ISBN: 978-81-989981-3-2

PROGRESSIVE TRENDS IN PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES VOLUME II

Editors:
Dr. Ghanshyam Parmar
Dr. Ganesh D. Satpute
Dr. Rakhi B. Shambharkar
Dr. N. Jyothi

Bhumi Publishing, India
First Edition: July 2025

Progressive Trends in Pharmaceutical, Chemical and Biological Sciences

Volume II

(ISBN: 978-81-989981-3-2)

Editors

Dr. Ghanshyam Parmar

Department of Pharmacy

Sumandeep Vidyapeeth Deemed to be

University, Piparia, Vadodara, Gujarat

Dr. Ganesh D. Satpute

Department of Chemistry,

Shri. Govindrao Munghate Arts and

Science College, Kurkheda, M.S.

Dr. Rakhi B. Shambharkar

Department of Botany,

Shri. Govindrao Munghate Arts

and Science College, Kurkheda, M.S.

Dr. N. Jyothi

Departmet of Chemistry,

Government Degree College,

Badangpet, Dist. Rangareddy, Telangana

Bhumi Publishing

July 2025

Title: Progressive Trends in Pharmaceutical, Chemical and Biological Sciences Volume II

Editors: Dr. Ghanshyam Parmar, Dr. Ganesh D Satpute,

Dr. Rakhi B. Shambharkar, Dr. N. Jyothi

First Edition: July 2025

ISBN: 978-81-989981-3-2

Published by:

Bhumi Publishing

BHUMI PUBLISHING

Nigave Khalasa, Tal – Karveer, Dist – Kolhapur, Maharashtra, INDIA 416 207

E-mail: bhumipublishing@gmail.com

PREFACE

We are delighted to present this book titled Progressive Trends in Pharmaceutical, Chemical and Biological Sciences, an edited volume that brings together emerging perspectives, innovative research, and recent advancements across these interconnected disciplines. The rapid pace of scientific progress in pharmaceutical, chemical, and biological sciences has led to significant breakthroughs impacting human health, environment, and industrial applications. This compilation aims to provide a comprehensive platform for academicians, researchers, industry professionals, and students to understand current developments and future directions in these fields.

The chapters included in this book address a diverse range of topics, including novel drug delivery systems, synthesis and characterization of new chemical entities, green chemistry approaches, molecular biology techniques, biotechnological applications, and interdisciplinary research trends. Each contribution has been rigorously reviewed to maintain academic integrity and relevance. The authors have shared their expertise, experimental insights, and critical analyses to foster an integrated understanding of concepts and their practical implications.

This book is designed to inspire young researchers to undertake multidisciplinary studies that address global challenges such as sustainable development, environmental safety, drug discovery for unmet medical needs, and improvement of quality of life. It serves as a valuable reference for postgraduate students, research scholars, and faculty members seeking updated information and research methodologies in these fast-evolving domains.

We express our sincere gratitude to all the contributing authors for their timely submissions and scholarly efforts, and to the editorial board members and reviewers for their meticulous evaluation, constructive suggestions, and support throughout the publication process. We are thankful to the publisher for their encouragement and professional assistance in bringing this book to fruition.

We hope that Progressive Trends in Pharmaceutical, Chemical and Biological Sciences will motivate its readers to explore new ideas, initiate collaborative research, and contribute effectively towards scientific advancement. We welcome constructive feedback and suggestions for future editions to further enrich the academic value of this work.

- Editors

TABLE OF CONTENT

Sr. No.	Book Chapter and Author(s)	Page No.
1.	**THERANOSTIC NANOMEDICINE FOR DRUG DELIVERY AND DIAGNOSIS** Piyushkumar Sadhu	1 – 13
2.	**AGE-ASSOCIATED PHARMACOKINETICS: IMPLICATIONS FOR SAFE PRESCRIBING** Dilsar Gohil, Rajesh Maheshwari	14 – 22
3.	**EGPA: A DISEASE OF MANY FACES—FROM AIRWAY INFLAMMATION TO SYSTEMIC VASCULITIS** Cyril Sajan, Krupa Joshi, Hemraj Singh Rajput	23 – 35
4.	**FUTURE PERSPECTIVE ON EPILEPSY** Varunsingh Saggu, Hemraj Singh Rajput	36 – 50
5.	**EXOSOME-BASED DRUG DELIVERY: NATURAL NANOCARRIERS IN PHARMACEUTICS** Mamta Kumari, Piyushkumar Sadhu, Chitrali Talele, Niyati Shah	51 – 63
6.	**GREEN NANOTECHNOLOGY IN DRUG DELIVERY FORMULATIONS** Chitrali Talele, Dipali Talele, Mamta Kumari, Nirmal Shah	64 – 74
7.	**NEUROBEHAVIORAL NURTURING: THE ROLE OF PHYSIOTHERAPY IN PRETERM INFANT DEVELOPMENT** DHWANI CHANPURA	75 – 84
8.	**ROS-RESPONSIVE NANOCARRIERS FOR INFLAMMATORY DISEASES** Chintan Aundhia	85 – 96
9.	**BOILING POINT: DEFINITION, MECHANISM, INFLUENCING FACTORS, AND APPLICATIONS IN CHEMICAL AND INDUSTRIAL PROCESSES** Shivkant Patel, Dillip Kumar Dash, Krupa Joshi, Surabhi Jain	97 – 107

10.	**GLP-1 RECEPTOR AGONISTS: THE NEXT-GENERATION APPROACH TO METABOLIC AND NEURODEGENERATIVE DISEASE TREATMENT** Aarti Sachin Zanwar, Dhanya B. Sen, Krupa Joshi Tamanna Chhabra	108 – 117
11.	**NEPHROBLASTOMA (WILMS TUMOR): A COMPREHENSIVE OVERVIEW** Kailashgiri I Goswami	118 – 123
12.	**RADIOPHARMACEUTICAL APPLICATIONS IN ONCOLOGY: DIAGNOSTICS AND THERAPEUTICS** Yuvraj Maharshi	124 – 134
13.	**HERBAL PLANTS AND THEIR ROLE IN PREVENTING RHEUMATOID ARTHRITIS** Sunil Kardani, Ghanshyam Parmar, Sunil Baile, Hadia Rajesh	135 – 147

Progressive Trends in Pharmaceutical, Chemical and Biological Sciences Volume II
(ISBN: 978-81-989981-3-2)

THERANOSTIC NANOMEDICINE FOR DRUG DELIVERY AND DIAGNOSIS

Piyushkumar Sadhu
Department of Pharmaceutics, Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara – 391760
Corresponding author E-mail: piyush.sadhu@yahoo.in

Abstract:
Theranostic nanomedicine represents a paradigm shift in personalized healthcare by integrating therapeutic and diagnostic functions into a single nanoplatform. These advanced nanosystems enable simultaneous drug delivery and real-time monitoring of therapeutic responses, offering unprecedented precision in disease management, particularly in oncology, neurodegenerative disorders, and cardiovascular diseases. Nanocarriers such as liposomes, dendrimers, polymeric nanoparticles, metal-organic frameworks, and quantum dots are engineered to encapsulate both therapeutic agents and imaging probes, allowing site-specific delivery and non-invasive tracking via modalities like MRI, PET, CT, and fluorescence imaging. The incorporation of targeting ligands further enhances the specificity of these systems, minimizing off-target effects and improving therapeutic indices. Recent advances have highlighted the role of stimuli-responsive theranostic carriers that release their payload in response to internal (pH, enzymes, redox) or external (temperature, light, magnetic field) stimuli. Despite the promising potential, challenges such as large-scale synthesis, regulatory hurdles, biosafety, and reproducibility limit their clinical translation. This chapter provides a comprehensive overview of theranostic nanomedicine, focusing on design principles, classification, mechanisms, imaging modalities, and therapeutic applications. It also critically analyzes current research trends, regulatory landscapes, and translational challenges, while offering insights into future directions for integrating artificial intelligence and personalized nanomedicine in theranostic development.

Keywords: Theranostics, Diagnostic Imaging, Targeted Therapy, Personalized Medicine, Stimuli-Responsive Systems, Dual-Function Nanocarriers

Introduction:

Theranostic nanomedicine is an interdisciplinary field that merges therapy and diagnostics within a single nanoscale platform, allowing for simultaneous disease treatment and real-time monitoring of therapeutic efficacy. The term *theranostics* originates from a combination of the words *therapy* and *diagnostics*, reflecting its dual-functional approach. The concept gained significant attention in the early 2000s, although its foundational idea can be traced back to the use of radioisotopes in nuclear medicine for both imaging and treatment. The integration of nanotechnology into theranostics marked a turning point, enabling enhanced delivery, cellular specificity, and the convergence of imaging and therapeutic capabilities at the molecular level

[1]. The evolution of nanomedicine brought forth a variety of nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, quantum dots, gold nanoparticles, and magnetic nanostructures, each capable of being engineered for both drug loading and imaging contrast enhancement. Early milestones in theranostics included the development of iron oxide nanoparticles for MRI-based tumor imaging combined with chemotherapy and gold nanoshells for photothermal ablation and imaging. These systems demonstrated not only improved pharmacokinetics and biodistribution but also opened new avenues for non-invasive, image-guided therapy [2].

Theranostic nanomedicine plays a crucial role in the advancement of precision and individual's genetic profile, disease subtype, and real-time response to therapy. Traditional one-size-fits-all approaches often result in suboptimal outcomes due to variability in patient response. Theranostic nanoplatforms address this gap by enabling targeted delivery of therapeutic agents to specific tissues or cells, while simultaneously providing diagnostic feedback through imaging signals. This dual-functionality allows clinicians to visualize biodistribution, monitor drug release, assess therapeutic efficacy, and adjust dosages dynamically, all of which are pivotal for personalized care. Moreover, theranostic systems can be functionalized with biomarkers or ligands that recognize disease-specific receptors, enhancing selectivity and minimizing systemic toxicity. In oncology, for instance, this enables the detection of tumor heterogeneity and metastasis, followed by real-time tracking of tumor regression during chemotherapy or radiotherapy. The integration of theranostics into clinical workflows fosters a more informed, adaptive, and individualized treatment approach, ultimately improving clinical outcomes and reducing healthcare costs. As technologies evolve, theranostic nanomedicine is expected to serve as a cornerstone in the era of next-generation personalized therapeutics and diagnostics [3,4].

Design Principles of Theranostic Nanocarriers

The successful integration of therapeutic and diagnostic functions within a single nanosystem relies heavily on sophisticated design strategies that ensure biocompatibility, stability, targeting capability, and multifunctionality. Theranostic nanocarriers must be engineered to encapsulate or conjugate therapeutic agents and imaging probes without compromising either functionality. The core design principles include core-shell architectures, surface modifications, and dual cargo loading mechanisms, each tailored to maximize therapeutic efficacy, imaging sensitivity, and target specificity.

Core-Shell Structures

Core-shell nanostructures represent a fundamental architectural design in theranostic systems, offering a compartmentalized framework for housing therapeutic and diagnostic components. Typically, the core serves as a reservoir for imaging agents (e.g., magnetic nanoparticles, quantum dots, radionuclides), while the shell encapsulates or conjugates therapeutic agents (e.g.,

chemotherapeutics, siRNA, peptides) and provides protection from premature degradation. This spatial separation enhances the stability of sensitive payloads and prevents unwanted interactions between therapeutic and diagnostic agents [5]. Furthermore, the shell can be designed to be stimuli-responsive, enabling controlled drug release upon exposure to specific triggers such as pH, temperature, redox potential, or enzyme activity. Examples of core-shell nanocarriers include gold nanoshells, silica-coated magnetic nanoparticles, and polymeric micelles with hydrophobic cores and hydrophilic coronas [6].

Surface Functionalization and Ligand Targeting

Surface engineering is critical for imparting targeting specificity, prolonged circulation time, and stealth properties to theranostic nanocarriers. Functionalization involves the attachment of specific ligands such as antibodies, peptides, aptamers, or small molecules that recognize and bind to overexpressed receptors on diseased cells (e.g., folate receptor, transferrin receptor, HER2). This ligand-receptor interaction facilitates active targeting, enhancing cellular uptake at the diseased site while minimizing off-target effects. Additionally, coating the nanoparticle surface with hydrophilic polymers like polyethylene glycol (PEG) helps evade the mononuclear phagocyte system (MPS), prolonging systemic circulation and improving bioavailability a concept known as PEGylation. Advanced strategies also include multifunctional surfaces, where multiple ligands or diagnostic markers are incorporated to achieve dual or multi-targeting capabilities, and cell-penetrating peptides (CPPs) are added to improve intracellular delivery [7,8].

Encapsulation of Therapeutics and Imaging Agents

An essential aspect of theranostic nanocarrier design is the co-delivery of drugs and imaging agents within a unified platform. The loading strategies depend on the physicochemical properties of the cargo and the carrier material. Hydrophilic drugs and imaging agents are typically encapsulated in the aqueous core or hydrophilic compartments, while hydrophobic molecules are loaded into the lipid bilayer or polymer matrix. Imaging agents such as gadolinium (MRI), fluorophores (optical imaging), radionuclides (PET/SPECT), or iron oxide nanoparticles (MRI) are either physically entrapped or chemically conjugated to the nanocarrier [8]. Therapeutic agents, on the other hand, are loaded using adsorption, encapsulation, or covalent linkage, depending on the release kinetics desired. Some platforms are designed for sequential or co-release of agents, triggered by stimuli at the target site, ensuring the diagnostic imaging occurs prior to or in synchrony with therapeutic action. This strategic co-loading allows for real-time monitoring of drug biodistribution, accumulation, and therapeutic response, making treatment highly adaptable and efficient [9].

Types of Theranostic Nanoplatforms

Theranostic nanomedicine encompasses a broad spectrum of nanocarriers engineered to simultaneously deliver therapeutic agents and diagnostic probes. The choice of nanoplatform depends on several factors, including drug loading capacity, biocompatibility, imaging modality, circulation time, and target specificity. The following section details the major classes of theranostic nanocarriers, highlighting their unique structural attributes and functional potential in integrated therapy and diagnostics.

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are one of the most versatile and extensively studied theranostic platforms, constructed from biodegradable and biocompatible polymers such as polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), polycaprolactone (PCL), and polyethylene glycol (PEG). These nanoparticles can be engineered as nanospheres or nanocapsules depending on the method of drug incorporation. Therapeutic agents are either encapsulated within the polymeric matrix or adsorbed on the surface, while imaging agents such as fluorophores, gadolinium, or iron oxide can be incorporated simultaneously. Functionalization with targeting ligands enables site-specific delivery and enhanced cellular uptake. The flexibility in polymer selection and surface modification makes PNPs ideal candidates for stimuli-responsive and multi-modal theranostic systems [10,11].

Liposomes and Micelles

Liposomes are spherical vesicles composed of phospholipid bilayers, capable of encapsulating both hydrophilic drugs (in the aqueous core) and hydrophobic drugs (within the lipid bilayer). Their biocompatibility and structural similarity to cell membranes make them suitable for clinical translation. Liposomes can be modified with targeting ligands or polyethylene glycol (PEG) to enhance stability and targeting efficiency. Micelles, in contrast, are formed by the self-assembly of amphiphilic block copolymers in aqueous media, resulting in a hydrophobic core and hydrophilic shell. This core can solubilize poorly water-soluble drugs, while imaging agents such as near-infrared dyes or radionuclides can be incorporated for real-time imaging. Micellar systems are particularly effective in passive tumor targeting through the enhanced permeability and retention (EPR) effect, and their small size (~10–100 nm) allows deep tissue penetration [12].

Metal-Based Nanoparticles (Gold, Iron Oxide, Quantum Dots)

Metal-based nanocarriers are widely employed in theranostics due to their unique optical, magnetic, and electronic properties, making them excellent contrast agents in various imaging modalities.

- Gold nanoparticles (AuNPs) possess strong surface plasmon resonance (SPR), enabling use in photoacoustic imaging, CT, and photothermal therapy (PTT). Their surface is easily functionalized for drug conjugation and targeting.
- Iron oxide nanoparticles (IONPs) are superparamagnetic materials used predominantly in magnetic resonance imaging (MRI). They can be combined with chemotherapeutics to form magnetically guided and image-trackable delivery systems.
- Quantum dots (QDs) are semiconductor nanocrystals with exceptional fluorescence stability and tunable emission, making them suitable for fluorescence imaging. However, concerns about heavy metal toxicity have limited their clinical applicability [13,14].

Dendrimers and Hybrid Nanostructures

Dendrimers are highly branched, monodisperse macromolecules with a well-defined core-shell structure and a large number of surface functional groups. Commonly used dendrimers include polyamidoamine (PAMAM) and polypropylene imine (PPI). Their architecture allows precise control over size, shape, and surface chemistry, enabling multi-drug loading, gene delivery, and conjugation with imaging agents or targeting ligands [15]. Hybrid nanostructures combine two or more nanomaterials such as polymers with metals, lipids with inorganic cores, or silica with magnetic elements to exploit the advantages of each component. For example, lipid-coated gold nanoparticles, silica-coated quantum dots, and polymer-metal hybrid micelles offer enhanced theranostic performance, improved stability, and tailored drug release profiles. These platforms are emerging as promising candidates for customized, multifunctional nanomedicine [16].

Mechanisms of Action

Theranostic nanocarriers employ sophisticated delivery mechanisms to ensure site-specific accumulation, controlled release, and efficient cellular internalization of both therapeutic and diagnostic agents. These mechanisms are crucial to maximize treatment efficacy, minimize systemic toxicity, and enable real-time monitoring of therapeutic response. This section discusses the primary strategies by which theranostic nanocarriers function at the biological interface.

Passive and Active Targeting

Passive targeting exploits the enhanced permeability and retention (EPR) effect, a phenomenon observed in tumors and inflamed tissues characterized by leaky vasculature and poor lymphatic drainage. Nanoparticles in the size range of 10–200 nm can accumulate preferentially in such pathological tissues due to their prolonged circulation and ability to extravasate through fenestrated blood vessels. This mechanism is particularly advantageous in solid tumors and inflammatory diseases, allowing non-specific but preferential delivery of nanotherapeutics without the need for targeting ligands [17].

In contrast, active targeting involves the surface functionalization of nanocarriers with ligands that bind specifically to overexpressed receptors on target cells (e.g., folate receptor, HER2, integrins). Ligands used include antibodies, peptides, aptamers, and small molecules, which facilitate receptor-mediated endocytosis and improve cellular specificity and uptake. Active targeting is often combined with passive targeting for synergistic effects, improving therapeutic index and enabling precise imaging of disease-specific biomarkers [18].

Stimuli-Responsive Release Mechanisms

Stimuli-responsive nanocarriers are designed to release their payloads selectively in response to specific internal or external stimuli, thus ensuring on-demand and site-specific drug activation. This intelligent release mechanism improves therapeutic outcomes and reduces systemic side effects [19].

Internal Stimuli-Responsive Systems:

- pH-sensitive nanocarriers exploit the acidic environment of tumors (pH ~6.5) or endosomes/lysosomes (pH ~5.0–5.5) to trigger release.
- Redox-responsive systems are designed to degrade in response to high intracellular glutathione (GSH) levels, common in cancer cells.
- Enzyme-sensitive carriers respond to overexpressed enzymes like matrix metalloproteinases (MMPs) or cathepsins for targeted degradation and drug release [20].

External Stimuli-Responsive Systems:

- Thermo-responsive systems release drugs in response to localized hyperthermia (e.g., ≥42°C).
- Photo-responsive nanocarriers respond to specific light wavelengths, enabling spatiotemporal control.
- Magnetic and ultrasound-responsive carriers can be guided or activated via external fields for controlled release and imaging enhancement [21].

Cellular Uptake and Intracellular Trafficking

Following accumulation at the target site, efficient cellular internalization and intracellular trafficking are critical for achieving therapeutic efficacy and diagnostic precision. Most theranostic nanocarriers are internalized through endocytic pathways, including clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, and phagocytosis, particularly in immune cells such as macrophages. Once inside the cell, these nanocarriers are typically sequestered in endosomes that may eventually fuse with lysosomes, where enzymatic degradation can compromise therapeutic payloads. To overcome this, advanced nanocarrier designs incorporate endosomal escape strategies, such as the proton sponge effect using cationic polymers like polyethylenimine, pH-sensitive membrane-disruptive materials, or fusogenic peptides that destabilize the endosomal membrane. Upon successful cytosolic release,

therapeutic agents can reach intracellular targets, including the cytoplasm, nucleus, or mitochondria, while embedded imaging agents facilitate real-time tracking of cellular localization and treatment response. This coordinated intracellular trafficking ensures maximal therapeutic benefit and enables integrated diagnostic feedback for precise and adaptive disease management [22,23].

Imaging Modalities in Theranostics

A critical component of theranostic nanomedicine is the integration of imaging functionality within the nanocarrier system to enable real-time, non-invasive visualization of disease sites, nanoparticle biodistribution, and therapeutic response. By incorporating imaging agents into the nanoplatforms, theranostic systems not only guide site-specific drug delivery but also offer valuable diagnostic insights that enhance clinical decision-making. Several imaging modalities are commonly employed in this context, each with its unique advantages in terms of resolution, sensitivity, and tissue penetration depth.

Magnetic Resonance Imaging (MRI)

MRI is a non-invasive, high-resolution imaging modality that provides detailed anatomical and functional information, particularly of soft tissues. It operates on the principles of nuclear magnetic resonance, using strong magnetic fields and radiofrequency pulses to generate contrast between tissues based on the behavior of hydrogen nuclei. In theranostic applications, superparamagnetic iron oxide nanoparticles (SPIONs) and gadolinium (Gd)-based contrast agents are commonly integrated into nanocarriers. SPIONs act as T2-weighted contrast agents, creating dark regions on MR images due to their influence on transverse relaxation time, while Gd-based agents offer T1-weighted contrast, enhancing signal intensity. The incorporation of MRI contrast agents into nanoparticles allows tracking of biodistribution, tumor accumulation, and drug release kinetics in vivo. Moreover, MRI is advantageous due to its deep tissue penetration, absence of ionizing radiation, and compatibility with longitudinal studies, making it a valuable modality for real-time monitoring in cancer, cardiovascular, and neurodegenerative diseases [24].

Positron Emission Tomography (PET) and Computed Tomography (CT)

PET and CT are powerful imaging modalities that provide functional and structural information, respectively. PET imaging is based on the detection of gamma rays emitted during the annihilation of positrons released by radioactive tracers, while CT employs X-rays to construct cross-sectional images of the body. In theranostics, PET imaging utilizes radiolabeled nanoparticles, commonly tagged with isotopes such as fluorine-18 (^{18}F), copper-64 (^{64}Cu), or zirconium-89 (^{89}Zr), which allow quantitative imaging of nanocarrier distribution and pharmacokinetics with high sensitivity. PET is particularly useful for detecting metabolic activity in tumors and monitoring disease progression or therapeutic response. CT, on the other hand, is

often used in hybrid imaging systems (e.g., PET/CT, SPECT/CT) to provide detailed anatomical reference alongside functional data. Nanocarriers functionalized with high atomic number elements such as gold (Au), bismuth, or iodine-based compounds serve as effective CT contrast agents due to their strong X-ray attenuation properties. The combination of PET and CT in theranostic nanomedicine enables high-resolution, quantitative, and real-time visualization of nanocarriers in deep tissues, enhancing both diagnostic precision and therapeutic planning [25].

Optical Imaging and Fluorescence Techniques

Optical imaging encompasses a variety of techniques, including fluorescence, bioluminescence, and near-infrared (NIR) imaging, which are widely used in preclinical research due to their high sensitivity, ease of use, and low cost. Among these, fluorescence imaging is the most prevalent modality in theranostic nanomedicine. Theranostic nanoparticles can be loaded or conjugated with fluorophores, quantum dots, upconversion nanoparticles (UCNPs), or NIR dyes that emit light upon excitation, allowing real-time visualization of nanoparticle localization, cellular uptake, and therapeutic response. The use of NIR dyes (650-900 nm) is particularly advantageous due to deeper tissue penetration and reduced background autofluorescence. Despite its limitations in clinical translation such as limited tissue penetration, photobleaching, and poor quantification optical imaging remains a powerful tool for tracking nanoparticle behavior in small animal models, optimizing nanoparticle design, and validating targeting strategies. Recent advancements in multimodal optical probes and photoacoustic imaging are extending the clinical applicability of optical techniques, offering functional and molecular-level imaging capabilities when combined with therapeutic agents [26].

Therapeutic Applications

Theranostic nanomedicine has demonstrated significant promise across a wide range of pathological conditions, particularly where precise diagnosis and site-specific therapy are essential. By integrating therapeutic and imaging functions into a single platform, theranostic systems enable real-time disease monitoring, individualized treatment regimens, and minimized off-target effects. This section highlights key therapeutic areas where theranostic nanocarriers are making impactful contributions.

Oncology

Oncology remains the primary and most extensively explored area for theranostic nanomedicine due to the urgent need for accurate tumor imaging and targeted therapy. Cancer heterogeneity, metastasis, and drug resistance often limit the effectiveness of conventional treatments [27]. Theranostic nanoparticles, engineered with tumor-specific ligands and contrast agents, provide enhanced tumor targeting, real-time tracking, and controlled drug release, making them ideal for cancer management. These systems improve tumor selectivity, allow non-invasive imaging of tumor margins, and enable adaptive therapeutic strategies. Moreover, theranostics support

combination therapies, such as chemo-photodynamic or chemo-immunotherapy, offering synergistic anti-cancer effects. Examples include:

- Gold nanoparticles and quantum dots for simultaneous imaging and photothermal therapy (PTT)
- Iron oxide-loaded liposomes for MRI-guided chemotherapy
- pH-responsive polymeric nanoparticles for targeted delivery of doxorubicin with fluorescence tracking.

Cardiovascular and Neurodegenerative Disorders

Cardiovascular diseases (CVDs) and neurodegenerative disorders are complex conditions that benefit from early detection, targeted intervention, and continuous monitoring, all of which are facilitated by theranostic platforms.In cardiovascular theranostics, nanoparticles functionalized with ligands targeting atherosclerotic plaques (e.g., VCAM-1, integrins) deliver anti-inflammatory drugs or thrombolytics, while simultaneously enabling imaging via MRI or PET to assess plaque burden and vascular remodeling [28]. For instance, iron oxide nanoparticles are used for MRI tracking of inflammation in atherosclerosis, while echogenic liposomes can deliver drugs and visualize thrombus dissolution under ultrasound guidance. In neurodegenerative diseases such as Alzheimer's and Parkinson's, the blood–brain barrier (BBB) poses a major obstacle. Theranostic nanoparticles can be engineered to cross the BBB using receptor-mediated transport mechanisms and deliver neuroprotective agents. Concurrently, they allow imaging of amyloid-beta plaques or dopaminergic neuron loss using PET, SPECT, or fluorescence, aiding in early diagnosis and therapeutic assessment [29].

Infectious Diseases and Inflammation

Infectious diseases and inflammatory conditions require rapid diagnosis and targeted therapy to prevent systemic spread and reduce resistance development. Theranostic nanomedicine offers a unique solution by combining antimicrobial delivery with real-time tracking of infection sites [30]. Nanoparticles can be loaded with antibiotics, antivirals, or anti-inflammatory agents, and conjugated with imaging agents such as NIR dyes or radionuclides for infection-site localization. The use of stimuli-responsive release systems, which respond to microbial enzymes, oxidative stress, or acidic pH at infection sites, further enhances specificity and reduces systemic toxicity. In inflammation, theranostic tools can distinguish between acute and chronic phases, enabling stage-specific interventions.

For example:

- Silver nanoparticles with antibacterial properties have been integrated with fluorescent tags to treat and image bacterial infections.
- Liposomes loaded with rifampicin and tagged with PET isotopes are being investigated for tuberculosis diagnosis and therapy.

- Macrophage-targeted nanoparticles allow visualization and modulation of chronic inflammation in diseases such as rheumatoid arthritis and inflammatory bowel disease [31].

Future Perspective and Challenges

Theranostic nanomedicine holds immense potential to revolutionize disease management by offering personalized, targeted, and image-guided therapeutic solutions; however, several challenges must be addressed to fully realize its clinical utility. Future perspectives include the development of multifunctional, stimuli-responsive nanocarriers with enhanced biocompatibility, precision targeting, and integration with artificial intelligence for real-time decision-making and predictive diagnostics. Additionally, advances in nanofabrication techniques and modular nanoparticle design are expected to enable scalable production and regulatory compliance. Despite significant preclinical success, clinical translation remains limited due to hurdles such as complex synthesis, long-term toxicity concerns, immunogenicity, regulatory ambiguities, and high production costs. Moreover, ensuring reproducibility, robust pharmacokinetic profiling, and comprehensive safety assessments are critical for widespread adoption. Overcoming these barriers through interdisciplinary collaboration, rigorous validation, and innovation will pave the way for next-generation theranostic platforms in precision medicine [32,33].

Conclusion:

Theranostic nanomedicine represents a transformative convergence of therapeutic and diagnostic modalities within a single, multifunctional nanosystem. By enabling targeted drug delivery and real-time imaging, theranostic platforms offer significant advantages over conventional treatments, including improved therapeutic efficacy, reduced systemic toxicity, and personalized patient care. The diversity of nanocarriers ranging from polymeric nanoparticles and liposomes to metal-based structures and hybrid systems provides a versatile toolkit to address complex pathologies such as cancer, cardiovascular diseases, neurodegenerative disorders, and infectious conditions. The integration of passive and active targeting strategies, along with stimuli-responsive release mechanisms and advanced imaging techniques such as MRI, PET, CT, and fluorescence, has enhanced the precision and adaptability of modern therapeutics. Despite these promising developments, challenges related to clinical translation, safety, scalability, and regulatory approval must be rigorously addressed. With continued innovation, interdisciplinary collaboration, and a focus on translational research, theranostic nanomedicine is poised to become a cornerstone of next-generation healthcare, driving the evolution toward more precise, efficient, and individualized therapeutic interventions.

References:

1. Singh V. Theranostics: Integrated Diagnostics and Therapy Using Nanomedicine. InNanomedicine 2024 (pp. 505-530). Springer, Cham.

2. Muthu MS, Mei L, Feng SS. Nanotheranostics: advanced nanomedicine for the integration of diagnosis and therapy. Nanomedicine. 2014 Jul 1;9(9):1277-80.
3. Siddhardha B, Parasuraman P. Theranostics application of nanomedicine in cancer detection and treatment. InNanomaterials for drug delivery and therapy 2019 Jan 1 (pp. 59-89). William Andrew Publishing.
4. Han Q, Du L, Zhu L, Yu D. Review of the application of dual drug delivery nanotheranostic agents in the diagnosis and treatment of liver cancer. Molecules. 2023 Oct 10;28(20):7004.
5. Bai RG, Muthoosamy K, Manickam S. Nanomedicine in theranostics. InNanotechnology applications for tissue engineering 2015 Jan 1 (pp. 195-213). William Andrew Publishing.
6. Alshehri S, Imam SS, Rizwanullah M, Akhter S, Mahdi W, Kazi M, Ahmad J. Progress of cancer nanotechnology as diagnostics, therapeutics, and theranostics nanomedicine: preclinical promise and translational challenges. Pharmaceutics. 2020 Dec 24;13(1):24.
7. Mukherjee A, Paul M, Mukherjee S. Recent progress in the theranostics application of nanomedicine in lung cancer. Cancers. 2019 Apr 29;11(5):597.
8. Fan Z, Fu PP, Yu H, Ray PC. Theranostic nanomedicine for cancer detection and treatment. Journal of food and drug analysis. 2014 Mar 1;22(1):3-17.
9. Sharma R, Mody N, Agrawal U, Vyas SP. Theranostic nanomedicine; a next generation platform for cancer diagnosis and therapy. Mini reviews in medicinal chemistry. 2017 Dec 1;17(18):1746-57.
10. Maheswaran T, Ganapathy N, DineshShankar J, Mohanapriya S, Ilayaraja V, Yoithapprabhunath TR, Yamunadevi AM. Theranostics an emerging paradigm—A review. IOSR J. Dent. Med. Sci. 2018 Oct;17:19-24.
11. Mukherjee S, Madamsetty VS, Bhattacharya D, Roy Chowdhury S, Paul MK, Mukherjee A. Recent advancements of nanomedicine in neurodegenerative disorders theranostics. Advanced Functional Materials. 2020 Aug;30(35):2003054.
12. Zhu W, Wei Z, Han C, Weng X. Nanomaterials as promising theranostic tools in nanomedicine and their applications in clinical disease diagnosis and treatment. Nanomaterials. 2021 Dec 10;11(12):3346.
13. Dessale M, Mengistu G, Mengist HM. Nanotechnology: a promising approach for cancer diagnosis, therapeutics and theragnosis. International Journal of Nanomedicine. 2022 Aug 26;17:3735.
14. Ruman U, Fakurazi S, Masarudin MJ, Hussein MZ. Nanocarrier-based therapeutics and theranostics drug delivery systems for next generation of liver cancer nanodrug modalities. International journal of nanomedicine. 2020 Mar 3:1437-56.

15. Alshamrani M. Broad-spectrum theranostics and biomedical application of functionalized nanomaterials. Polymers. 2022 Mar 17;14(6):1221.
16. Karthikeyan L, Sobhana S, Yasothamani V, Gowsalya K, Vivek R. Multifunctional theranostic nanomedicines for cancer treatment: Recent progress and challenges. Biomedical Engineering Advances. 2023 Jun 1;5:100082.
17. Li P, Wang D, Hu J, Yang X. The role of imaging in targeted delivery of nanomedicine for cancer therapy. Advanced Drug Delivery Reviews. 2022 Oct 1;189:114447.
18. Huang H, Lovell JF. Advanced functional nanomaterials for theranostics. Advanced functional materials. 2017 Jan;27(2):1603524.
19. Al-Thani AN, Jan AG, Abbas M, Geetha M, Sadasivuni KK. Nanoparticles in cancer theragnostic and drug delivery: A comprehensive review. Life sciences. 2024 Jul 9:122899.
20. Jani P, Subramanian S, Korde A, Rathod L, Sawant KK. Theranostic nanocarriers in cancer: dual capabilities on a single platform. Functional Bionanomaterials: From Biomolecules to Nanoparticles. 2020:293-312.
21. Jani P, Subramanian S, Korde A, Rathod L, Sawant KK. Theranostic nanocarriers in cancer: dual capabilities on a single platform. Functional Bionanomaterials: From Biomolecules to Nanoparticles. 2020:293-312.
22. Shete MB, Patil TS, Deshpande AS, Saraogi G, Vasdev N, Deshpande M, Rajpoot K, Tekade RK. Current trends in theranostic nanomedicines. Journal of Drug Delivery Science and Technology. 2022 May 1;71:103280.
23. Toader C, Dumitru AV, Eva L, Serban M, Covache-Busuioc RA, Ciurea AV. Nanoparticle strategies for treating CNS disorders: a comprehensive review of drug delivery and theranostic applications. International Journal of Molecular Sciences. 2024 Dec 11;25(24):13302.
24. Gautam L, Jain A, Vishwakarma N, Sharma R, Mody N, Dubey S, Vyas SP. Nanomedicine for the diagnosis and treatment of cancer. InNanomedicine for the Treatment of Disease 2019 Sep 25 (pp. 395-422). Apple Academic Press.
25. Rout SK, Priya V, Setia A, Mehata AK, Mohan S, Albratty M, Najmi A, Meraya AM, Makeen HA, Tambuwala MM, Muthu MS. Mitochondrial targeting theranostic nanomedicine and molecular biomarkers for efficient cancer diagnosis and therapy. Biomedicine & Pharmacotherapy. 2022 Sep 1;153:113451.
26. Peng H, Liu X, Wang G, Li M, Bratlie KM, Cochran E, Wang Q. Polymeric multifunctional nanomaterials for theranostics. Journal of Materials Chemistry B. 2015;3(34):6856-70.

