that leads to control glucose in blood and appetite[4].Drug is taken by oral route and it is absorbed from the stomach/intestine into the bloodstream that reaches GLP-1 receptor which is a G-protein-coupled receptor acts on pancreatic β-cells, pancreatic α-cells and brain to glucose and appetite control[3,4].GLP-1 agonist binds to GLP-1(GLP-1R) on pancreatic cells which activates intracellular signaling pathway thereby increasing in cAMP (cyclic adenosine monophosphate) and activation of protein Kinase A (PKA) and Epac2 which produces glucose-dependent insulin secretion. In response to high glucose in blood, insulin is released and which helps to reduce hyperglycemia as well as lower the risk of hypoglycemia compared to some other drugs [3,4,5]. Activation of GLP-1R takes place in pancreatic α-cells which result in suppression of glucagon secretion [3,4].

Generally, glucagon increases blood glucose by stimulating hepatic glucose production in the liver. When GLP-1 based drugs reduces glucagon release, less glucose is produced in liver, which supports to lower blood glucose levels and promotes overall glycemic control[3,4].In gastric emptying section GLP-1 agonist delays gastric emptying and slows nutrient delivery to bloodstream which increases postprandial glucose it takes place through nerve-mediated pathway and direct muscular effects in the gastrointestinal tract[3,4].The effect in central nervous system is by activation of GLP-1R in hypothalamus and other brain regions triggers satiety and as well as suppresses appetite, reduced intake of food and decreased body mass with therapeutic benefit[3,4].

The first clinically approved oral GLP-1 drug was oral semaglutide which was developed by combining peptide with permeation

enhancer, the enhancer used is (sodium N-(8-[2-hydroxybenzoyl]amino)caprylate) it stimulates absorption of drug through stomach lining, tackling the challenge that peptides are usually degraded in the GIT,this allows the drug reach systemic circulation effectively and the dosing with once-daily oral administration is clinically beneficial[3].Oral semaglutide has same mechanism as injectable GLP-1 analogs, it acts via the GLP-1 receptor activation, promotes insulin secretion and glucose control whereas it requires special administration condition such as fasting and delay before eating to improve absorption of drug and to increase effectiveness[3,5].

Table 1: Incretin hormones and their role

Hormones	Source	Main Role
GLP-1	Intestinal L-cells	It stimulates insulin secretion
GIP	Intestinal K-cells	Enhances insulin release after meals

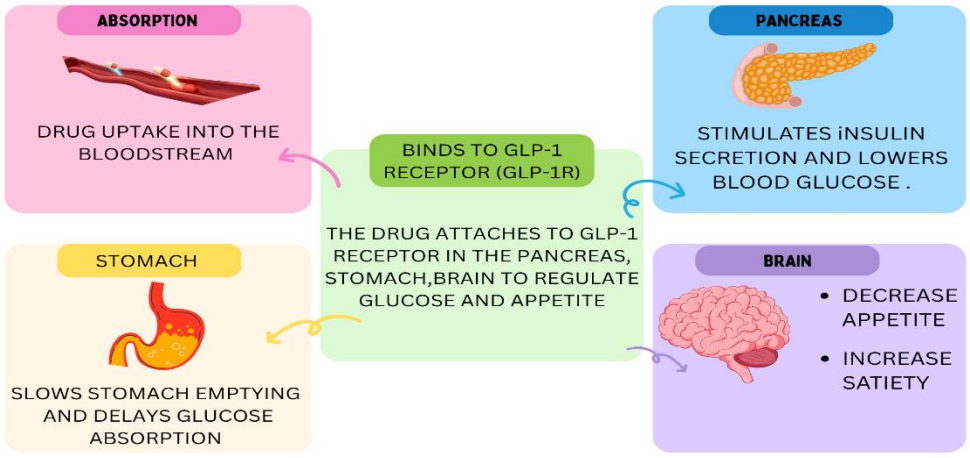

Figure 1: Mechanism of action of Oral GLP-1 Receptor Agonist

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4. Development and Pharmaceutical Challenges of Oral Glp-1 Drugs

GLP-1 is a peptide hormone which controls the blood glucose level and its action is to increase insulin and decrease glucagon and its slow gastric emptying and increase postprandial fullness [6,7]. The peptide drugs are difficult to give orally because of its stability issues like its degraded by stomach acid and digestive enzymes. In addition, their large molecules have poor intestinal permeability which lower the absorption.so this is why GLP-1 therapy was previously available only as injections form [6,7].

To overcome this absorption enhancers is used to improve oral delivery. The main enhancers used is SNAC (sodium-(8-[2-hydroxybenzoyl] amino) caprylate), the role is to protect peptide from enzymatic degradation and temporarily increases intestinal permeability [7,6]. This is possible to develop a oral semaglutide [7,6]. This was the first approved oral GLP-1 receptor agonist. In pharmacokinetics studies they observed SNAC which helps increase drug absorption and absorption is better in bloodstream, maintain plasma concentration and it is effective after oral administration. [7,9]. The several pharmaceutical challenges are faced in oral GLP-1 drug delivery other than degradation and poor absorption it also includes difficulty in maintaining peptide stability in acidic gastric environment, prevent the drug from digestive enzymes, and overcoming epithelial barrier and mucus barrier in GI all these factors limit the drug entry and which leads to limited oral bioavailability [6,8].

To overcome these issues, researchers have introduced additional pharmaceutical challenges such as PH modulation to reduce acidity

in stomach, modification of peptide backbone to improve stability, to enhance intestinal transport by mucus penetrating delivery systems and protective polymers and hydrogels are used to shield peptide from enzymes[6,8].Even with these development still some limitations are present namely poor absorption in the gut based on GI condition, low oral bioavailability, and is still very challenging to convert lab research to treat patients for good result[6,8,9].

5. Current and Emerging Glp-1 Therapies

Currently, oral glucagon-like peptide-1 receptor agonists (GLP-1 RAs) shows major development in the treatment of type 2 diabetes mellitus, offering user friendly administration compared to traditional injectable forms. Among these, oral semaglutide (Rybelsus®) is the only clinically approved available for clinical use by FDA[10].oral semaglutide is a peptide based agonist designed with absorption enhancer SNAC to improve gastrointestinal uptake and it is consumed once daily at doses of 3mg,7mg,or14mg[10].For optical bioavailability, the tablet need to be taken with water on empty stomach, must avoid food or other oral liquids for at least 30minutes after ingestion[10].In addition to peptide-based therapy, many oral non-peptide small-molecule GLP-1 RAs currently under formulation, includes danuglipron, lotiglipron, orforglipron(LY3502970)[12].these small molecules aims to mimic the therapeutic effects of GLP-1 agonists, but are easier to take and has fewer rules to consume. In clinical studies orforglipron has shown promising results, helps to lower blood sugar (HbA1c) and body mass in adults with type 2 diabetes [12]. These drugs are not yet approved for regular use, but they are the next type oral GLP-1 therapies and may have may have advantages in contrast to current peptide-based therapies [10,12].

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Table 2: Current GLP-1 receptor agonists for type 2 diabetes

Drug	Type	Route	Status
Semaglutide	GLP-1 agonist	Oral	FDA approved
Semaglutide	GLP-1 agonist	Injection	FDA approved
Liraglutide	GLP-1 agonist	Injection	FDA Approved

Figure 2: Representation of oral and injectable GLP-1 receptor agonist formulations used in the treatment of type 2 diabetes

6. Safety Profile Adverse Effects

These drugs are generally considered safe for adults patients , but few people may experience stomach-related side effects such as vomiting, nausea, or diarrhea[14,17].In elderly patients, the drugs show similar effectiveness and considered safe, but close clinical monitoring is recommended because they may have multiple medical conditions or may have increased sensitivity to drugs[13].In pediatric patients, these drugs shows good tolerability though limited information is available on long term safety so close clinical monitoring is advised[17].

7. Comparison with Injectable Glp-1 Ras

semaglutide is present in both oral and injectable forms; it differs from other GLP-1receptor agonists because it is available in injectable form and allowing physicians to choose suitable therapeutic approach depending on patients' needs and clinical factors [19]. Both oral and injectable form contribute a better control in people with type 2 diabetes mellitus. Whereas injectable form may produce slightly higher reductions in HbA1c, but oral formulations still provide clinically. Compared with any other antidiabetic agent's injectable semaglutide has shown greater result in weight loss whereas oral form also helps but in weight loss [19]. Both oral and injectable forms have a low risk of causing hypoglycemia, especially when they are not used together with insulin or sulfonylureas[20].In once a week injectable semaglutide is given which improves patient adherence and helps patients to continue the treatment compared with medicine that need to be consumed daily[19].Also tablet form of semaglutide offers a needle-free alternative, improve patient preference and supports earlier treatment initiation in T2DM management [20].these both form of semaglutide shows the same mechanism of action and therapeutic effects which includes glycemic control and weight reduction. The only difference is route of administration and dosing frequency, where injectable semaglutide offers less frequent dosing and sometimes slightly greater efficacy while oral semaglutide allows a non-injectable option in glycemic and weight outcomes [19,20].

8. Future Perspective

Future studies will evaluate cost-effectiveness and accessibility and help to reduce healthcare burden of diabetes[18].They may reduce the risk of cardiovascular problems and improve overall metabolic

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health, which can help long term diabetes treatment[15,10].In addition more easiest forms of medicines may help patients follow their treatment more ,without difficulty and simpler process of taking medicines may allow doctors to begin treatment at earlier stage[16,19].

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Chapter 10

CRISPR-Cas9 Genome Editing in Zebrafish for Modeling Human Diseases: A Narrative Review

Tejaswini Rah Raman[a], V.Jayashree[b*]

[1]*B.Pharm Student, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

[2]**Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institutes of Science, Technology & Advanced Studies, Chennai*

** Corresponding Author: jeya.sps@vistas.ac.in*

Abstract

Genome editing technologies have come a long way in terms of modern biological research by now allowing precise modification of genetic material. Various tools are under review, among which, CRISPR-Cas9 has emerged as one of the most efficient and widely used systems. This is due to its simplicity, The zebrafish, Danio rerio, has become a prominent vertebrate model for genetic studies because of its rapid embryonic development, optical transparency, and strong genetic similarity to humans. In recent years, CRISPR-Cas9 has been extensively applied in zebrafish to investigate gene function, generate targeted mutations, and establish models of human disease. This review summarizes the fundamental principles of CRISPR-Cas9–mediated genome editing and discusses its application in zebrafish research. Particular emphasis is placed on experimental workflows, including guide RNA design, embryo microinjection, and mutant screening strategies. In addition, the review highlights major research applications such as functional genomics, disease modeling, and

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drug discovery. Despite its numerous advantages, certain technical challenges, including off-target effects and mosaic mutations, remain important considerations. Continued improvements in genome editing strategies are expected to further enhance the utility of zebrafish as a model system for biomedical research. Overall, the integration of CRISPR-Cas9 technology with zebrafish biology provides a powerful platform for understanding gene function and advancing studies related to human health and disease.

Keywords: CRISPR; CRISPR-Cas9; genome; zebrafish; modification; genome editing.

1. Introduction

Genome editing technologies have transformed modern biological research by enabling precise manipulation of genetic material. One of the most influential breakthroughs in this field is the development of CRISPR-Cas9, a genome editing system derived from a bacterial adaptive immune mechanism that protects microorganisms against invading viral DNA [1,2]. The discovery and development of CRISPR-Cas9 have revolutionized molecular biology by providing researchers with a powerful tool capable of introducing targeted genetic modifications with high precision and efficiency [3,4].

Compared with earlier genome editing technologies such as zinc-finger nucleases and transcription activator-like effector nucleases, CRISPR-Cas9 offers several advantages, including easier design, reduced cost, and the ability to edit multiple genes simultaneously [5,6]. These characteristics have enabled the rapid adoption of CRISPR technology across a wide range of research disciplines, including genetics, biotechnology, and biomedical sciences [7,8]. In recent years, CRISPR-based genome editing has been applied

extensively to investigate gene function and to develop experimental models for human diseases [9].

One organism that has significantly benefited from the implementation of CRISPR technology is the zebrafish, Danio rerio. Zebrafish have become an important vertebrate model organism due to their rapid embryonic development, optical transparency during early life stages, and genetic similarity to humans [10]. Approximately seventy percent of human genes have at least one zebrafish orthologue, making this organism highly suitable for modeling human diseases and studying gene function in vivo [11].