27. Song S, Shen H, Wang Y, Chu X, Xie J, Zhou N, Shen J. Biomedical application of graphene: From drug delivery, tumor therapy, to theranostics. Colloids and Surfaces B: Biointerfaces. 2020 Jan 1;185:110596.
28. Das MK, editor. Multifunctional theranostic nanomedicines in cancer. Academic Press; 2021 Mar 16.
29. Kasi PB, Mallela VR, Ambrozkiewicz F, Trailin A, Liška V, Hemminki K. Theranostics nanomedicine applications for colorectal cancer and metastasis: recent advances. International journal of molecular sciences. 2023 Apr 27;24(9):7922.
30. Lajevardi MS, Ashrafpour M, Mubarak SM, Rafieyan B, Kiani A, Noori E, Roayaei Ardakani M, Montazeri M, Kouhi Esfahani N, Asadimanesh N, Khalili S. Dual roles of extracellular vesicles in acute lymphoblastic leukemia: implications for disease progression and theranostic strategies. Medical Oncology. 2024 Nov 22;42(1):11.
31. Xue Y, Gao Y, Meng F, Luo L. Recent progress of nanotechnology-based theranostic systems in cancer treatments. Cancer Biology & Medicine. 2021 May 1;18(2):336-51.
32. Shoaib A, Javed S, Tabish M, Khan ME, Zaki M, Alqahtani SS, Sultan MH, Ahsan W, Afzal M. Applications of nanomedicine-integrated phototherapeutic agents in cancer theranostics: A comprehensive review of the current state of research. Nanotechnology Reviews. 2024 May 24;13(1):20240023.
33. Lin Y, Liu J, Chong SY, Ting HJ, Tang X, Yang L, Zhang S, Qi X, Pei P, Yi Z, Huang C. Dual-Function Nanoscale Coordination Polymer Nanoparticles for Targeted Diagnosis and Therapeutic Delivery in Atherosclerosis. Small. 2024 Nov;20(47):2401659.

AGE-ASSOCIATED PHARMACOKINETICS: IMPLICATIONS FOR SAFE PRESCRIBING

Dilsar Gohil*, Rajesh Maheshwari
Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India. 391760
*Corresponding author E-mail: gohildilsar9624@gmail.com

Abstract:
As global life expectancy rises, the management of pharmacotherapy in elderly populations has become a growing concern in clinical practice. The physiological and biochemical changes that accompany aging significantly alter drug pharmacokinetics and pharmacodynamics, necessitating customized approaches to medication use. Renal and hepatic functions critical for drug metabolism and excretion tend to decline with age, often leading to prolonged drug half-life and increased risk of toxicity. Additionally, altered receptor sensitivity can heighten vulnerability to central nervous system (CNS) depressants such as benzodiazepines and antipsychotics. Polypharmacy is another pressing issue among older adults due to the prevalence of chronic comorbidities, increasing the likelihood of drug-drug interactions, adverse reactions, and non-compliance. To minimize risks, prescribers must adopt age-sensitive strategies such as initiating therapy at low doses ("start low, go slow"), routine monitoring of liver and renal function, and regular medication reviews with a focus on deprescribing unnecessary or inappropriate drugs. The goal of geriatric pharmacology is not just to manage disease but to improve quality of life and preserve functional independence. By understanding the unique challenges of drug therapy in the elderly, healthcare professionals can ensure more effective, safer, and patient-centered care. This article explores the clinical implications, common issues, and practical strategies for optimizing pharmacotherapy in the aging population.

Keywords: Geriatric Pharmacology, Polypharmacy, Drug Metabolism in Elderly, CNS Drug Sensitivity, Deprescribing

Introduction:

The aging population is rapidly expanding, with individuals aged 65 and older representing a significant proportion of healthcare recipients worldwide. This demographic shift underscores the urgent need for a focused approach to pharmacotherapy in older adults. Aging affects nearly every organ system in the body and leads to considerable changes in how drugs are processed and how the body responds to them. These changes influence both the safety and effectiveness of pharmacological treatments, making geriatric pharmacology an essential discipline in modern healthcare. One of the most pronounced age-related changes involves a decline in renal and hepatic function. These organs are pivotal in drug clearance, and their diminished capacity in the

elderly can result in drug accumulation and increased toxicity. Additionally, alterations in body composition such as increased fat and reduced lean muscle mass affect drug distribution, while changes in receptor sensitivity can amplify or blunt drug effects [1].

Compounding these physiological challenges is the issue of polypharmacy. Older adults often take multiple medications simultaneously to manage chronic illnesses like diabetes, hypertension, and arthritis. While necessary, polypharmacy raises the risk of adverse drug reactions, drug-drug interactions, and patient non-compliance. Effective pharmacotherapy in elderly patients demands a personalized and cautious approach. Strategies such as starting with low doses, adjusting therapy based on renal and hepatic function, and discontinuing non-essential medications are crucial. This tailored approach enhances therapeutic outcomes and minimizes harm, helping older individuals maintain their health and independence. The present discussion delves into the unique aspects of pharmacology in the elderly and offers evidence-based practices for safe and effective drug use [2].

1. Pharmacology in Pregnancy: A Clinical Overview

Pregnancy presents a complex and delicate physiological state in which the safety and effectiveness of pharmacological therapy must be critically evaluated. The therapeutic approach for pregnant individuals is not merely a modification of standard adult dosing, but rather a calculated balance between maternal health needs and fetal safety. Changes in maternal physiology, as well as the potential for drug-induced fetal harm, make this a uniquely sensitive area in pharmacological science [3].

Placental Drug Transfer

One of the central concerns in maternal pharmacotherapy is the ability of drugs to cross the placental barrier. The placenta, though serving as a selective filter, does not completely block the passage of exogenous substances. Lipophilic, low molecular weight, and non-ionized drugs easily cross the placenta and can reach fetal circulation. Some of these drugs may be harmless, while others carry the risk of disrupting fetal development. The extent of placental drug transfer depends on various factors including drug properties, gestational age, placental blood flow, and transport mechanisms.

Teratogenic Risks and Fetal Sensitivity

Teratogenicity refers to a drug's potential to interfere with fetal development and cause structural or functional abnormalities. The first trimester, particularly between the third and eighth week of gestation, is the most critical period, as major organ systems are forming during this window. Exposure to harmful drugs during this time can lead to irreversible birth defects or even miscarriage. Some drugs, such as thalidomide, have historically caused severe congenital malformations, emphasizing the importance of rigorous drug safety assessment.

It is also important to note that teratogenic risk varies not only by the drug's pharmacological action but also by the timing and duration of exposure. For example, drugs that are relatively safe

in later trimesters may pose significant risks in the early stages of pregnancy. Similarly, chronic exposure over several weeks may be more harmful than a single, short-term dose [4].

Maternal Physiological Changes and Their Impact on Pharmacokinetics

Pregnancy is associated with profound physiological alterations that influence the pharmacokinetics absorption, distribution, metabolism, and excretion of drugs. These changes may alter both the effectiveness and toxicity of medications:

- Increased plasma volume (by up to 50%) results in the dilution of drugs, potentially lowering their plasma concentrations and therapeutic effects.
- Enhanced renal blood flow and glomerular filtration rate accelerate the excretion of renally-cleared drugs, often requiring dosage adjustments.
- Changes in hepatic enzyme activity, particularly cytochrome P450 isoenzymes, may either increase or decrease the metabolism of various drugs.
- Delayed gastric emptying and altered gastrointestinal pH may affect oral drug absorption, although the clinical significance of this is variable.

Understanding these changes is crucial for adjusting drug regimens and ensuring optimal maternal and fetal outcomes [5].

Drug Safety Classification in Pregnancy

To assist clinicians in prescribing safely during pregnancy, the U.S. Food and Drug Administration (FDA) had traditionally used a risk categorization system (A, B, C, D, X):

- Category A: Controlled studies in humans show no risk.
- Category B: Animal studies show no risk, but no well-controlled human studies exist.
- Category C: Animal studies show adverse effects; no adequate human studies available.
- Category D: Positive evidence of human fetal risk, but potential benefits may warrant use.
- Category X: Contraindicated in pregnancy; risks outweigh benefits.

However, this system has been phased out and replaced by the Pregnancy and Lactation Labeling Rule (PLLR), which provides more detailed narrative information regarding drug use in pregnancy, lactation, and effects on fertility. The PLLR aims to improve decision-making by presenting evidence-based data in a clearer, more clinically meaningful format [6].

Examples of Drugs Considered Safe or Harmful

While some medications are considered generally safe during pregnancy, others are strictly avoided due to established teratogenic or toxic effects:

- Commonly accepted safe drugs include paracetamol (acetaminophen) for pain and fever, and penicillin-based antibiotics, which have shown minimal risk in multiple studies.
- Contraindicated or high-risk drugs include:
    - Thalidomide, which caused severe limb deformities when used as an antiemetic in the 1950s and 60s.

- Isotretinoin, a retinoid used for severe acne, is associated with central nervous system and craniofacial anomalies.
- Warfarin, a commonly used anticoagulant, is linked to fetal bleeding and malformations when administered during the first trimester.

When treatment with essential drugs is necessary, safer alternatives should be considered, and the lowest effective dose should be used.

Pharmacological management during pregnancy is a nuanced and cautious practice that must account for physiological changes, drug safety profiles, and timing of exposure. Clinicians must weigh the therapeutic needs of the mother against the potential risks to the fetus, relying on updated guidelines such as the PLLR and evidence-based data. A strong understanding of drug behavior during pregnancy is essential to prevent fetal harm while ensuring maternal well-being [7].

2. Pharmacology in Pediatrics: A Specialized Approach to Drug Therapy

Pharmacology in the pediatric population presents a unique and complex landscape that differs significantly from adult pharmacotherapy. Children are not merely "small adults" — they possess distinct physiological characteristics that influence drug behavior and therapeutic responses. This makes the accurate selection, dosing, and monitoring of medications in children a critical aspect of pediatric care [8].

Challenges in Pediatric Pharmacology

Administering drugs to infants and children poses numerous challenges, primarily due to ongoing developmental changes in organ systems, which directly affect how drugs are processed. The most notable concern is the immaturity of the liver and kidneys, the primary organs responsible for drug metabolism and elimination.

In addition, dosing accuracy is a major hurdle. Unlike adults, where standardized doses are commonly applied, pediatric doses must often be calculated individually based on weight or body surface area. Errors in these calculations can lead to subtherapeutic effects or toxic side effects. Moreover, as children grow, their pharmacokinetic profiles change, necessitating continuous dosage adjustments.

Another critical issue is the lack of robust clinical data for many drugs in the pediatric population. Ethical concerns and legal limitations often prevent the inclusion of children in clinical trials, leaving physicians to rely on off-label use, extrapolated data, or adult studies practices that may not accurately predict pediatric responses [9].

Pharmacokinetic Differences in Children

Pharmacokinetics how the body absorbs, distributes, metabolizes, and eliminates drugs varies considerably in pediatric patients, especially in neonates and infants. These variations are crucial for clinicians to understand to ensure drug safety and efficacy.

1. Absorption

Drug absorption in neonates and infants is influenced by several developmental factors:

- Delayed gastric emptying can slow the onset of action for orally administered drugs.
- Altered gastric pH (higher than in adults) affects the solubility and ionization of certain medications, particularly weak acids and bases.
- Immature digestive enzymes and bile salt production can impair the breakdown and absorption of lipophilic drugs.

2. Distribution

In pediatric patients, particularly neonates:

- Total body water content is significantly higher than in adults, which increases the volume of distribution for hydrophilic drugs. As a result, water-soluble drugs may require larger per-kilogram doses to achieve therapeutic plasma levels.
- Lower fat stores reduce the volume of distribution for lipophilic drugs, potentially enhancing their plasma concentration and effects.
- Plasma protein levels, such as albumin, are reduced in infants, which can lead to a higher free (active) drug concentration, especially for protein-bound medications [10].

3. Metabolism

The liver's enzymatic systems, particularly the cytochrome P450 family, are underdeveloped at birth. This immature metabolism:

- Reduces the rate of drug biotransformation, potentially leading to prolonged drug half-lives and accumulation.
- Matures gradually, with enzyme activity typically increasing during the first year of life, altering drug clearance as the child grows.

4. Excretion

Renal function in newborns is also immature, with:

- Lower glomerular filtration rate (GFR)
- Reduced tubular secretion and reabsorption

These factors contribute to slower elimination of renally excreted drugs, requiring dosage adjustments and extended dosing intervals for medications cleared through the kidneys (e.g., aminoglycosides) [11].

Dosage Calculations in Pediatrics

Because of the physiological variability among children, dosing must be individualized. The two most common approaches are:

1. Body Weight-Based Dosing (mg/kg)

- This is the most widely used method in pediatric practice.
- It ensures that the dose is proportional to the child's mass, reducing the risk of over- or under-dosing.

2. Body Surface Area (BSA)-Based Dosing (mg/m²)

- More accurate for certain drugs, especially those with narrow therapeutic ranges like chemotherapy agents.
- BSA is considered to correlate better with metabolic rate than weight alone.

3. Pediatric Dosage Formulas

When the exact pediatric dose isn't available, various formulas can be used to approximate it from adult doses:

- Clark's Rule: Dose = (Weight in lbs ÷ 150) × Adult dose
- Young's Rule: Dose = (Age ÷ [Age + 12]) × Adult dose

While helpful, these formulas are approximations and should be supplemented with clinical judgment, especially in neonates and critically ill children.

Pediatric pharmacology is a specialized and evolving field that demands careful consideration of developmental physiology, organ maturity, and metabolic differences. A thorough understanding of age-specific pharmacokinetics is vital to optimize therapeutic outcomes and minimize adverse effects in young patients. As the medical community continues to advocate for more pediatric-specific research and drug approvals, the ultimate goal remains the safe and effective use of medications tailored to the unique needs of children [12].

3. Pharmacology in the Elderly: A Geriatric Perspective

As the global population ages, the safe and effective use of medications in older adults has become a central focus of clinical pharmacology. Geriatric pharmacology deals with how aging affects the way drugs are handled by the body, how sensitive the body becomes to certain medications, and how polypharmacy and comorbidities complicate treatment regimens. With age-related physiological changes, drug therapy in the elderly requires careful adjustment to prevent adverse outcomes.

Age-Related Physiological Changes and Their Impact

One of the primary challenges in geriatric pharmacology is the progressive decline in renal and hepatic function. These organs play a vital role in drug metabolism and excretion. In elderly patients, glomerular filtration rate (GFR), renal blood flow, and tubular function often decline significantly, even in the absence of diagnosed kidney disease. As a result, drugs that are primarily excreted through the kidneys such as aminoglycosides or digoxin can accumulate in the body, increasing the risk of toxicity if dosages are not appropriately adjusted.

Similarly, hepatic metabolism slows with age, particularly affecting Phase I reactions (oxidation, reduction, hydrolysis) that are mediated by the cytochrome P450 enzyme system. Though Phase II reactions (conjugation) are generally preserved, slower liver function means that drugs requiring hepatic metabolism, such as certain beta-blockers and benzodiazepines, may have prolonged half-lives in elderly individuals [13].

Altered Drug Sensitivity and Pharmacodynamics

Aging not only changes how drugs are processed but also how the body responds to them. The sensitivity of drug receptors may be altered with age, leading to either increased or decreased responsiveness. For example, older adults often show enhanced sensitivity to central nervous system (CNS) depressants, such as benzodiazepines and opioids, which can cause sedation, confusion, and increased fall risk at doses that are well-tolerated in younger adults.

On the other hand, the responsiveness to beta-adrenergic agents may decrease, affecting the efficacy of medications like beta-blockers in the management of hypertension or heart failure. These pharmacodynamic changes necessitate a more cautious approach to drug therapy in geriatric populations.

Polypharmacy and Drug Interactions

Polypharmacy, defined as the concurrent use of multiple medications, is a widespread issue among older adults due to the presence of multiple chronic conditions such as diabetes, hypertension, arthritis, and cardiovascular disease. Taking numerous medications increases the likelihood of drug-drug interactions, which can enhance toxicity or diminish therapeutic effects.

Beyond interactions, polypharmacy raises the risk of medication non-adherence, prescription cascades (treating side effects of one drug with another), and cognitive decline. Clinicians must critically assess the necessity of each medication and weigh its benefits against potential harms in the context of the patient's overall health status and goals of care [14].

Common Pharmacological Issues in Older Adults

Due to physiological and pharmacokinetic differences, elderly individuals are more prone to adverse drug reactions (ADRs). Some frequent concerns include:

- Increased sensitivity to CNS-acting drugs, such as benzodiazepines and antipsychotics, leading to drowsiness, delirium, and impaired balance.
- Delayed clearance of renally eliminated medications, such as aminoglycosides, resulting in nephrotoxicity or ototoxicity.
- Greater risk of gastrointestinal bleeding from non-steroidal anti-inflammatory drugs (NSAIDs), especially when used without gastroprotective agents.

These complications highlight the importance of age-adjusted prescribing practices and continuous drug monitoring [15].

Strategies for Safer Medication Use in the Elderly

To minimize the risks associated with pharmacotherapy in older adults, several key principles should be followed:

Start Low and Go Slow

Initiating treatment with a lower-than-standard dose and gradually increasing it allows the clinician to gauge drug tolerance and reduce the risk of side effects.

Routine Monitoring of Organ Function

Regular assessment of renal and liver function is essential for guiding dosage adjustments, especially for medications with narrow therapeutic indices or significant renal clearance. Creatinine clearance (CrCl) or estimated GFR should be used instead of serum creatinine alone, which may be misleading due to reduced muscle mass in the elderly [16].

Deprescribing and Medication Review

Routine medication reconciliation and deprescribing the planned discontinuation of medications that are no longer necessary or potentially harmful can greatly improve the quality of life in older patients. This includes stopping drugs with high anticholinergic burdens, redundant therapies, or those no longer aligned with the patient's treatment goals.

The practice of pharmacology in elderly patients requires a nuanced approach that goes beyond simply adjusting doses. It demands a thorough understanding of age-related physiological changes, an appreciation of the increased vulnerability to side effects, and an ongoing commitment to rational, patient-centered prescribing. By individualizing therapy and vigilantly monitoring treatment outcomes, healthcare providers can ensure that medications remain beneficial rather than burdensome in this sensitive population [17].

Conclusion:

Pharmacological management in the elderly is a multifaceted process requiring an in-depth understanding of age-associated physiological changes and the risks posed by polypharmacy. Declining renal and hepatic function, altered drug receptor sensitivity, and increased susceptibility to central nervous system effects make elderly patients particularly vulnerable to drug-related complications. Incorporating principles such as starting treatment with lower doses, closely monitoring organ function, and systematically reviewing medication regimens is essential to minimizing risks. Deprescribing thoughtful discontinuation of unnecessary medications has emerged as a key strategy in reducing polypharmacy-related harm and improving quality of life. Geriatric pharmacology is not only about managing disease but also about preserving independence and promoting well-being in older adults. With evidence-based and patient-centered strategies, healthcare professionals can optimize drug therapy to meet the unique needs of this growing population segment.

References:

1. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol. 2004;57(1):6–14.
2. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003;38(8):843–853.
3. Spinewine A, Schmader KE, Barber N, *et al.* Appropriate prescribing in elderly people. Lancet. 2007;370(9582):173–184.

4. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther. 2009;85(1):86–88.
5. Hanlon JT, Schmader KE, Ruby CM, Weinberger M. Suboptimal prescribing in older inpatients and outpatients. J Am Geriatr Soc. 2001;49(2):200–209.
6. American Geriatrics Society. AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674–694.
7. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17(6):571–584.
8. O'Mahony D, Gallagher P, Ryan C, *et al.* STOPP/START criteria for potentially inappropriate prescribing in older people. Age Ageing. 2015;44(2):213–218.
9. Tinetti ME, Bogardus ST Jr, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med. 2004;351(27):2870–2874.
10. Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation. King's Fund; 2013.
11. Wawruch M, Fialova D, Zikavska M, *et al.* Factors influencing the use of inappropriate medication in older patients. J Clin Pharm Ther. 2008;33(5):461–472.
12. Onder G, Petrovic M, Tangiisuran B, *et al.* Development and validation of a score to assess risk of adverse drug reactions in hospitalized older patients. Arch Intern Med. 2010;170(13):1142–1148.
13. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Med. 2015;13:74.
14. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: “There's got to be a happy medium”. JAMA. 2010;304(14):1592–1601.
15. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57–65.
16. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults. Arch Intern Med. 2010;170(18):1648–1654.
17. Campanelli CM. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616–631.

EGPA: A DISEASE OF MANY FACES — FROM AIRWAY INFLAMMATION TO SYSTEMIC VASCULITIS

Cyril Sajan*, Krupa Joshi, Hemraj Singh Rajput
Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Piparia, Waghodia, Vadodara- 391760
*Corresponding author E-mail: cyrilsajan97@gmail.com

Abstract:
Eosinophilic Granulomatosis with Polyangiitis (EGPA), previously known as Churg-Strauss Syndrome, is a rare multisystem disorder characterized by widespread inflammation of blood vessels, marked by granulomatous inflammation rich in eosinophils, and necrotizing vasculitis involving small- and medium-sized arteries. A hallmark feature of this disease is a personal history of asthma and elevated eosinophil levels in the blood. EGPA generally progresses through three distinct clinical stages: an initial phase dominated by allergic conditions like asthma and nasal polyps; a second phase distinguished by high eosinophil counts and infiltration of tissues by these cells; and a final phase defined by necrotizing vasculitis that can damage various organs, including the lungs, skin, peripheral nerves, and digestive tract. The precise cause of EGPA remains elusive, but it is believed to result from a complex interaction between genetic susceptibility, immune system abnormalities, and environmental exposures. Diagnosis relies on recognizing characteristic clinical manifestations, laboratory evidence of eosinophilia and elevated IgE, and histopathological confirmation demonstrating vasculitis with eosinophilic infiltration. Treatment is typically initiated with systemic corticosteroids, with the addition of immunosuppressive medications in more severe or treatment-resistant cases. The emergence of biologic therapies, particularly those targeting interleukin-5, has broadened the therapeutic landscape and improved patient outcomes. Early detection and timely intervention are critical to reducing disease complications and enhancing the long-term prognosis for patients with EGPA.

Keywords: Churg-Strauss Syndrome, Eosinophilic Granulomatosis with Polyangiitis, EGPA, Vasculitis, Eosinophilia, Asthma, Granulomatous Inflammation, Necrotizing Vasculitis, Immunosuppressive Therapy, Biologics.

Introduction:
Eosinophilic Granulomatosis with Polyangiitis (EGPA), formerly referred to as Churg-Strauss Syndrome, is an uncommon systemic vasculitis that predominantly targets small- to medium-sized arteries and veins. First detailed by Jacob Churg and Lotte Strauss in 1951, this disease is defined by a hallmark triad: asthma, elevated eosinophil levels in the peripheral blood, and systemic vasculitis featuring granulomatous inflammation. Although determining its exact

prevalence remains challenging due to frequent underdiagnosis and symptom overlap with other eosinophilic conditions, it is generally believed to affect between 10 and 15 individuals per million.

EGPA typically progresses through three clinical stages. The initial phase often manifests as allergic symptoms, including asthma and rhinitis. This phase transitions into an eosinophilic stage, characterized by significant infiltration of eosinophils into various tissues such as the lungs and gastrointestinal system. The final phase involves widespread necrotizing vasculitis, which can impact multiple organ systems, leading to serious complications like peripheral nerve damage, cutaneous involvement, and cardiac abnormalities.

While the precise causes of EGPA remain incompletely understood, current research points to a multifactorial origin involving genetic predisposition, environmental exposures, and immune system dysregulation. Approximately 40% of patients exhibit anti-neutrophil cytoplasmic antibodies (ANCAs), particularly those directed against myeloperoxidase (MPO), which are linked to specific clinical features such as renal disease and peripheral neuropathy.

Prompt diagnosis is crucial, as untreated EGPA can lead to significant disability and increased mortality. Diagnosis is based on clinical suspicion supported by laboratory data showing marked eosinophilia and elevated immunoglobulin E (IgE), as well as histopathological confirmation of eosinophil-rich granulomatous inflammation and vasculitis. Management centers on the early initiation of systemic corticosteroids to control inflammation, while additional immunosuppressive or biologic therapies are considered for severe or refractory cases.

This introduction serves as a foundation for an in-depth discussion of EGPA, exploring its epidemiology, disease mechanisms, clinical presentation, diagnostic challenges, and the latest advances in therapeutic approaches.[1]

Epidemiology:

Eosinophilic Granulomatosis with Polyangiitis (EGPA), previously termed Churg-Strauss Syndrome, is a rare systemic vasculitis that predominantly targets small- and medium-sized blood vessels. Due to its infrequent occurrence and clinical similarities with other eosinophilic and vasculitic conditions, establishing precise incidence and prevalence rates remains challenging.

1. **Incidence and Prevalence:**

   EGPA is an uncommon disease, with annual incidence estimates ranging from 0.5 to 6.8 cases per million people globally. Its overall prevalence is also low, typically reported between 10 and 30 cases per million.[2] This rarity places EGPA among the least common of the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, alongside granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

2. **Age Distribution:**
   The condition most frequently emerges in middle adulthood, with an average onset age between 40 and 50 years. Nonetheless, cases have been documented throughout the lifespan, including in pediatric and elderly populations. While uncommon, childhood cases generally mirror adult presentations, featuring asthma and marked eosinophilia.
3. **Sex Distribution:**
   Both men and women can develop EGPA, though a slight male predominance is observed in most studies, with reported male-to-female ratios ranging from 1.2:1 to 1.6:1. The reasons behind this subtle sex difference remain uncertain.
4. **Geographic Distribution:**
   EGPA has been identified worldwide, without a clear pattern of regional or ethnic clustering. However, most of the available epidemiological data originate from Europe and North America, likely reflecting differences in healthcare infrastructure, diagnostic capabilities, and reporting practices. Some studies indicate a higher prevalence in Western nations, possibly correlating with the greater burden of asthma—a major risk factor—in these regions.
5. **Association with Asthma and Atopy:**
   Asthma is a hallmark of EGPA, preceding vasculitic symptoms in over 90% of cases. Many patients also have a history of atopic conditions, such as allergic rhinitis, nasal polyps, or atopic dermatitis, supporting a role for Th2-dominated immune responses in disease pathogenesis. The high rates of asthma in industrialized countries may partly explain the geographic variation in EGPA diagnosis.
6. **ANCA Status:**
   Around 30–40% of patients with EGPA are positive for anti-neutrophil cytoplasmic antibodies (ANCAs), most commonly those targeting myeloperoxidase (MPO). ANCA-positive patients often present with more classic vasculitic features, such as kidney involvement and peripheral neuropathy. Conversely, ANCA-negative patients are more likely to develop cardiac or pulmonary complications.
7. **Diagnostic Considerations:**
   EGPA typically progresses through distinct phases—beginning with asthma and eosinophilia before advancing to systemic vasculitis—which can complicate early diagnosis. Its rarity, coupled with symptom overlap with other eosinophilic and vasculitic diseases, contributes to diagnostic delays and potential underrecognition.

Conclusion:

Although EGPA is rare, it is increasingly acknowledged as a significant cause of systemic vasculitis, particularly in patients with adult-onset asthma and eosinophilia. Understanding its

epidemiology underscores the importance of clinical vigilance in asthma patients who develop new systemic features, enabling earlier diagnosis and appropriate therapy.

Etiology:

The precise etiology of Eosinophilic Granulomatosis with Polyangiitis (EGPA) remains elusive, but current understanding points to a multifaceted origin involving genetic, immune, and environmental components that collectively foster eosinophilic inflammation and systemic vasculitis.

1. **Genetic Predisposition:**

   While no single gene mutation has been conclusively identified as the cause of EGPA, genetic factors appear to contribute to disease risk. Notably, certain human leukocyte antigen (HLA) haplotypes—especially HLA-DRB4—have been implicated, suggesting roles in antigen presentation and immune modulation. Additionally, genome-wide association studies have identified potential links between EGPA and polymorphisms in the interleukin-5 (IL5) gene, a cytokine pivotal for eosinophil growth and survival. These findings support the idea that inherited traits may increase susceptibility to EGPA, particularly in the presence of environmental stimuli.

2. **Immune System Dysregulation:**

   EGPA is marked by significant immune imbalances, particularly a skewed Th2 immune response. Elevated levels of IL-5 are consistently found in patients with EGPA and correlate with disease severity, highlighting its central role in driving eosinophilic proliferation and activation. Additionally, around 30–40% of patients have anti-neutrophil cytoplasmic antibodies (ANCAs), particularly those directed against myeloperoxidase (MPO-ANCA). These autoantibodies can provoke neutrophil activation, leading to the release of reactive oxygen species and subsequent damage to blood vessel walls, thereby contributing to the vasculitic component of the disease.

3. **Environmental Influences:**

   Environmental exposures are thought to act as potential triggers in genetically susceptible individuals. Asthma and atopic conditions, which precede vasculitic manifestations in over 90% of patients, are among the most consistent associations. Chronic exposure to environmental allergens and respiratory irritants may perpetuate Th2-biased immune responses, fostering eosinophilic inflammation. Certain medications—such as leukotriene receptor antagonists like montelukast—have been reported to precipitate EGPA in some patients, though this remains a topic of debate. Additionally, infections, particularly those affecting the respiratory tract, have been proposed as potential initiating factors through mechanisms of immune activation and loss of tolerance.

4. **Autoantibodies and Disease Pathogenesis:**
   The detection of MPO-ANCA in a subset of EGPA patients suggests overlapping features with other ANCA-associated vasculitides, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). These antibodies can activate neutrophils, which release enzymes and free radicals that damage the endothelium, leading to small-vessel inflammation. However, EGPA is distinct from other vasculitides due to its pronounced eosinophilic infiltration and granuloma formation, indicating that both cellular and humoral immune mechanisms contribute to its pathogenesis.

Conclusion:

In essence, EGPA emerges from the interplay of genetic vulnerability, immune dysregulation—dominated by Th2 responses and eosinophil activation—and environmental exposures. These interconnected factors give rise to the defining features of EGPA: asthma, eosinophilia, and systemic vasculitis. Understanding these mechanisms is essential for advancing targeted therapies and optimizing disease management strategies.[3]

Pathophysiology:

The underlying mechanisms of Eosinophilic Granulomatosis with Polyangiitis (EGPA) are complex and multifaceted, involving a dynamic interplay of immune dysregulation, eosinophil-driven inflammation, and small- to medium-vessel vasculitis.[4] Although the complete pathophysiology has not been fully delineated, several key processes have been identified.

1. **Immune System Imbalance and Th2 Dominance:**
   A hallmark feature of EGPA is the predominance of a Th2-mediated immune response, characterized by elevated levels of interleukin-5 (IL-5), interleukin-4 (IL-4), and interleukin-13 (IL-13). These cytokines facilitate the differentiation, activation, and prolonged survival of eosinophils, leading to significant peripheral eosinophilia—a defining feature of the condition. Eosinophils then migrate to tissues such as the lungs, skin, nerves, and gastrointestinal tract, where they release cytotoxic granule proteins (e.g., major basic protein and eosinophil cationic protein), resulting in tissue injury and inflammation.
2. **Tissue Eosinophilic Infiltration:**
   Chemokines like eotaxin and RANTES recruit eosinophils to sites of inflammation, where they accumulate and release their granular contents. This local degranulation leads to tissue necrosis, granulomatous reactions, and the histological appearance of eosinophil-rich infiltrates. These processes contribute to the characteristic manifestations of EGPA, including asthma, pulmonary infiltrates, and eosinophilic involvement of the gastrointestinal tract.

3. **ANCA-Related Vasculitis:**
   Approximately one-third of patients with EGPA exhibit circulating anti-neutrophil cytoplasmic antibodies (ANCAs), predominantly those against myeloperoxidase (MPO-ANCA). These autoantibodies bind to neutrophils, triggering their activation and degranulation, which releases proteolytic enzymes and reactive oxygen species. This cascade damages the endothelial lining of blood vessels, leading to fibrinoid necrosis and necrotizing vasculitis affecting small- to medium-sized vessels. Patients with ANCA positivity are more likely to exhibit prominent vasculitic features such as kidney involvement and peripheral nerve dysfunction.
4. **Granulomatous Inflammation:**
   Another key pathological finding in EGPA is the formation of granulomas, which are composed of activated macrophages, multinucleated giant cells, lymphocytes, and eosinophils. These structures are believed to arise from persistent immune stimulation in response to either environmental or endogenous antigens.
5. **Disease Phases:**
   EGPA typically progresses through three interrelated clinical phases:
   • **Prodromal Phase:** Characterized by atopic manifestations, including asthma, allergic rhinitis, and nasal polyps.
   • **Eosinophilic Phase:** Marked by elevated eosinophil counts and infiltration of various organs, notably the lungs and gastrointestinal tract.
   • **Vasculitic Phase:** Involves systemic necrotizing vasculitis, granuloma formation, and the potential involvement of multiple organs such as the skin, nervous system, heart, and kidneys.
6. **Emerging Immune Pathways:**
   Recent studies have highlighted additional immune mechanisms in EGPA pathogenesis, including the involvement of B cells, immunoglobulin E (IgE), and other autoantibodies, underscoring the disease's heterogeneity. The critical role of IL-5 in disease progression has paved the way for targeted therapies, such as mepolizumab, which selectively blocks IL-5 activity and has shown clinical efficacy in EGPA patients.

Conclusion:

Overall, EGPA's pathogenesis represents a unique convergence of Th2-mediated eosinophilic inflammation and ANCA-associated vasculitis, with a variable degree of granulomatous involvement. This duality necessitates a tailored therapeutic approach that addresses both the eosinophilic and vasculitic elements of the disease to achieve optimal clinical outcomes.

Clinical Presentation and Diagnosis of EGPA

Eosinophilic Granulomatosis with Polyangiitis (EGPA) typically follows a three-phase course, though not every patient progresses through all phases distinctly. The disease presents with a broad array of symptoms resulting from eosinophil-mediated tissue damage and small- to medium-vessel vasculitis.[5]

1. Prodromal (Allergic) Phase

- **Asthma:** Present in over 90% of cases, asthma is often the initial and most consistent symptom. It usually begins in adulthood and may be severe or difficult to manage.
- **Upper Airway Disease:** Chronic sinusitis, nasal congestion, and recurrent nasal polyps are frequently observed.
- **Other Atopic Conditions:** Patients may also report eczema or similar allergic disorders.

2. Eosinophilic Phase

- **Blood Eosinophilia:** Elevated eosinophil counts typically exceed 1,500/μL or represent more than 10% of the total white blood cell count.
- **Pulmonary Findings:** Non-fixed, transient opacities on chest imaging often reflect eosinophilic pneumonia.
- **Gastrointestinal Symptoms:** Eosinophilic infiltration of the GI tract can cause abdominal pain, diarrhea, or bleeding.
- **Cardiac Manifestations:** Some patients develop eosinophilic myocarditis, endomyocardial fibrosis, or pericarditis.

3. Vasculitic Phase

- **Systemic Symptoms:** Fever, unintentional weight loss, and malaise are common.
- **Cutaneous Signs:** Patients may develop palpable purpura, nodules, or urticarial-like rashes.
- **Peripheral Neuropathy:** Mononeuritis multiplex is a hallmark, presenting with asymmetric motor and sensory deficits.
- **Kidney Involvement:** Though less common than in other ANCA-associated vasculitides, manifestations may include mild proteinuria, hematuria, or renal dysfunction.
- **Cardiac Complications:** Vasculitis of coronary vessels or eosinophilic infiltration can cause pericarditis or heart failure.
- **Other Organs:** Rare cases involve the central nervous system, potentially leading to strokes or encephalopathy.

Diagnosis

A comprehensive approach incorporating clinical evaluation, laboratory findings, imaging, and histopathology is essential for diagnosing EGPA. Although the 1990 ACR criteria were initially intended for classification, they are frequently referenced in clinical practice.

1. Clinical Assessment

- Detailed patient history and physical examination, focusing on asthma, allergic features, and systemic manifestations.
- Examination for skin lesions, neuropathy, and other systemic signs.