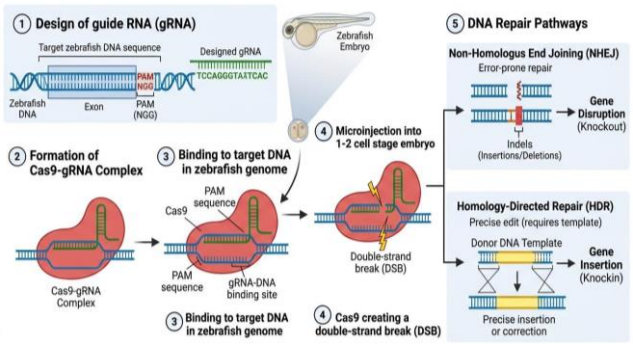

Figure 1: CRISPR-Cas9 Mechanism applied to Zebrafish Genome Editing

The integration of CRISPR-Cas9 genome editing with zebrafish biology has accelerated the generation of targeted genetic mutations and disease models. This technology allows researchers to efficiently knock out genes, introduce disease-associated mutations, and study the resulting phenotypic effects in living organisms [12,13]. Consequently, CRISPR-based zebrafish models have become valuable tools for investigating the genetic basis of diseases and for identifying potential therapeutic strategies.

This review discusses the mechanisms underlying CRISPR-Cas9 genome editing and highlights its applications in zebrafish models for

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studying human diseases. The review also examines current challenges associated with CRISPR technology and explores potential future developments in genome editing research.

2. Zebrafish as a Model Organism in Biomedical Research

The zebrafish has emerged as one of the most widely used vertebrate model organisms in biological and biomedical research. Several biological and experimental characteristics contribute to its popularity, particularly in genetic studies.

Zebrafish embryos develop externally and remain transparent during early developmental stages, allowing direct observation of cellular and developmental processes in real time [10]. Major organ systems such as the heart, brain, and digestive system develop rapidly, often within the first two to three days following fertilization. This rapid development enables efficient analysis of gene function and early disease phenotypes.

Another significant advantage of zebrafish is their high reproductive capacity. A single breeding pair can produce hundreds of embryos within a week, enabling large-scale genetic screening experiments and high-throughput analyses [11]. These characteristics make zebrafish particularly well suited for reverse genetics approaches using CRISPR-Cas9 genome editing.

Genetically, zebrafish share a considerable degree of conservation with humans. Many genes associated with human diseases have functional homologues in zebrafish, enabling researchers to investigate disease mechanisms using this model organism [13]. In addition, zebrafish are highly suitable for drug discovery studies because therapeutic compounds can easily be administered through the surrounding aquatic environment.

These advantages have established zebrafish as a powerful platform for studying developmental biology, disease pathogenesis, and therapeutic interventions.

3. Mechanism of CRISPR-Cas9 Genome Editing

The CRISPR-Cas9 genome editing system functions through an RNA-guided DNA cleavage mechanism. The system consists primarily of a Cas9 endonuclease enzyme and a single-guide RNA (sgRNA), which directs the Cas9 protein to a complementary DNA sequence within the genome [14,15].

The sgRNA contains a sequence that is complementary to the target DNA region, allowing the Cas9 enzyme to recognize and bind to specific genomic sites. Successful targeting requires the presence of a short DNA sequence known as the protospacer adjacent motif, or PAM, which is recognized by the Cas9 protein [4]. Once the sgRNA binds to its target sequence, Cas9 introduces a double-strand break in the DNA.

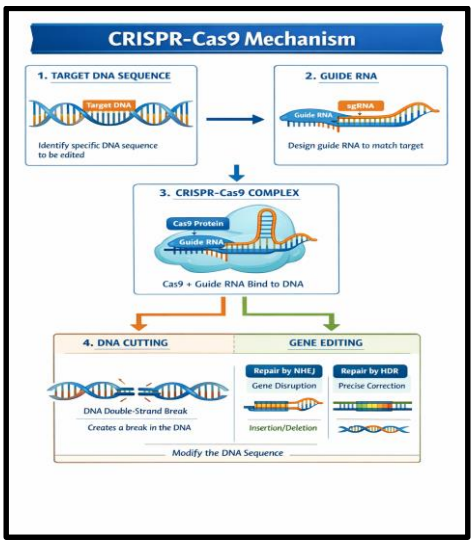

Figure 2: CRISPR-Cas9 Mechanism

Following DNA cleavage, cellular DNA repair mechanisms are activated to repair the damage. Two primary repair pathways are

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involved in this process: non-homologous end joining and homology-directed repair. Non-homologous end joining is an error-prone repair pathway that frequently introduces insertions or deletions at the break site, often resulting in gene disruption [5]. This process is commonly used to generate gene knockout mutations.

In contrast, homology-directed repair utilizes a homologous DNA template to repair the break accurately. By providing an artificial donor DNA template, researchers can introduce precise genetic modifications such as point mutations or reporter gene insertions [17].

The combination of programmable RNA targeting and efficient DNA cleavage makes CRISPR-Cas9 one of the most versatile genomes editing technologies currently available.

4. CRISPR-Cas9 Editing Strategies in Zebrafish

Genome editing in zebrafish using CRISPR-Cas9 typically involves the microinjection of Cas9 mRNA or Cas9 protein along with sgRNA into fertilized embryos at the one-cell stage. Delivering genome editing components at this stage ensures that the modifications occur before extensive cell division, increasing the likelihood that the genetic changes will be present in most cells of the developing organism [10].

The experimental workflow begins with the identification of a target gene and the design of guide RNAs capable of recognizing specific genomic sequences. Bioinformatics tools are often used to minimize off-target effects and improve targeting efficiency [11].

Following microinjection, embryos are allowed to develop normally. Researchers then screen the embryos for mutations using molecular techniques such as polymerase chain reaction amplification and DNA sequencing [12].

Advancements in CRISPR technology have further improved genome editing efficiency in zebrafish. For instance, alternative Cas9 variants have expanded the range of genomic targets that can be edited [13]. These improvements have enhanced the ability of researchers to generate stable mutant lines for disease modeling studies.