2. Laboratory Investigations

- **Eosinophilia:** Peripheral eosinophil count often >1,500/μL.
- **Serum IgE:** Typically elevated.
- **ANCA Testing:** Positive in about 30–40% of patients, predominantly showing MPO-ANCA (p-ANCA). ANCA positivity is associated with a higher likelihood of vasculitic features like neuropathy and renal involvement.
- **Inflammatory Markers:** ESR and CRP are usually elevated.

3. Imaging Studies

- **Chest X-ray or CT:** Reveals transient, patchy infiltrates.
- **Sinus Imaging:** May show chronic sinusitis or nasal polyps.

4. Histopathological Examination (Gold Standard)

- Tissue biopsy (skin, nerve, lung) typically demonstrates:
    - Eosinophil-rich granulomatous inflammation.
    - Necrotizing vasculitis of small- to medium-sized vessels.
    - Extravascular granulomas with eosinophils.

5. ACR 1990 Classification Criteria

(Requires at least four of the following six criteria for classification):

1. Asthma
2. Peripheral eosinophilia >10%
3. Neuropathy (mononeuritis multiplex or polyneuropathy)
4. Non-fixed pulmonary infiltrates
5. Paranasal sinus abnormalities
6. Extravascular eosinophils on biopsy

Differential Diagnosis

- Other ANCA-associated vasculitides (e.g., GPA, MPA)
- Hypereosinophilic syndrome
- Parasitic infections
- Allergic bronchopulmonary aspergillosis
- Eosinophilic pneumonia

Conclusion

Timely identification of the characteristic triad—adult-onset asthma, eosinophilia, and systemic vasculitis—coupled with laboratory and histopathological confirmation, is crucial for prompt

diagnosis and management. Given the disease's variable presentation, clinicians should maintain a high level of suspicion in patients with new systemic symptoms and a history of adult-onset asthma.

Pharmacological Treatment of EGPA

The primary strategy for managing Eosinophilic Granulomatosis with Polyangiitis (EGPA) centers on systemic immunosuppression. Treatment typically begins with corticosteroids, often supplemented by other immunosuppressive or biologic therapies based on disease severity and organ involvement.[6]

1. Corticosteroids

• **First-line therapy:** Oral prednisone, typically at an initial dose of 0.5 to 1 mg/kg/day, is the cornerstone of treatment. The dosage is gradually reduced over several months as symptoms stabilize.

• **Severe or organ-threatening disease:** For patients with critical organ involvement—such as cardiac, renal, or neurological complications—initial therapy may include high-dose intravenous methylprednisolone (e.g., 500–1000 mg/day for 3 consecutive days) followed by a switch to high-dose oral therapy.

2. Conventional Immunosuppressants

Reserved for patients with severe disease, organ involvement, or relapses.

• **Cyclophosphamide:** Recommended for life-threatening or severe organ involvement; usually administered as monthly intravenous infusions (0.5–1 g/m²) or daily oral doses (1.5–2 mg/kg/day).

• **Azathioprine or Methotrexate:** Often used as maintenance therapy or to minimize long-term steroid use, particularly in patients with less severe disease.

• **Mycophenolate mofetil:** Sometimes utilized when azathioprine or methotrexate are not tolerated or contraindicated.

3. Biologic Agents

• **Mepolizumab (anti-IL-5 antibody):** Approved for EGPA management; helps reduce eosinophil levels, controls asthma symptoms, and lowers the risk of relapses.

• **Rituximab (anti-CD20 antibody):** May be considered in select patients, especially those who are ANCA-positive or have refractory disease.

4. Additional Therapies

• **Plasmapheresis:** Generally reserved for severe cases with complications like renal or pulmonary hemorrhage.

• **Supportive Care:** Includes prophylactic antibiotics, such as cotrimoxazole, to prevent opportunistic infections in patients on intensive immunosuppressive therapy.

Non-Pharmacological Management of EGPA

Non-drug interventions are a critical component of comprehensive care for patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA). These approaches help manage symptoms, mitigate complications, and enhance quality of life alongside medical treatment.

1. Patient Education

• Educating patients about the nature of EGPA, its progression, and possible complications empowers them to actively participate in their care.

• Emphasize the importance of consistent medication use and teach strategies to manage asthma and allergic symptoms effectively.

2. Asthma and Allergy Management

• Use inhaled corticosteroids and bronchodilators to control asthma symptoms as needed.

• Recommend allergen avoidance measures and nasal saline irrigation to manage allergic rhinitis.

3. Monitoring and Prevention

• Regular follow-up with a multidisciplinary team—rheumatologists, pulmonologists, cardiologists—is essential to monitor disease activity and address potential side effects of treatment.

• Implement screening for infections, osteoporosis, and cardiovascular risk factors, as these are increased by long-term corticosteroid use.

4. Physical and Occupational Therapy

• For patients with peripheral neuropathy or musculoskeletal issues, customized rehabilitation programs can maintain function and mobility.

• Teaching joint protection techniques and ergonomic adjustments supports independence in daily activities.

5. Cardiovascular Risk Reduction

• Manage hypertension, diabetes, and elevated cholesterol, as both the disease and its treatments can increase cardiovascular risks.

6. Psychosocial Support

• Offer counseling, peer support groups, and social services to help patients and families manage the psychological and social challenges of living with a chronic condition.

Summary

An integrated approach that combines early and aggressive medical therapy with a broad spectrum of non-pharmacological strategies is essential to achieve disease control, prevent relapses, and improve long-term outcomes for patients with EGPA.[7]

Pharmacists' Role in Managing Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Pharmacists are essential members of the multidisciplinary team caring for patients with EGPA. They ensure the safe and effective use of medications, promote adherence, educate patients, and

monitor for potential side effects. Their expertise supports optimal treatment outcomes and enhances patients' overall quality of life.[8]

1. Medication Management and Safety

• Corticosteroid Use:

o Educate patients on the correct use of corticosteroids, including tapering regimens, potential side effects like hyperglycemia, osteoporosis, and mood swings, and the risk of infections.
o Monitor long-term complications such as adrenal suppression and advise on appropriate calcium and vitamin D supplementation.

• Immunosuppressive Agents:

o Oversee dosing of medications like cyclophosphamide, azathioprine, and methotrexate.
o Stress the need for regular laboratory tests (e.g., liver function, complete blood count) to detect potential hematologic or liver toxicities.
o Discuss infection risks and the importance of vaccinations.

• Biologic Therapies (e.g., mepolizumab, rituximab):

o Provide guidance on administration (subcutaneous or IV), possible side effects, and the need for infection screening (e.g., TB testing before rituximab).
o Reinforce adherence and the importance of follow-up to monitor efficacy and safety.

2. Patient Education and Counseling

• Therapy Adherence:

o Highlight the importance of consistent medication use, even when symptoms improve, to maintain disease control and prevent relapse.

• Asthma and Allergy Control:

o Educate on correct inhaler use and adherence to allergy treatments to manage respiratory symptoms effectively.

• Managing Side Effects:

o Provide advice on managing corticosteroid-related issues like weight gain, hyperglycemia, and mood changes.
o Offer guidance on minimizing side effects from immunosuppressive therapies, including infection prevention and gastrointestinal symptom management.

3. Drug Interaction and Polypharmacy Management

• Evaluate potential drug-drug interactions, especially in patients on multiple therapies including corticosteroids, immunosuppressants, or biologics.
• Review interactions with common over-the-counter medicines (e.g., NSAIDs) or herbal supplements that could affect disease control or cause adverse reactions.

4. Vaccination and Infection Prevention

• Recommend appropriate vaccinations (e.g., influenza, pneumococcal, herpes zoster) before starting immunosuppressive therapy.

• Educate patients on avoiding live vaccines during periods of high-dose immunosuppression.

5. Supportive Lifestyle and Bone Health

• Advise on smoking cessation, balanced nutrition, and exercise to lower cardiovascular risks.

• Recommend calcium and vitamin D supplementation and monitoring for corticosteroid-induced osteoporosis.

6. Care Coordination and Interprofessional Collaboration

• Serve as a bridge between patients and other healthcare providers (e.g., rheumatologists, pulmonologists, primary care) to coordinate care.

• Participate in treatment planning, offering insights on medication safety, adherence, and cost-effectiveness.

7. Specialty Pharmacy Services and Access to Therapies

• Assist patients in navigating insurance approvals and obtaining high-cost biologics like mepolizumab.

• Provide education on storage, administration, and handling of specialty medications to ensure proper use.[9]

Conclusion:

Eosinophilic Granulomatosis with Polyangiitis (EGPA), previously known as Churg-Strauss Syndrome, is an uncommon systemic vasculitis that presents a diagnostic challenge due to its diverse clinical manifestations. It typically progresses through distinct phases: initial adult-onset asthma, marked eosinophilia, and subsequent systemic vasculitis affecting various organs.[10] Early detection and prompt treatment initiation are essential to prevent irreversible organ damage and to enhance patient outcomes.

The management of EGPA requires a coordinated, multidisciplinary strategy. Systemic corticosteroids remain the primary treatment modality, effectively controlling inflammation. Additional immunosuppressive therapies—such as cyclophosphamide—and biologic agents, including mepolizumab, are particularly important for patients with severe or treatment-resistant disease. Non-drug measures, such as optimal asthma control, comprehensive supportive care, and robust patient education, are indispensable components of patient-centered management.

Pharmacists play a crucial role in this multidisciplinary care team, offering essential expertise in medication optimization, educating patients, monitoring side effects, and fostering adherence. Their collaboration with rheumatologists, pulmonologists, and other healthcare professionals ensures a comprehensive and integrated approach to care.

Ongoing research aimed at elucidating the underlying mechanisms of EGPA and developing novel targeted therapies continues to enhance our ability to manage this complex disease effectively.[11] A personalized, team-based approach remains the cornerstone of EGPA management, offering the best chance of improved prognosis and enhanced quality of life for affected patients.

References:

1. Mahr A, Moosig F, Neumann T, *et al.* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolving concepts. Allergy. 2013;68(9):1190-1198.
2. Groh M, Pagnoux C, Baldini C, *et al.* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): revisiting the classification criteria. Medicine (Baltimore). 2015;94(22):e2098.
3. Comarmond C, Pagnoux C, Khellaf M, *et al.* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term follow-up of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheumatol. 2013;65(1):270-281.
4. Vaglio A, Moosig F, Zwerina J. Churg-Strauss syndrome: update on pathophysiology and treatment. Curr Opin Rheumatol. 2012;24(1):24-30.
5. Wechsler ME, Akuthota P, Jayne D, *et al.* Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017;376(20):1921-1932.
6. Guillevin L, Cohen P, Gayraud M, *et al.* Churg-Strauss syndrome: clinical study and long-term follow-up of 96 patients. Medicine (Baltimore). 1999;78(1):26-37.
7. Hellmich B, Ehlers S, Csernok E, *et al.* Update on the pathogenesis of Churg-Strauss syndrome. Clin Exp Rheumatol. 2003;21(6 Suppl 32):S69-S77.
8. Samson M, Puéchal X, Devilliers H, *et al.* Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Rheumatology (Oxford). 2019;58(6):1007-1015.
9. Cottin V, Bel E, Bottero P, *et al.* Revisiting the role of eosinophils in EGPA: implications for treatment. Eur Respir Rev. 2021;30(160):210043.
10. Jennette JC, Falk RJ, Bacon PA, *et al.* 2012 Revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1-11.
11. Watts R, Lane S, Hanslik T, *et al.* Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. 2007;66(2):222-227.

Bhumi Publishing, India
July 2025

FUTURE PERSPECTIVE ON EPILEPSY

Varunsingh Saggu*, Hemraj Singh Rajput
Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India
*Corresponding author E-mail: varunsvdu@gmail.com

Abstract:
Epilepsy, affecting over 70 million people worldwide, poses a significant global health burden marked by disability, mortality, comorbidities, stigma, and substantial costs. Recent advancements in understanding the pathophysiological mechanisms of epilepsy have led to a paradigm shift, characterizing it as a symptom complex with diverse risk factors and a strong genetic predisposition Seizures, characterized by sudden electrical disruptions in the brain, manifest through diverse symptoms, while epilepsy is defined by recurrent, unprovoked seizures. The incidence and prevalence of epilepsy vary globally, influenced by factors such as healthcare quality and infection risks. The classification of epileptic seizures and epilepsies has evolved, emphasizing the importance of a detailed clinical history and reliable eyewitness accounts for accurate diagnosis. The International League against Epilepsy (ILAE) provides a classification system based on seizure occurrence, epilepsy syndrome identification, and recurrent seizure likelihood. The pathophysiology includes the mechanisms triggering seizures, emphasizing the imbalance between neuronal excitation and inhibition. Abnormalities in ions, neurotransmitters, and membrane properties contribute to hyperexcitation and hypersynchronization in neuronal networks, culminating in seizures. A variety of anti-seizure medications (ASDs), detailing their mechanisms of action, doses provide insights about different drug choice approaches. It also extends to newer treatment approaches, encompassing drugs like Vigabatrin, Rufinamide, Perampanel, Eslicarbazepine, and others.

Keywords: Epilepsy, Health, Pathophysiological Mechanism

Introduction:

A seizure is a sudden, temporary disruption of electrical signals in the brain that can lead to changes in behavior, movement, feelings, and consciousness. This signal overload leads to diverse symptoms such as abnormal sensations, loss of consciousness, and involuntary muscle movements, as affected brain cells transmit signals uncontrollably to surrounding areas.(1) It can last for a few seconds to a few minutes and may vary in severity. Epilepsy, in contrast, is a neurological disorder characterized by recurrent, unprovoked seizures. The distinction lies in the frequency and nature of seizures; a single seizure does not necessarily indicate epilepsy.(2) Conclusively, seizures are a symptom, epilepsy is a distinct disorder characterized by recurrent,

unprovoked seizures. Physicians typically diagnose epilepsy when there is no other discernible underlying cause for the seizures, such as a head injury or infection. A minimum of two seizures occurring at least 24 hours apart is a key diagnostic criterion, with multiple seizures within a 24-hour period not necessarily indicative of epilepsy.(3)

While "seizure disorder" and "epilepsy" are often used interchangeably, the term "provoked" distinguishes seizures resulting from identifiable causes, like severe hypoglycemia, which are not classified as forms of epilepsy. The key criterion for epilepsy is the occurrence of recurrent, unprovoked seizures, emphasizing the importance of distinguishing between different types of seizure events.(4)

Epilepsy incidence varies globally, with high-income countries experiencing a consistent rate of around 50 per 100,000 annually, exhibiting bimodal distribution in infants (<1 year) and individuals over 50, peaking after 70. Low-income countries face higher incidence (>80–100 per 100,000) possibly due to substandard healthcare and increased infection risks. Active epilepsy prevalence ranges from 4–12 per 1000, with risk factors differing by age. In high-income countries, over two-thirds achieve long-term remission, often attributed to anti seizure medication. Drug-resistant epilepsy affects up to a third, with limited improvement despite available drugs. Global variations stem from diverse risk factors, including infections and inadequate care, influencing both incidence and prevalence.(5, 6)

The International League against Epilepsy (ILAE) characterizes epilepsy through the occurrence of:

(1) A minimum of two unprovoked (or reflex) seizures with a gap of more than 24 hours between them

(2) A single unprovoked (or reflex) seizure along with a likelihood of subsequent seizures comparable to the typical recurrence risk (at least 60%) following two unprovoked seizures within the next decade

(3) The identification of an epilepsy syndrome.(7)

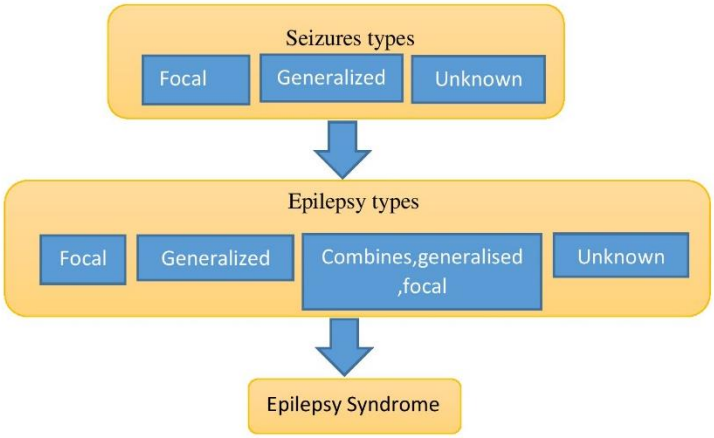

Figure 1 :ILAE Classification of epilepsy(8)

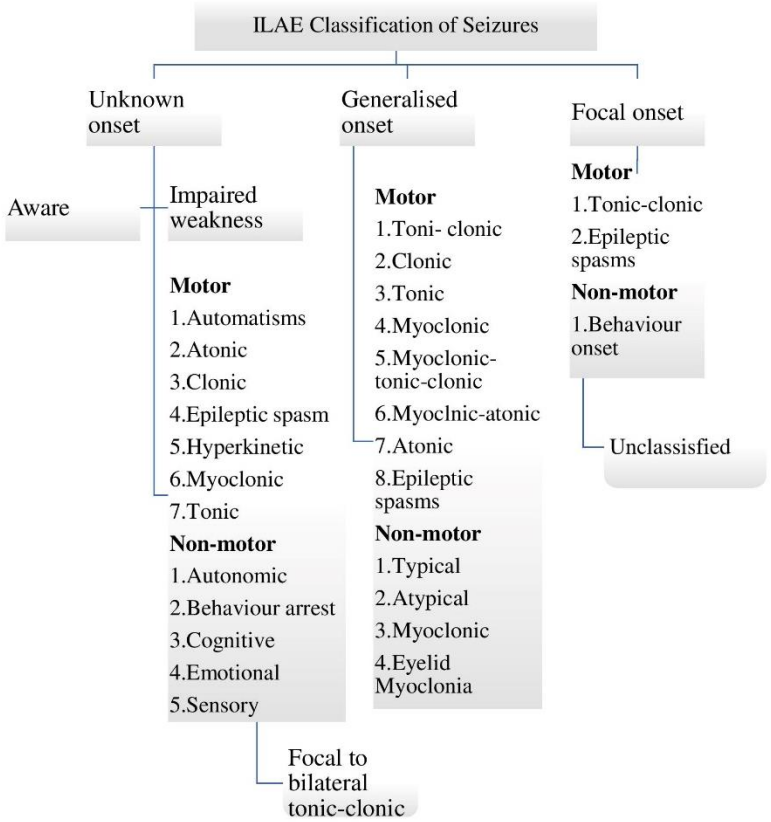

Figure 2 :ILAE Classification of seizure(7) (9)

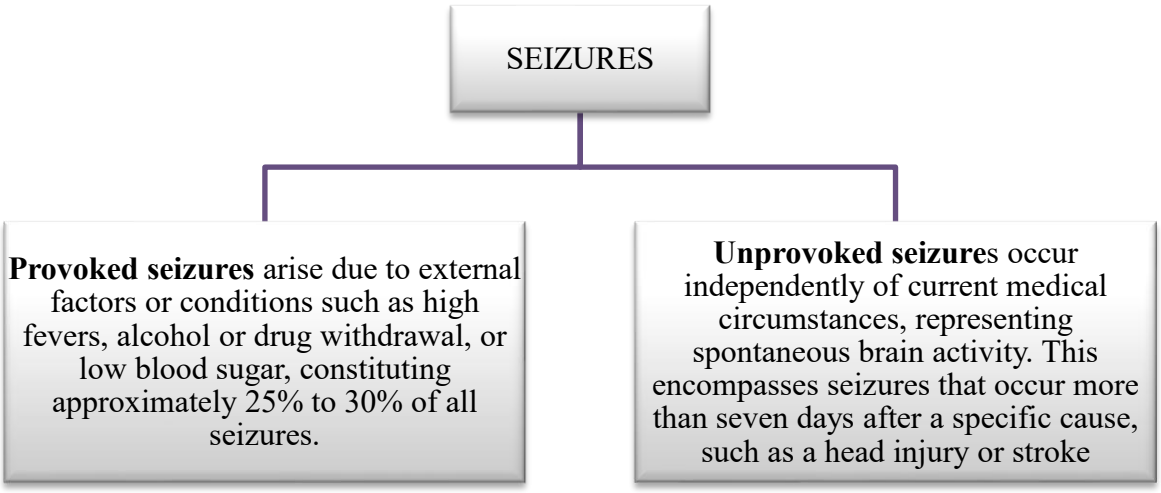

Figure 3 : Classification of seizures(10)

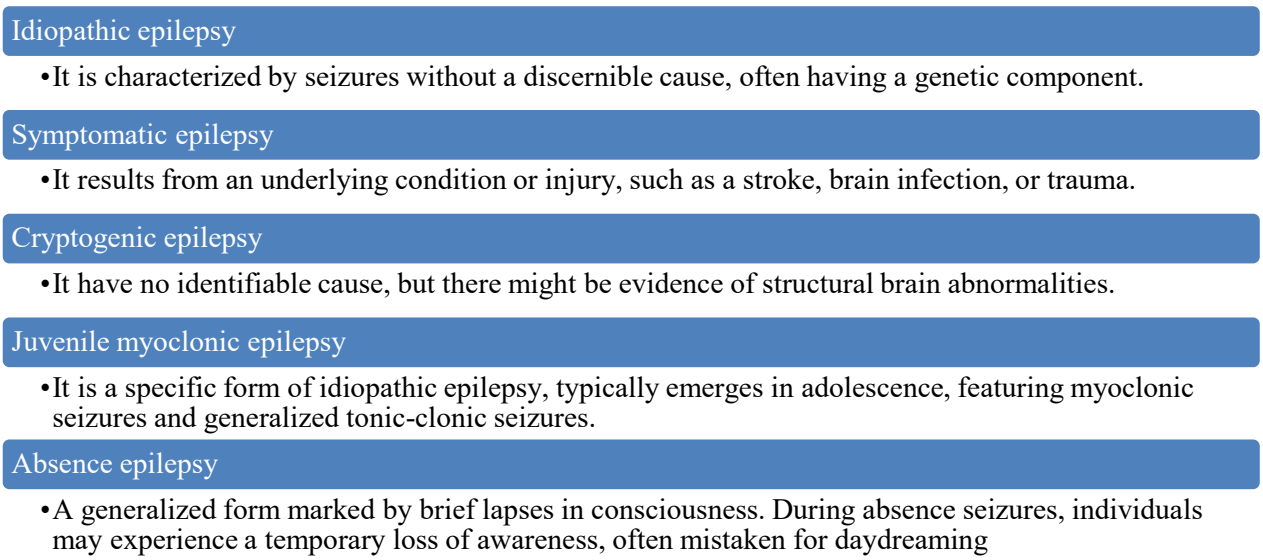

Figure 4 :Types of epilepsy(11)

Pathophysiology

Seizures result from sudden, uncontrolled depolarization of neurons, causing abnormal motor or sensory activity, often with loss of consciousness. The exact cellular mechanisms initiating seizures involve theories of altered membrane permeability, reduced inhibitory control, and neurotransmitter imbalances. A seizure arises from an imbalance between neuronal excitation and inhibition, marked by hyperexcitation and hypersynchronization within a neuronal network. Changes in ions, neurotransmitters, and neuronal membrane properties, influenced by factors like hypoxia or abnormal neurotransmitter levels, can trigger seizures.(12)

Clinical manifestations of abnormal neuronal discharge include alterations in motor function, sensation, autonomic function, consciousness, and behavior. Neurons in the epileptogenic focus are hyperexcitable, with a lower stimulation threshold easily triggered by physiological changes.(13)

Synchronized bursts from an adequate number of neurons generate a spike discharge on the EEG. At the individual neuron level, epileptiform activity involves a sustained depolarization leading to a burst of action potentials, followed by a plateau-like depolarization, rapid repolarization, and hyperpolarization—collectively termed the paroxysmal depolarizing shift (PDS). This burst results from prolonged depolarization due to extracellular Ca++ influx, activating voltage-dependent Na+ channels, causing Na+ influx, and initiating repetitive action potentials. The subsequent hyperpolarizing after potential is facilitated by GABA receptors and Cl− influx or K+ efflux, depending on the cell type.

Normally, intact hyperpolarization and the presence of inhibitory neurons in the surrounding region prevent the spread of bursting activity. However, with sufficient activation, neighboring neurons are recruited through various mechanisms. Repetitive discharges result in:

1) An increase in extracellular K+, reducing the effectiveness of hyperpolarizing outward K+ currents and potentially depolarizing nearby neurons

2) Accumulation of Ca++ in presynaptic terminals, enhancing neurotransmitter release

3) Depolarization-triggered activation of the NMDA subtype of the excitatory amino acid receptor, leading to increased Ca++ influx and subsequent neuronal activation.(14)

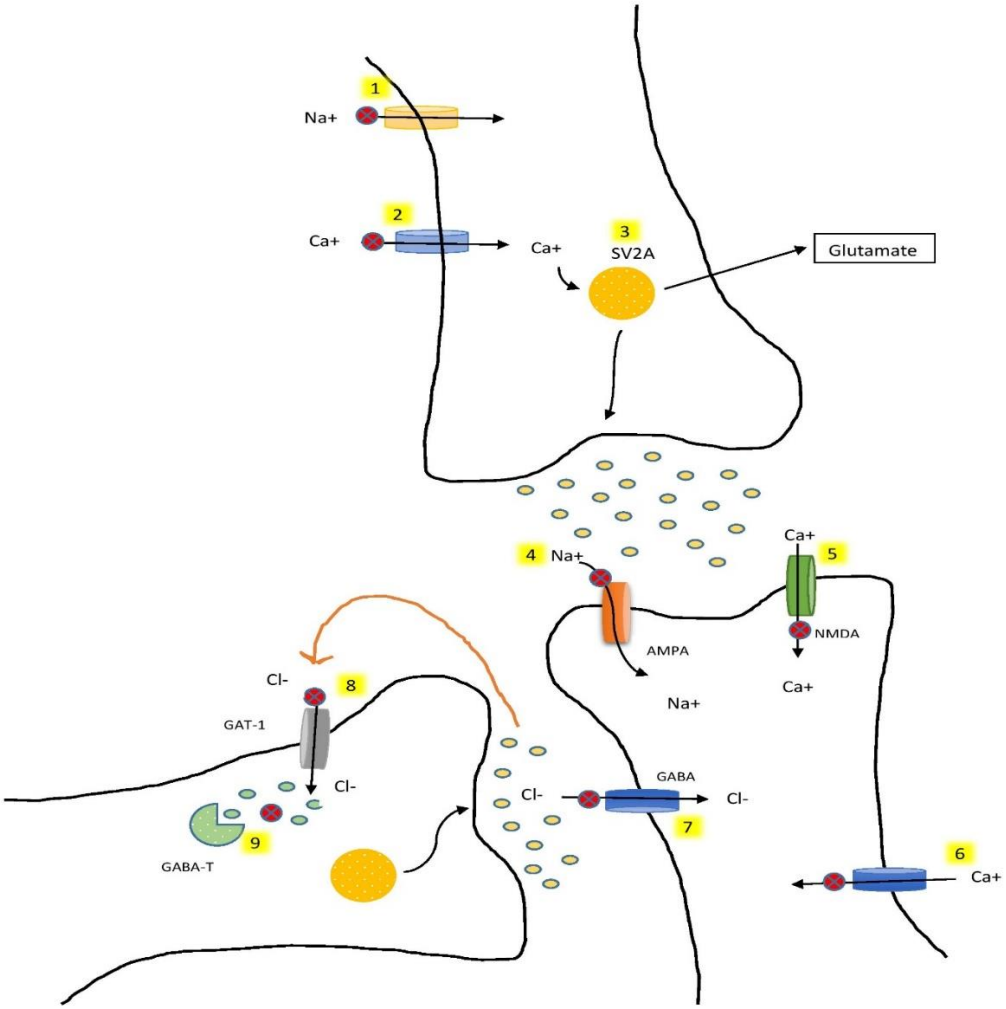

Figure 5: Pathophysiology of epilepsy and site of action of AED

1. Na+ channel blockers-phenytoin,Carbamazepine,Oxcarbamazepine,Valproic acid
2. Ca+ channel blockers-Ethosuximide,Zonisamide
3. SV2A blockers-Leviteracetam
4. AMPA receptor blockers-topiramate
5. NMDA receptor blockers-felbamate
6. Low voltage Ca+ T-type channels blockers-Valproic acid,zonisamide
7. Cl- channels blockers-benzodiazepines,barbiturates
8. GABA reuptake inhibitor-Tiagabine
9. GABA aminotransferase inhibitor-Vigabatrin

Etiology

Causes	**Condition**
Vascular	Hypotension, hypertension, PRESS, Acute ischemic stroke, Intracerebral hemorrhage, subarachnoid hemorrhage, hypoxemia
Infectious	Meningitis, Encephalitis, Brain abscess
Traumatic	Epidural hematoma, sub Dural hematoma
Autoimmune	SLE, Paraneoplastic syndrome
Metabolic	Decrease in Vitamin B1, glucose, Na+, Ca+, Mg+, PO4 Increase in urea, waste, ammonia, hyperthyroidism
Idiopathic	West syndrome, Lennox-Gastaut syndrome, Juvenile myoclonic epilepsy
Neoplastic	Glioblastoma, meningioma, malignancy
Drugs	Opioids, TCAs, Isoniazid, Salicylic toxicity, cocaine, caffeine, amphetamines, metronidazole, penicillin, Benzodiazepines, Bupropion, Lithium(15, 16)

Signs and Symptoms

Table 1: Comparative signs and symptoms

	Muscle stiffness	**Muscle twitching and jerking**	**Awareness**
Tonic	Yes	No	Normally or slightly altered
Clonic	No	Yes	Normally or slightly altered
Tonic Clonic	yes	Yes	loss

Table 2: Signs and symptoms of epilepsy(17) (13) (18) (19) (20) (21)

Epilepsy type	***Key Features***	***Onset***	***Consciousness***	***Motor symptoms***	***Other symptoms***
Generalized tonic-clonic	Loss of consciousness, stiffening, rhythmic jerking, confusion, fatigue, incontinence.	Sudden	Loss	Stiffening, jerking	Postictal state (confusion, fatigue)

Absence(Petit mal)	Brief lapses, staring, subtle movements, no memory of episode.	Sudden	Impaired for a few seconds	Subtle movements	No memory of the episode
Myoclonic	Sudden, brief muscle jerks or twitches, often in clusters.	Sudden	Preserved	Jerking movements	May occur individually or in clusters
Tonic	Stiffening of muscles, falls, injuries.	Sudden	Impaired	Stiffening	Falls and potential injuries
Clonic	Rhythmic jerking movements, typically in the face and limbs.	Sudden	Impaired	Rhythmic jerking	May affect one or both sides of the body
Focal(Variable)	Varies based on affected brain region.	Variable	Variable	Variable, depending on area	Variable, based on affected brain region

Genetic

Epilepsies with genetic origins typically manifest in infancy or childhood. Examples include Dravet syndrome (SCN1A mutations), Childhood Absence Epilepsy (mutations in T-type Ca2+ channels and GABA-receptor subunits), and Juvenile Myoclonic Epilepsy (mutations in EFHC1 and ICK). Formerly labeled as idiopathic generalized epilepsy, these disorders are now recognized as genetic generalized epilepsies, reflecting molecular-level abnormalities. Genetic etiologies may be inherited or arise from sporadic mutations but are not acquired post-birth.(22) Genetic research in epilepsy has identified over 30 mutated genes linked to rare autosomal dominant monogenic epilepsies, primarily involving ion channels but also neuronal receptors, transcription factors, and enzymes. Familial monogenic epilepsies constitute 5–10% of genetic epilepsy cases, with the majority of presumed genetic generalized epilepsies, like juvenile

myoclonic epilepsy, lacking known causes. Focal epilepsies may have a genetic basis, often involving genes in the mTOR pathway or voltage/ligand-gated channels.(5)

Diagnosis

1. EEG-identify type and location of seizure
2. MRI-detect changes in structure of brain
3. Single photo emission computed tomography(SPECT)-detect changes in blood flow
4. PET scan-detect alterations in glucose uptake and metabolism
5. Video EEG-differentiate between different type of seizures(5, 13, 16)

Treatment

Managing patients after a single isolated seizure involves a careful consideration of factors influencing the likelihood of recurrent seizures. The decision to initiate antiseizure drug (ASD) therapy is based on findings such as abnormal brain imaging, epileptiform EEG, or a history of nocturnal seizures, with the probability of recurrence being 2 to 2.5 times higher in the presence of these factors. Clinicians may differ in their approach, but generally, patients with two or more unprovoked seizures should start ASDs.

Once the decision to initiate therapy is made, accurate identification of seizure type and epilepsy diagnosis is crucial. ASD selection is then tailored to the specific epilepsy syndrome, considering patient characteristics such as age, gender, comorbidities, and potential adverse effects. For example, patients with childhood absence epilepsy may benefit from ethosuximide, while those with comorbid conditions like migraine or bipolar disorder may be prescribed drugs like topiramate or lamotrigine.(23)

Pharmacokinetic drug interactions further complicate ASD selection, requiring an understanding of metabolic pathways and effects on liver enzymes. Care must be taken when adding or withdrawing ASDs from a drug regimen to avoid complications.

Patient adherence to a prescribed regimen and insurance coverage are also critical factors. Complex dosing regimens may lead to nonadherence, affecting seizure control. Additionally, the cost of therapy or lack of insurance coverage may present challenges for patients.

After selecting an ASD, the optimization of the dose involves titrating to a therapeutic maintenance dose based on individual recommendations. The titration speed depends on factors like age, comorbidities, and the urgency of achieving therapeutic levels. While ASD monotherapy is preferred, some patients may require dual or polytherapy if seizures persist.(24)

Table 3: Anti epileptic drugs(25-32)

	MOA	DOSE	USE
First Generation			
Carbamazepine	Sodium channel blocker	100-200mg	Focal seizures, TC
Clonazepam	GABA augmentation	0.5mg	Absence, myoclonic
Ethosuximide	Calcium channel modification	250mg	Absence
Phenobarbital	GABA augmentation	30mg	Focal, general
Phenytoin	Sodium channel blocker	200mg	Focal, TC
Valproic acid	Calcium and Sodium channel blocker	200mg	Generalised (includes absence or myoclonic)
Primidone	GABA augmentation	125mg	Partial, TC
Second Generation			
Gabapentin	Unknown, may increase the synthesis of GABA	300mg	Focal
Leviteracetam	Modulation of synaptic vesicle protein	250mg	Focal, myoclonic, tonic-clonic
Topiramate	Sodium channel blocker, GABA-A receptors enhancers, AMPA-type glutamate antagonist, effect on calcium channels	100-200mg daily	Focal, generalized, Lennox-Gastaut syndrome, West syndrome, TC
Lamotrigine	Sodium channel blocker, calcium channel blocker	50mg	Focal, generalized, TC, Idiopathic epilepsy, symptomatic epilepsy, Myoclonic, Absence
Oxcarbazepine	Sodium channel blocker, calcium channel blocker	150-300mg	Focal, TC
Zonisamide	Sodium channel blocker, calcium channel blocker	367mg/day(100mg/day)	Focal, generalized, TC, absence, tonic, myoclonic
Tiagabine	GABA re-uptake inhibitor	5mg	Focal
Felbamate	NMDA receptor blocker, sodium channel modulator, GABA-A transmission enhancer	400mg	Focal, TC, Lennox-Gastaut syndrome

Third Generation			
Clobazam	GABA augmentation	10mg	Lennox-Gastaut syndrome
Pregabalin	Calcium channel modulation	50mg	Focal
Brivaracetam	Sodium channel blocker	25–50 mg twice daily	Focal, myoclonic
Pregabalin	Calcium channel modulation	150 mg daily in 2 or 3 divided doses. Maximum 600 mg daily in 2 or 3 divided doses	Focal, TC

Newer Treatment Approahces

Table 4: Newer Anti-epileptic drugs(9, 33-36)

DRUGS	MOA	DOSE	USE
Vigabatrin	Blocking the breakdown of GABA (gamma-aminobutyric acid) by irreversibly inhibiting GABA transaminase	200mg/kg/day	Focal, TC, West syndrome
Rufinamide	Sodium channel blocker	Start with 200–400 mg per day and increase by 200–400 mg per day after 2 weeks; further increases, if indicated, by 400 mg per day every 2 weeks	Focal, TC
Perampanel	Noncompetitive antagonist of the ionotropic !-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)-type glutamate receptors on postsynaptic neurons	Commence with a daily dosage of 2 mg, gradually raising it to a maintenance dose ranging from 4 to 8 mg once daily. The maximum allowable daily dose is 12 mg.	Focal, general

Eslicarbazepine	Sodium channel blocker	800mg, 1200mg	Partial-onset seizure
Lacosamide	Slow inactivation of Na+ channels	Begin with a dosage of 50 mg administered twice daily, gradually escalating to a maximum dose of 200 mg taken twice daily.	Focal
Retigabine	K+ channel modulator	200mg	Partial onset, drug resistant epilepsy
Stiripentol	GABA enhancer	250, 500mg	Dravet syndrome in patient taking clobazam
Ganaxolone	GABA receptor modulator	50-1500mg	Infantile spasma, partial-onset
Losigamone	Unknown, Maybe NMDA blocker, Na+ channel blocker	1500mg/day	Partial
Safinamide	Sodium channel blocker, calcium channel blocker, MAO-B inhibitor	50, 100mg	Partial, generalised

Future Perspective on Epilepsy

Epilepsy, a chronic neurological disorder characterized by recurrent unprovoked seizures, affects millions of individuals worldwide. Despite significant progress in its diagnosis and treatment, a substantial proportion of patients continue to experience uncontrolled seizures or endure the long-term side effects of antiepileptic drugs. As research advances and technology becomes increasingly sophisticated, the future of epilepsy care is expected to undergo revolutionary changes that focus not only on seizure suppression but also on prevention, precision therapy, and improved quality of life.

1. Precision Medicine and Genetic Insights

One of the most promising developments in the future management of epilepsy lies in the field of precision medicine. With growing access to genetic testing and whole-genome sequencing, clinicians are now beginning to identify specific mutations responsible for various epilepsy syndromes. This approach enables a better understanding of disease mechanisms at the

molecular level, allowing for targeted interventions. In the future, individualized treatment plans based on a patient's genetic profile could become standard practice, particularly in pediatric cases where early identification of genetic causes could significantly alter prognosis.

For example, certain forms of epilepsy such as Dravet syndrome, caused by mutations in the SCN1A gene, may benefit from therapies specifically designed to modulate sodium channel function. Gene therapy, antisense oligonucleotides (ASOs), and CRISPR-based genome editing are emerging as potential curative strategies for monogenic epilepsies. Although currently in experimental stages, these therapies could one day replace long-term medication in selected patients, offering the possibility of disease modification or even cure.

2. Advancements in Neurotechnology and Brain Interfaces

Technological innovation is also reshaping the way epilepsy is diagnosed and managed. High-resolution neuroimaging techniques such as functional MRI (fMRI), magnetoencephalography (MEG), and advanced EEG analyses are enabling more precise localization of seizure foci. This is especially beneficial for surgical candidates, where accurate mapping of epileptogenic zones is critical for achieving seizure freedom while preserving vital brain functions.

In addition, neuromodulation therapies are expected to become more refined and accessible. Devices like responsive neurostimulation (RNS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) already offer hope to individuals with drug-resistant epilepsy. These technologies are designed to detect abnormal brain activity and deliver electrical stimulation in real-time to prevent seizures. Future iterations of these systems will likely incorporate machine learning algorithms to improve their responsiveness, accuracy, and adaptability to the patient's neural patterns.

Brain-computer interfaces (BCIs) may also play a transformative role in epilepsy care. By continuously monitoring neural signals and adapting in real time, BCIs could potentially predict seizures before they occur, allowing timely intervention or alerting caregivers. Integration of BCIs with wearable or implantable devices may eventually make real-time seizure forecasting a practical reality.

3. Artificial Intelligence and Digital Health

The integration of artificial intelligence (AI) and digital health tools is another area with transformative potential. AI-driven platforms can process vast datasets from EEG recordings, imaging studies, and clinical histories to assist in diagnosis, seizure prediction, and treatment optimization. These tools are particularly valuable in reducing diagnostic delays and minimizing human error in interpreting complex neurophysiological data.

Wearable technologies, such as smartwatches and biosensors, are being developed to monitor physiological markers that may precede seizures, such as changes in heart rate, skin conductance, or movement patterns. These devices can alert patients and caregivers to impending seizures,

potentially reducing injury and allowing for more timely medical interventions. In the future, integration of wearable data with AI platforms could form closed-loop systems for seizure detection and automatic treatment delivery.

Moreover, telemedicine and mobile health applications are expected to improve access to care, particularly in remote or underserved regions. These tools can facilitate regular follow-up, medication tracking, remote EEG monitoring, and patient education, thereby enhancing continuity of care and adherence to treatment.

4. Holistic and Multidisciplinary Care Models

Beyond technological advances, the future of epilepsy care must also address the broader psychosocial and quality-of-life issues faced by patients. Chronic epilepsy is often accompanied by comorbidities such as depression, anxiety, cognitive dysfunction, and social stigma. A holistic approach that incorporates mental health services, cognitive rehabilitation, social support systems, and vocational counseling will be vital in delivering comprehensive care.

Multidisciplinary epilepsy centers, combining the expertise of neurologists, psychiatrists, neuropsychologists, social workers, and genetic counselors, are likely to become central hubs for personalized epilepsy management. These centers may also play a key role in patient and caregiver education, thereby empowering individuals to actively participate in treatment decisions and lifestyle modifications.

5. Global Health and Equity Considerations

While many of these advancements are being developed in high-resource settings, it is essential that the future of epilepsy care addresses global health disparities. In many low- and middle-income countries, epilepsy remains underdiagnosed and undertreated due to lack of access to diagnostic tools, medications, and trained professionals. The expansion of affordable generic medications, simplified diagnostic algorithms, and digital health solutions could bridge this gap.

Additionally, global initiatives must aim to raise awareness, reduce stigma, and improve health literacy about epilepsy. Public health campaigns, international collaborations, and government support will be crucial in ensuring that the benefits of modern epilepsy care reach all populations, regardless of socioeconomic status.

Conclusion:

The future of epilepsy care is rich with possibility. From gene-targeted therapies and AI-enhanced diagnostics to wearable seizure detectors and personalized care pathways, we are entering an era of unprecedented innovation. However, realizing this future requires continued investment in research, cross-disciplinary collaboration, and a commitment to equitable healthcare delivery. As our understanding of epilepsy deepens and technologies evolve, the ultimate goal remains clear: to not only control seizures but to restore independence, dignity, and quality of life for every individual living with epilepsy.

References:

1. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. The Lancet. 2019;393(10172):689-701.
2. Banerjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy—a review. Epilepsy research. 2009;85(1):31-45.
3. Hauser WA. Seizure disorders: the changes with age. Epilepsia. 1992;33:6-14.
4. Scambler G. Epilepsy: Routledge; 2005.
5. Moshé SL, Perucca E, Ryvlin P, Tomson T. Epilepsy: new advances. The Lancet. 2015;385(9971):884-98.
6. Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020;54(2):185-91.
7. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, *et al.* ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475-82.
8. Fisher RS, Boas WVE, Blume W, Elger C, Genton P, Lee P, *et al.* Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470-2.
9. Gastaut H, Zifkin BG. Classification of the epilepsies. Drugs for the Control of Epilepsy: CRC Press; 2019. p. 349-59.
10. McAfee AT, Chilcott KE, Johannes CB, Hornbuckle K, Hauser WA, Walker AM. The incidence of first provoked and unprovoked seizure in pediatric patients with and without psychiatric diagnoses. Epilepsia. 2007;48(6):1075-82.
11. Falco-Walter J, editor Epilepsy—definition, classification, pathophysiology, and epidemiology. Seminars in neurology; 2020: Thieme Medical Publishers, Inc. 333 Seventh Avenue, 18th Floor, New York, NY ….
12. Raedt R, Durand DM, Boon P, Vonck K, Krames ES. Epilepsy: anatomy, physiology, pathophysiology, and disorders. Neuromodulation: Elsevier; 2018. p. 987-97.
13. Lawal M, Omobayo H, Lawal K. Epilepsy: pathophysiology, clinical manifestations and treatment options. British Journal of Neuroscience Nursing. 2018;14(2):58-72.
14. Stafstrom CE. Recognizing seizures and epilepsy: insights from pathophysiology. epilepsy. 2014:1-9.
15. Shorvon SD, Andermann F, Guerrini R. The causes of epilepsy: common and uncommon causes in adults and children: Cambridge University Press; 2011.
16. Milligan TA. Epilepsy: a clinical overview. The American Journal of Medicine. 2021;134(7):840-7.
17. Matthews W. Tonic seizures in dissaminated sclerosis. Brain. 1958;81(2):193-206.
18. Panayiotopoulos C. Typical absence seizures and their treatment. Archives of disease in childhood. 1999;81(4):351-5.

19. Duchowny MS. Atonic seizures. Pediatrics in Review. 1987;9(2):43-9.
20. Striano P, Belcastro V. Treatment of myoclonic seizures. Expert Review of Neurotherapeutics. 2012;12(12):1411-8.
21. Wong M, Trevathan E. Infantile spasms. Pediatric neurology. 2001;24(2):89-98.
22. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. The Lancet. 2006;367(9516):1087-100.
23. Ghosh S, Sinha JK, Khan T, Devaraju KS, Singh P, Vaibhav K, *et al.* Pharmacological and therapeutic approaches in the treatment of epilepsy. Biomedicines. 2021;9(5):470.
24. Liu G, Slater N, Perkins A. Epilepsy: treatment options. American family physician. 2017;96(2):87-96.
25. Perucca E. An introduction to antiepileptic drugs. Epilepsia. 2005;46:31-7.
26. Sander JW. The use of antiepileptic drugs—principles and practice. Epilepsia. 2004;45:28-34.
27. Czapinski P, Blaszczyk B, Czuczwar SJ. Mechanisms of action of antiepileptic drugs. Current topics in medicinal chemistry. 2005;5(1):3-14.
28. Sankaraneni R, Lachhwani D. Antiepileptic drugs—a review. Pediatric annals. 2015;44(2):e36-e42.
29. Perucca E. Introduction to the choice of antiepileptic drugs. The treatment of epilepsy. 2015:365-75.
30. Levy RH. Antiepileptic drugs: Lippincott Williams & Wilkins; 2002.
31. Macdonald RL, Kelly KM. Antiepileptic drug mechanisms of action. Epilepsia. 1995;36:S2-S12.
32. Das N, Dhanawat M, Shrivastava SK. An overview on antiepileptic drugs. Drug discoveries & therapeutics. 2012;6(4):178-93.
33. LaRoche SM, Helmers SL. The new antiepileptic drugs: clinical applications. Jama. 2004;291(5):615-20.
34. French JA, Gazzola DM. Antiepileptic drug treatment: new drugs and new strategies. CONTINUUM: Lifelong Learning in Neurology. 2013;19(3):643-55.
35. Macdonald RL. Antiepileptic drug actions. Epilepsia. 1989;30:S19-S28.
36. LaRoche SM, Helmers SL. The new antiepileptic drugs: scientific review. Jama. 2004;291(5):605-14.

EXOSOME-BASED DRUG DELIVERY: NATURAL NANOCARRIERS IN PHARMACEUTICS

Mamta Kumari*, Piyushkumar Sadhu, Chitrali Talele, Niyati Shah
Department of Pharmaceutics, Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara – 391760
*Corresponding author E-mail: mamtastar36@gmail.com

Abstract:
Exosomes are nanoscale, membrane-bound extracellular vesicles ranging from 30 to 150 nanometers in diameter, naturally secreted by various cell types. These vesicles originate from the endosomal pathway, particularly from multivesicular bodies (MVBs), and are released into the extracellular environment through exocytosis. Exosomes serve as natural mediators of intercellular communication, carrying and transferring biologically active molecules including proteins, lipids, mRNA, microRNA, and other non-coding RNAs between cells. Their inherent features such as high biocompatibility, low immunogenicity, and natural origin offer distinct advantages over synthetic nanocarriers. Remarkably, exosomes possess the ability to cross physiological barriers, including the notoriously selective blood-brain barrier, positioning them as powerful tools for targeted drug delivery to difficult-to-reach tissues. Over the past decade, significant strides have been made in exosome engineering, isolation techniques, and drug loading methodologies. These developments have expanded their application to a broad spectrum of therapeutic agents, ranging from conventional small-molecule drugs to complex biologics like siRNA, mRNA, CRISPR/Cas components, and therapeutic proteins. Furthermore, surface modification strategies such as ligand conjugation or PEGylation can be employed to enhance their tissue specificity, cellular uptake, and circulation time. Exosomes also display immune-evasive behavior, which contributes to their prolonged systemic presence and reduced clearance by phagocytic cells. However, despite their potential, several challenges impede their clinical translation, including issues with large-scale production, vesicle heterogeneity, and regulatory classification. This chapter aims to present an in-depth analysis of the biological properties, fabrication strategies, therapeutic potential, and translational hurdles associated with exosome-based drug delivery systems.

Keywords: Exosomes, Nanocarriers, Extracellular Vesicles, Targeted Drug Delivery, RNA Delivery, Exosome Engineering

Introduction:

The effective delivery of therapeutic agents remains one of the most critical challenges in modern pharmaceutics. Conventional drug delivery systems often suffer from limitations such as

poor bioavailability, lack of target specificity, systemic toxicity, and the inability to cross physiological barriers like the blood-brain barrier (BBB). Additionally, many drugs, especially biologics such as peptides, proteins, and nucleic acids, face enzymatic degradation and rapid clearance before reaching their intended site of action. These issues necessitate the development of advanced drug delivery systems that can improve pharmacokinetics, enhance therapeutic efficacy, and minimize adverse effects. Nanocarrier-based approaches have gained prominence, yet synthetic systems often present concerns related to biocompatibility, immunogenicity, and clearance mechanisms. In response to the limitations of synthetic carriers, attention has increasingly shifted toward natural nanocarriers that offer improved biological compatibility and functional versatility. Among these, exosomes have emerged as highly promising vectors for drug delivery. As endogenous carriers, they are naturally equipped to interact with biological systems, enabling efficient cellular uptake, tissue penetration, and even immune modulation. Their ability to encapsulate and protect therapeutic payloads, coupled with inherent targeting and signaling functions, makes them an attractive platform for delivering a diverse range of drugs, including small molecules, RNA, DNA, and proteins [1].

In response to the limitations of synthetic carriers, attention has increasingly shifted toward natural nanocarriers that offer improved biological compatibility and functional versatility. Among these, exosomes have emerged as highly promising vectors for drug delivery. As endogenous carriers, they are naturally equipped to interact with biological systems, enabling efficient cellular uptake, tissue penetration, and even immune modulation. Their ability to encapsulate and protect therapeutic payloads, coupled with inherent targeting and signaling functions, makes them an attractive platform for delivering a diverse range of drugs, including small molecules, RNA, DNA, and proteins [2,3].

Biogenesis and Composition of Exosomes

Exosomes are biologically derived nanovesicles that originate from intracellular pathways and carry a specific molecular cargo reflective of their parent cells. Understanding their biogenesis and composition is crucial for harnessing their potential as drug delivery vehicles, especially in designing targeted and efficient therapeutic systems.

Formation Pathways: Endosomal and MVB Mechanisms

The biogenesis of exosomes is a multistep process initiated in the endosomal compartment of the cell. It begins with the invagination of the plasma membrane, forming early endosomes. These early endosomes mature into late endosomes, during which intraluminal vesicles (ILVs) are formed by inward budding of the endosomal membrane. This results in the development of multivesicular bodies (MVBs) containing multiple ILVs, these ILVs are what become exosomes. MVBs can either fuse with lysosomes for degradation or with the plasma membrane to release ILVs into the extracellular space as exosomes. Two major pathways regulate ILV formation:

- The ESCRT-dependent pathway (Endosomal Sorting Complex Required for Transport), involving a series of protein complexes (ESCRT-0 to ESCRT-III) that sort and sequester cargo into ILVs.
- ESCRT-independent mechanisms, which rely on lipids (e.g., ceramide) and tetraspanins (e.g., CD63, CD81) for membrane budding and cargo selection [4,5].

Molecular Composition: Lipids, Proteins, and Nucleic Acids

Exosomes are characterized by a distinct molecular signature composed of:

- Lipids: Including cholesterol, sphingomyelin, phosphatidylserine, and ceramides, which confer membrane rigidity, curvature, and signaling properties.
- Proteins: Enriched with tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70, HSP90), Alix, TSG101, and adhesion molecules. These proteins are involved in vesicle trafficking, cell targeting, and membrane fusion.
- Nucleic acids: Exosomes carry diverse genetic material such as mRNA, microRNA (miRNA), long non-coding RNA (lncRNA), and DNA fragments, which are functionally active in recipient cells and can modulate gene expression and cellular behavior [6,7].

Exosome Secretion and Cellular Uptake

Once formed within MVBs, exosomes are released into the extracellular environment through exocytosis, a process regulated by Rab GTPases (e.g., Rab27a, Rab11, Rab35), SNARE proteins, and cytoskeletal dynamics. These versatile uptake pathways allow exosomes to function as natural intercellular shuttles, facilitating targeted and efficient delivery of bioactive molecules. Their ability to be taken up by specific cells or tissues is influenced by surface markers and engineered modifications, which is key to designing targeted drug delivery systems. These secreted exosomes interact with recipient cells via several mechanisms:

- Receptor-ligand interactions on the cell surface, initiating signal transduction.
- Membrane fusion, leading to direct cytoplasmic delivery of contents.
- Endocytosis or phagocytosis, where the exosomes are internalized and processed intracellularly [8,9].

Isolation and Characterization Techniques

Accurate isolation and characterization of exosomes are essential steps for ensuring reproducibility, functional integrity, and clinical safety in drug delivery applications. Due to their nanoscale size and heterogeneous nature, the selection of appropriate methods is critical to distinguish exosomes from other extracellular vesicles (EVs) and contaminants such as proteins or apoptotic bodies. This section outlines the major techniques employed for exosome purification and characterization.

Ultracentrifugation and Density Gradient Methods

Differential ultracentrifugation is the most widely used method for exosome isolation, leveraging sequential centrifugation steps to progressively remove cells, debris, and larger vesicles. Final ultracentrifugation at 100,000 × g sediments exosomes based on their small size and density. This method is cost-effective and scalable but may cause vesicle deformation or co-purification of contaminants. To enhance purity, density gradient ultracentrifugation (e.g., using sucrose or iodixanol gradients) is employed. This technique separates exosomes based on their buoyant density (~1.13–1.19 g/mL), improving the isolation of intact and functionally active vesicles. However, these methods are time-consuming and require expensive equipment and operator expertise. [10]

Size-Exclusion Chromatography and Microfluidics

Size-exclusion chromatography (SEC) separates exosomes from soluble proteins and smaller particles by passing the sample through porous beads, allowing vesicles to elute based on size. SEC offers high purity, preserves vesicle integrity, and is well-suited for clinical-grade applications. Microfluidic devices represent a next-generation platform that enables rapid, high-throughput exosome isolation with minimal sample volume. Techniques such as immunoaffinity capture (targeting CD63, CD9, or CD81), acoustic nanofiltration, and on-chip filtration allow for precise and reproducible isolation [11]. Microfluidics are ideal for point-of-care and diagnostic applications but may be limited by throughput in large-scale preparations.

Characterization: DLS, NTA, TEM, and Western Blotting

The characterization ensures that isolated vesicles are indeed exosomes and provides insights into their size, morphology, surface markers, and functionality:

- Dynamic Light Scattering (DLS): Measures average particle size and polydispersity index; suitable for quick assessment but less accurate for heterogeneous populations.
- Nanoparticle Tracking Analysis (NTA): Tracks Brownian motion of individual particles to determine size distribution and concentration; widely used for exosome quantification.
- Transmission Electron Microscopy (TEM): Provides high-resolution images of exosome morphology and confirms vesicle size and bilayer structure.
- Western Blotting: Confirms exosome identity by detecting characteristic protein markers (e.g., CD63, CD81, TSG101, Alix) and absence of cellular contaminants (e.g., calnexin) [12,13].

Table 1: Comparative Overview of Exosome Isolation Techniques

Technique	Principle	Advantages	Limitations	Suitability
Differential Ultracentrifugation	Size and density-based sedimentation	Widely used; simple; scalable for lab use	Time-consuming; potential vesicle damage; co-isolation of protein aggregates	Research-grade applications
Density Gradient Ultracentrifugation	Buoyant density separation (e.g., sucrose or iodixanol gradients)	Higher purity than differential ultracentrifugation; good for functional studies	Labor-intensive; requires experience; expensive equipment	High-purity research; preclinical use
Size-Exclusion Chromatography (SEC)	Size-based separation through porous beads	Gentle on vesicles; reproducible; high purity	Lower yield; limited sample volume	Clinical and diagnostic applications
Ultrafiltration	Membrane filtration based on size cut-off	Fast and simple; scalable	Potential clogging and vesicle loss; low purity	Pre-enrichment step or combination use
Precipitation (e.g., PEG-based)	Polymer-induced aggregation	Quick and easy; no specialized equipment	Co-precipitates proteins; low purity	High-throughput screening
Immunoaffinity Capture	Antibody recognition of surface markers (e.g., CD63, CD81)	High specificity; marker-based enrichment	Expensive; not suitable for bulk recovery	Biomarker studies; diagnostic panels
Microfluidics	On-chip filtration, acoustics, or antibody-based separation	Fast; minimal sample; portable; automation-compatible	Limited throughput; high cost of chips	Point-of-care diagnostics; research

Drug Loading Strategies in Exosomes

Efficient drug loading is a critical step in developing exosome-based delivery systems. The method used to encapsulate therapeutic agents whether small molecules, nucleic acids, or proteins greatly influences the stability, release profile, and targeting efficiency of the final formulation. Drug loading strategies can be broadly categorized into passive, active, and endogenous (genetic engineering) approaches, each with distinct advantages and limitations.

Passive Loading (Incubation, Diffusion)

Passive loading is a straightforward method that involves the co-incubation of isolated exosomes with therapeutic cargo under controlled conditions, utilizing concentration gradients and membrane diffusion to facilitate drug incorporation. This technique is particularly effective for hydrophobic small molecules such as paclitaxel and curcumin, which readily integrate into the lipid bilayer of exosomes. The primary advantages of passive loading include its technical simplicity, gentle handling, and the preservation of exosome integrity and surface markers. However, it is limited by its relatively low loading efficiency, especially for hydrophilic or large biomolecules, and does not enable active targeting of the cargo into the exosomal lumen. Although optimization of parameters such as temperature, pH, and incubation time can modestly enhance loading efficiency, the method remains best suited for lipophilic drugs and exploratory applications [14,15].

Active Loading (Electroporation, Sonication, Freeze–Thaw)

Active loading methods involve the temporary disruption of the exosome membrane to facilitate the entry of drug molecules into the vesicle interior. Techniques such as electroporation use electrical pulses to generate transient pores, allowing the incorporation of nucleic acids like siRNA, miRNA, and plasmid DNA, though they may risk RNA degradation or cargo aggregation. Sonication employs ultrasonic waves to momentarily disturb membrane integrity, enabling the encapsulation of both small and large molecules with relatively high efficiency, albeit with the potential to alter exosome structure. Another approach, freeze–thaw cycles, relies on repeated freezing and thawing to destabilize the membrane and promote drug diffusion; although considered gentle, this method may lead to vesicle fusion or aggregation. Therefore, active loading techniques typically offer higher encapsulation efficiency than passive methods but require precise optimization to maintain the structural and functional integrity of exosomes [16].

Genetic Engineering for Endogenous Loading

Genetic engineering for endogenous loading involves modifying donor cells so that therapeutic molecules are naturally incorporated into exosomes during their biogenesis. This is typically achieved by transfecting cells with plasmid or viral vectors encoding the desired therapeutic cargo, such as RNA or proteins. To enhance specificity and efficiency, exosomal sorting signals like Lamp2b or CD63 fusion tags are often fused to the cargo, directing it into forming

exosomes. This strategy enables highly selective and reproducible incorporation of complex or sensitive biologics, particularly RNA-based therapeutics, while preserving the structural integrity and native functionality of the exosomes. Its key advantages include scalability, precision, and compatibility with personalized or cell-specific treatments. However, it also presents challenges, notably the requirement for genetic modification of source cells and the associated biosafety and regulatory concerns. Despite these hurdles, endogenous loading has become increasingly attractive for developing targeted, next-generation exosome therapeutics [17,18].

Surface Modification and Targeting

To enhance the therapeutic efficiency of exosome-based drug delivery systems, surface modification strategies are employed to improve target specificity, circulation stability, and cellular uptake. Native exosomes already display certain targeting capabilities due to inherited membrane proteins from their parent cells. However, further engineering of their surface allows for precise and customizable delivery to specific tissues, making them more suitable for clinical applications.

Ligand Conjugation and Receptor

Ligand conjugation is a targeted delivery strategy that involves attaching specific molecules such as antibodies, peptides, aptamers, or small ligands to the surface of exosomes to direct them toward specific cell types. These ligands bind selectively to overexpressed receptors on target cells, such as the folate receptor in cancer cells, thereby enhancing the specificity and efficiency of exosome internalization [19]. Common methods for ligand attachment include covalent coupling techniques like click chemistry or EDC/NHS reactions, as well as genetic engineering approaches where targeting peptides are fused to exosomal membrane proteins, such as Lamp2b. This targeted strategy has shown promise in applications like HER2-directed delivery in breast cancer or RVG peptide-mediated targeting of neurons for brain drug delivery. Therefore, ligand conjugation significantly improves cell-type specificity and reduces off-target accumulation and systemic toxicity, making it a powerful tool in exosome-based therapeutic design [20,21].

PEGylation and Surface Engineering

PEGylation involves the covalent attachment of polyethylene glycol (PEG) chains to the surface of exosomes to enhance their colloidal stability, prolong circulation time, and reduce recognition by the immune system. The PEG forms a steric barrier around the exosome, minimizing protein opsonization and subsequent clearance by the mononuclear phagocyte system (MPS), thereby extending the half-life of the exosomes in systemic circulation. This modification offers several advantages, including reduced immunogenicity, improved pharmacokinetics, and prevention of vesicle aggregation during storage. Beyond PEGylation, additional surface engineering techniques can be employed, such as the incorporation of other polymers, charge alterations, or lipid modifications to impart pH-responsiveness, enzyme-triggered release, or enhanced endosomal escape further optimizing exosomes for controlled drug delivery and specific

targeting [22,23]. In parallel, a novel approach involves the fusion of exosomes with synthetic nanoparticles like liposomes, polymeric carriers, or gold nanoshells. This hybrid strategy aims to merge the natural targeting and biocompatibility of exosomes with the structural versatility and functional tunability of synthetic systems. Fusion can be achieved through methods such as co-extrusion, freeze–thaw cycles, or sonication, resulting in hybrid vesicles with enhanced drug loading capacity, controlled release kinetics, and potential for multifunctionality, including simultaneous therapeutic and diagnostic (theranostic) applications. These engineered hybrid systems represent a cutting-edge frontier in nanomedicine, offering promising solutions for precision drug delivery and personalized therapeutic interventions [24].

Therapeutic Applications

Exosomes have emerged as highly versatile carriers in a wide range of therapeutic applications due to their ability to protect and deliver diverse bioactive molecules, cross biological barriers, and interact selectively with target cells. Their endogenous origin and customizable surface properties allow for precise and efficient drug delivery in multiple disease contexts, including cancer, neurological disorders, autoimmune diseases, and gene-based therapies.

Cancer Therapy

In oncology, exosome-based systems are being explored for the targeted delivery of chemotherapeutic agents, RNA therapeutics, and immune modulators. Exosomes can be engineered to deliver small-molecule drugs such as paclitaxel or doxorubicin directly to tumor cells, minimizing off-target toxicity and enhancing therapeutic efficacy. Furthermore, tumor-derived exosomes can be modified to deliver siRNA or miRNA that silence oncogenes or reprogram the tumor microenvironment. Their natural tropism and ability to evade immune detection also make them ideal candidates for delivering checkpoint inhibitors and tumor antigens in cancer immunotherapy [25,26].

Neurological Disorders and Brain Delivery

Exosomes possess the remarkable ability to cross the blood–brain barrier (BBB), making them excellent vehicles for treating neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and glioblastoma. By engineering exosomes with targeting peptides (e.g., RVG peptide), they can deliver therapeutic RNA, proteins, or small molecules directly to neurons and glial cells. Studies have demonstrated successful delivery of anti-inflammatory agents, neuroprotective miRNAs, and CRISPR components into the brain, showing promise in halting or reversing disease progression [26,27].

Autoimmune and Inflammatory Diseases

Exosome-based therapies are being developed for diseases characterized by immune dysregulation, such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease. Exosomes derived from mesenchymal stem cells (MSCs) exhibit intrinsic immunomodulatory properties, capable of suppressing pro-inflammatory cytokines and

promoting regulatory T-cell responses. When loaded with anti-inflammatory drugs or nucleic acids, these exosomes can further enhance targeted delivery to inflamed tissues, reducing systemic side effects and improving therapeutic outcomes [28].

Gene and RNA-based Therapies

Exosomes offer a non-immunogenic and efficient platform for delivering genetic materials, including siRNA, miRNA, mRNA, and plasmid DNA, for gene silencing or expression. Their natural capacity to encapsulate and protect nucleic acids enables high transfection efficiency without the toxicity commonly associated with viral vectors or synthetic carriers. Genetic engineering of donor cells allows for precise packaging of therapeutic RNA, which can then be directed toward specific tissues using surface-modified exosomes. Applications in cancer gene therapy, genetic disorders, and infectious diseases are actively being explored, highlighting exosomes as next-generation vectors for safe and targeted gene delivery [29,30].

Clinical Translation and Regulatory Landscape

Despite their immense potential, the clinical translation of exosome-based drug delivery systems remains in its nascent stages, challenged by scientific, technical, and regulatory complexities. While numerous preclinical studies have confirmed the safety, biocompatibility, and therapeutic efficacy of exosomes across diverse applications, their advancement into clinically approved products requires overcoming significant barriers related to large-scale manufacturing, standardization, quality assurance, and compliance with regulatory frameworks. Currently, a growing number of early-phase clinical trials are assessing the safety and feasibility of exosome-based therapies in areas such as oncology, wound healing, neurological disorders, and immune modulation, with mesenchymal stem cell (MSC)-derived exosomes showing promise due to their regenerative and anti-inflammatory properties. Trials involving exosomes for treating conditions like graft-versus-host disease (GvHD), COVID-19-associated pneumonia, and pancreatic cancer have yielded encouraging preliminary outcomes [31]. However, the absence of standardized and scalable methods for exosome isolation, purification, and characterization remains a major bottleneck, as variations in cell source, purification techniques (e.g., ultracentrifugation, chromatography), and storage protocols can significantly impact product quality. Regulatory agencies like the FDA and EMA mandate Good Manufacturing Practice (GMP) compliance, including stringent process control, reproducibility, and potency evaluation. Moreover, safety assessments must consider immunogenicity, sterility, tumorigenicity, and long-term toxicity, with regulatory classification dependent on factors such as source origin, manipulation level, and intended use. Although no unified global standards currently exist for exosome therapeutics, organizations like the International Society for Extracellular Vesicles (ISEV) have introduced MISEV guidelines to aid in defining quality benchmarks. Looking forward, broader clinical adoption will depend on the development of automated production platforms, standardized protocols, validated potency assays, and interdisciplinary collaboration between academia,

industry, and regulatory bodies. Integrating regulatory science with advances in exosome engineering will be key to enabling the safe, effective, and scalable deployment of exosome-based drug delivery systems in clinical settings [32].

Future Perspectives and Challenges

Exosome-based drug delivery systems represent a transformative advancement in nanomedicine, offering highly biocompatible, targeted, and versatile platforms for the delivery of a wide range of therapeutic agents. Their intrinsic ability to mediate intercellular communication, cross biological barriers, and protect bioactive cargo from enzymatic degradation positions them as ideal candidates for applications in cancer therapy, neurodegenerative disorders, gene therapy, and immunomodulation. As the field rapidly evolves, promising future directions include the development of personalized therapies using patient-derived exosomes to minimize immunogenicity and enhance targeting precision [33]. Advances in synthetic biology and genetic engineering are expected to improve control over cargo loading and surface modification, while hybrid exosome-nanoparticle systems may offer enhanced therapeutic payloads and multifunctionality, including theranostic capabilities. Integrating bioinformatics, omics technologies, and AI-driven tools will further deepen understanding of exosome biology and improve targeting strategies. Additionally, the emergence of GMP-compliant, automated production platforms may help resolve scalability limitations and support commercial viability. However, several challenges remain that could hinder clinical translation. Standardized protocols for isolation, purification, and characterization are still lacking, contributing to batch variability and inconsistent efficacy. Exosome heterogeneity, based on source cells and physiological states, further complicates reproducibility and regulatory compliance. Ensuring long-term safety, controlling biodistribution, and avoiding off-target effects are essential for systemically administered exosomes. Regulatory uncertainty, due to the absence of harmonized global guidelines, alongside unresolved issues of intellectual property, biosafety, and ethics, particularly in donor-derived products, also present significant hurdles. Finally, the high cost and complexity of producing sterile, high-purity, and functionally validated exosomes may restrict widespread access, underscoring the need for innovations that enhance cost-efficiency and production scalability [34].

Conclusion:

Exosome-based drug delivery systems offer a groundbreaking approach in pharmaceutics, combining the advantages of natural biocompatibility, targeted delivery, and the ability to cross biological barriers. Their versatility in carrying diverse therapeutic agents including small molecules, proteins, and nucleic acids makes them highly promising for treating a wide range of diseases, from cancer to neurodegenerative and inflammatory disorders. Advances in isolation techniques, surface engineering, and cargo loading strategies have significantly expanded their potential applications. However, despite encouraging preclinical and early clinical results,

several challenges such as large-scale production, standardization, and regulatory approval must be overcome to enable their full clinical translation. Continued interdisciplinary collaboration and innovation in biotechnology, manufacturing, and regulatory science will be essential to address these limitations. With sustained research and development efforts, exosomes are poised to play a pivotal role in the future of precision medicine and targeted therapeutics, potentially transforming the landscape of modern drug delivery.

References:

1. Sen S, Xavier J, Kumar N, Ahmad MZ, Ranjan OP. Exosomes as natural nanocarrier-based drug delivery system: recent insights and future perspectives. 3 Biotech. 2023 Mar;13(3):101.
2. Zhang M, Zang X, Wang M, Li Z, Qiao M, Hu H, Chen D. Exosome-based nanocarriers as bio-inspired and versatile vehicles for drug delivery: recent advances and challenges. Journal of Materials Chemistry B. 2019;7(15):2421-33.
3. Song H, Liu B, Dong B, Xu J, Zhou H, Na S, Liu Y, Pan Y, Chen F, Li L, Wang J. Exosome-based delivery of natural products in cancer therapy. Frontiers in cell and developmental biology. 2021 Mar 2;9:650426.
4. Yong T, Zhang X, Bie N, Zhang H, Zhang X, Li F, Hakeem A, Hu J, Gan L, Santos HA, Yang X. Tumor exosome-based nanoparticles are efficient drug carriers for chemotherapy. Nature communications. 2019 Aug 23;10(1):3838.
5. Butreddy A, Kommineni N, Dudhipala N. Exosomes as naturally occurring vehicles for delivery of biopharmaceuticals: insights from drug delivery to clinical perspectives. Nanomaterials. 2021 Jun 3;11(6):1481.
6. Ferreira D, Moreira JN, Rodrigues LR. New advances in exosome-based targeted drug delivery systems. Critical reviews in oncology/hematology. 2022 Apr 1;172:103628.
7. Lee J, Lee JH, Chakraborty K, Hwang J, Lee YK. Exosome-based drug delivery systems and their therapeutic applications. RSC advances. 2022;12(29):18475-92.
8. Orefice NS, Di Raimo R, Mizzoni D, Logozzi M, Fais S. Purposing plant-derived exosomes-like nanovesicles for drug delivery: patents and literature review. Expert Opinion on Therapeutic Patents. 2023 Feb 1;33(2):89-100.
9. Barzin M, Bagheri AM, Ohadi M, Abhaji AM, Salarpour S, Dehghannoudeh G. Application of plant-derived exosome-like nanoparticles in drug delivery. Pharmaceutical Development and Technology. 2023 May 28;28(5):383-402.
10. Koh HB, Kim HJ, Kang SW, Yoo TH. Exosome-based drug delivery: translation from bench to clinic. Pharmaceutics. 2023 Jul 29;15(8):2042.
11. Salem D, Abdel-Ghany S, Mohamed E, Alahmady NF, Alqosaibi A, Al-Dhuayan IS, Alnamshan MM, Arneth R, Arneth B, Sabit H. Natural Nanoparticles for Drug Delivery:

Proteomic Insights and Anticancer Potential of Doxorubicin-Loaded Avocado Exosomes. Pharmaceuticals. 2025 Jun 4;18(6):844.