5. Applications of CRISPR-Cas9 in Zebrafish Disease Models

5.1 Cancer Research

Cancer research has benefited significantly from CRISPR-based zebrafish models. Targeted mutations in tumor suppressor genes and oncogenes can induce tumor formation in zebrafish, enabling researchers to study tumor initiation, progression, and metastasis in a living organism [16].

5.2 Cardiovascular diseases

Zebrafish are widely used to study cardiovascular diseases because their heart structure and development share similarities with humans. CRISPR-induced mutations in genes associated with cardiac development can lead to abnormalities in heart morphology and function, providing valuable insights into congenital heart diseases [17].

5.3 Neurological Disorders

Zebrafish models have also been developed for studying neurological disorders. CRISPR-mediated mutations affecting neuronal signaling pathways can produce behavioral and physiological phenotypes that resemble human neurological conditions [9]. These models are particularly useful for high-throughput screening of neuroactive compounds.

5.4 Metabolic Disorders

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CRISPR technology has also enabled the development of zebrafish models for metabolic and genetic disorders. Mutations affecting metabolic pathways can lead to phenotypes similar to human metabolic diseases, allowing researchers to study disease progression and evaluate therapeutic strategies [18].

6. Limitations and Challenges

Despite its advantages, CRISPR-Cas9 genome editing also presents several challenges. One significant concern is the occurrence of off-target mutations, which may introduce unintended genetic changes in the genome. Another limitation is mosaicism, which occurs when genome editing events happen after the first cell division, resulting in organisms containing both edited and unedited cells. This phenomenon can complicate early phenotypic analysis.[25]

In addition, precise genome editing through homology-directed repair remains relatively inefficient compared with non-homologous end joining, making accurate gene insertion experiments more difficult.

Ethical considerations related to genome editing technologies must also be considered as CRISPR approaches move closer to clinical applications [26].

7. Future Perspectives

Continuous improvements in genome editing technologies are expected to expand the applications of CRISPR-Cas9 in biomedical research. Emerging approaches such as base editing and prime editing allow precise nucleotide modifications without introducing double-strand breaks, potentially reducing off-target effects [17].

The integration of CRISPR genome editing with advanced genomic technologies and imaging techniques will likely enhance our

understanding of gene function and disease mechanisms.

Ultimately, insights gained from zebrafish disease models may contribute to the development of novel gene therapies and personalized medicine strategies in human healthcare [21].

8. Discussion

One of the most significant contributions of CRISPR-based zebrafish models is the ability to replicate human disease-associated mutations and observe their effects during development and adulthood. Unlike traditional genetic approaches that required extensive time and resources, CRISPR technology enables the rapid generation of targeted mutations, allowing researchers to study gene function more efficiently [4,10]. This has facilitated the development of disease models for cancer, cardiovascular disorders, neurological diseases, and metabolic conditions.

Despite these advantages, several challenges remain in the application of CRISPR technology. Off-target mutations represent a major concern because unintended DNA modifications may lead to inaccurate experimental results or unexpected phenotypes [25]. Although improvements in guide RNA design and high-fidelity Cas9 variants have reduced these risks, careful validation of edited organisms is still required.

Nevertheless, ongoing technological improvements continue to enhance the reliability and efficiency of CRISPR-based genome editing. Advances such as base editing, prime editing, and improved Cas9 variants are expected to address many of the current limitations and expand the potential applications of genome editing technologies in zebrafish models and other experimental systems [17].

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9. Conclusion

In summary, the CRISPR-Cas9 genome editing system has become an indispensable tool for modern biological and biomedical research. Its ability to introduce targeted genetic modifications with high precision has significantly accelerated the study of gene function and disease mechanisms. The zebrafish model organism provides an ideal platform for applying CRISPR technology due to its genetic similarity to humans, rapid development, and suitability for large-scale genetic screening.

The integration of CRISPR-Cas9 with zebrafish genetics has enabled the generation of numerous disease models that replicate human genetic disorders. These models have provided valuable insights into the molecular basis of diseases and have facilitated the identification of potential therapeutic targets. In addition, zebrafish-based CRISPR studies have contributed to advances in drug discovery and translational research.

Although challenges such as off-target effects, mosaicism, and limited efficiency of precise genome editing remain, continued technological developments are expected to improve the accuracy and applicability of CRISPR-based approaches. Future innovations in genome editing tools and experimental methodologies will likely expand the role of zebrafish models in biomedical research.

Overall, the combination of CRISPR-Cas9 genome editing and zebrafish biology represents a powerful approach for advancing our understanding of human diseases and developing novel therapeutic strategies for improving human health.

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Chapter 11

Pharmacognosy of Medicinal Plants: Phytochemical Profiling and Therapeutic Applications

S.Jayakumari[a]*, Pooja Bal Krishna[b], Anugu Mamatha[c]

[a]*Professor, Department of Pharmacognosy, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Chennai*

[b]*Assistant Professor, KCT'S Krishna College of Pharmacy Malkapur, Karad 415539*

Assistant Professor, Vijay College of Pharmacy, Nizamabad, Telangana

** Corresponding Author: nisajayaa@gmail.com*

Abstract

Medicinal plants remain a cornerstone of global healthcare systems, contributing significantly to both traditional medicine and modern drug discovery. According to the World Health Organization, nearly 80% of the world's population relies on plant-based medicines for primary healthcare needs. More than 25% of modern pharmaceutical drugs are derived directly or indirectly from plant sources, and approximately 50,000–70,000 plant species are estimated to be used medicinally worldwide. Pharmacognosy, the study of crude drugs obtained from natural sources, integrates botanical, chemical, and pharmacological approaches to identify bioactive compounds and validate therapeutic claims. This chapter presents a comprehensive overview of pharmacognosy with emphasis on phytochemical profiling techniques and their therapeutic applications. Quantitative data on phytochemical classes, extraction efficiencies, and bioactivity

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correlations are discussed. Advanced analytical tools such as chromatography and spectroscopy have enabled precise characterization of secondary metabolites, accelerating the development of plant-based therapeutics. The chapter also highlights challenges, sustainability concerns, and future prospects in medicinal plant research.