12. Wang Y, Wei Y, Liao H, Fu H, Yang X, Xiang Q, Zhang S. Plant exosome-like nanoparticles as biological shuttles for transdermal drug delivery. Bioengineering. 2023 Jan 12;10(1):104.
13. Kim H, Jang H, Cho H, Choi J, Hwang KY, Choi Y, Kim SH, Yang Y. Recent advances in exosome-based drug delivery for cancer therapy. Cancers. 2021 Sep 2;13(17):4435.
14. Kar R, Dhar R, Mukherjee S, Nag S, Gorai S, Mukerjee N, Mukherjee D, Vatsa R, Chandrakanth Jadhav M, Ghosh A, Devi A. Exosome-based smart drug delivery tool for cancer theranostics. ACS biomaterials science & engineering. 2023 Jan 9;9(2):577-94.
15. Palakurthi SS, Shah B, Kapre S, Charbe N, Immanuel S, Pasham S, Thalla M, Jain A, Palakurthi S. A comprehensive review of challenges and advances in exosome-based drug delivery systems. Nanoscale Advances. 2024.
16. Gutierrez-Millan C, Calvo Díaz C, Lanao JM, Colino CI. Advances in exosomes-based drug delivery systems. Macromolecular Bioscience. 2021 Jan;21(1):2000269.
17. Antimisiaris SG, Mourtas S, Marazioti A. Exosomes and exosome-inspired vesicles for targeted drug delivery. Pharmaceutics. 2018 Nov 6;10(4):218.
18. Madhan S, Dhar R, Devi A. Plant-derived exosomes: a green approach for cancer drug delivery. Journal of Materials Chemistry B. 2024.
19. Cai Y, Zhang L, Zhang Y, Lu R. Plant-derived exosomes as a drug-delivery approach for the treatment of inflammatory bowel disease and colitis-associated cancer. Pharmaceutics. 2022 Apr 8;14(4):822.
20. Pullan JE, Confeld MI, Osborn JK, Kim J, Sarkar K, Mallik S. Exosomes as drug carriers for cancer therapy. Molecular pharmaceutics. 2019 Apr 5;16(5):1789-98.
21. Vázquez-Ríos AJ, Molina-Crespo Á, Bouzo BL, López-López R, Moreno-Bueno G, de la Fuente M. Exosome-mimetic nanoplatforms for targeted cancer drug delivery. Journal of nanobiotechnology. 2019 Dec;17:1-5.
22. Lu M, Huang Y. Bioinspired exosome-like therapeutics and delivery nanoplatforms. Biomaterials. 2020 Jun 1;242:119925.
23. Liu F, Meng F, Yang Z, Wang H, Ren Y, Cai Y, Zhang X. Exosome-biomimetic nanocarriers for oral drug delivery. Chinese Chemical Letters. 2024 Sep 1;35(9):109335.
24. Patil SM, Sawant SS, Kunda NK. Exosomes as drug delivery systems: A brief overview and progress update. European Journal of Pharmaceutics and Biopharmaceutics. 2020 Sep 1;154:259-69.
25. Jiang XC, Gao JQ. Exosomes as novel bio-carriers for gene and drug delivery. International journal of pharmaceutics. 2017 Apr 15;521(1-2):167-75.

26. Amiri A, Bagherifar R, Ansari Dezfouli E, Kiaie SH, Jafari R, Ramezani R. Exosomes as bio-inspired nanocarriers for RNA delivery: preparation and applications. Journal of Translational Medicine. 2022 Mar 14;20(1):125.
27. Shinge SA, Xiao Y, Xia J, Liang Y, Duan L. New insights of engineering plant exosome-like nanovesicles as a nanoplatform for therapeutics and drug delivery. Extracellular Vesicles and Circulating Nucleic Acids. 2022 Jun 29;3(2):150.
28. Kathait P, Patel PK, Sahu AN. Harnessing exosomes and plant-derived exosomes as nanocarriers for the efficient delivery of plant bioactives. Nanomedicine. 2024 Dec 19;19(30):2679-97.
29. Bashyal S, Thapa C, Lee S. Recent progresses in exosome-based systems for targeted drug delivery to the brain. Journal of Controlled Release. 2022 Aug 1;348:723-44.
30. Anusha R, Priya S. Dietary exosome-like nanoparticles: An updated review on their pharmacological and drug delivery applications. Molecular Nutrition & Food Research. 2022 Jul;66(14):2200142.
31. Yang J, Ai X, Zhang C, Guo T, Feng N. Application of plant-derived extracellular vesicles as novel carriers in drug delivery systems: A review. Expert Opinion on Drug Delivery. 2025 Jun 3;22(6):787-803.
32. Feng T, Karges J, Liao X, Ji L, Chao H. Engineered exosomes as a natural nanoplatform for cancer targeted delivery of metal-based drugs. Coordination Chemistry Reviews. 2022 Mar 1;454:214325.
33. Shao J, Zaro J, Shen Y. Advances in exosome-based drug delivery and tumor targeting: from tissue distribution to intracellular fate. International journal of nanomedicine. 2020 Nov 24:9355-71.
34. Sajnani SL, Zhang Y, Vllasaliu D. Exosome-based therapies for mucosal delivery. International journal of pharmaceutics. 2021 Oct 25;608:121087.

Bhumi Publishing, India
July 2025

GREEN NANOTECHNOLOGY IN DRUG DELIVERY FORMULATIONS

Chitrali Talele[1], Dipali Talele*[2], Mamta Kumari[1], Nirmal Shah[1]

[1]Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India 391760

[2]School of Pharmacy,

Vishwakarma University, Survey No 2,3,4 Laxmi Nagar, Kondhwa, Budruk, Pune 411048.

*Corresponding author E-mail: dipalitalele93@gmail.com

Abstract:

Green nanotechnology represents a sustainable and eco-conscious approach to the design and development of nanomaterials for drug delivery applications. By incorporating principles of green chemistry and engineering, this approach minimizes the use of hazardous substances and reduces environmental impact while improving the safety, biocompatibility, and therapeutic efficacy of nanocarriers. Green-synthesized nanoparticles utilize natural resources such as plant extracts, biopolymers, and benign solvents, offering an environmentally friendly alternative to conventional synthesis methods. This chapter explores the conceptual foundation of green nanotechnology, the materials and methods used in the synthesis of green nanocarriers, and their applications in targeted drug delivery. It also discusses the advantages of green nanotechnology over traditional methods, along with challenges related to scalability, reproducibility, and regulatory compliance. The integration of green nanotechnology into pharmaceutical formulation science has the potential to revolutionize drug delivery by providing cleaner, safer, and more efficient therapeutic platforms aligned with global sustainability goals.

Keywords: Green Nanotechnology, Biocompatibility, Biodegradable Polymers, Environmental Impact, Nanomaterials

1. Introduction to Green Nanotechnology:

1.1 Definition and Scope

Green nanotechnology is an interdisciplinary field that merges the principles of green chemistry with nanoscale science and engineering to create safer, more environmentally sustainable technologies. In the context of pharmaceutical sciences, green nanotechnology focuses on the design, synthesis, and application of nanomaterials for drug delivery that are both effective and eco-friendly. This approach aims to minimize toxic reagents, reduce energy consumption, and utilize renewable resources during the manufacturing process. Unlike conventional nanotechnology, which often relies on hazardous solvents and non-biodegradable materials, green nanotechnology leverages benign reaction conditions, plant-derived biomolecules, and biodegradable polymers to fabricate functional nanocarriers. The growing demand for safer therapeutics and environmentally responsible production has accelerated the integration of green

nanotechnology into drug delivery research. It addresses not only the ecological impact of pharmaceutical manufacturing but also enhances the biocompatibility and clinical acceptability of nanomedicines. As the pharmaceutical industry moves toward more sustainable models, green nanotechnology offers a strategic advantage in developing next-generation drug delivery systems that are aligned with global health and environmental priorities (1).

1.2 Relevance to Pharmaceutical Sciences

The relevance of green nanotechnology in pharmaceutical sciences stems from its potential to revolutionize drug formulation, delivery efficiency, and patient safety. Traditional drug delivery systems often suffer from poor solubility, limited bioavailability, and systemic toxicity. Nanocarriers can overcome these limitations by improving pharmacokinetics, enabling targeted delivery, and facilitating controlled release. However, concerns about the long-term toxicity and environmental fate of synthetic nanomaterials have prompted a shift toward greener alternatives (2). Green nanotechnology aligns well with the pharmaceutical industry's increasing emphasis on eco-design, quality-by-design (QbD) frameworks, and regulatory compliance with environmental and safety standards. Moreover, the use of natural biomaterials and biosynthesis methods enhances the therapeutic potential of nanocarriers by reducing immunogenicity and improving patient compatibility. This is particularly important for chronic therapies, pediatric formulations, and injectable systems. Green nanotechnology thus plays a crucial role in creating safe, sustainable, and patient-centric drug delivery platforms.

2. Principles of Green Chemistry and Engineering

2.1 Twelve Principles of Green Chemistry

The foundation of green nanotechnology lies in the twelve principles of green chemistry, a framework established by Paul Anastas and John Warner to guide the development of safer chemical processes and products. These principles emphasize waste minimization, energy efficiency, renewable feedstocks, and the reduction of hazardous substances. When applied to nanomaterial synthesis, these principles encourage the avoidance of toxic solvents and reagents, the use of environmentally benign reducing agents, and the design of biodegradable end-products. In drug delivery formulations, adherence to green chemistry principles results in nanocarriers that are not only effective in transporting therapeutic agents but are also safer for human use and the environment. For example, the use of water or ethanol as solvents, plant extracts as reducing and stabilizing agents, and biodegradable polymers like chitosan or alginate exemplify how the principles of green chemistry are translated into nanotechnology practices. Atom economy and process efficiency are also prioritized, leading to scalable, reproducible, and cost-effective production processes suitable for industrial application (3). Moreover, the principle of designing safer chemicals ensures that the materials used in the formulation of nanocarriers exhibit minimal toxicity while maintaining therapeutic function. The principle of degradation

ensures that the nanocarriers break down into innocuous by-products after fulfilling their role, thus avoiding bioaccumulation and long-term ecological risks. These principles provide a holistic strategy for designing nanocarrier systems that are both effective and sustainable.

2.2 Application in Nanomaterial Design

The application of green chemistry principles in nanomaterial design necessitates a paradigm shift from traditional chemical synthesis to more sustainable methodologies. In nanomedicine, this means replacing synthetic surfactants and reducing agents with natural biomolecules such as polyphenols, proteins, or sugars. These natural substances not only drive nanoparticle formation but often impart additional therapeutic or targeting properties to the final product. One of the most significant contributions of green chemistry to nanomaterial design is the development of "one-pot" synthesis techniques, which reduce the number of steps and reagents involved, thus lowering waste and energy consumption. For example, plant-mediated synthesis of metallic nanoparticles is a well-established approach that utilizes the phytochemicals in plant extracts as both reducing and capping agents. This method eliminates the need for toxic chemicals and high-temperature reactions, making it suitable for producing nanoparticles intended for biological use.

Another important consideration is the lifecycle analysis (LCA) of nanocarriers, which assesses their environmental impact from synthesis through disposal. By evaluating each stage of the nanomaterial's life, researchers can identify and mitigate potential ecological risks (4). This includes choosing raw materials that are renewable, minimizing emissions during production, and ensuring complete biodegradation post-use. Incorporating green engineering principles into process development also supports energy conservation and operational safety. Reactions carried out at ambient temperature and pressure not only reduce energy input but also enhance the stability and reproducibility of the final product. Microfluidic and solvent-free systems, as well as mechanochemical synthesis, are emerging techniques in this field that align closely with both green chemistry and engineering goals.

3. Green Synthesis Approaches for Nanocarriers

3.1 Plant-Mediated Synthesis

Plant-mediated synthesis is one of the most widely researched and applied green strategies for fabricating nanocarriers due to its simplicity, cost-effectiveness, and ecological compatibility. This method leverages the rich phytochemical profile of plant extracts including flavonoids, alkaloids, terpenoids, and polyphenols as reducing and stabilizing agents in the synthesis of metallic and polymeric nanoparticles. These bioactive compounds not only facilitate the formation of nanoparticles but can also impart therapeutic functionalities such as antioxidant, anti-inflammatory, or antimicrobial effects. The aqueous extracts of various plant parts leaves, stems, flowers, fruits, or roots are typically mixed with metal salts or polymer precursors under mild conditions. For example, silver or gold nanoparticles synthesized using green tea, neem, or

aloe vera extracts have demonstrated potent antimicrobial and anticancer properties. The absence of harsh chemicals and the use of renewable biomass make this method highly suitable for biomedical applications, including drug delivery. Moreover, the biocompatibility of the resulting nanocarriers is significantly improved, reducing the risk of cytotoxicity and immune reactions. In addition to metals, plant-mediated synthesis can also be employed for producing polymeric nanoparticles. Polymers such as cellulose, starch, and pectin can be extracted from plants and used to form nanoparticles that serve as drug reservoirs. The inherent bioactivity of some plant-based materials further enhances their therapeutic potential, allowing for synergistic effects when used in conjunction with conventional drugs. The scalability and reproducibility of plant-mediated synthesis remain areas of ongoing research, with advances in standardization protocols contributing to its future clinical viability.

3.2 Microbial and Enzyme-Based Synthesis

Microorganisms such as bacteria, fungi, and algae have also been utilized as biological factories for the green synthesis of nanocarriers. These organisms possess inherent biochemical machinery that can reduce metal ions and synthesize biopolymers under controlled conditions. Microbial synthesis offers advantages such as high yield, specificity, and the possibility of intracellular or extracellular nanoparticle production.

Fungal strains like *Aspergillus*, *Fusarium*, and *Penicillium* have been successfully used to synthesize gold and silver nanoparticles with uniform size distribution and desirable surface characteristics. Bacterial species such as *Bacillus subtilis* and *Escherichia coli* can reduce metal salts enzymatically, producing nanoparticles with high purity and stability. Algae-mediated synthesis is particularly attractive for large-scale production due to the ease of cultivation and minimal nutrient requirements. Enzyme-based synthesis is another elegant approach in green nanotechnology. Enzymes such as nitrate reductase, laccase, and tyrosinase can catalyze the formation of nanomaterials under physiological conditions. This bio-catalytic route eliminates the need for extreme pH or temperature and allows for highly selective synthesis (5).

3.3 Biopolymer-Assisted Synthesis

Biopolymers such as chitosan, alginate, gelatin, hyaluronic acid, and starch are increasingly being used in the synthesis and formulation of green nanocarriers. These materials are naturally derived, biodegradable, and generally recognized as safe (GRAS) by regulatory authorities. Their use aligns well with the principles of green chemistry and offers multiple functional benefits, including mucoadhesiveness, sustained release, and bioadhesive properties. Chitosan, derived from the deacetylation of chitin found in crustacean shells, has been extensively studied for its ability to form nanoparticles through ionic gelation or polyelectrolyte complexation. These nanoparticles are suitable for oral, nasal, and ocular drug delivery due to their mucoadhesive nature and ability to open tight junctions in epithelial tissues. Similarly, alginate, extracted from

brown seaweed, forms nanoparticles through gelation with divalent cations like calcium and is widely used for encapsulating proteins and live cells (6). Biopolymer-assisted synthesis often involves mild reaction conditions and aqueous media, minimizing the need for organic solvents or surfactants. These systems can be further functionalized with ligands for targeted delivery or modified to respond to environmental stimuli such as pH or temperature. In addition to their inherent biocompatibility, many biopolymers possess bioactivity that can complement the therapeutic effects of the drug cargo. For instance, hyaluronic acid has an affinity for CD44 receptors, commonly overexpressed in tumor cells, enabling passive targeting in cancer therapy. The versatility of biopolymers in forming a wide range of nanostructures nanogels, micelles, and nanoparticles makes them indispensable tools in the formulation of green drug delivery systems. Their abundant availability and low environmental impact further solidify their role in advancing the goals of sustainable nanomedicine.

4. Types of Green Nanocarriers for Drug Delivery

4.1 Metallic Nanoparticles

Metallic nanoparticles such as silver, gold, zinc oxide, and iron oxide have garnered significant attention in drug delivery due to their unique physicochemical properties, including high surface area, tunable size, and ease of surface modification. When synthesized via green routes, these nanoparticles offer an environmentally friendly alternative to those produced through conventional chemical methods. Green synthesis methods, particularly those employing plant extracts or microbial cultures, provide nanoparticles with improved stability and biocompatibility while eliminating the use of toxic reagents (7). Silver nanoparticles (AgNPs), for instance, have been synthesized using tea, neem, or clove extracts and demonstrated enhanced antibacterial and anticancer properties when used as drug carriers. Gold nanoparticles (AuNPs), known for their chemical inertness and facile conjugation with biological molecules, have been successfully developed using green reducing agents such as ascorbic acid or flavonoids. These nanoparticles can be engineered for passive or active targeting, making them suitable for cancer therapy and imaging. Moreover, zinc oxide and iron oxide nanoparticles synthesized via biogenic routes have shown potential for oral and topical delivery, especially in antimicrobial and antioxidant applications. Their ability to respond to external stimuli, such as magnetic fields (in the case of iron oxide), enables site-specific drug release. However, the long-term toxicity and biodistribution of metallic nanoparticles remain active areas of research, necessitating rigorous biocompatibility testing before clinical application.

4.2 Polymeric and Lipid-Based Nanocarriers

Polymeric nanoparticles and lipid-based systems represent the most clinically advanced nanocarriers due to their high drug-loading efficiency, controlled release profiles, and established safety profiles. In the realm of green nanotechnology, the focus has shifted to using

biodegradable and natural polymers such as chitosan, alginate, polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers (PLGA). These polymers can be processed in aqueous media without the need for organic solvents, aligning with green chemistry principles. Chitosan nanoparticles prepared via ionic gelation or reverse micellar methods have demonstrated utility in delivering peptides, DNA, and small-molecule drugs. Their positive surface charge enables interaction with negatively charged cell membranes and mucosal tissues, enhancing bioavailability. Similarly, alginate-based nanoparticles, when combined with calcium or barium ions, provide stable, biocompatible carriers for oral and injectable formulations. Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), have also been adapted to green synthesis protocols. These systems typically use natural lipids and emulsifiers derived from plant or animal sources, processed under mild conditions. Liposomes, composed of phospholipid bilayers, mimic biological membranes and have been employed extensively in anticancer and antifungal drug delivery. Their capacity to encapsulate both hydrophilic and hydrophobic drugs makes them versatile tools for systemic and localized therapy. Green synthesis approaches for lipid-based nanocarriers often involve high-shear homogenization or ultrasonication in aqueous systems, avoiding toxic organic solvents. Such methods yield stable, reproducible formulations that are amenable to scale-up and regulatory approval (8).

4.3 Hybrid and Composite Systems

Hybrid nanocarriers integrate the advantages of different material classes to create multifunctional delivery platforms with improved performance. In green nanotechnology, hybrid systems often involve the combination of metallic, polymeric, or lipidic components synthesized through sustainable methods. These systems are designed to overcome specific challenges in drug delivery, such as premature degradation, poor solubility, or lack of targeting specificity. For example, a hybrid nanoparticle consisting of a gold core (synthesized using plant extract) encapsulated within a biodegradable polymer shell (such as PLGA or chitosan) offers the dual benefits of enhanced stability and controlled release. Such systems can also be functionalized with ligands for active targeting or fluorophores for diagnostic imaging. Composite systems, such as nanofibers or nanogels formed by integrating polymers with bioactive plant materials, have shown promise in wound healing and transdermal delivery. These structures can be loaded with antibiotics, anti-inflammatory agents, or growth factors and applied topically, where they provide sustained drug release and promote tissue regeneration. The development of green-synthesized hybrid and composite nanocarriers is still in its early stages but holds substantial potential for personalized and multifunctional therapy. Their design requires careful consideration of compatibility among components, synthesis parameters, and scalability for pharmaceutical use.

5. Applications in Drug Delivery

5.1 Targeted Cancer Therapy

One of the most prominent applications of green nanocarriers is in targeted cancer therapy. The tumor microenvironment presents several unique features, including leaky vasculature and an acidic extracellular pH, that can be exploited for selective drug delivery using nanoparticles. Green-synthesized nanoparticles, especially those derived from plant-mediated or biopolymer-based systems, are particularly suited for this application due to their improved biocompatibility and reduced systemic toxicity. For instance, gold nanoparticles synthesized using plant extracts such as *Terminalia catappa* or *Azadirachta indica* have demonstrated the ability to selectively accumulate in tumor tissues and enhance the cytotoxicity of loaded chemotherapeutics like doxorubicin or paclitaxel. Similarly, chitosan-based polymeric nanoparticles, loaded with anticancer agents, have shown increased cellular uptake in tumor cells via receptor-mediated endocytosis. Targeted delivery is further enhanced by functionalizing green nanocarriers with ligands such as folic acid, transferrin, or antibodies, which bind to overexpressed receptors on cancer cells. This active targeting approach minimizes off-target effects, enhances therapeutic index, and overcomes multidrug resistance mechanisms by improving intracellular drug concentration. In addition, the biodegradability of the green carrier matrix ensures that once the drug is released, the carrier safely degrades without eliciting adverse effects.

5.2 Antimicrobial and Antiviral Delivery

The rise of antimicrobial resistance (AMR) has necessitated the exploration of innovative delivery platforms that can enhance the efficacy of existing antibiotics while reducing their side effects. Green nanocarriers offer a promising solution by improving drug solubility, bioavailability, and retention at the site of infection. Silver nanoparticles synthesized using green methods exhibit intrinsic antimicrobial activity, which can synergistically enhance the effect of encapsulated antibiotics. Plant-derived nanoparticles often carry bioactive phytochemicals with antibacterial or antiviral properties, further augmenting their therapeutic potential. For instance, green-synthesized zinc oxide nanoparticles have shown efficacy against bacterial strains like *Staphylococcus aureus* and *Escherichia coli* when used in wound dressings or topical gels. Similarly, polymeric nanoparticles made from natural polymers like gelatin or starch have been used to deliver antiviral drugs such as acyclovir with improved pharmacokinetics.

5.3 Transdermal and Mucosal Drug Delivery

Green nanocarriers have shown considerable promise in transdermal and mucosal delivery systems, where biocompatibility and reduced irritation are critical requirements. The use of biodegradable and non-toxic materials such as chitosan, alginate, or hyaluronic acid enhances their compatibility with skin and mucosal tissues, making them ideal for local or systemic administration through non-invasive routes. Chitosan nanoparticles, for example, have

mucoadhesive properties that allow them to adhere to mucosal membranes in the nasal, oral, or vaginal cavity, thereby improving drug residence time and absorption. In transdermal applications, lipid-based green nanocarriers like liposomes and nanostructured lipid carriers have been used to encapsulate anti-inflammatory drugs, analgesics, or hormones for controlled dermal penetration. Moreover, nanogels and nanofibers fabricated through green synthesis are being incorporated into patches or films for sustained transdermal delivery. These systems are especially beneficial for patients requiring chronic therapy, as they improve compliance and reduce the frequency of dosing. The environmental safety of green nanocarriers also supports their use in over-the-counter or cosmetic formulations, where long-term exposure is a concern (9).

6. Advantages Over Conventional Nanotechnology

6.1 Environmental Benefits

One of the foremost advantages of green nanotechnology in drug delivery is its reduced environmental impact compared to conventional nanotechnology. Traditional nanoparticle synthesis often involves the use of toxic solvents, high energy inputs, and hazardous reagents that generate harmful byproducts and contribute to environmental pollution. Green synthesis approaches, on the other hand, utilize water or ethanol as solvents, renewable raw materials, and mild reaction conditions, thereby minimizing energy consumption and hazardous waste generation. The use of plant extracts, microbial cultures, and biopolymers in nanocarrier fabrication avoids synthetic stabilizers and surfactants, which are difficult to degrade and pose long-term ecological risks. Furthermore, green nanocarriers are typically biodegradable, breaking down into non-toxic byproducts after their therapeutic function is complete. This not only reduces their environmental footprint but also supports the principles of sustainable pharmaceutical development and circular economy practices in the healthcare sector. From an industrial standpoint, adherence to green chemistry and engineering principles ensures regulatory compliance and reduces the costs associated with waste disposal and environmental remediation. As environmental sustainability becomes an integral part of pharmaceutical manufacturing and product lifecycle management, green nanotechnology is emerging as a responsible and forward-looking approach.

6.2 Improved Biocompatibility and Safety

Biocompatibility is a critical parameter in drug delivery systems, directly influencing the safety, efficacy, and patient acceptability of therapeutic formulations. Conventional nanocarriers, especially those synthesized using synthetic surfactants, organic solvents, or heavy metals, may induce cytotoxicity, oxidative stress, or immunogenic responses. Green nanotechnology addresses these concerns by employing naturally derived and biologically compatible materials.

Nanocarriers fabricated using plant extracts or biopolymers such as chitosan, gelatin, and alginate exhibit enhanced tolerability and reduced risk of adverse immune reactions. The absence of residual toxic solvents or surfactants in green-synthesized formulations further improves their safety profile. Additionally, green-synthesized metallic nanoparticles often show greater stability in biological environments due to the presence of naturally occurring stabilizing agents like phenolics and proteins. Clinical safety is further enhanced through the use of endogenous or food-grade components in the formulation, which are well-accepted by regulatory authorities. For example, lipid-based carriers synthesized using natural phospholipids or fatty acids have demonstrated excellent safety in parenteral and oral applications. Overall, green nanocarriers contribute to safer drug delivery options, particularly for sensitive patient populations such as children, the elderly, and those with chronic conditions (10).

6.3 Cost-Effectiveness and Accessibility

Green nanotechnology not only provides environmental and biological advantages but also improves the economic feasibility of nanoparticle-based drug delivery systems. By eliminating the need for expensive and hazardous chemicals, high-temperature reactions, and complex purification steps, green synthesis significantly lowers production costs. Many green synthesis methods can be conducted at room temperature using readily available materials, making them suitable for low-resource settings and decentralized manufacturing. For instance, plant-mediated nanoparticle synthesis can be carried out using local biomass without requiring extensive infrastructure or specialized equipment. Similarly, polymeric nanocarriers based on starch, pectin, or other agricultural byproducts offer a low-cost alternative to synthetic polymers while maintaining functional properties. In addition to lower material and energy costs, green nanocarriers reduce the regulatory burden associated with toxicological evaluation, waste disposal, and environmental impact assessment. This can accelerate product development timelines and reduce the financial barriers to market entry. For global health initiatives and public sector programs, the cost-effectiveness and sustainability of green nanocarriers make them particularly appealing for applications in infectious disease control, maternal health, and non-communicable disease management.

7. Challenges and Future Prospects

Despite the promising advantages of green nanotechnology, its widespread adoption in drug delivery is hindered by several technical and scientific challenges. One of the primary limitations is the variability and lack of reproducibility in green synthesis processes, particularly those involving biological materials such as plant extracts or microbial cultures. The composition of these extracts can vary depending on the source, season, and extraction conditions, leading to inconsistencies in nanoparticle size, shape, and surface characteristics. Moreover, there is a need for standardized protocols and robust quality control measures to ensure batch-to-batch

consistency. Unlike conventional chemical synthesis, which allows precise stoichiometric control, green methods often rely on complex and poorly defined mixtures of biomolecules (11). This complexity can complicate scaling up processes for industrial manufacturing. Furthermore, the lack of comprehensive mechanistic understanding of biosynthesis routes limits the rational design of green nanocarriers for specific therapeutic goals. Analytical techniques such as dynamic light scattering (DLS), zeta potential analysis, transmission electron microscopy (TEM), and high-performance liquid chromatography (HPLC) are essential for thorough characterization, but these tools are not always accessible in low-resource settings where green synthesis might otherwise be advantageous. Addressing these challenges requires interdisciplinary collaboration among chemists, biologists, pharmacologists, and engineers to optimize synthesis parameters and establish reproducible, scalable methods (12).

Conclusion:

Green nanotechnology represents a paradigm shift in the field of drug delivery, integrating the principles of sustainability, safety, and efficacy into the design and development of advanced therapeutic systems. By leveraging renewable resources, biocompatible materials, and environmentally benign synthesis methods, green nanocarriers address several critical challenges associated with conventional nanotechnology, including toxicity, ecological impact, and scalability. This chapter has explored the foundational principles of green chemistry and their application in developing various types of nanocarriers—metallic, polymeric, lipid-based, and hybrid systems each offering unique advantages for specific drug delivery applications.

Green synthesis approaches, including plant-mediated, microbial, enzymatic, and biopolymer-assisted techniques, offer innovative pathways for producing nanoparticles under mild conditions without hazardous reagents. These carriers have demonstrated promise in treating a range of diseases from cancer and infections to chronic inflammatory conditions while providing site-specific targeting, improved bioavailability, and minimal side effects. Their utility in non-invasive delivery routes such as transdermal and mucosal administration further enhances patient compliance and therapeutic outcomes. While the field continues to face challenges related to standardization, regulatory acceptance, and reproducibility, emerging technologies such as synthetic biology, smart polymers, and AI-driven formulation tools are poised to bridge these gaps. With growing global emphasis on environmentally responsible healthcare and personalized medicine, green nanotechnology stands at the forefront of next-generation drug delivery strategies. As interdisciplinary research and industrial investment in this area expand, green nanocarriers are likely to transition from the bench to the bedside, offering safer, more effective, and more sustainable treatment options for diverse patient populations.

References:

1. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. Oxford: Oxford University Press; 1998.
2. Iravani S. Green synthesis of metal nanoparticles using plants. Green Chem. 2011;13(10):2638-50.
3. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arab J Chem. 2017;12(7):908-31.
4. Singh P, Kim YJ, Zhang D, Yang DC. Biological synthesis of nanoparticles from plants and microorganisms. Trends Biotechnol. 2016;34(7):588-99.
5. Kharissova OV, Dias HR, Kharisov BI, Pérez BO, Pérez VM. The greener synthesis of nanoparticles. Trends Biotechnol. 2019;37(7):747-59.
6. Thakkar KN, Mhatre SS, Parikh RY. Biological synthesis of metallic nanoparticles. Nanomedicine. 2010;6(2):257-62.
7. Patra JK, *et al.* Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnol. 2018;16:71.
8. Siddiqi KS, Husen A, Rao RAK. A review on biosynthesis of silver nanoparticles and their biocidal properties. J Nanobiotechnol. 2018;16(1):1-28.
9. Sharma D, *et al.* Green synthesis and characterization of iron oxide nanoparticles for antimicrobial applications. Nanomaterials (Basel). 2019;9(11):1714.
10. Dreaden EC, *et al.* The golden age: gold nanoparticles for biomedicine. Chem Soc Rev. 2012;41(7):2740-79.
11. Kumar A, *et al.* Green synthesis of metal nanoparticles using plants: An eco-friendly approach. J Chem Rev. 2020;2(2):56-69.
12. Ahmed S, *et al.* Green synthesis of silver nanoparticles using Azadirachta indica aqueous leaf extract. J Radiat Res Appl Sci. 2016;9(1):1-7.

NEUROBEHAVIORAL NURTURING: THE ROLE OF PHYSIOTHERAPY IN PRETERM INFANT DEVELOPMENT

Dhwani Chanpura
College of Physiotherapy,
Sumandeep Vidyapeeth Deemed-to-be-University, Piparia, Vadodara, Gujarat 391760
Corresponding author E-mail: dhwanichanpura232@gmail.com

Abstract:
Preterm birth poses significant challenges to the neurobehavioral development of infants due to the interruption of intrauterine maturation and exposure to the complex environment of the neonatal intensive care unit (NICU). In this critical period, physiotherapists play an essential role in supporting the behavioral, motor, sensory, and autonomic systems of preterm neonates. This chapter explores the evolving role of physiotherapy in nurturing neurobehavioral development from a developmental care perspective.
It begins with an overview of neurobehavioral functioning in preterm infants, highlighting common difficulties such as impaired state regulation, motor coordination, and sensory modulation. The chapter outlines how physiotherapy in the NICU has shifted from a passive, medically focused model to an active, family-centered, and cue-based approach grounded in frameworks like the Synactive Theory and NIDCAP. Key physiotherapy interventions are discussed in detail, including developmentally supportive positioning, movement facilitation, sensory modulation, kangaroo care, and oral-motor coordination.
The chapter also emphasizes the importance of standardized assessment tools such as the General Movements Assessment and Infant Positioning Assessment Tool in guiding individualized care. The critical role of parental involvement is examined through the lens of education, empowerment, and emotional support.
Finally, the chapter addresses current challenges, emerging technologies, and future directions in neonatal physiotherapy. By integrating clinical expertise with compassionate, developmentally sensitive care, physiotherapists not only improve immediate NICU outcomes but also contribute meaningfully to the lifelong developmental trajectory of preterm infants.

Introduction:
Preterm birth, occurring before 37 completed weeks of gestation, introduces a delicate start to life, often marked by a series of medical and developmental challenges. Among the most vulnerable aspects impacted by early birth is the infant's neurobehavioral development, which includes how the baby moves, responds to the environment, regulates internal states, and begins forming the earliest foundations for interaction and learning. Unlike full-term infants, who complete critical periods of brain and sensory development in the womb, preterm neonates must

adapt to the unfamiliar and often overstimulating environment of the neonatal intensive care unit (NICU). There, they are exposed to bright lights, loud noises, and frequent handling factors that can disrupt their immature neurological systems.

During this delicate phase, physiotherapists play a crucial role not only in addressing the infant's physical needs but also in shaping their neurobehavioral development. Through specialized knowledge and gentle, developmentally appropriate care, physiotherapists assist preterm infants in developing essential skills, including self-regulation, postural control, sensory integration, and motor coordination. They also create opportunities for bonding and interaction, both with caregivers and the environment, laying the foundation for long-term developmental health. This chapter examines the diverse and essential ways physiotherapy supports the neurobehavioral development of preterm infants, beginning in the NICU and continuing into early life.

Neurobehavioral development in early life is a complex, interwoven process involving the maturation of the brain, the emergence of motor abilities, the integration of sensory input, and the infant's capacity to regulate behavior and physiological states. In full-term infants, much of this development unfolds in the final weeks of gestation within the protective environment of the womb. However, for preterm neonates—born before these critical periods are complete—this developmental trajectory is disrupted and reshaped by the realities of extrauterine life.

Preterm infants often face the challenge of neurological immaturity, where their central nervous system is not yet fully equipped to manage the demands of life outside the womb. In the neonatal intensive care unit (NICU), they are suddenly exposed to bright lights, loud alarms, frequent medical interventions, and irregular handling routines—all of which differ dramatically from the quiet, dark, and rhythmically regulated uterine environment. Additionally, their sleep-wake cycles may be fragmented, and opportunities for consistent maternal bonding through touch, voice, and eye contact are frequently limited.

As a result of these stressors, preterm neonates may struggle with several aspects of neurobehavioral function:

- **State regulation**, or the ability to transition smoothly between different levels of arousal such as quiet sleep, active alertness, or drowsiness, can be erratic or delayed.
- **Sensory modulation** may be impaired, with infants either overreacting or underreacting to touch, sound, or movement.
- **Motor coordination** is often immature, marked by jerky movements, low muscle tone, or asymmetrical posture.
- **Autonomic functions** such as heart rate, respiratory patterns, and body temperature regulation may show instability, particularly during handling or stressful procedures.

This early period of life represents both a risk and an opportunity. It is precisely within this vulnerable window that physiotherapists can make a profound difference. By using developmentally appropriate, infant-led interventions, physiotherapists help shape

neurobehavioral organization, facilitating smoother transitions between behavioral states, encouraging regulated sensory experiences, supporting emerging motor control, and promoting a sense of safety and comfort. Their interventions are not just physical; they are also deeply relational and environmental, recognizing that the brain's development is influenced not only by biological processes but also by the quality of interaction and care an infant receives.

Physiotherapy in the NICU: A Developmental Perspective

The practice of physiotherapy in neonatal intensive care units (NICUs) has undergone a significant transformation over the past few decades. Once considered a reactive or adjunctive service—primarily addressing musculoskeletal issues or respiratory function—physiotherapy is now firmly embedded within a developmentally supportive care model. This shift acknowledges that the preterm infant is not just a small patient with medical needs, but a developing human whose sensory, motor, and behavioral systems are exquisitely sensitive to both harm and healing during this early window of life.

In the current developmental framework, the role of the physiotherapist **is** active, intentional, and deeply attuned to the infant's cues and capabilities. Rather than imposing movement or addressing problems after they arise, physiotherapists work proactively to nurture the infant's emerging self-regulation, movement patterns, and postural control, all while minimizing physiological and behavioral stress.

Key components of this developmental approach include:

- **Developmentally Supportive Positioning**: Proper positioning is not merely about comfort—it is foundational for neurodevelopment. Physiotherapists ensure that preterm infants are positioned in ways that support flexion, containment, midline orientation, and symmetrical posture, closely mimicking the supportive environment of the womb. This enhances motor learning, reduces energy expenditure, and helps prevent positional deformities.
- **Facilitated Movements Reflecting Intrauterine Experience**: Gentle, guided movements offered by the physiotherapist can simulate the kinds of input a fetus would experience through the uterine walls. These movements help reinforce postural stability, encourage active engagement, and support the integration of primitive reflexes into more organized motor patterns.
- **Stress Reduction and State Regulation**: A key principle in developmental care is recognizing and responding to signs of stress in the infant. Physiotherapists are trained to read behavioral cues—such as changes in skin color, breathing patterns, or facial expressions—and modify their interactions accordingly. Through calming touch, slow transitions, and respectful handling, they help infants maintain stability and develop smoother transitions between sleep and wake states.

- **Environmental Modulation**: Beyond direct interaction, physiotherapists advocate for changes in the infant's environment that promote development—such as reducing excessive light and sound, using supportive bedding, and ensuring gentle, consistent handling.

This approach is strongly grounded in two key theoretical models:

- The Synactive Theory of Development (Als, 1982) conceptualizes the infant as a dynamic system with five interdependent subsystems: autonomic, motor, state, attention/interaction, and self-regulation. Physiotherapists use this model to observe how these subsystems interact, and to guide interventions that support rather than overwhelm the infant.
- The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) builds on this theory and promotes care that is tailored to each infant's behavioral signals and neurological maturity. Physiotherapists trained in NIDCAP principles use their skills to adapt not only the therapy session, but also to guide caregivers and staff in developmentally sensitive handling.

By incorporating these principles, physiotherapists in the NICU do far more than manage physical impairments; they actively participate in shaping the infant's neurobehavioral trajectory, optimizing brain development through every movement, position, and interaction. This developmental lens reinforces the idea that early physiotherapy is not simply about function it is about fostering potential in the most formative days of life.

Assessment Tools for Neurobehavioral and Motor Development

Accurate assessment forms the cornerstone of individualized intervention. Key tools used by physiotherapists include:

- **Neurobehavioral Assessment of the Preterm Infant (NAPI)**
  Measures neurological maturation, motor development, and state behavior.
- **Neonatal Behavioral Assessment Scale (NBAS)**
  Assesses reflexes, muscle tone, habituation, and autonomic regulation.
- **Assessment of Preterm Infant Behavior (APIB)**
  Detailed observation of infant's interaction with the environment.
- **General Movements Assessment (GMA)**
  Detects spontaneous movement patterns predictive of neurological outcome.
- **Infant Positioning Assessment Tool (IPAT)**
  Evaluates the postural quality and positioning appropriateness in NICU settings.

These tools guide physiotherapists in tailoring interventions that are developmentally congruent and behaviorally sensitive.

Core Physiotherapy Interventions Supporting Neurobehavioral

Below are the core domains of physiotherapy intervention that directly support neurobehavioral organization in preterm neonates:

A. Positioning and Handling

Positioning and handling are foundational components of neonatal physiotherapy, as they directly influence the infant's comfort, movement patterns, and physiological regulation.

- **Promotes flexor tone and midline orientation**: Preterm infants often exhibit hypotonia and extension postures due to their early separation from the intrauterine environment. Developmentally supportive positioning fosters flexor tone**,** alignment of limbs toward the midline, and postural symmetry, which are essential for motor organization and calming behavior.
- **Prevents secondary musculoskeletal complications**: Improper or prolonged positioning may lead to issues such as plagiocephaly, torticollis, or hip dysplasia. Physiotherapists regularly assess and adjust positioning to mitigate these risks and support skeletal integrity.
- **Enhances behavioral state regulation**: Thoughtful handling techniques—such as slow transitions, swaddled containment, and nesting—reduce stress and support the infant in maintaining a calm, alert state conducive to interaction and learning.

B. Sensory Modulation

Preterm infants are highly sensitive to external stimuli. Their developing nervous systems can easily become overwhelmed, leading to disorganized behavior or physiological instability.

- **Graded sensory input**: Physiotherapists introduce tactile (gentle touch), vestibular (movement), and auditory stimuli in a carefully titrated manner, respecting the infant's readiness and tolerance. This facilitates sensory system maturation and improves the infant's ability to engage with their environment.
- **Avoidance of sensory overload**: Strategies such as dimming lights, reducing ambient noise, and using slow, deliberate handling are critical in protecting the infant from overstimulation. By creating a soothing sensory environment, physiotherapists help support autonomic stability and behavioral organization.

C. Movement Facilitation

Movement is a crucial driver of early brain development. Physiotherapists provide gentle facilitation of movements that mimic natural intrauterine motion and promote emerging motor skills.

- **Passive and active motor stimulation**: Depending on the infant's condition, therapists may use controlled passive range of motion exercises or encourage spontaneous, active movements to enhance neuromuscular coordination and build early motor patterns.

- **Early interventions**: Techniques such as infant massage, facilitated rolling, and tummy time are introduced post-medical stabilization to stimulate proprioceptive feedback, muscle activation, and postural control, which all contribute to enhanced neurobehavioral performance.

D. Kangaroo Care Support

Kangaroo Mother Care (KMC) or skin-to-skin contact is one of the most powerful, evidence-based interventions supporting both physiological and behavioral regulation in preterm infants.

- **Promotes emotional and physiological bonding**: Skin-to-skin contact enhances parent-infant bonding**,** stabilizes vital signs, and supports temperature regulation, all of which are fundamental to neurobehavioral development.
- **Guidance on safe positioning**: Physiotherapists work closely with nursing staff and parents to ensure that the infant is safely and optimally positioned during kangaroo care, maximizing developmental benefits while minimizing strain on the infant's musculoskeletal or respiratory systems.

E. Oral Motor and Respiratory Coordination

Feeding is one of the most complex neurobehavioral tasks for a preterm infant, requiring synchronized coordination between sucking, swallowing, and breathing.

- **Preparation for oral feeding**: Physiotherapists assess oral tone, rooting reflexes, and sucking strength, preparing infants for safe and effective oral feeding when they are developmentally ready.
- **Interdisciplinary coordination**: Physiotherapists often collaborate with speech-language pathologists, occupational therapists, and neonatologists to optimize feeding readiness and respiratory coordination, ensuring that interventions are safe and developmentally supportive.

These interventions are more than routine care—they are intentional, evidence-informed strategies designed to optimize the infant's short- and long-term developmental outcomes. By focusing on comfort, control, sensory harmony, and parent-infant bonding, physiotherapists help guide preterm neonates through the fragile transitions of early life with greater resilience and organization.

Family-Centered and Cue-Based Care

In the journey of a preterm infant's development, the family—especially parents—is not a passive observer, but an essential part of the care team. Recognizing the profound emotional, psychological, and developmental impact of early parent-infant interaction, modern neonatal care places strong emphasis on family-centered and cue-based care models. Physiotherapists are uniquely positioned to bridge clinical expertise with empathetic education, empowering caregivers to actively support their infant's neurobehavioral development from the earliest stages.

Educating Caregivers on Infant Cues and Behaviors

Preterm infants often express their needs, stress, or comfort not through words or cries but through subtle behavioral and physiological cues—changes in skin color, limb movement, gaze aversion, or breathing patterns. These cues can be difficult for new parents to interpret, especially in the intimidating environment of the NICU. Physiotherapists play a crucial role in:

- Teaching parents to recognize signs of stress (e.g., yawning, hiccupping, finger splaying) and comfort behaviors (e.g., bringing hands to mouth, calm breathing).
- Helping families read and respond to these signals, fostering early attunement and responsiveness, which are foundational for emotional bonding and neurodevelopment.

Training in Developmental Care Techniques

Physiotherapists offer hands-on coaching in gentle, supportive techniques that promote the infant's sense of security and organization. These include:

- Swaddling to provide tactile and proprioceptive containment.
- Containment holding, where caregivers use their hands to gently support the infant's head and feet, simulating the boundaries of the womb.
- Positioning strategies that enhance comfort and reduce stress during caregiving tasks like diaper changes or feeding.

By involving parents in these techniques, physiotherapists not only support the infant's well-being but also boost parental confidence and competence, especially important for parents who may feel helpless or anxious in the NICU environment.

Promoting Meaningful Parental Involvement

Active parental involvement has been shown to improve both short- and long-term outcomes for preterm infants. Physiotherapists encourage and facilitate:

- Kangaroo care and skin-to-skin contact.
- Participation in therapeutic positioning and handling during routine care.
- Daily rituals that strengthen emotional connection and continuity of care, such as soothing touch or soft verbal interactions.

This empowerment is critical—not only for the infant's development, but also for the emotional resilience and mental health of caregivers navigating the stress of preterm birth.

The Essence of Cue-Based Care

Cue-based care means that interventions are timed and adjusted according to the infant's own signals of readiness and tolerance, rather than being dictated by rigid schedules. For physiotherapists, this requires a flexible and respectful approach—pausing therapy when signs of stress appear, modifying touch or movement based on the infant's alertness, and working collaboratively with nursing and medical staff to ensure the infant's needs are always prioritized.

By honoring the infant's cues and involving the family as empowered partners, physiotherapists help create a therapeutic environment where the infant feels safe, supported, and understood.

This not only promotes healthier neurobehavioral development but also lays the emotional groundwork for secure attachment and developmental resilience.

Interdisciplinary Collaboration and Continuity of Care

Physiotherapists function as part of a larger neonatal multidisciplinary team. Their collaboration ensures:

- Timely identification of developmental delays
- Shared planning for transition to home care
- Coordination with early intervention services post-discharge

They contribute to individualized care plans that integrate the infant's medical needs with developmental priorities.

Challenges, Innovations, and Future Directions

Despite the growing recognition of physiotherapy's importance in neonatal care, several challenges limit its optimal implementation. High patient loads and a shortage of physiotherapists with specialized neonatal training often led to limited individualized interventions. Additionally, parental anxiety and limited confidence in handling medically fragile infants can reduce caregiver involvement, an essential component of developmental care. Variability in physiotherapy practices across NICUs, both nationally and globally, further complicates efforts to standardize care and measure outcomes effectively.

In response, several innovations are transforming the landscape of neonatal physiotherapy. Smart neonatal positioning devices now offer real-time posture feedback, helping ensure safe, developmentally appropriate alignment. Wearable movement sensors enable continuous monitoring of motor activity, allowing early detection of delays or abnormalities. Emerging artificial intelligence (AI) tools can analyze video footage of neonatal behavior and movements, offering objective insights into neurobehavioral patterns.

Looking ahead, the integration of telehealth platforms is expected to expand access to post-discharge physiotherapy, especially in underserved areas. Ongoing research into early physiotherapy interventions continues to highlight their role in shaping brain plasticity and improving developmental outcomes. Importantly, efforts are underway to develop standardized physiotherapy protocols for the NICU, ensuring evidence-based, consistent care that is responsive to each infant's unique needs.

Together, these advances signal a shift toward more personalized, accessible, and data-informed physiotherapy. By overcoming current barriers and embracing innovation, physiotherapists can continue to play a transformative role in improving neurodevelopmental outcomes for preterm infants.

Physiotherapists play a pivotal role in the delicate journey of neurobehavioral development in preterm neonates. Far beyond traditional notions of movement rehabilitation, their work is deeply rooted in developmental science, emotional attunement, and family empowerment. By

conducting nuanced assessments and delivering individualized, developmentally appropriate interventions, physiotherapists support the emerging behavioral, sensory, and motor systems of infants born far too soon. Their presence in the NICU is not just therapeutic—it is transformative.

Through gentle touch, therapeutic positioning, and cue-based engagement, they help these infants organize their bodies, regulate their states, and interact meaningfully with their environment. Equally important is the physiotherapist's role in guiding and empowering families, educating caregivers, easing anxieties, and fostering confident, nurturing bonds that strengthen both the infant's and the family's trajectory.

In doing so, physiotherapists don't just improve short-term medical outcomes; they help shape the foundation for long-term developmental health, learning, and quality of life. As neonatal care continues to advance, the integration of physiotherapy into early neurobehavioral support is not just beneficial—it is essential.

References:

1. Aarnoudse-Moens CS, Weisglas-Kuperus N, Van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2019 Aug 1;124(2):717-28.
2. Orton J, Spittle A, Doyle L, Anderson P, Boyd R. Do early intervention programmes improve cognitive and motor outcomes for preterm infants after discharge? A systematic review. Developmental Medicine & Child Neurology. 2019 Nov;51(11):851-9.
3. Brown NC, Inder TE, Bear MJ, Hunt RW, Anderson PJ, Doyle LW. Neurobehavior at term and white and gray matter abnormalities in very preterm infants. The Journal of pediatrics. 2019 Jul 1;155(1):32-8.
4. Nakano H, Kihara H, Nakano J, Konishi Y. The influence of positioning on spontaneous movements of preterm infants. Journal of Physical Therapy Science. 2010;22(3):337-44.
5. Tang X, Bei F, Sha S, Qin Y. The effects of a postural supporting "New Nesting Device" on early neurobehavioral development of premature infants. Journal of Neonatal Nursing. 2021 Jun 1;27(3):191-9.
6. Toso BR, Viera CS, Valter JM, Delatore S, Barreto GM. Validation of newborn positioning protocol in Intensive Care Unit. Revista brasileira de enfermagem. 2019 Nov;68:1147-53.
7. Madlinger-Lewis L, Reynolds L, Zarem C, Crapnell T, Inder T, Pineda R. The effects of alternative positioning on preterm infants in the neonatal intensive care unit: a randomized clinical trial. Research in developmental disabilities. 2020 Feb 1;35(2):490-7.
8. Ferrari F, Bertoncelli N, Gallo C, Roversi MF, Guerra MP, Ranzi A, Hadders-Algra M. Posture and movement in healthy preterm infants in supine position in and outside the nest. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2017 Sep 1;92(5):F386-90.

9. Eskandari Z, Seyedfatemi N, Haghani H, Almasi-Hashiani A, Mohagheghi P. Effect of Nesting on Extensor Motor Behaviors in Preterm Infants: A Randomized Clinical Trial. Iranian Journal of Neonatology IJN. 2020;11(3):64-70.
10. Tane R, Rustina Y, Waluyanti FT. Nesting with Fixation and Position to Facilitate Quiet Sleep and Oxygen Saturation on Low-Birth Weight Infants. Comprehensive child and adolescent nursing. 2019 Mar 29;42(sup1):29-37.
11. Sweeney JK, Heriza CB, Blanchard Y, Dusing SC. Neonatal physical therapy. Part II: Practice frameworks and evidence-based practice guidelines. Pediatric Physical Therapy. 2010 Apr 1;22(1):2-16.
12. McManus BM, Chambliss JH, Rapport MJ. Application of the NICU practice guidelines to treat an infant in a level III NICU. Pediatric Physical Therapy. 2013 Jul 1;25(2):204-13.
13. Sathish Y, Edward Lewis L, Angelitta Noronha J, George A, Snayak B, S Pai M, Bhat R, Purkayastha J. Clinical outcomes of snuggle up position using positioning aids for preterm (27-32 weeks) infants. Iranian Journal of Neonatology. 2017 Mar 1;8(1):1-6.
14. Johnston CC, Fernandes AM, Campbell-Yeo M. Pain in neonates is different. Pain. 2011 Mar 1;152(3):S65-73.
15. McEwen BS, Gray JD, Nasca C. Recognizing resilience: Learning from the effects of stress on the brain. Neurobiology of stress. 2018 Jan 1;1:1-1.
16. Prasanna K, Radhika M. Effectiveness of Nesting on Posture and Motor Performance Among Newborn babies. Nursing. 2021 Jun;4(6).
17. Zahed M, Berbis J, Brevaut-Malaty V, Busuttil M, Tosello B, Gire C. Posture and movement in very preterm infants at term age in and outside the nest. Child's Nervous System. 2017 Dec;31:2333-40.
18. Samsom JF, de Groot L. The influence of postural control on motility and hand function in a group of ‘high risk’preterm infants at 1 year of age. Early Human Development. 2005 Dec 1;60(2):101-13.
19. Radwan RI, Mohammed AA. Effect of nesting position on behavioral organization among preterm neonates. International Journal of Novel Research in Healthcare and Nursing. 2019;6(3):803-18.

ROS-RESPONSIVE NANOCARRIERS FOR INFLAMMATORY DISEASES

Chintan Aundhia
Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat 391760 India
Corresponding author E-mail: aundhia@gmail.com

Abstract:
Inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and chronic obstructive pulmonary disease, are characterized by excessive production of reactive oxygen species (ROS), which contribute to tissue damage and chronic inflammation. Traditional anti-inflammatory therapies often suffer from systemic toxicity, poor bioavailability, and lack of site-specificity. In recent years, ROS-responsive nanocarriers have emerged as a novel platform for targeted drug delivery, leveraging the pathological oxidative environment of inflamed tissues for controlled and site-specific release of therapeutic agents. These nanocarriers are designed to remain stable under physiological conditions and release their payload in response to elevated ROS levels, thereby enhancing therapeutic efficacy while minimizing off-target effects. This chapter explores the design principles, types of ROS-sensitive materials, fabrication strategies, and therapeutic applications of ROS-responsive nanocarriers in the management of inflammatory diseases. It also highlights recent advances, preclinical studies, and the challenges that must be addressed to facilitate clinical translation. By capitalizing on redox imbalances as a natural trigger, ROS-responsive nanocarriers represent a promising strategy to overcome the limitations of conventional therapies and revolutionize inflammation-targeted drug delivery.

Keywords: ROS-Responsive Nanocarriers, Inflammatory Diseases, Targeted Drug Delivery, Oxidative Stress, Polymeric Nanoparticles, Redox-Sensitive Systems, Site-Specific Release, Rheumatoid Arthritis

1. Introduction:

1.1 Inflammatory Diseases: Pathogenesis and Challenges

Inflammatory diseases comprise a wide range of chronic and acute conditions marked by dysregulated immune responses and sustained tissue injury. These disorders include rheumatoid arthritis (RA), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), and systemic lupus erythematosus (SLE), among others (1). The pathogenesis of these diseases involves persistent activation of immune cells, overproduction of pro-inflammatory cytokines, and release of oxidative mediators, all of which culminate in damage to structural and functional components of affected tissues.

Despite significant advances in the development of immunomodulatory drugs and biologics, the effective management of inflammatory diseases remains a clinical challenge. Many current

therapies are associated with systemic side effects, poor bioavailability, and limited efficacy due to nonspecific distribution. Furthermore, conventional dosage forms often fail to respond to the fluctuating and heterogeneous nature of the inflammatory microenvironment. These issues underscore the need for intelligent drug delivery systems capable of achieving site-specific action while minimizing harm to healthy tissues (2).

1.2 Role of Reactive Oxygen Species in Inflammation

Reactive oxygen species (ROS) are chemically reactive molecules derived from molecular oxygen, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH). Under physiological conditions, ROS function as secondary messengers in various cellular processes, including signal transduction, host defense, and apoptosis. The intracellular redox environment is tightly regulated by an array of antioxidant defense systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. However, during inflammation, immune cells such as neutrophils, macrophages, and eosinophils become activated and generate excessive quantities of ROS through mechanisms like the respiratory burst. This overproduction overwhelms endogenous antioxidant systems and leads to oxidative stress a state characterized by an imbalance between ROS generation and neutralization. ROS can induce lipid peroxidation, protein denaturation, and DNA damage, thereby contributing to tissue destruction and perpetuation of the inflammatory response. Moreover, ROS act as key signaling molecules in inflammatory pathways (3). They activate redox-sensitive transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), which regulate the expression of pro-inflammatory cytokines, adhesion molecules, and matrix-degrading enzymes. This molecular cascade creates a self-sustaining loop that amplifies inflammation and exacerbates tissue injury. Therefore, controlling ROS levels or using them as triggers for localized drug release represents a rational strategy in managing inflammatory diseases.

1.3 Need for ROS-Responsive Drug Delivery Systems

Traditional anti-inflammatory therapies, including corticosteroids, NSAIDs, and biologics, have several limitations related to poor target specificity, frequent dosing requirements, and systemic toxicity. In chronic inflammatory diseases, continuous administration of these agents often leads to drug resistance, immune suppression, and adverse effects on non-target tissues. Furthermore, the dynamic nature of inflammation with its spatial and temporal fluctuations in molecular markers demands a more adaptable therapeutic approach (4). ROS-responsive drug delivery systems offer a novel solution to these challenges by enabling selective and controlled release of therapeutic agents in oxidative environments. These systems are designed with redox-sensitive moieties that undergo cleavage or structural transformation upon exposure to elevated ROS levels. This allows for the payload to be released precisely at sites of inflammation, thereby enhancing therapeutic efficacy and reducing systemic exposure.

2. Design and Mechanism of ROS-Responsive Nanocarriers

2.1 Types of ROS and Their Pathological Relevance

Reactive oxygen species (ROS) encompass a family of chemically reactive molecules that include both radical and non-radical oxygen derivatives. The most commonly encountered ROS in biological systems are superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and singlet oxygen ($^1O_2$). These molecules are primarily generated through mitochondrial respiration, NADPH oxidase activity, xanthine oxidase reactions, and during inflammatory responses by activated leukocytes. In healthy cells, basal levels of ROS are tightly regulated and serve important physiological functions such as cell signaling, regulation of gene expression, and defense against pathogens. However, in pathological states such as chronic inflammation, the balance between ROS generation and antioxidant defenses is disrupted, resulting in oxidative stress. Inflamed tissues consistently exhibit elevated concentrations of ROS, which can reach several micromoles, especially in localized microenvironments such as the synovial fluid in rheumatoid arthritis or the mucosal lining in inflammatory bowel disease (5).

2.2 Design Principles for ROS-Responsive Systems

The conceptual framework of ROS-responsive nanocarriers is based on the incorporation of molecular components that undergo a physicochemical transformation in the presence of ROS. The most common strategy involves incorporating ROS-labile linkers within the carrier matrix or drug-conjugate structure. These linkers remain stable under physiological conditions but degrade upon encountering elevated ROS levels, leading to the disassembly of the carrier or the cleavage of drug conjugates. Several essential criteria govern the design of effective ROS-responsive systems. Firstly, the sensitivity and selectivity of the carrier must align with ROS concentrations present in inflamed tissues while remaining inert in normal tissue environments (6). Secondly, the structural transformation whether it is degradation, swelling, or polarity shift should be rapid and irreversible to ensure efficient drug release. Thirdly, the materials used must be biocompatible, non-immunogenic, and ideally biodegradable. Architecturally, nanocarriers can be designed as micelles, liposomes, dendrimers, polymersomes, or inorganic-organic hybrids, depending on the drug's physicochemical properties and therapeutic requirements. These architectures may encapsulate drugs physically or attach them covalently through redox-sensitive bonds. For enhanced specificity, surface functionalization with targeting ligands such as antibodies, peptides, or small molecules can be employed to direct the carrier to inflamed tissues or immune cell subsets.

2.3 Common ROS-Responsive Linkers and Materials

A variety of chemical moieties have been exploited to create ROS-responsive linkers in nanocarrier systems. One of the most widely used groups is the thioketal linkage, which undergoes cleavage in the presence of ROS such as hydroxyl radicals and hydrogen peroxide (7).

Thioketal-containing polymers are particularly attractive due to their stability under acidic and enzymatic conditions, ensuring specificity to oxidative triggers. Boronate esters represent another class of ROS-labile bonds, especially sensitive to hydrogen peroxide. Upon exposure, boronate groups are oxidized to phenols, resulting in structural breakdown and cargo release. These linkers are frequently incorporated into self-assembling block copolymers or drug conjugates. Proline and thioether-based systems also demonstrate ROS sensitivity. Thioethers are oxidized to sulfoxides or sulfones in the presence of ROS, causing a shift in hydrophilicity and often triggering the disintegration of the nanostructure. Diselenide bonds, which are cleaved by singlet oxygen, have also been used for redox-responsive designs, though their clinical relevance is still under investigation due to potential toxicity concerns.

3. Types of ROS-Responsive Nanocarriers

3.1 Polymeric Nanoparticles

Polymeric nanoparticles are among the most extensively studied and versatile platforms for ROS-responsive drug delivery. These systems are typically composed of biodegradable polymers that incorporate redox-sensitive linkages within their backbone or side chains. Polymers such as poly(thioketal), poly(propylene sulfide), and boronate-based block copolymers are commonly employed due to their ability to undergo ROS-induced cleavage or structural transformation (8). The use of polymers offers considerable flexibility in terms of nanoparticle architecture, allowing for the formation of nanospheres, nanocapsules, micelles, or dendritic structures. In many designs, hydrophobic drugs are encapsulated within the core of the polymer matrix, and release is triggered upon ROS-mediated degradation of the carrier. These systems offer the benefit of tunable size, surface charge, and drug release profiles, all of which can be optimized for specific inflammatory disease targets.

3.2 Liposomes and Micelles

Liposomes and micelles are amphiphilic nanostructures that have also been engineered for ROS-responsiveness (9). These systems typically incorporate redox-sensitive lipids or surfactants into their bilayer or core-shell architecture, enabling them to respond selectively to oxidative environments. In the case of liposomes, incorporation of thioketal- or boronate-containing phospholipids allows for membrane destabilization upon exposure to ROS, resulting in rapid drug release. Micelles, on the other hand, are formed by self-assembly of amphiphilic block copolymers. When these polymers include ROS-sensitive segments such as thioether or poly(propylene sulfide) domains the micelles can disintegrate in oxidative environments, facilitating drug release. Micelles are particularly suitable for delivering poorly water-soluble drugs, and their small size (~10–100 nm) facilitates deep tissue penetration and accumulation in inflamed microvasculature via the enhanced permeability and retention (EPR) effect.

3.3 Inorganic and Hybrid Nanocarriers

Inorganic nanocarriers, including mesoporous silica nanoparticles (MSNs), gold nanoparticles, and cerium oxide nanostructures, have also been employed for ROS-responsive drug delivery. These systems typically achieve responsiveness either by loading redox-sensitive materials within the porous matrix or by modifying the surface with ROS-cleavable linkers. MSNs are particularly attractive due to their high surface area, tunable pore size, and biocompatibility. When functionalized with thioketal or boronate groups at the pore openings, these particles can effectively retain drugs under normal conditions and release them in oxidative environments. Gold nanoparticles can be used as cores for hybrid systems, with redox-sensitive polymers or ligands attached to the surface (10). These platforms not only enable controlled release but also offer imaging capabilities due to the optical properties of gold. Cerium oxide nanoparticles possess intrinsic ROS-scavenging properties due to their redox-active surface, making them unique dual-function systems that can simultaneously deliver drugs and modulate oxidative stress. However, concerns regarding their long-term safety and clearance profiles must be addressed before clinical translation.

4. Synthesis and Characterization

The synthesis of ROS-responsive nanocarriers involves careful selection of materials and linkers that respond selectively to elevated ROS levels. Various fabrication techniques have been employed, depending on the type of nanocarrier, drug payload, and intended application. For polymeric nanoparticles, common methods include nanoprecipitation, emulsion-solvent evaporation, and self-assembly of amphiphilic block copolymers. These processes allow for the formation of well-defined nanostructures with controllable size, surface characteristics, and encapsulation efficiency. ROS-responsive polymers used in these systems are often synthesized through step-growth polymerization or ring-opening polymerization, incorporating redox-labile bonds such as thioketal, boronate, or thioether linkages. These functional groups are either integrated within the backbone of the polymer or grafted onto side chains, enabling triggered degradation in response to ROS.

In the case of liposomes and micelles, film hydration, reverse-phase evaporation, and solvent injection methods are commonly employed. For hybrid or inorganic nanocarriers, sol-gel synthesis, hydrothermal treatment, or templating strategies are used to form cores that are subsequently functionalized with ROS-sensitive moieties. Surface modification is often accomplished through click chemistry or carbodiimide crosslinking to attach linkers or targeting ligands, ensuring specificity and biocompatibility. Thorough physicochemical characterization of ROS-responsive nanocarriers is essential for evaluating their performance and stability. Particle size and zeta potential are routinely measured using dynamic light scattering (DLS), which provides insights into colloidal stability and aggregation behavior. Transmission electron

microscopy (TEM) and scanning electron microscopy (SEM) offer detailed information about particle morphology and surface features. The chemical composition and structure of the responsive materials are confirmed using nuclear magnetic resonance (NMR) spectroscopy, Fourier-transform infrared (FTIR) spectroscopy, and mass spectrometry (11). The successful incorporation of redox-sensitive linkers is typically verified by ^{1}H-NMR or FTIR based on specific bond signatures. Thermal and mechanical properties may also be assessed via differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), particularly for polymer-based systems. Drug loading efficiency and encapsulation capacity are evaluated using high-performance liquid chromatography (HPLC) or ultraviolet-visible (UV-Vis) spectrophotometry. These techniques determine how much drug is incorporated into the nanocarriers and how effectively it can be retained prior to release. An essential aspect of ROS-responsive nanocarrier characterization is the evaluation of release kinetics in the presence of ROS. In vitro release studies typically involve exposing the nanocarriers to various concentrations of ROS-generating agents such as hydrogen peroxide (H_2O_2), tert-butyl hydroperoxide (t-BHP), or hypochlorous acid (HOCl). Drug release is monitored over time using UV-Vis or HPLC analysis.

Comparative studies under physiological and oxidative stress conditions help validate the specificity of the carrier's response. Ideally, minimal drug leakage should occur under normal conditions, while rapid and substantial release should be observed in ROS-rich environments. Furthermore, responsive degradation or disassembly can be assessed via DLS or TEM by measuring size changes or morphological transformations following ROS exposure. Advanced techniques such as fluorescent labeling of the nanocarrier or encapsulated cargo allow real-time tracking of release kinetics and cellular uptake. These approaches provide critical insights into the temporal and spatial dynamics of drug delivery and are often coupled with cytotoxicity and efficacy assays in cell culture models of inflammation.

5. Applications In Inflammatory Diseases

5.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation, joint destruction, and systemic oxidative stress. Activated macrophages, neutrophils, and fibroblast-like synoviocytes in the synovial tissue produce elevated levels of reactive oxygen species (ROS), which not only contribute to tissue degradation but also activate redox-sensitive signaling pathways such as NF-κB and STAT3. This creates a localized pro-inflammatory and oxidative microenvironment, making RA an ideal target for ROS-responsive drug delivery (12). Several studies have demonstrated the effectiveness of ROS-responsive nanocarriers in delivering disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, or natural antioxidants directly to the inflamed joints. For instance, thioketal-based polymeric

nanoparticles loaded with methotrexate have shown superior retention in arthritic joints, leading to significant reductions in joint swelling and inflammatory cytokines with reduced systemic toxicity. ROS-triggered release ensures that the drug is delivered preferentially to inflamed tissues while sparing healthy joints, thereby enhancing therapeutic outcomes and minimizing adverse effects.

5.2 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is marked by chronic inflammation of the gastrointestinal tract, with ROS playing a pivotal role in mucosal damage and immune dysregulation. Infiltrating immune cells such as neutrophils and macrophages generate high levels of ROS in the colonic epithelium, which contributes to barrier dysfunction and perpetuation of inflammation. The harsh and variable conditions of the gastrointestinal tract pose significant challenges for traditional drug delivery approaches. ROS-responsive nanocarriers offer a unique solution by remaining stable in the acidic gastric environment and releasing their payload in the oxidative conditions of the inflamed intestine (13). Boronate-containing micelles, for example, have been developed to encapsulate corticosteroids or anti-inflammatory phytochemicals like curcumin. These systems exhibit minimal release under normal conditions but disassemble rapidly upon exposure to H_2O_2 in inflamed colonic tissues, enabling targeted therapy with improved mucosal healing and reduced systemic absorption.

5.3 Pulmonary Inflammation and COPD

Chronic obstructive pulmonary disease (COPD) and other pulmonary inflammatory disorders such as asthma are characterized by airway remodeling, neutrophilic infiltration, and increased oxidative burden in the lungs. Cigarette smoke, environmental pollutants, and recurrent infections further amplify ROS production, leading to progressive lung damage and impaired gas exchange. Inhalable ROS-responsive nanocarriers represent a promising strategy for delivering anti-inflammatory agents directly to the respiratory tract. Polymeric nanoparticles incorporating redox-labile moieties such as thioethers or diselenide bonds can encapsulate corticosteroids or small interfering RNAs (siRNAs) and be formulated as aerosols for pulmonary administration (14). Upon reaching inflamed alveolar or bronchial tissues, these carriers respond to elevated ROS levels by releasing their cargo, thereby reducing local inflammation and oxidative injury. The use of biodegradable and biocompatible materials in these carriers ensures safety and minimizes accumulation in lung tissues over repeated dosing.

5.4 Emerging Indications

Beyond well-established inflammatory conditions, ROS-responsive nanocarriers have begun to show promise in treating other diseases where oxidative stress plays a central role. These include neuroinflammatory conditions such as multiple sclerosis and Parkinson's disease, where

microglial activation and mitochondrial dysfunction generate high ROS levels that contribute to neuronal damage. Similarly, atherosclerosis, characterized by oxidative modification of low-density lipoproteins (LDL) and endothelial inflammation, is another potential target for ROS-triggered drug delivery. In these emerging applications, ROS-responsive systems are being explored for the delivery of neuroprotective agents, antioxidants, and anti-inflammatory cytokines. Multifunctional nanoparticles that can cross biological barriers like the blood–brain barrier (BBB) or arterial endothelium are particularly valuable. Although these applications are still in early stages, they offer a glimpse into the broad versatility and translational potential of ROS-responsive nanomedicine in the management of chronic inflammatory and oxidative disorders.