Keywords: Pharmacognosy, Medicinal Plants, Phytochemical Profiling, Bioactive Compounds, Therapeutic Applications.

1. Introduction

Pharmacognosy is a multidisciplinary branch of pharmaceutical sciences that deals with the study of medicinal plants, natural drugs, and their bioactive constituents. Historically, medicinal plants have played a pivotal role in the treatment of human diseases, forming the basis of traditional systems such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine. Archaeological evidence suggests that medicinal plant use dates back over 5,000 years, with documented records in ancient texts.

In recent decades, renewed interest in plant-based medicines has emerged due to the limitations of synthetic drugs, including adverse effects, drug resistance, and high development costs. Natural products offer structural diversity and biological specificity, making them valuable leads for novel therapeutics. Pharmacognostic studies ensure the correct identification, standardization, and quality control of crude drugs, thereby safeguarding efficacy and safety.

Phytochemical profiling, a core component of pharmacognosy, involves qualitative and quantitative analysis of secondary metabolites such as alkaloids, flavonoids, phenolics, terpenoids, glycosides, and saponins. These compounds are responsible for a

wide range of pharmacological activities including antioxidant, antimicrobial, anti-inflammatory, anticancer, and antidiabetic effects.

2. Medicinal Plants and Their Bioactive Constituents

Medicinal plants synthesize a vast array of secondary metabolites as defense mechanisms against environmental stress, pests, and pathogens. These metabolites, although not directly involved in primary metabolic processes, possess significant therapeutic potential.

2.1 Major Classes of Phytochemicals

Alkaloids constitute nearly 20% of plant-derived bioactive compounds and are known for potent pharmacological effects on the nervous system. Flavonoids and phenolic compounds account for approximately 40% of identified phytochemicals and exhibit strong antioxidant and anti-inflammatory properties. Terpenoids, representing the largest class, contribute to antimicrobial and anticancer activities, while glycosides and saponins are associated with cardioprotective and immunomodulatory effects.

2.2 Quantitative Distribution

Studies indicate that medicinal plant extracts typically contain 5–15% phenolic compounds by dry weight, while alkaloid content ranges from 0.1–5% depending on species and extraction method. Such quantitative variations significantly influence therapeutic efficacy.

3. Phytochemical Profiling Techniques

Phytochemical profiling refers to the systematic identification and quantification of chemical constituents present in plant materials.

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Accurate profiling is essential for standardization and reproducibility of herbal formulations.

3.1 Extraction Methods

Common extraction techniques include maceration, Soxhlet extraction, and percolation. Modern methods such as microwave-assisted extraction and supercritical fluid extraction have demonstrated 20–40% higher yield efficiency and reduced solvent consumption compared to conventional techniques.

3.2 Analytical Techniques

Chromatographic methods such as thin-layer chromatography, high-performance liquid chromatography, and gas chromatography are widely used for separation and quantification. Spectroscopic techniques including UV–Visible, infrared, nuclear magnetic resonance, and mass spectrometry provide structural elucidation. Combined hyphenated techniques enhance sensitivity and accuracy, enabling detection of compounds at microgram levels.

4. Therapeutic Applications of Medicinal Plants

Medicinal plants exhibit diverse pharmacological activities validated through in vitro, in vivo, and clinical studies.

4.1 Antioxidant and Anti-inflammatory Activities

Oxidative stress is implicated in over 60% of chronic diseases. Plant-derived antioxidants such as flavonoids and phenolic acids demonstrate free radical scavenging activity ranging from 50–90% in standard assays, reducing inflammation and cellular damage.

4.2 Antimicrobial and Anticancer Properties

Approximately 30% of plant extracts screened globally show antimicrobial activity against pathogenic bacteria and fungi. Several

anticancer drugs, including those derived from plants, have demonstrated cytotoxicity with IC50 values below 10 µg/mL against cancer cell lines.

4.3 Metabolic and Cardioprotective Effects

Medicinal plants used in traditional medicine have shown significant antidiabetic effects, with reductions in blood glucose levels by 20–40% in experimental models. Cardioprotective compounds improve lipid profiles and reduce oxidative stress markers.

5. Quality Control and Standardization

Quality control is critical for ensuring safety and efficacy of herbal drugs. Pharmacognostic evaluation includes macroscopic and microscopic analysis, physicochemical parameters, and chromatographic fingerprinting. Standardization minimizes batch-to-batch variation and enhances clinical reliability.

6. Sustainability and Conservation of Medicinal Plants

Overharvesting and habitat loss threaten nearly 15% of medicinal plant species worldwide. Sustainable cultivation, good agricultural and collection practices, and conservation strategies are essential to preserve biodiversity while meeting increasing demand.

7. Discussion

Pharmacognosy bridges traditional knowledge and modern science, enabling systematic validation of medicinal plants. Advances in analytical technologies have improved phytochemical characterization and therapeutic correlation. However, challenges remain in standardization, clinical validation, and sustainable sourcing. Integrating pharmacognosy with biotechnology and computational approaches can accelerate drug discovery and ensure

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long-term viability of plant-based medicines.

8. Conclusion

Pharmacognosy of medicinal plants plays a vital role in healthcare and pharmaceutical development. Phytochemical profiling provides scientific evidence for therapeutic claims and supports quality assurance of herbal drugs. With increasing global reliance on natural medicines, robust pharmacognostic research, sustainable practices, and interdisciplinary collaboration are essential for translating traditional remedies into safe and effective therapeutics.

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Chapter 12

Fabry Disease: Molecular Mechanisms and Emerging Therapeutic Approaches

Albin Binu[1], Sri Ram Chandru.A[2], V.Jayashree[3*]

[1,2]Pharm D Student, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai, India

*[3]*Associate Professor, Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai, India*

ABSTRACT:

Fabry Disease is a rare X-linked inherited metabolic disorder caused by mutations in the *GLA* gene, which result in deficient activity of the lysosomal enzyme α-galactosidase A. The enzymatic deficiency leads to progressive accumulation of glycosphingolipids, particularly globotriaosylceramide (Gb3), within lysosomes of various cell types. This accumulation contributes to multisystem involvement affecting the kidneys, heart, nervous system, and skin. Clinical manifestations may include neuropathic pain, angiokeratomas, renal dysfunction, cardiomyopathy, and cerebrovascular complications. Due to the variability of symptoms and lack of awareness, the disease is frequently underdiagnosed, especially in developing countries. Advances in molecular biology have improved the understanding of the underlying pathogenic mechanisms and facilitated the development of targeted therapeutic strategies. Current treatment primarily involves enzyme replacement therapy aimed at restoring α-galactosidase A activity and reducing substrate accumulation. In addition, emerging therapeutic approaches such as pharmacological

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chaperone therapy, gene therapy, and substrate reduction therapy are being investigated to provide more effective and long-term management options. This chapter discusses the molecular mechanisms underlying Fabry disease, its clinical manifestations, diagnostic approaches, and recent advances in therapeutic strategies, highlighting future perspectives for improved patient outcomes.