6. Therapeutic Benefits and Limitations

6.1 Site-Specific and Controlled Drug Release

One of the foremost advantages of ROS-responsive nanocarriers is their capacity to achieve site-specific drug release in inflamed tissues where ROS concentrations are markedly elevated. This targeted activation ensures that therapeutic agents are delivered preferentially to diseased sites, minimizing drug exposure to healthy tissues and thereby reducing off-target effects (15). Such spatiotemporal control is especially critical in managing chronic inflammatory conditions where prolonged systemic drug exposure often leads to toxicity and therapeutic resistance. The ROS-responsiveness of these systems also allows for stimulus-triggered, on-demand drug release, which can be fine-tuned by manipulating the chemical structure of redox-sensitive linkers. This feature is particularly useful in diseases with fluctuating inflammatory severity, such as rheumatoid arthritis or IBD, where the nanocarrier's responsiveness can dynamically match the local oxidative environment, ensuring optimal dosing at the site of inflammation.

6.2 Improved Pharmacokinetics and Bioavailability

ROS-responsive nanocarriers significantly improve the pharmacokinetic profiles of many therapeutic agents. Poorly soluble drugs, labile biomolecules, and macromolecular therapeutics can be effectively protected and solubilized within the nanocarrier matrix, resulting in enhanced systemic stability and prolonged circulation time. These improvements increase bioavailability and reduce the frequency of dosing, both of which are crucial for patient compliance in long-term therapies. Additionally, many ROS-responsive systems are designed using materials that exhibit stealth characteristics, such as PEGylation, to evade immune surveillance and extend blood half-life. This contributes to higher accumulation in inflamed tissues via both passive (enhanced permeability and retention) and active targeting strategies, improving therapeutic efficacy and reducing dosage requirements.

6.3 Multifunctionality and Combination Therapy

Modern ROS-responsive platforms are not limited to drug delivery but can incorporate multifunctional capabilities such as diagnostic imaging, real-time monitoring, and combination therapy. Co-delivery of antioxidants along with anti-inflammatory drugs within the same carrier offers synergistic effects neutralizing excessive ROS while simultaneously modulating inflammatory pathways (16). This dual-action strategy can disrupt the feedback loop of inflammation and oxidative stress more effectively than monotherapy. Further, these nanocarriers can be functionalized with ligands or antibodies that target specific immune cells, enhancing the selectivity and efficacy of treatment. Integration of imaging agents enables tracking of biodistribution and drug release, paving the way for theranostic applications where therapy and diagnostics are unified in a single platform.

6.4 Limitations and Challenges

Despite their promising attributes, ROS-responsive nanocarriers face several challenges that limit their clinical translation. One major concern is the heterogeneity of ROS levels in different patients and disease stages, which can result in variable drug release and inconsistent therapeutic responses. Designing systems that are selectively activated by pathological levels of ROS, while remaining inert in healthy tissues, requires precise engineering and characterization. Another limitation lies in the potential immunogenicity and long-term safety of the materials used. Although many redox-sensitive polymers are biodegradable, the safety profile of degradation products must be thoroughly assessed. Regulatory hurdles for nanoparticle-based systems are also significant, with stringent requirements for reproducibility, scalability, and cost-effectiveness in manufacturing. Furthermore, while in vitro and small-animal studies have demonstrated efficacy, the translation of these systems to large animal models and human trials remains limited. Issues such as stability in biological fluids, clearance mechanisms, and interactions with the immune system must be comprehensively addressed through preclinical research.

7. Future Perspectives

The integration of ROS-responsive nanocarriers into mainstream inflammatory disease treatment holds transformative potential, but their broader clinical adoption will depend on strategic advancements in both science and technology. One of the key future directions is the development of *precision nanomedicine* strategies that incorporate patient-specific ROS profiles to guide therapy. Since oxidative stress levels vary between individuals and across disease stages, personalized ROS-responsive systems that adapt to these differences could markedly enhance treatment efficacy and safety. Further innovation in *multi-responsive nanocarriers* is another exciting frontier. While current designs primarily respond to ROS, emerging systems are being engineered to react to multiple stimuli such as pH, enzymes, or temperature alongside

ROS. These systems offer the possibility of even tighter spatial and temporal control over drug release, especially in complex inflammatory microenvironments where multiple physiological aberrations coexist. By integrating two or more triggers, dual or synergistic responses can be harnessed for highly selective and potent therapeutic actions. c. Nanocarriers embedded with fluorescent dyes, MRI contrast agents, or PET tracers could allow clinicians to visualize carrier distribution, track drug release, and adjust dosages accordingly, ushering in a new era of dynamic and responsive treatment regimens. The combination of ROS-responsive systems with *emerging therapeutic modalities*, such as gene therapy, siRNA delivery, and immune checkpoint inhibitors, also presents promising opportunities. These novel payloads are often unstable or require targeted intracellular delivery challenges that ROS-responsive nanocarriers are well-equipped to address (17). Particularly in autoimmune or chronic inflammatory disorders, targeted suppression of immune signaling using gene silencing agents delivered via redox-sensitive vectors may offer more durable and disease-modifying outcomes. However, for these advancements to translate from concept to clinic, substantial challenges must be overcome. *Scalability and manufacturing reproducibility* remain key bottlenecks, especially for complex multifunctional nanocarriers. Standardized synthesis protocols, quality control metrics, and regulatory pathways specific to responsive nanomedicines must be established to facilitate approval and commercialization. Moreover, *in vivo stability, biodistribution, and clearance* mechanisms of these systems must be rigorously studied in large animal models before human trials can be initiated.

Conclusion:

ROS-responsive nanocarriers represent a compelling advancement in the field of targeted drug delivery, particularly for the treatment of inflammatory diseases marked by elevated oxidative stress. By leveraging the pathological overproduction of reactive oxygen species at inflamed sites, these smart delivery systems enable site-specific, controlled, and efficient therapeutic release, thereby minimizing systemic exposure and associated side effects. The design and synthesis of such nanocarriers ranging from polymeric nanoparticles and liposomes to inorganic hybrids have demonstrated promising preclinical success across various conditions including rheumatoid arthritis, inflammatory bowel disease, and chronic obstructive pulmonary disease. These systems not only improve the pharmacokinetic profiles and bioavailability of encapsulated drugs but also offer multifunctionality, such as co-delivery of synergistic agents and potential integration with diagnostic imaging for theranostic applications. Despite these advantages, several challenges remain, including the need for precise control of ROS-responsiveness, standardized characterization protocols, and scalable manufacturing methods that meet clinical regulatory standards. Moreover, the interpatient variability in ROS expression and the

complexity of inflammatory microenvironments necessitate the future development of adaptable and personalized delivery platforms.

Continued research in multi-stimuli responsive systems, patient-specific nanomedicine, and the integration of novel therapeutic agents such as biologics and nucleic acids will further enhance the clinical utility of ROS-responsive nanocarriers. With sustained interdisciplinary collaboration and translational focus, these innovative drug delivery vehicles hold great promise to redefine therapeutic strategies for managing chronic inflammatory diseases and improving patient outcomes in the years to come.

References:

1. Fedorchenko Y, Zimba O, Yatsyshyn R, Doskaliuk B, Zaiats L, Fedorchenko M. The interplay between rheumatic diseases and pulmonary health. Rheumatology International. 2024;44(7):1179-84.
2. Stielow M, Witczyńska A, Kubryń N, Fijałkowski Ł, Nowaczyk J, Nowaczyk A. The bioavailability of drugs—the current state of knowledge. Molecules. 2023;28(24):8038.
3. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria journal of medicine. 2018;54(4):287-93.
4. He L, He T, Farrar S, Ji L, Liu T, Ma X. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cellular Physiology and Biochemistry. 2017;44(2):532-53.
5. Edge R, Truscott TG. The reactive oxygen species singlet oxygen, hydroxy radicals, and the superoxide radical anion—examples of their roles in biology and medicine. Oxygen. 2021;1(2):77-95.
6. Park H, Saravanakumar G, Kim J, Lim J, Kim WJ. Tumor microenvironment sensitive nanocarriers for bioimaging and therapeutics. Advanced Healthcare Materials. 2021;10(5):2000834.
7. Rinaldi A, Caraffi R, Grazioli MV, Oddone N, Giardino L, Tosi G, *et al.* Applications of the ROS-responsive thioketal linker for the production of smart nanomedicines. Polymers. 2022;14(4):687.
8. Debnath SK, Singh B, Agrawal N, Srivastava R. EPR-Selective Biodegradable Polymer-Based Nanoparticles for Modulating ROS in the Management of Cervical Cancer. Handbook of Oxidative Stress in Cancer: Therapeutic Aspects: Springer; 2022. p. 2863-89.
9. Liang J, Liu B. ROS-responsive drug delivery systems. Bioengineering & translational medicine. 2016;1(3):239-51.
10. Esmailzadeh F, Taheri-Ledari R, Salehi MM, Zarei-Shokat S, Ganjali F, Mohammadi A, *et al.* Bonding states of gold/silver plasmonic nanostructures and sulfur-containing active

biological ingredients in biomedical applications: a review. Physical Chemistry Chemical Physics. 2024.

11. Kristinaitytė K, Dagys L, Kausteklis J, Klimavicius V, Doroshenko I, Pogorelov V, *et al.* NMR and FTIR studies of clustering of water molecules: From low-temperature matrices to nano-structured materials used in innovative medicine. Journal of Molecular Liquids. 2017;235:1-6.
12. Nag S, Mohanto S, Ahmed MG, Subramaniyan V. "Smart" stimuli-responsive biomaterials revolutionizing the theranostic landscape of inflammatory arthritis. Materials Today Chemistry. 2024;39:102178.
13. Wan X, Zhang C, Lei P, Wang H, Chen R, Yang Q, *et al.* Precision therapeutics for inflammatory bowel disease: advancing ROS-responsive nanoparticles for targeted and multifunctional drug delivery. Journal of Materials Chemistry B. 2025.
14. Gulin-Sarfraz T. Design of Multifunctional Nanoparticles for Cellular Labeling and Tracking, Delivery and Scavenging of Active Substances in vivo. 2019.
15. Srinivasarao M, Low PS. Ligand-targeted drug delivery. Chemical reviews. 2017;117(19):12133-64.
16. Muhammad W, Zhang Y, Zhu J, Xie J, Wang S, Wang R, *et al.* Co-delivery of azithromycin and ibuprofen by ROS-responsive polymer nanoparticles synergistically attenuates the acute lung injury. Biomaterials Advances. 2023;154:213621.
17. Malla RR, Kamal MA. ROS-responsive nanomedicine: towards targeting the breast tumor microenvironment. Current Medicinal Chemistry. 2021;28(28):5674-98.

BOILING POINT: DEFINITION, MECHANISM, INFLUENCING FACTORS, AND APPLICATIONS IN CHEMICAL AND INDUSTRIAL PROCESSES

Shivkant Patel*[1], Dillip Kumar Dash[1], Krupa Joshi[1], Surabhi Jain[2]

[1]Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, 391760, Vadodara, Gujarat

[2]Monark Goswami College of Pharmacy Gandhinagar, Gujarat, India

*Corresponding author E-mail: shivapatel2609@gmail.com

Abstract:

The boiling point is a critical thermodynamic property of liquids, defined as the temperature at which the vapor pressure of a liquid equals the external atmospheric pressure, initiating a phase change from liquid to gas. Unlike evaporation, which occurs only at the liquid's surface, boiling is a bulk phenomenon characterized by the formation of vapor bubbles throughout the liquid's body. This transformation occurs when thermal energy overcomes intermolecular forces holding the molecules together in the liquid phase. The boiling point is influenced by factors such as atmospheric pressure and molecular interactions, and it serves as a key parameter in the identification, purity assessment, and characterization of chemical substances. Furthermore, this property is indispensable in various separation and purification techniques, particularly distillation. Its relevance extends across multiple industries, including pharmaceuticals, petrochemicals, and food technology, where precise thermal regulation is essential. This article provides a detailed exploration of the principles, mechanisms, and practical significance of boiling point in both laboratory and industrial settings.

Keywords: Boiling Point, Vapor Pressure, Phase Transition, Intermolecular Forces, Evaporation, Distillation, Purity Analysis, Thermodynamic Property, Separation Techniques, Chemical Characterization, Pharmaceutical Industry, Thermal Control

1. Introduction:

The boiling point of a substance is defined as the specific temperature at which the vapor pressure of the liquid becomes equal to the external atmospheric pressure, facilitating a phase transition from the liquid state to the gaseous state. At this critical point, the thermal energy supplied to the liquid overcomes the cohesive intermolecular forces that hold the molecules in the liquid phase. As a result, vapor bubbles form not only at the surface but also within the bulk of the liquid. These bubbles, composed of vaporized molecules, grow in size and rise through the liquid column to escape into the surrounding atmosphere. This process is markedly different from evaporation, which is a surface phenomenon occurring at temperatures below the boiling point, where only the molecules at the liquid–air interface gains sufficient energy to escape into

the vapor phase. In contrast, boiling is a bulk phenomenon, involving the entire body of the liquid. The boiling point is influenced by several factors, including external pressure and the strength of intermolecular forces within the substance. It is a fundamental physical property and is extensively used in both qualitative and quantitative analysis for the identification, purity assessment, and characterization of chemical compounds. Moreover, because different substances have distinct boiling points, this property plays a crucial role in separation techniques such as distillation, recrystallization, and solvent recovery. Understanding the boiling behavior of substances is also critical in various practical applications across industries, including pharmaceuticals, petrochemicals, and food processing, where precise thermal control is essential for maintaining the quality and stability of products [1].

2. Principles of Boiling

2.1 Vapor Pressure

Vapor pressure refers to the pressure exerted by the vapor molecules in equilibrium with their corresponding liquid phase in a closed system at a specific temperature. It arises from the tendency of liquid molecules, which are constantly in motion, to escape into the gaseous phase. At any given temperature, a fraction of the molecules at the surface of the liquid possesses sufficient kinetic energy to overcome the intermolecular forces (such as hydrogen bonding, van der Waals forces, or dipole-dipole interactions) and enter the vapor phase. As the temperature increases, the average kinetic energy of the liquid molecules also increases. This causes a greater number of molecules to transition into the vapor phase, thereby increasing the vapor pressure. The relationship between temperature and vapor pressure is exponential and can be described by the Clausius–Clapeyron equation, which is commonly used to estimate changes in vapor pressure with temperature. Boiling occurs when the vapor pressure of the liquid becomes equal to the external atmospheric pressure. Under this condition, the molecules within the liquid no longer need to rely solely on surface escape; instead, vapor formation can occur throughout the entire volume of the liquid. This defines the boiling point of the substance.

Boiling Point Condition: Vapor Pressure of Liquid=Atmospheric Pressure

At this equilibrium point, the liquid can freely transition into vapor, and the process of boiling becomes energetically favorable [2].

2.2 Boiling Process

The boiling process is a dynamic and energy-dependent phase transition that occurs when a liquid is heated to its boiling point. It involves the following sequential steps:

- Absorption of Heat Energy: As the liquid is heated, it absorbs thermal energy from the external source. This energy increases the kinetic energy of the molecules throughout the liquid.

- Overcoming Intermolecular Forces: With the rise in kinetic energy, the molecules begin to overcome the intermolecular attractions that maintain the liquid's structure. In polar molecules like water, this means overcoming strong hydrogen bonds, whereas in nonpolar substances, it involves weaker van der Waals forces.
- Formation of Vapor Bubbles: Once the vapor pressure equals atmospheric pressure, molecules within the bulk of the liquid have enough energy to form tiny vapor pockets or bubbles. Unlike evaporation, which only involves surface molecules, boiling involves vapor formation within the interior of the liquid.
- Growth and Rise of Bubbles: These bubbles, initially formed at nucleation sites (such as container walls or impurities), expand due to continued vaporization and reduced surrounding pressure. The buoyant force pushes them upward through the liquid.
- Escape to Atmosphere: Upon reaching the surface, the bubbles burst and release vapor into the atmosphere. This phase transition from liquid to gas continues as long as heat is supplied and the liquid remains at its boiling point.

Throughout the boiling process, the temperature of the liquid remains constant despite continuous heat input. This is because the added energy is consumed in breaking intermolecular bonds and facilitating the phase change, rather than increasing temperature a concept known as latent heat of vaporization. In summary, boiling is a bulk phase transition characterized by energy absorption, vapor bubble formation, and vapor release. It is a critical phenomenon not only in laboratory and industrial processes but also in everyday life, such as cooking, sterilization, and distillation [3].

3. Types of Boiling Points

The boiling point of a substance is not a fixed value but depends on the surrounding atmospheric or external pressure. Therefore, boiling points are often classified based on the pressure at which the boiling occurs. Two commonly referenced types are the normal boiling point and the standard boiling point.

3.1 Normal Boiling Point

The normal boiling point is defined as the temperature at which a liquid changes to vapor when the external pressure is exactly 1 atmosphere (atm), equivalent to 760 mmHg or 101.325 kPa. This condition represents the traditional, widely used standard for comparing boiling points of substances under typical laboratory conditions.

At the normal boiling point:

- The vapor pressure of the liquid becomes equal to 1 atm, allowing the formation of vapor bubbles within the liquid bulk.
- Boiling occurs uniformly throughout the liquid, not just at the surface.

- The temperature remains constant during the boiling process, even with continuous heating, as the energy is used for the phase transition.

Example:

Water has a normal boiling point of 100°C (373.15 K) at 1 atm pressure. This is the basis for many physical chemistry calculations and calibration of thermometers.

The normal boiling point is particularly significant in fields such as:

- Analytical chemistry for identifying pure compounds.
- Chemical engineering for designing distillation columns.
- Pharmaceuticals for selecting suitable solvents based on their boiling behavior [4].

3.2 Standard Boiling Point

The standard boiling point is the temperature at which a liquid boils when the external pressure is 1 bar (100 kPa), a pressure unit slightly lower than 1 atmosphere. This definition aligns with International System of Units (SI), which recommends using 1 bar as the reference pressure for thermodynamic data instead of 1 atm.

Since 1 bar < 1 atm, the standard boiling point of a substance is typically slightly lower than its normal boiling point.

Example:

Water's standard boiling point is approximately 99.61°C (372.76 K), slightly below its normal boiling point of 100°C at 1 atm.

The use of standard boiling points is particularly prevalent in:

- Thermodynamic tables and phase diagrams,
- SI-compliant scientific literature,
- Global databases and computational chemistry software [5].

4. Factors Affecting Boiling Point

The boiling point of a substance is not solely determined by its intrinsic chemical structure. It is influenced by several external and internal factors, including environmental conditions and molecular characteristics. Understanding these factors is crucial in predicting boiling behavior and designing processes such as distillation, solvent selection, and formulation development.

4.1 Atmospheric Pressure

The external atmospheric pressure plays a pivotal role in determining the temperature at which boiling occurs. Since boiling happens when the vapor pressure of a liquid equals the surrounding pressure, any change in atmospheric pressure will directly affect the boiling point.

- At Higher Altitudes: Atmospheric pressure is lower at elevated locations (e.g., mountains), resulting in a lower boiling point. For instance, water may boil at 90°C instead of 100°C, which can affect cooking times and chemical reactions.

- In Pressure Cookers: The internal pressure is increased above atmospheric pressure, which raises the boiling point of water to about 120°C. This enables food to cook faster due to the higher temperature of the cooking medium.

4.2 Intermolecular Forces

The nature and strength of intermolecular forces between molecules significantly affect the boiling point:

- Hydrogen Bonding: Strong attractions exist in molecules like water (H_2O), where hydrogen bonds cause a significant elevation in boiling point.
- Dipole–Dipole Interactions: Polar molecules with permanent dipoles (e.g., acetone) also have higher boiling points compared to non-polar molecules of similar molecular mass.
- Van der Waals (London Dispersion) Forces: Though weak individually, these forces become significant in larger, non-polar molecules, contributing to higher boiling points.

Example:

Water (H_2O) has a boiling point of 100°C, whereas methane (CH_4), with similar molar mass but no hydrogen bonding, boils at –161.5°C.

4.3 Molecular Weight and Molecular Size

In general, boiling point increases with molecular size and mass. Larger molecules have greater surface area, which enhances London dispersion forces, thus requiring more energy (heat) to vaporize [6].

- Straight-chain hydrocarbons (e.g., n-hexane) have higher boiling points than their branched isomers due to more surface contact.
- Heavy or bulky molecules take more energy to break intermolecular attractions.

Example:

Butane (C_4H_{10}) boils at –0.5°C, whereas octane (C_8H_{18}) boils at 125.6°C due to greater molecular mass and size.

4.4 Polarity

Polarity affects boiling points through the strength of dipole-dipole interactions. Polar molecules have partial positive and negative charges, which attract adjacent molecules, increasing the energy needed to transition into the gas phase.

- Polar compounds like ethanol exhibit hydrogen bonding and dipole interactions, resulting in higher boiling points.
- Non-polar compounds like benzene have lower boiling points if molecular weights are similar.

4.5 Presence of Impurities

The addition of non-volatile impurities or solutes to a liquid causes an elevation in its boiling point, a phenomenon known as boiling point elevation, which is a colligative property [7].

- The presence of solutes lowers the vapor pressure of the solution.
- A higher temperature is required for the vapor pressure to equal atmospheric pressure.

Example:

When salt (NaCl) is added to water, the boiling point increases slightly. This is exploited in cooking (e.g., adding salt to boiling water for pasta) and in industrial processes like antifreeze formulation.

5. Boiling Point Determination Methods

The boiling point of a compound is an important physical constant used for identification, purity assessment, and characterization of organic and inorganic substances. Several experimental techniques are employed to determine the boiling point, each suited to specific types of samples and applications. The most commonly used methods include the capillary tube method, distillation, and thermometric techniques.

5.1 Capillary Tube Method (Siwoloboff's Method)

The capillary tube method, also known as Siwoloboff's method, is a simple and widely used laboratory technique, especially suited for small samples and routine boiling point determination of organic liquids.

Procedure:

- A small quantity of the liquid sample is introduced into a small test tube or a specially designed boiling point tube.
- A thin-walled capillary tube, sealed at one end, is inserted open end down into the liquid sample.
- The assembly is placed in a liquid heating bath (commonly silicone oil or concentrated sulfuric acid), which is gradually heated.
- As the temperature increases, vapor from the liquid enters the capillary tube.
- The boiling point is recorded as the temperature at which a continuous stream of bubbles emerges from the open end of the capillary tube.
- Upon cooling, the temperature at which the bubble formation stops is often taken as the confirmation of the boiling point.

Advantages:

- Requires very small sample volumes.
- Simple, quick, and cost-effective.
- Suitable for routine laboratory use.

Limitations:

- Less accurate for high-boiling or thermally unstable compounds.
- Requires visual observation, which may introduce human error [8]

5.2 Distillation Method

Distillation is a classical method used not only for determining the boiling point but also for purifying liquids based on differences in volatility. It is particularly effective for larger volumes and for substances with high boiling points or impurities.

Procedure:

- The liquid is placed in a round-bottom distillation flask connected to a condenser and thermometer.
- Upon heating, the liquid vaporizes and condenses in the cooling arm, and the temperature at which distillation begins (i.e., a steady stream of vapor is observed) is recorded as the boiling point.
- The thermometer bulb must be positioned properly at the opening of the distillation head to ensure accurate temperature measurement.

Types of Distillation:

- Simple Distillation – for pure compounds or mixtures with widely differing boiling points.
- Fractional Distillation – for separating mixtures of liquids with close boiling points.
- Vacuum Distillation – used when boiling points are too high under atmospheric pressure.

Advantages:

- Highly accurate for pure substances.
- Provides both boiling point data and purified product.

Limitations:

- Requires larger sample size.
- Time-consuming and involves more equipment [9].

5.3 Thermometric Methods

For more accurate and sophisticated applications, thermometric methods using electronic sensors are employed. These methods are especially useful for high-boiling, toxic, corrosive, or volatile substances, where traditional techniques may be impractical or unsafe.

Instruments Used:

- Digital Thermometers – Provide direct, precise temperature readings.
- Thermocouples – Made of two dissimilar metals, generate voltage corresponding to temperature.
- Infrared Thermometers – Non-contact devices useful for hazardous or reactive materials.
- Boiling Point Apparatus – Automated systems with built-in temperature controls and detectors for reproducible results.

Procedure:

- The liquid sample is placed in a sealed or semi-open container.

- A sensor is immersed in the sample or placed near the vapor stream.
- As the liquid heats up, the boiling point is recorded when steady vapor formation occurs.

Advantages:

- High accuracy and reproducibility.
- Useful for industrial, research, and hazardous environments.
- Suitable for automated data logging.

Limitations:

- Requires calibration and specialized equipment.
- May not be economical for small-scale or routine applications [10].

6. Significance and Applications of Boiling Point

The boiling point is a fundamental physical property with widespread applications across chemical, industrial, pharmaceutical, and analytical sciences. It serves not only as a tool for substance identification and characterization but also plays a crucial role in process design, purity assessment, and quality control. Below are some of the key areas where boiling point measurements are critically important [11].

6.1 Purity Analysis

Boiling point is highly sensitive to the presence of impurities, making it a reliable indicator of purity for many liquid compounds.

- Pure substances exhibit a sharp and well-defined boiling point.
- The presence of non-volatile impurities typically leads to a boiling point elevation, while volatile impurities may cause either elevation or depression depending on their nature.
- In organic chemistry laboratories, this property is frequently used as a preliminary check for the success of synthesis and purification steps.

Example:

A sample of ethanol with water contamination will boil over a range of temperatures instead of the pure ethanol boiling point of 78.37°C, indicating impurity [12]

6.2 Substance Identification

The boiling point serves as a distinctive physical property, useful in the identification of unknown compounds, especially in combination with other properties like melting point, refractive index, and density.

- In qualitative organic analysis, the boiling point is used alongside spectroscopic data (NMR, IR, MS) to confirm the identity of compounds.
- Boiling point databases provide reference values that can be matched to experimentally determined results to suggest the most likely identity of an unknown liquid.

Example:

A colorless liquid with a boiling point close to 100°C may be suspected to be water, but further analysis would confirm its identity and rule out other candidates like methanol or acetone [12].

6.3 Distillation Techniques

Boiling point differences form the basis of distillation, one of the oldest and most essential separation and purification techniques in chemistry.

- Simple Distillation: Utilized when the boiling point difference between components is large (typically >25°C).
- Fractional Distillation: Employed for mixtures with closely spaced boiling points, using a fractionating column to allow multiple vaporization-condensation cycles.
- Vacuum Distillation: Used for heat-sensitive compounds or those with very high boiling points, where lowering the pressure decreases the boiling point.

Applications:

- Petroleum refining: Fractional distillation separates crude oil into components like gasoline, kerosene, and diesel.
- Ethanol purification: Distillation helps remove water and concentrate ethanol for fuel or pharmaceutical use.
- Solvent recycling: In laboratories and industries, solvents are purified by distillation based on their boiling ranges [13].

6.4 Pharmaceutical Industry

In the pharmaceutical sector, boiling point plays an important role in:

a. *Thermal Stability Studies*

- Boiling point provides insight into the volatility and degradation risk of drug molecules under heat.
- High-boiling solvents or compounds are preferred for formulations requiring long-term thermal stability.

b. Storage and Packaging Design

- Compounds with low boiling points are more volatile and prone to evaporation, requiring airtight containers and cold storage.
- For instance, inhalation drugs or volatile anesthetics (e.g., isoflurane) are stored in specially designed pressurized containers [14].

c. Process Engineering

- During synthesis and formulation, boiling point helps in selecting appropriate solvents that evaporate easily after the reaction but remain chemically compatible with the active pharmaceutical ingredient (API).

d. Quality Control

- Consistent boiling points during quality checks ensure that there has been no solvent contamination, decomposition, or improper formulation [15].

Conclusion:

The boiling point is a vital and widely studied physical property in the field of chemistry, as well as in various interdisciplinary sciences such as materials science, environmental science, chemical engineering, and pharmaceutical research. It marks the temperature at which a liquid's vapor pressure becomes equal to the surrounding atmospheric pressure, allowing it to transition into the gaseous phase. This seemingly simple transition holds profound implications in both theoretical and practical applications. Boiling point is fundamentally governed by several key factors, including the strength of intermolecular forces (such as hydrogen bonding, dipole-dipole interactions, and van der Waals forces), external atmospheric pressure, molecular structure, molecular mass, and chemical composition. A deeper understanding of these factors not only enables accurate prediction of boiling behavior but also aids in the design of chemical processes and the development of temperature-sensitive materials.

The accurate measurement of boiling point is crucial for:

- Substance identification, especially in organic and analytical chemistry,
- Purity analysis, where deviations in boiling point can indicate contamination or improper formulation,
- Separation and purification techniques, such as distillation in both laboratory and industrial settings, and
- Pharmaceutical and chemical industries, where thermal behavior directly impacts formulation, storage, stability, and process control.

Additionally, methods like Siwoloboff's capillary technique, distillation, and modern thermometric approaches ensure boiling points can be determined with high precision depending on the nature of the substance and the scale of application. In conclusion, the boiling point is not merely a textbook parameter; it is an essential metric that reflects the interplay between molecular characteristics and environmental conditions. Mastery over its determination and interpretation is fundamental to the success of both experimental and applied sciences.

References:

1. Chang H. The myth of the boiling point. Sci Prog. 2008;91(3):219-40.
2. Mewes JM, Smits OR. Accurate elemental boiling points from first principles. Phys Chem Chem Phys. 2020;22(41):24041-50.
3. Washburn EW, Read JW. THE LAWS OF "CONCENTRATED" SOLUTIONS. VI. THE GENERAL BOILING-POINT LAW. J Am Chem Soc. 1919;41(5):729-41.

4. Sanghvi R, Yalkowsky SH. Estimation of the normal boiling point of organic compounds. Ind Eng Chem Res. 2006;45(8):2856-61.
5. Struyf J. An analytical approach for relating boiling points of monofunctional organic compounds to intermolecular forces J Chem Educ. 2011;88(7):937-43.
6. Larson RF. Factors Affecting Boiling in a Liquid. Ind Eng Chem. 1945;37(10):1004-9.
7. Smith RL, Watson KM. Boiling points and critical properties of hydrocarbons. Ind Eng Chem. 1937;29(12):1408-14.
8. Karr C, Childers EE. An Improved Siwoloboff Micro Boiling Point Method. Anal Chem. 1961;33(4):655-6.
9. Saidur R, Elcevvadi ET, Mekhilef S, Safari A, Mohammed HA. An overview of different distillation methods for small scale applications. Renewable Sustainable Energy Rev. 2011;15(9):4756-64.
10. Phansi P, Danchana K, Cerdà V. Kinetic thermometric methods in analytical chemistry. Trend Anal Chem. 2017;97:316-25.
11. Héberger K, Kowalska T. Thermodynamic significance of boiling point correlations for alkylbenzenes in gas chromatography: Extension of Trouton's rule. J Chromatogr A. 1999;845(1-2):13-20.
12. Lai WY, Chen DH, Maddox RN. Application of a nonlinear group-contribution model to the prediction of physical constants. 1. Predicting normal boiling points with molecular structure. Ind Eng Chem Res. 1987;26(6):1072-9.
13. Murphy PM. Teaching structure–property relationships: Investigating molecular structure and boiling point. J Chem Educ. 2007;84(1):97.
14. Simamora P, Yalkowsky SH. Group contribution methods for predicting the melting points and boiling points of aromatic compounds. Ind Eng Chem Res. 1994;33(5):1405-9.
15. Satou M, Yokoyama S, Sanada Y. Structural analysis and estimation of boiling point of hydrocarbons in a coal-derived liquid by a group contribution method. Fuel. 1992;71(5):565-74.

Bhumi Publishing, India
July 2025

GLP-1 RECEPTOR AGONISTS: THE NEXT-GENERATION APPROACH TO METABOLIC AND NEURODEGENERATIVE DISEASE TREATMENT

Aarti Sachin Zanwar*[1], Dhanya B. Sen[1], Krupa Joshi[1], Tamanna Chhabra[2]

[1]Department of Pharmacy,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara-391760, Gujarat, India

[2]Department of Prosthodontics and Crown and Bridge,

K M Shah Dental College and Hospital,

Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara-391760

*Corresponding author E-mail: aarti.zanwar@gmail.com

Abstract:

Glucagon-like peptide-1 (GLP-1) is essential for controlling glucose metabolism and energy balance, also called as incretin. Its action collectively contributes to enhance weight regulation and glycemic control. The dual action of GLP-1 receptor agonists and DPP-4 inhibitors have emerged as is a boom to metabolic disease, owing to the rapid breakdown of native GLP-1 by DPP-4. Besides improving blood sugar levels, these therapies offer cardiovascular and metabolic benefits, with recent investigation in other conditions like neurodegenerative diseases and NAFLD. It holds great potential for the future management of diabetes mellitus, supported by their proven clinical effectiveness, broadening range of therapeutic applications, and continuous advancements in treatment strategies.

Keywords: GLP-1 agonist, diabetes mellitus, obesity, semaglutide, DPP4 inhibitors

Introduction:

Diabetes, is a collection of long-term metabolic diseases marked by consistently increasing more blood sugar (glucose) levels than normal level. This disorder develops as a result of either the body's cells becoming resistant to the response of insulin or the pancreas producing insufficient amounts of insulin, for controlling blood glucose. [1]

About 589 million human being, globally have diabetes as of 2025, making up 1 in 9 or 11.1% of the adult population worldwide. By 2050, it is anticipated that there will be 853 million diabetics patients worldwide. The prevalence of diabetes has increased from 4.0% in 1995 to 10.5% in 2021, and is expected to continue climbing. [2]

Type 1 diabetes mellitus (T1DM), prevalent form of diabetes diagnosed in patients under the age of 20, affects approximately 1.8 million children and young adults worldwide (3–4). Type 2 diabetes rates have surged significantly since 1960, closely correlated with global obesity. In 1985, 30 million people were diagnosed, but by 2015, it had reached 392 million. By 2017, over

6.28% of the global population, were affected forming global health emergency that has a big impact on public health systems and economy around the world. [5–6]

More than four out of ten persons with diabetes, or over 252 million people, are unaware of their health condition, thereby raising their risk of repercussions. Every year, diabetes causes more than 3.4 million fatalities. For the first time, global diabetes-related health spending exceeded one trillion US dollars in 2024. Compared to people without diabetes, people withT2DM have an 84% more risk of cardiopulmonary arrest. Urban areas and younger age groups are increasingly affected by the biggest rises in diabetes prevalence that are taking place in developing nations. India, China, the United States, Indonesia, and Pakistan are the nations with the highest rates of diabetes. [7] Figure 1 summarizes the different kinds of diabetes mellitus.

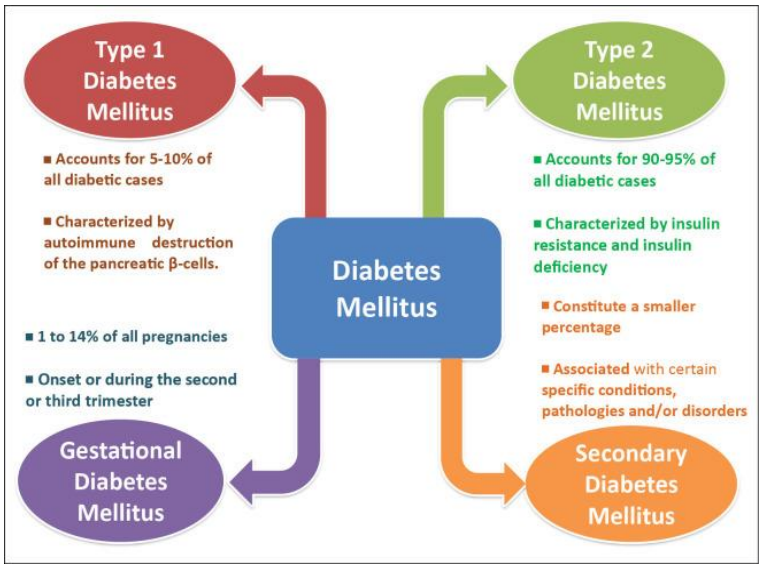

Figure 1: Types of diabetes mellitus [8]

The first line of treatment for diabetes mellitus includes healthy eating, increased physical activity, and weight loss. Metformin is the most common initial medication, reducing glucose production in the liver. [9–10]

Depending on the needs of each patient, additional oral medications may include thiazolidinediones, Gliptins, Gliflozins, and sulfonylureas. GLP-1 receptor agonists, such as tirzepatide and semaglutide, increase insulin synthesis, decrease glucagon, and aid in weight loss. [11]

With significant effects on both health and the treatment of disease, the peptide hormone GLP-1 has become a enter as a regulator of human metabolism. In response to dietary intake, it is mainly released by certain neurons in the brainstem and enteroendocrine cells in the colon. (12) GLP-1 is a key target in the management of T2 DM and obesity as it is essential for maintaining glucose homeostasis. A key player in the body's metabolic reaction to fed intake, as it response to nutrient absorption. [13–14]

Secretion and Structure

GLP-1 is released is likely triggered by brain signals, gut peptides, or neurotransmitters for short time (10-15 min) while the second phase is likely stimulated by digested nutrients.