Keywords: *Fabry disease, α-galactosidase A deficiency, globotriaosylceramide (Gb3), enzyme replacement therapy, gene therapy.*

1. INTRODUCTION:

Fabry disease is an X-linked genetic disorder that impacts glycosphingolipid metabolism. The disorder arises from alterations in the galactosidase alpha (GLA) gene found on the X chromosome. The GLA gene encodes an enzyme known as α-galactosidase (AGAL), which is located in lysosomes. AGAL's role is to metabolize a sphingolipid known as globotriaosylceramide, referred to as Gb3 or GL3. Consequently, in Fabry disease, Gb3 is not broken down, leading to its accumulation in various tissues, including lysosomes. Lysosomes exist in various cell types in the heart (cardiomyocytes and fibroblasts), the kidneys (podocytes, tubular cells and glomerular endothelium), capillary endothelial cells, and neurons.

Endothelial cell growth and swelling are common in patients with this illness, which can result in heart disease, stroke, and renal failure in their third or fourth decade of life, or early death. The primary illness process is expected to start in infancy, while some experts suggest that it may have started during foetal life. Still, many people with Fabry disease do not exhibit any symptoms throughout their early

years of life, despite the evolution of many other lysosomal storage illnesses. Between the ages of three and ten, the first indications and symptoms that affect a child's overall condition and performance typically manifest in boys a few years earlier than in girls. Over time, cell damage and lysosomal accumulation worsen, impacting essential organs and eventually resulting in organ failure. End-stage kidney failure and cardiovascular consequences are the most serious and potentially fatal conditions.

Fabry disease was long thought to primarily affect men; women were only thought to be “carriers of the affected gene”. However, a number of studies show that women can exhibit a range of symptoms, from almost asymptomatic to the "classical" phenotype, with varying degrees of intensity and variability. Males typically have the "classical" phenotype, but cases with more severe cardiac involvement or renal manifestations.

Preventing permanent organ damage and stopping the disease's progression are the fundamental objectives of FD therapy. Enzyme replacement therapy (ERT) and the pharmacological chaperone migalastat are examples of disease-specific treatments that are essential. ERT has greatly improved the management of FD, reduced a number of symptoms and extended life expectancy by replacing or restoring inadequate enzyme activity. For FD patients with vulnerable mutations linked to low residual α-Gal A activity, migalastat, an oral chaperone, has been found to be especially helpful.

2. EPIDEMIOLOGY

In total, over fifty lysosomal storage diseases have been identified and described biochemically and genetically, including Fabry disease. Fabry disease is ranked second after Gaucher disease in terms of the

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frequency of these lysosomal storage disorders. The precise incidence of this illness is unknown, and because some people are not diagnosed, the prevalence may be underestimated in the existing data. Many individuals with Fabry disease do not receive an accurate diagnosis and their symptoms are mistakenly attributed to other disorders due to limited access of genetic testing.

The incidence of Fabry hemizygotes was reported to be 1:117 000. Although the incidence of heterozygotes was not indicated, a combined incidence of 1:58 000 can be calculated by projecting the finding in hemizygotes.

Other research revealed different numbers, but the methods employed to figure out them also differed. A notable high prevalence of the condition was discovered when attempting to calculate the incidence using newborn screening, such as in Italy, where one in 3100 people had the illness. One in 1500 newborn men had Fabry disease, according to another study, and the majority of them had the IVS4+919G>A mutation, which is thought to determine cardiac phenotype with later onset.

It was thought to look for individuals with Fabry disease among people with end-stage renal disease (ESRD) receiving haemodialysis because renal failure and cardiovascular illnesses are the most prevalent symptoms. The prevalence of Fabry disease in haemodialysis patients was found to be 0.22% in retrospective research involving 105 male patients. Based on similar assumptions, a Japanese study found that 1.2% of male dialysis patients had Fabry disease.

3. Genetic Basis:

A result of a mutation in the GLA gene, FD is a monogenic, recessive

inheritance condition associated with the X chromosome. This gene, which is found at location Xq22 on the long arm of the X chromosome, codes for the α-GAL enzyme. New mutations are uncommon, and the majority of instances are inherited. The disease has been linked to more than 900 distinct mutations.

Gb3 is broken down into galactose and lactosylceramide in the lysosomes by α-GAL, which has about 429 amino acids. As a result, GB3 accumulates in several tissues in FD patients. It has a preference for kidney podocytes and the vascular endothelium and smooth muscle cells of the cardiovascular system, which explains why these organs are more frequently affected by clinical symptoms.

The α-GAL gene is roughly 12 kb long and has seven exons. A variety of molecular mutations in this gene, including missense (57%), nonsense (11%), partial deletions (6%), insertions (6%), and abnormalities in RNA processing that result in aberrant splicing's (6%), can cause FD. Because diverse clinical symptoms might result from the same mutation, the relationship between genotype and phenotype is complicated. Both the blood group and environmental variables may be responsible for this. Due to an extra buildup of glycosphingolipids in the membrane of blood group B erythrocytes, patients with blood groups AB or B may exhibit more severe illness presentations.

4. PATHOPHYSIOLOGY:

Despite the accumulation of Gb3 during α-GalA deficiency is known to occur in lysosomes, not much information is known regarding the mechanisms that lead to cellular malfunction and ultimately to symptoms. Lipid-laden lysosomes may affect autophagic flux, including mitophagy, as with other inherited glycosphingolipidoses,

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which may contribute to the mitochondrial dysfunction seen in FD patients' fibroblasts. In a similar way the observed elevation of the unfolded protein response in cells of certain FD patients may indicate endoplasmic reticulum malfunction. Oxidative stress, inflammation, and fibrosis appear to be important pathogenic factors.

LysoGb3 has been proposed as a potential pathogenic factor in FD. For both classic male and female FD patients, lysoGb3 lifetime exposure was found to be significantly correlated with overall disease severity. In fact, lysoGb3 stimulates the growth of smooth muscle cells, which is consistent with the increased arterial stiffness and intima media thickness in FD. Additionally, it has been demonstrated that lysoGb3 destroys nociceptive neurones at the levels found in FD males, which is compatible with the reported pain in the extremities of classic FD males. The upper limb's thermal sensory limen and cold detection threshold were found to be highly correlated with lifetime exposure to lysoGb3. Following that, it is believed that lysoGb3 plays a role in glomerulus fibrosis and podocyte loss, two significant features of renal illness in FD patients. Finally, it has been discovered that lysoGb3 inhibits endothelial nitric oxide synthase (eNOS) at concentrations similar to those in FD patients, potentially contributing to the vasculopathy in FD.

5. Clinical Manifestations:

The build-up of Gb3 in the nervous systems tiny nerve fibres is what causes the initial symptoms to manifest in early childhood. One of the first signs of Fabry disease is pain, which is reported by 60–80% of boys and girls who are classically affected. Boys typically exhibit symptoms at younger ages. The Fabry disease is characterised by two forms of pain: (i) episodic crises, also referred to as "Fabry crises,"

which are defined as burning pain that starts in the extremities of the body (ii) persistent discomfort with burning sensations and paraesthesia in the extremities. Fabry crises can be brought on by a number of things, including exhaustion, stress, physical activity, fever, and abrupt temperature changes.

Gastrointestinal symptoms, which begin in childhood and persist until adulthood, are typical after pain. They include diarrhoea, nausea, vomiting, and stomach pain, particularly after eating. Gb3 buildup in the mesenteric blood vessels may be the cause of these symptoms, which could result in anorexia.

Skin lesions, such as angiokeratoma and clusters of red-purple capillary vascular lesions, are another very distinctive characteristic that can be seen from childhood. They are seen on the buttocks, upper thighs, inguinal region, umbilical zone, and even mucosal areas like the mouth. These are tiny superficial angiomas, and the injury to the vascular endothelial cells causes the skin's vessels to dilate. They range in size from a pinpoint to several millimetres, and as they become older, both their size and quantity increase.

6. DIAGNOSIS:

The clinical management of FD patients depends on the monitoring of disease symptoms and the effectiveness of FD treatment. Clinical, radiographic, and laboratory analysis can be used to determine the beginning and course of a disease. However, because patient variability is so significant, it might be difficult to evaluate a therapeutic treatment's effectiveness. Furthermore, some severe effects of FD, like advanced renal failure, cannot be reversed. However, biomarkers are crucial for monitoring illness and treatment.

Identification of GLA gene mutations causing a missing or clearly

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defective α-GalA protein is a simple way to diagnose classic FD in men. Using artificial water-soluble substrates like 4-methylumbelliferyl-α-galactoside, it is easy to demonstrate extremely low α-GalA activity in leukocytes, fibroblasts, and dried blood spots. To further confirm the diagnosis, increased levels of Gb3 and lysoGb3 in plasma and urine can be found. For FD females, especially those with negatively skewed X-inactivation, enzyme activity tests are not usually useful. The diagnosis of FD in females can then be confirmed with the detection of increased lysoGb3. The diagnosis of atypical FD patients who arrive with an uncommon symptom (such as albuminuria, left ventricular enlargement, or white matter abnormalities) in addition to a GLA gene mutation with unclear effect is challenging. This is frequently accompanied by a comparatively high residual enzyme activity in cells and no obvious anomaly in the amounts of Gb3 and lysoGb3 in the plasma or urine. In difficult situations, biopsy analysis and Gb3 deposit demonstration are thought to be useful in supporting diagnosis.

Biopsies of various FD patients' tissues may also indicate the illness. The presence of cytoplasmic vacuoles containing the lipids can be observed using optical microscopy. Electronic microscopy reveals lysosomal inclusions with a lamellar structure. Immunoelectron microscopy can be used to look for anti-Gb3 antibodies when these results are contradictory.

7. Current Treatment:

Approved treatments such as enzyme replacement therapy (ERT) and chaperone therapy work to reduce intracellular Gb3 accumulation by replacing the deficient α-galactosidase A enzyme or stabilizing misfolded enzyme forms, thereby enhancing their transport and

enzymatic activity within lysosomes.

7.1. Enzyme Replacement Therapy (ERT): Purified human placental AGAL was successfully given to two FD patients by Brady and others in 1973, marking the first attempts at ERT. The infusion was well tolerated by both patients, and AGAL activity rose by roughly 68% over pre-infusion values. Over time, two brothers with FD were given human plasma and spleen-derived AGAL. Up to 70% of Gb3 was cleared after plasma-derived AGAL was administered. Clinical research advancement was constrained by the difficult purification and restricted supply of human AGAL for infusion. Agalsidase-alfa which is produced in a human cell line (human fibrosarcoma cells HT-1080) with an approved dosage of 0.2 mg/kg body weight and an infusion duration of about 40 minutes, and agalsidase-beta (Fabrazyme, Sanofi Genzyme), which is produced in Chinese hamster ovary (CHO) cells with a recommended dose of 1.0 mg/kg body weight and an infusion duration of about 240 minutes. The following therapeutic effects can be achieved with ERT, depending on the patients and their manifestations: stabilisation of kidney function or delay of progression to terminal kidney failure, stabilisation of the thickness of the heart wall and function or reduction of left ventricular hypertrophy, and improvement in sweating.

7.2. Chaperone Therapy: Reduced intracellular AGAL activities are frequently caused by missense mutations in the GLA gene, which produce an unstable and misfolded protein. Misfolded proteins will prematurely degrade before they reach the lysosomes because they cannot pass the endoplasmic reticulum's (ER) protein quality-control process. Pharmacological chaperones, which bind reversibly to the protein's active core, can be employed to restore the protein's folding and stability. It is initially discovered as a competitive inhibitor of the

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AGAL enzyme, the small molecule 1-deoxygalactonojirimycin (DGJ) is an iminosugar. The binding to the catalytic center of the enzyme (wild-type and susceptible mutations) enhances protein folding in the ER and accelerates maturation and trafficking to the lysosome at sub-inhibitory concentrations (extracellular: 20–100 μM). This causes an increase in enzymatic AGAL activity in both healthy control cells.

8. Emerging Therapeutic Approaches:

8.1. Next Generation ERTs: Pegunigalsidase alfa is a new version of AGAL that is covalently cross-linked and PEGylated (PEG, polyethylene glycol). It was created as an ERT for FD and made in tobacco cells with longer in vitro stability and a tenfold longer half-life in male Fabry mice (581 min) than licensed medications, pegunigalsidase appears to behave similarly to the ERTs currently on the market. Increased efficacy was found in a 1-year phase I/II clinical trial (dose-finding study) as a result of decreased immunogenicity and a longer plasma half-life (80 h). Because PEGylation stabilises the AGAL homodimer and improves its half-life (80 h), it may be possible to lengthen the infusion interval (monthly IV administration).

8.2. Substrate Reduction Therapy: While migalastat increases endogenous enzyme activities of AGAL due to amenable mutations and ERT seeks to replace missing or defective AGAL through the infusion of a genetically engineered enzyme, substrate reduction therapy (SRT) aims to reduce the substrate and, consequently, inhibit Gb3 accumulation in the cells. Lucerastat (Idorsia) is a low molecular weight iminosugar that inhibits the manufacture of glycosphingolipids, including downstream Gb3, by blocking the upstream-located glucosylceramide synthase (GCS). This suggests a

possible new oral therapy option. The initial in vitro research showed that fibroblasts generated from FD patients successfully reduced Gb3 and improved abnormal cellular membranes.

8.3. Gene Therapy: DNA containing the genetic code for the AGAL protein is introduced into patients' cells as part of gene therapy. The safety of gene therapy for FD is now being assessed in a number of clinical trials using varying therapeutic modalities. The lentiviral ex vivo transduction of haematopoietic stem cells is the foundation of the first interventional, multicenter, global, open-label trial. The goal of this strategy is to produce functional AGAL using transfected haematopoietic stem cell-derived cells, which will then be released into the plasma and taken up by AGAL-deficient cells. Adeno-associated virus (AAV) in vivo transduction of hepatocytes, utilising these cells as an AGAL-secreting platform rather than cells produced from haematopoietic stem cells, is the basis for two more clinical investigations.

9. Conclusion

Fabry disease is a rare X-linked lysosomal storage illness caused by mutations in the GLA gene that result in a shortage of the enzyme α-galactosidase A. Globotriaosylceramide (Gb3) gradually builds up in many tissues as a result of this enzymatic deficiency, causing multisystem involvement that affects the kidneys, heart, nervous system, and vascular endothelium. From early symptoms like neuropathic pain, gastrointestinal issues, and angiokeratomas to serious consequences including renal failure, cardiomyopathy, and cerebrovascular accidents, Fabry disease's clinical presentation is quite varied.

Recent advancements in gene therapy, substrate reduction therapy,

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and next-generation enzyme replacement medicines present encouraging opportunities for enhancing long-term illness management. These new methods seek to improve therapeutic efficacy, lessen the burden of treatment, and possibly offer longer-lasting repair of the underlying enzyme deficiency. To enhance clinical results and quality of life for Fabry disease patients, early diagnosis, prompt therapeutic intervention, and ongoing research into innovative treatment approaches are crucial.

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Dr.V.Jayashree is an Associate Professor of Pharmacology at the School of Pharmaceutical Sciences, VISTAS, Chennai. She holds a Ph.D. in Pharmacology and has over a decade of teaching and research experience. Her primary research interest lies in oncology studies. She has published 31 research papers in reputed databases, four books, and eleven book chapters, and holds patents in pharmaceutical innovations. She has guided around 3 Ph.D scholars, guiding 5 Ph.D Scholars and guided 7 undergraduate projects. Dr. Jayashree has received several prestigious awards for excellence in teaching and research, recognizing her significant contributions to pharmaceutical education and cancer research.

Dr. Jaya Vasavi G is an Assistant Professor in the Department of Pharmaceutics at the School of Pharmaceutical Sciences, VISTAS, Chennai, Tamil Nadu, with 14 years of teaching and research experience. She completed her M.Pharm and Ph.D. in Pharmaceutics from Vels University, VISTAS. Her research focuses on nano drug delivery systems. She has authored 6 books, 2 book chapters, holds 6 patents, and published 20 research and review papers in national and international journals. She has received the Icon of Tamil Nadu Award (2023), Research Excellence and Young Teacher Awards (2024), and Young Scientist Award (2025). She is a Registered Pharmacist (Reg. No: 056961/A1) and a Life Member of APTI.

Dr. Vijayakumar Murugesan He is an experienced professional in technology transfer, holding a Master's degree in Pharmacy from BITS Pilani. With over 19 years of expertise, he has significantly contributed to Research & Development and technology transfer, particularly in the area of cancer drug formulations. His core competencies include process optimization, scale-up, and ensuring regulatory compliance, facilitating a seamless transition from development to commercialization. Currently pursuing a Ph.D. in Regulatory Affairs, specializing in cosmetics, he is deepening his understanding of global regulatory standards. He is also actively engaged in pioneering research focused on advancing cancer drug formulations, with a strong emphasis on enhancing efficacy, safety, and patient outcomes.

Dr.S.Hemalatha, Professor and Head of Pharmacy Practice at Karpagam Academy of Higher Education, Coimbatore, specializes in chronic disease management, clinical pharmacokinetics, therapeutic drug monitoring, and patient-centered care. Her research focuses on tuberculosis, diabetes, cardiovascular disorders, HIV/AIDS, and adverse drug reactions. She has published extensively, contributed book chapters, and holds patents in healthcare innovations. Dr. Hemalatha has supervised numerous Pharm.D projects and organizes academic programs. Her current interests include artificial intelligence, machine learning, and digital tools to enhance clinical pharmacy practice and research.

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