It inhibits stomach emptying, which slows down its own secretion (negative feedback) when it is activated postprandially. [12, 15]

Numerous signaling pathways have been linked to sugars, which cause the L-cell membrane to depolarize, raising the cytosolic Ca2+ concentration and ultimately triggering the release of GLP-1. [16–19]

These drugs work similarly as endogenou Gs LP-1 by promoting satiety, suppressing glucagon, boosting insulin production, and postponing stomach emptying.

GLP-1, a proglucagon molecule, is created by enzymes during nutrient consumption. Only 10–15% of GLP-1 remains in the circulation after DPP-4 breaks down the active versions. GLP-1 receptor agonists and DPP-4 inhibitors have been created to address this. Patients with type 2 diabetes who get GLP-1-based medication have been shown to lose weight and have a lower risk of hypoglycemia. [20–21]

Mechanism of Action

The GLP-1 receptor, present on pancreatic β-cells and other tissues, is where GLP-1 works. Its presence will elevate insulin secretion, downregulating glucagon release, and other metabolic consequences result from this binding's activation of intracellular signaling cascades, such as the cAMP/PKA and PI3K/Akt pathways. [22-23]

As a glucose-dependent incretin hormone, is essential for maintaining glucose equilibrium in the body because it stimulates insulin production from pancreatic β-cells and inhibits glucagon release, both of which lower blood glucose levels.

GLP-1 has attracted a lot of attention for its wider physiological functions in addition to its impact on glucose metabolism. By affecting the central nervous system, it decreases hunger, improves satiety, and slows down stomach emptying, making it a viable target for treatments related to obesity and weight loss. The hormone's natural duration of effect is limited to 1-2 minutes due to its fast circulatory breakdown, mainly by DPP-4. To extend its therapeutic benefits, GLP-1 receptor agonists and DPP-4 inhibitors were developed.

With benefits including decrease in body weight and risk of hypoglycemia as compared to conventional therapy, GLP-1 and its analogs have completely changed the way type 2 diabetes and obesity are treated in recent years. Additionally, new studies demonstrate how GLP-1-based treatments can be used to treat a variety of illnesses, related to heart, liver and neurons. It highlights the hormone's complex role in human physiology and growing importance in contemporary medicine. [24–25] Table 1 summarizes the various approved GLP1 agonist therapies.

Table1: Major FDA-Approved GLP-1 Receptor Agonists

Sr. No.	Drug Name	Approval year	Company	Brand Names	Indication	Dosing Frequency	HbA1c reduction	Remark
1	Exenatide	2005, 2012	Astra Zeneca	Byetta, Bydureon	Type 2 diabetes	Twice daily, weekly (5 or 10 mcg).	Moderate	Short-acting, postprandial effect
2	Liraglutide	2010	Novo Nordisk	Victoza (diabetes), Saxenda (obesity)	Type 2 diabetes, obesity	Daily (SC inj. 0.6 mg once daily after week to 1.2 mg then increased to 1.8 mg nce daily)	Good	Long-acting, fasting glucose effect
3	Albiglutide	2014	GSK	Tanzeum	Type 2 diabetes	Weekly (withdrawn from the market in 2018 due to commercial reason)	-	-
4	Dulaglutide	2014	Eli Lilly	Trulicity	Type 2 diabetes	Weekly	Good	Long-acting
5	Lixisenatide	2016	Sanofi	Adlyxin (US), Lyxumia (EU)	Type 2 diabetes	Once daily (SC injection 10 mcg for 10 day then 20 mcg)	Good	Short-acting
6	Semaglutide	2017	Novo Nordisk	Ozempic (diabetes) Rybelsus (oral, diabetes), Wegovy (obesity)	Type 2 diabetes, obesity	Weekly subcutaneously, daily orally	High	Long-acting, oral form available
7	Tirzepatide (Dual GLP1 and GIP agonist)	2022	Eli Lilly	Mounjaro (diabetes), Zepbound (obesity)	Type 2 diabetes, obesity	Once weekly injection	Highest	Newest, strong data

Physiological Functions of GLP-1

1. **Increased Insulin Secretion:** GLP-1 stimulates the glucose-dependent release of insulin from pancreatic β-cells, which is a key strategy for lowering postprandial blood glucose levels.

2. **Suppression of Glucagon Release:** High glucose inhibits the release of glucagon, which reduces the quantity of glucose the liver produces.

3. **Delay of stomach emptying**: GLP-1 promotes satiety and prolongs nutrition absorption by postponing stomach emptying, which aids in weight management.

4. **Promotion of β-cell Health**: It suppresses apoptosis and promotes β-cell proliferation and neogenesis, which maintains or increases the number of β-cells. Diabetes therapy benefits greatly from this impact.

5. **Improvement of Insulin Sensitivity**: GLP-1 improves the effectiveness of insulin, which aids in glycemic control. [26]

Exenatide:

As the first approved drug in its class, exenatide is a first-generation sold under the Byetta (twice-daily injectable) brand by Amylin Pharmaceuticals and Eli Lilly & Company. Once-weekly, extended-release formulation sold under the brand name Bydureon (Amylin, Alkermes, and Eli Lilly). Byetta is administered subcutaneously twice a day. Exenatide decreases hunger, slows stomach emptying, inhibits incorrect glucagon secretion, and boosts glucose (dependent insulin) secretion. In people with type 2 diabetes, it enhances glycemic control (HbA1c decrease), particularly when used in conjunction with thiazolidinediones or conventional drug. [27]

Lixisenatide:

Developed initially by Sanofi, lixisenatide is sold under the trade names Adlyxin (in the US) and Lyxumia (in the EU). For 14 days, 10 mcg of lixisenatide is injected subcutaneously once day; after that, the dosage is increased to 20 mcg once daily. In instance, it decreases postprandial glucose excursions by postponing stomach emptying. [28]

Liraglutide:

Novo Nordisk developed and marketed it initially under the brand names Saxenda and Victoza. Liraglutide, a drug for managing weight, starts at 0.6 mg per day and goes up to 3.0 mg per day. It makes the stomach empty more slowly, causes glucagon to be released incorrectly, and makes insulin release more quickly when glucose is present**.** [29]

Dulaglutide:

Dulaglutide, a second-generation GLP-1 receptor agonist, offers a once-weekly subcutaneous dosage and greater ease compared to first-generation treatments. Its structural fusion of an IgG4-Fc fragment with a GLP-1 analogue provides a longer half-life for weekly dosage. Eli Lilly and Company develops and markets dulaglutide under the Trulicity trademark. It increases glucose-

dependent insulin secretion, inhibits glucagon release, delays stomach emptying, and reduces appetite in a manner similar to that of endogenous GLP-1. [30]

Semaglutide:

Novo Nordisk created the weight-loss drug semaglutide, a second-generation GLP-1 receptor agonist. It is marketed under the names Ozempic, Rybelsus, and Wegovy. By imitating endogenous GLP-1, semaglutide inhibits appetite, glucagon secretion, and stomach emptying while triggering insulin secretion. Additionally, it reduces the risk of serious cardiovascular events in people with documented heart disease and type 2 diabetes. [31-32]

Tirzepatide:

As a dual agonist of GLP-1 and GIP receptors, tirzepatide promotes improved glycaemic management and weight reduction. It delays stomach emptying, suppresses glucagon secretion, increases insulin secretion, and reduces appetite. Tirzepatide, developed and marketed by Eli Lilly and Company, is available once a week subcutaneously in a range of dosages. By reducing food consumption and promoting weight reduction, it also helps obese or overweight people control their weight over the long run. [33]

Neurodegenerative Diasease:

Early intervention with GLP-1 receptor agonists (GLP-1RAs) can significantly prevent irreversible neuronal loss in neurodegenerative diseases like Alzheimer's and Parkinson's. By preserving neuronal populations before extensive damage occurs, GLP-1RAs maximize neuroprotection potential. They can reduce pathological protein accumulation in Alzheimer's, potentially slowing or halting disease progression by reducing the aggregation of amyloid-beta and tau proteins.[34] GLP-1RAs suppress pro-inflammatory cytokines and promote an anti-inflammatory environment. They preserve synaptic function and neurogenesis, which are more robust in the early stages of disease, allowing for better support before ongoing degeneration overwhelms these mechanisms. GLP-1RAs improve brain insulin signaling and mitochondrial function, potentially preventing or delaying metabolic dysfunction in neurodegenerative diseases. They also support a healthy brain microenvironment by improving neurovascular coupling and endothelial function, ensuring blood-brain barrier integrity and cerebral blood flow. GLP-1RAs reduce neuronal loss, protein aggregation, and inflammation better before or at the start of dementia. [35,36]

Liver Disease: Decrease in Steatosis and Liver Fat

GLP-1RAs significantly improve hepatic steatosis and decrease hepatic fat buildup, with liraglutide and exenatide showing a 42% decrease in liver fat content in clinical trials. They also reduce fibrosis and hepatic inflammation by enhancing metabolic parameters and lowering tissue and systemic inflammation. They also lower chronic inflammatory markers, such as TNF-α, IL-6, and CRP, which contribute to liver damage. GLP-1 prevents hepatocyte apoptosis and

encourages autophagy by lowering endoplasmic reticulum stress and breaking down harmful lipid species. These medications indirectly reduce liver inflammation and fibrosis by improving metabolic dysfunction, reducing inflammation, promoting weight loss, and preventing hepatocyte injury and death. [37-39]

Kidney Disease

GLP-1 RAs induce natriuresis and diuresis, largely by inhibiting the sodium–hydrogen exchanger 3 (NHE3) in proximal tubular cells. They reduce renal oxidative stress and inflammation, likely through cAMP/PKA signaling and by decreasing NAD(P)H oxidase activity. It may decrease intraglomerular pressure and hyperfiltration, contributing to slower eGFR decline. Experimental studies suggest reduced intrarenal RAAS activation and angiotensin II levels. They may improve renal endothelial function and have anti-atherogenic actions. The most consistent clinical effect of GLP-1 RAs is a reduction in albuminuria, an important marker of kidney damage and predictor of disease progression. [40-42]

Conclusion:

GLP-1 is a complicated hormone that plays crucial functions in metabolic regulation, β-cell maintenance, and appetite control. The discovery of GLP-1 receptor agonists and DPP-4 antagonists, which also offer other benefits including weight loss and cardiovascular protection, has revolutionised the management of type 2 diabetes and obesity. Ongoing research continues to broaden the therapeutic potential of GLP-1-based medications, including their application in neurodegenerative and other chronic illnesses.

References:

1. Riddle MC, Bakris G, Blonde L, Boulton AJ, D'alessio D, De Groot M *et al.* Introduction: standards of medical care in diabetes—2018. Diabetes Care.2018 ;41(Suppl 1):S1-2.
2. Ogle GD, Wang F, Haynes A, Gregory GA, King TW, Deng K, *et al.* Global type 1 diabetes prevalence, incidence, and mortality estimates 2025: Results from the International diabetes Federation Atlas, and the T1D Index Version 3.0. Diabetes Research and Clinical Practice. 2025; 22:112277.
3. Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors.2013. Cell metabolism ;17(1):20-33.
4. Kumar V, Abbas A, Aster J (2021). *Robbins & Cotran Pathologic Basis of Disease* (10th ed.). Pennsylvania: Elsevier. pp. 1065–1132.
5. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. Nature medicine. 2006 ;12(1):75-80.
6. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF *et al.* Projections of type 1 and type 2 diabetes burden in the US population aged< 20 years through 2050:

dynamic modeling of incidence, mortality, and population growth. Diabetes care. 2012 ;35(12):2515-2520.

7. Kumar PJ, Clark ML, Zammitt NN, Sandilands EA, editors. Essentials of Kumar & Clark's Clinical Medicine. Elsevier; 2021.
8. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med. 2020;10(04):174-188.
9. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs. 2005;65:385-411.
10. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016;65(2):20-9.
11. Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician. 2009 ;79(1):29-36.
12. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007 May 1;132(6):2131-2157.
13. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C *et al.* Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct Target Ther. 2024 ;9(1):234.
14. Reed J, Bain SC, Kanamarlapudi V. Recent advances in understanding the role of glucagon-like peptide 1. F1000 Research. 2020 Apr 6;9:F1000-Faculty Rev-239.
15. Marathe CS, Rayner CK, Jones KL, Horowitz M. Glucagon-like peptides 1 and 2 in health and disease: a review. Peptides. 2013 ;44:75-86.
16. MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes. 2002 Dec 1; 51(suppl_3):S434-442.
17. Bu T, Sun Z, Pan Y, Deng X, Yuan G. Glucagon-like peptide-1: new regulator in lipid metabolism. Diabetes & Metabolism Journal. 2024 Apr 1;48(3):354-372.
18. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. Diabetes spectrum. 2017 Aug 1;30(3):202-10.
19. Ma X, Guan Y, Hua X. Glucagon-like peptide 1-potentiated insulin secretion and proliferation of pancreatic β-cells GLP-1. Journal of diabetes. 2014 Sep;6(5):394-402.
20. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. Diabetes. 1995 ;44(9):1126-1131.
21. Montrose-Rafizadeh C, Yang H, Rodgers BD, Beday A, Pritchette LA, Eng J. High potency antagonists of the pancreatic glucagon-like peptide-1 receptor. J Biol Chem 1997;272(34):21201-21206.

22. Kaihara KA, Dickson LM, Jacobson DA, Tamarina N, Roe MW, Philipson LH, *et al.* β-Cell-specific protein kinase A activation enhances the efficiency of glucose control by increasing acute-phase insulin secretion. Diabetes. 2013 May;62(5):1527-36.
23. Bhalla S, Mehan S, Khan A, Rehman MU. Protective role of IGF-1 and GLP-1 signaling activation in neurological dysfunctions. Neurosci Biobehav Rev.2022;142:104896.
24. Rowlands J, Heng J, Newsholme P, Carlessi R. Pleiotropic Effects of GLP-1 and Analogs on Cell Signaling, Metabolism, and Function. Front Endocrinol . 2018;9:672.
25. Donnelly D. The structure and function of the glucagon-like peptide-1 receptor and its ligands. Br J Pharmacol. 2012;166(1):27-41.
26. Holst JJ. The physiology of glucagon-like peptide 1. Physiological reviews. 2007 ;(4):1409-1439.
27. Genovese S, Mannucci E, Ceriello A. A review of the long-term efficacy, tolerability, and safety of exenatide once weekly for type 2 diabetes. Adv Ther. 2017 ;34:1791-1814.
28. McCarty D, Coleman M, Boland CL. Lixisenatide: a new daily GLP-1 agonist for type 2 diabetes management. Ann Pharmacother. 2017 May;51(5):401-409.
29. Tilinca MC, Tiuca RA, Burlacu A, Varga A. A 2021 update on the use of liraglutide in the modern treatment of 'diabesity': a narrative review. Medicina. 2021; 57(7): 669.
30. Scott LJ. Dulaglutide: a review in type 2 diabetes. Drugs. 2020;80(2):197-208.
31. Chao AM, Tronieri JS, Amaro A, Wadden TA. Semaglutide for the treatment of obesity. Trends in cardiovascular medicine. 2023;33(3):159-166.
32. Andreadis P, Karagiannis T, Malandris K, Avgerinos I, Liakos A, Manolopoulos A, *et al.* Semaglutide for type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2018;20(9):2255-2263.
33. Sokary S, Bawadi H. The promise of tirzepatide: A narrative review of metabolic benefits. Primary Care Diabetes. 2025;9: 229–237.
34. Hong CT, Chen JH, Hu CJ. Role of glucagon-like peptide-1 receptor agonists in Alzheimer's disease and Parkinson's disease. J. Biomed. Sci. 2024 ;31(1):102.
35. Dzidic-Krivic A, Fajkic A, Farhat EK, Lekic L, Ejubovic A, Vukas SK, *et al.* Linking Metabolic Syndrome to Neurodegeneration Mechanisms and Potential Treatments. Mol. Neurobiol. 2025; 24:1-23.
36. Monti G, Gomes Moreira D, Richner M, Mutsaers HAM, Ferreira N, Jan A. GLP-1 Receptor Agonists in Neurodegeneration: Neurovascular Unit in the Spotlight. Cells. 2022 ;11(13):2023.
37. Kathryn J Potter, Jackie Phinney, Tasha Kulai, Vicki Munro. Effects of GLP-1 receptor agonist therapy on resolution of steatohepatitis in non-alcoholic fatty liver disease: a systematic review and meta-analysis, J. Can. Assoc. Gastroenterol. 2025;8(2); 47–57.

38. Wong C, Lee MH, Yaow CY, Chin YH, Goh XL, Ng CH, *et al.* Glucagon-like peptide-1 receptor agonists for non-alcoholic fatty liver disease in type 2 diabetes: a meta-analysis. Frontiers in endocrinology. 2021;12:609110.
39. Wang XC, Gusdon AM, Liu H, Qu S. Effects of glucagon-like peptide-1 receptor agonists on non-alcoholic fatty liver disease and inflammation. World J Gastroenterol. 2014;20(40):14821.
40. Pan HC, Chen JY, Chen HY, Yeh FY, Sun CY, Huang TT, Wu VC. GLP-1 receptor agonists' impact on cardio-renal outcomes and mortality in T2D with acute kidney disease. Nature Communications. 2024 Jul 13;15(1):5912.
41. Michos ED, Bakris GL, Rodbard HW, Tuttle KR. Glucagon-like peptide-1 receptor agonists in diabetic kidney disease: A review of their kidney and heart protection. Am J Prev Cardiol. 2023 May 24;14:100502.
42. Kawanami D, Takashi Y. GLP-1 receptor agonists in diabetic kidney disease: from clinical outcomes to mechanisms. Frontiers in Pharmacology. 2020 Jun 30;11:967.

NEPHROBLASTOMA (WILMS TUMOR): A COMPREHENSIVE OVERVIEW

Kailashgiri I Goswami
Department of General Surgery,
Sumandeep Vidyapeeth Deemed to be University, Vadodara

Abstract:
Nephroblastoma, commonly known as Wilms tumor, is the most prevalent renal malignancy in children, typically diagnosed between ages 3 and 5. This chapter delves into its epidemiology, etiology, clinical presentation, diagnostic approaches, staging, treatment modalities, prognostic factors, and future directions. Emphasis is placed on the importance of multidisciplinary management and the advancements that have led to improved survival rates.

Keywords: Nephroblastoma, Nephron Sparing

Introduction:

Nephroblastoma, or Wilms tumor, is a malignant renal tumor predominantly affecting children. It accounts for approximately 6% of pediatric cancers. The tumor arises from metanephric blastemal cells, reflecting its embryonic origin.

Epidemiology

- **Incidence**: Approximately 8 cases per 1 million children under 15 years annually.
- **Age**: Peak incidence between 3 and 4 years.
- **Gender**: Slight female predominance.
- **Geographical Variation**: Higher incidence in African populations compared to East Asians.

Etiology and Risk Factors

- **Genetic Factors**:
    - **WT1 Gene Mutations**: Associated with syndromes like WAGR (Wilms tumor, Aniridia, Genitourinary anomalies, and mental Retardation).
    - **WT2 Locus Alterations**: Linked to Beckwith-Wiedemann syndrome.
- **Syndromic Associations**:
    - **Denys-Drash Syndrome**: Characterized by nephropathy, male pseudohermaphroditism, and Wilms tumor.
    - **Perlman Syndrome**: A rare overgrowth syndrome with a high risk of Wilms tumor.

Clinical Presentation

- **Common Symptoms**:
    - Abdominal mass or swelling.
    - Hematuria.

  - Hypertension.
  - Fever.
  - Anorexia.
- **Bilateral Involvement**: Occurs in approximately 5-10% of cases.

Diagnostic Evaluation

- **Imaging**:
  - **Ultrasound**: Initial modality to assess renal masses.
  - **CT/MRI**: Detailed evaluation of tumor extent and metastasis.
- **Laboratory Tests**:
  - Complete blood count.
  - Renal function tests.
  - Liver function tests.
- **Histopathology**:
  - **Triphasic Pattern**: Blastemal, epithelial, and stromal components.
  - **Anaplasia**: Indicates unfavorable histology and poorer prognosis.

Staging

Staging is crucial for treatment planning:

- **Stage I**: Tumor limited to the kidney and completely resected.
- **Stage II**: Tumor extends beyond the kidney but is completely resected.
- **Stage III**: Residual non-hematogenous tumor confined to the abdomen.
- **Stage IV**: Hematogenous metastases (e.g., lung, liver).
- **Stage V**: Bilateral renal involvement at diagnosis.

Treatment Modalities

- **Surgery**:
  - **Nephrectomy**: Standard treatment for unilateral tumors.
  - **Nephron-Sparing Surgery**: Considered in bilateral tumors to preserve renal function.
- **Chemotherapy**:
  - Agents like vincristine, dactinomycin, and doxorubicin are commonly used.
- **Radiation Therapy**:
  - Indicated in advanced stages or residual disease post-surgery.
- **Multidisciplinary Approach**:
  - Collaboration among pediatric oncologists, surgeons, radiologists, and nephrologists is essential for optimal outcomes.

Prognosis

- **Favorable Histology**: 5-year survival rate exceeds 90%.

- **Unfavorable Histology (Anaplastic)**: Lower survival rates, necessitating more aggressive treatment.
- **Prognostic Factors**:
    - Stage at diagnosis.
    - Histological subtype.
    - Age at diagnosis.
    - Response to initial therapy.

Follow-Up and Surveillance

Regular monitoring is vital to detect recurrence and manage late effects:

- **Imaging**: Periodic abdominal ultrasounds and chest X-rays.
- **Renal Function Tests**: Especially important in patients with solitary kidneys or those who received nephrotoxic treatments.
- **Monitoring for Secondary Malignancies**: Due to chemotherapy and radiation exposure.

Future Directions

- **Genetic Research**: Understanding molecular pathways to develop targeted therapies.
- **Risk Stratification**: Personalizing treatment intensity based on genetic and histological markers.
- **Global Health Initiatives**: Addressing disparities in diagnosis and treatment access worldwide.

Molecular Targets & Pathwayas

Wnt/β-catenin Pathway

- 15–20% of Wilms tumors show activation via WTX/CTNNB1 mutations
- Preclinical: FZD7 antibodies reduced growth in xenograft models
- Evolving CINNAB inhibitors (e.g., tegavivint) in other cancers

IGF2/IGF-1R & PI3K/AKT Signaling

- Frequently overexpressed; under trial with IGF1R/AKT inhibitors

Tyrosine Kinase Inhibitors

- Larotrectinib & entrectinib for NTRK-fusion tumors

microRNA-based Approaches

- Circulating miRNAs (miR-100-5p, miR-130b-3p, miR-143-3p) for diagnostics/prognostics
- Preclinical miR-200c-3p inhibits invasion
- RNAi and epigenetic modulation (e.g., XPO1 inhibitors) in early trials

DNA Damage Response Inhibitors

- ATR inhibitor M6620 enhances chemo cytotoxicity; Phase II underway

Immunotherapy

Checkpoint Inhibitors

- PD-1/PD-L1 agents like pembrolizumab being evaluated

CAR-T / T-Cell Therapies

- Experimental CAR-T designs and multi-tumor antigen CTL (MTAA-CTL) with early-phase success

Vaccine & Tumor Antigen Approaches

- WT1 peptide vaccines + HLA peptides show promise

Anti-GD2 Therapy

- Emerging interest in GD2-targeted antibodies (e.g., naxitamab) that have been used in pediatric solid tumors

Advanced Localized Therapies

Nephron-Sparing & Minimally Invasive Surgery

- Laparoscopic-assisted & NSS strategies reduce morbidity

High-Intensity Focused Ultrasound (HIFU)

- MRI-guided, non-invasive thermal ablation under development for select renal tumors

Smart Nanocarriers & Drug Delivery

- Nanotherapy (e.g., protein-corona nanoparticles) and targeted DDS show potential
- **Stem-Cell Rescue & Supportive Innovations**
- Autologous stem-cell transplantation post high-dose chemo improves salvage for relapse

Diagnostic Precision & Surveillance

Liquid Biopsies & ctDNA

- Digital droplet PCR and circulating tumor DNA for real-time monitoring

Biomarkers & Imaging

- LOH at 1p/16q as prognostic markers

Clinical Trials & Future Directions

- Numerous Phase I/II trials targeting IGF2, Wnt, microRNAs, ATR, TKIs, immunotherapies
- Vision: integrated 'multi-omic' predictive framework (genomic + transcriptomic + radiomic + epigenetic)
- Several cutting-edge techniques and technologies being developed or studied for nephroblastoma (Wilms tumor):

In silico "Oncosimulator" for Personalized Treatment Planning

- The *Nephroblastoma Oncosimulator* integrates patient MRI, histology, and treatment data to simulate tumor growth and predict individualized treatment responses. Early

results demonstrate accurate stratification by risk group and could guide personalized therapy plans

Advanced Genomic Profiling and Liquid Biopsies

- Ultra-high-resolution sequencing techniques (nanoseq + single-cell organoids) revealed that Wilms tumors harbor millions of somatic mutations—much more than previously known
- Identifying rare subclonal mutations (e.g., FOXR2) could allow classification into treatment-responsive subgroups and open avenues for repurposing adult immunotherapies
- Liquid biopsies (ctDNA, miRNAs) are emerging tools for minimal-residual-disease detection and real-time monitoring. Early studies are promising but require larger validation

MicroRNA-Based Diagnostics and Therapeutics

- Circulating miRNA signatures (e.g., miR-100-5p, -130b-3p, -143-3p) can differentiate Wilms tumor patients from healthy controls (~85% accuracy) and stratify relapse risk
- miR-200c-3p directly suppresses tumor cell invasion and may become a therapeutic target

Immunotherapy & Neoantigen Vaccines

- Personalized neoantigen vaccines (iNeST) designed from tumor-specific mutations have shown early promise in kidney cancers, training T-cells to detect residual disease post-surgery.
- WT1 peptide vaccines, possibly paired with checkpoint inhibitors (anti–PD-1/PD-L1), are in phase I/II pediatric trials.
- Though immune checkpoint inhibitors alone have shown low response rates in relapsed Wilms tumors, subgroups (e.g., TP53-mutated) may benefit due to higher neoantigen loads.

Combining Ablation Techniques with Immunotherapy

- "Combinatorial ablation"—using cryo-, RF-, HIFU or hyperthermia—can induce immunogenic tumor destruction, releasing antigenic debris to prime immune responses when combined with checkpoint inhibitors or CAR-T therapies
- Particularly, MR-guided HIFU (with AI-driven biomarkers) enables non-invasive, image-guided tumor ablation.

Minimally Invasive & Robotic Surgery

- **Laparoscopic radical and nephron-sparing surgeries (NSS)** offer faster recovery but require careful patient selection to avoid intraoperative tumor spill
- **Robotic-assisted laparoscopy (RAL)** is emerging, though experience in children is limited. Future focus: smaller robotic instruments and centralized expertise

Smart Nanoparticle Drug Delivery

- Multifunctional nanocarriers (e.g., protein-corona-coated, pH-responsive) are under development to deliver chemotherapy agents precisely to tumor cells, minimizing systemic toxicity.

Targeting Anaplastic (TP53-Mutant) Subtypes

- Diffuse anaplasia Wilms tumors often carry TP53 mutations that make standard chemotherapy less effective
- New strategies being explored include DNA damage pathway modulators and precision agents to sensitize these resistant tumors.

Summary of the Emerging Clinical Landscape

These novel approaches—from in silico modeling to nano-immunotherapy—are converging toward **precision medicine** for nephroblastoma. However, most are still in early clinical or experimental stages. Validated biomarkers and subtyping (TP53 status, neoantigens) will be critical to making these innovations both safe and effective.

References:

1. Johnson *et al.* Current recommendations and novel approaches in Wilms Tumor. Georgetown Med Rev. 2025.
2. Hong H, Dong J. Targeted therapy and immunotherapy of Wilms Tumor. Transl Cancer Res. 2021;10(12):5293-303.
3. MDPI. Personalized care strategies for Wilms Tumor. MDPI. 2024.
4. Columbia Doctors; National Cancer Institute. Larotrectinib, entrectinib, high-dose chemotherapy with stem-cell rescue for Wilms Tumor. PDQ Pediatric Treatment Editorial Board. [Internet]. Available from: https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq
5. PubMed. Advances in laparoscopic nephron-sparing surgery, imaging, and biomarker risk stratification in Wilms Tumor. PubMed. 2022-2023. Available from: https://pubmed.ncbi.nlm.nih.gov/

Bhumi Publishing, India
July 2025

RADIOPHARMACEUTICAL APPLICATIONS IN ONCOLOGY: DIAGNOSTICS AND THERAPEUTICS

Yuvraj Maharshi
Department of Paramedical Science,
Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat
Corresponding author E-mail: yuvrajmaharshi.201@gmail.com

Abstract:
Targeted radiopharmaceutical therapy has gained considerable traction as a cutting-edge modality in the oncologic therapeutic landscape. The strategic identification and exploitation of novel molecular targets—such as tumour-associated antigens, upregulated transmembrane receptors, and specific intracellular biomarkers—through the use of monoclonal antibodies, receptor-binding peptides, or engineered small molecules have significantly broadened the therapeutic reach and precision of radiopharmaceutical interventions. Notably, alpha-particle-emitting radionuclides have garnered increasing attention due to their superior radiobiological properties, including high linear energy transfer (LET) and minimal tissue penetration range. These characteristics confer enhanced tumoricidal efficacy while minimizing off-target cytotoxicity to surrounding healthy tissue. This review delineates the recent progress in the discovery and validation of innovative molecular targets for radiopharmaceutical therapy and highlights emerging clinical and preclinical applications of alpha emitters in the context of highly selective cancer treatment.

Keywords: Alpha Emitter, Theragnostic, Radiopharmaceutical Therapy, Molecular Imaging and Therapy.

Introduction:

Radiopharmaceutical therapy (RPT) originated from the foundational discovery of radioactivity by Henri Becquerel in 1896, followed by the seminal contributions of Marie and Pierre Curie.[1] Initial applications of radioactive elements in medicine were largely diagnostic; however, it was not until the mid-20th century that RPT began to gain recognition as a viable therapeutic modality in oncology. Mechanistically, RPT functions by delivering systemically administered radionuclides that induce DNA damage and subsequent cellular apoptosis through α- or β-particle emissions. The first instance of targeted radionuclide therapy occurred in 1941, with the administration of radioactive iodine for thyroid disease,[1] catalysing subsequent exploration of isotope-based strategies for selective tumour cytotoxicity while sparing normal tissue.

The 1950s marked significant strides in radiopharmaceutical development, particularly with the emergence of radiolabelled agents for both diagnostic imaging and therapy. However, achieving

tumour-specific targeting remained a formidable barrier, limiting broader clinical translation. Iodine-based therapies initially dominated due to the inherent biological compatibility between iodide and the sodium-iodide symporter, a naturally expressed thyroid membrane protein.[2-3] In contrast, contemporary RPT has evolved with advances in chelation chemistry, enabling flexible conjugation of targeting vectors with various radionuclides and facilitating rational design strategies for tumour-specific delivery.

This evolution is exemplified by the clinical success of agents such as ^{177}Lu-DOTATATE, approved for the treatment of neuroendocrine tumours, and ^{177}Lu-PSMA-617, which has demonstrated efficacy in metastatic castration-resistant prostate cancer (mCRPC). These developments have expanded the therapeutic landscape and prompted investigations into earlier-stage indications. Market analyses project that the global RPT sector will grow at a compound annual growth rate of up to 20%, reaching an estimated valuation of $13.07 billion by 2030.[4-6]

Despite these advances, RPT continues to face several critical challenges. From a logistical perspective, obstacles include radionuclide production and supply chain limitations, workforce shortages, and evolving regulatory frameworks. Biologically, concerns persist regarding incomplete tumour cell eradication, off-target toxicity, heterogeneous tumour receptor expression, suboptimal delivery kinetics, and differential radiosensitivity. The therapeutic efficacy of RPT is ultimately governed by both the physical decay characteristics of the radionuclide and the pharmacodynamic behaviour of the targeting ligand.[7]

To overcome these limitations, ongoing research is focusing on the identification of novel molecular targets, development of innovative targeting vectors, and utilization of next-generation α-emitting radionuclides. Strategies to protect non-tumour tissues from collateral radiation damage are also being actively explored. Collectively, these innovations aim to enhance the selectivity, potency, and safety profile of RPT, ensuring its continued evolution as a cornerstone of personalized oncology.[8]

Novel Targets

Currently, several FDA-approved radiopharmaceutical therapy (RPT) agents are integrated into standard clinical practice, including These agents have demonstrated clinical efficacy across various malignancies.[9] However, the therapeutic landscape has also witnessed the decline or discontinuation of earlier agents that, while initially beneficial, were ultimately superseded by more efficacious therapies or encountered insurmountable barriers in production, logistical distribution, or clinical adoption. [10]

Although advancements such as personalized dosimetry and combinatorial therapeutic strategies hold promise for optimizing the use of currently approved RPT agents, there remains an urgent need to develop novel therapeutics. This need is especially pronounced in the context of tumour types not addressed by existing therapies, as well as the significant intra- and inter-tumoral

heterogeneity that limits the uniform efficacy of single-agent interventions. One emerging paradigm is 'cocktail' RPT, which involves the simultaneous use of multiple agents or radionuclides to engage distinct molecular targets or biological pathways, thereby enhancing therapeutic coverage and efficacy.[11-15]

While a comprehensive enumeration of emerging agents under preclinical evaluation is beyond the scope of this review, we highlight a selection of clinically advanced RPT candidates that are directed against promising molecular targets. Although this discussion primarily centres on the target biology, it is critical to recognize the diversity of vector platforms—including small molecules, peptides, minibodies, and full-length antibodies—each of which possesses distinct pharmacokinetic and biodistribution profiles that influence clinical applicability. A detailed comparison of these vector classes and their physicochemical characteristics, though important, is also outside the purview of this manuscript.[16]

FAP:

Fibroblast Activation Protein (FAP) is a membrane-bound serine protease that is markedly overexpressed in more than 90% of epithelial-derived malignancies as well as in various sarcomas. Under physiological conditions, FAP expression is minimal or virtually absent in most normal adult tissues. In the tumour microenvironment, however, its overexpression is predominantly attributed to its abundant presence on cancer-associated fibroblasts (CAFs), though in a subset of neoplasms, tumour cells themselves may also express FAP. Neoplastic lesions exceeding 1–2 mm in diameter require stromal support, which often constitutes a substantial portion of the tumour mass. Notably, elevated FAP expression has been correlated with unfavourable clinical outcomes across multiple solid tumour types.[17] This widespread overexpression across histological subtypes has positioned FAP as a compelling target for the development of tumour-agnostic theragnostic agents, generating significant interest in its potential as a pan-cancer molecular target. Among the malignancies garnering the most attention for FAP-directed interventions are pancreatic carcinoma, soft tissue sarcoma (STS), non-small cell lung cancer (NSCLC), and head and neck squamous cell carcinoma (HNSCC).[18]

The development of FAP-targeted radioligands, particularly those labelled with ^{68}Ga, has yielded highly encouraging imaging results, characterized by exceptionally high tumour-to-background contrast. For example, uptake of ^{68}Ga-FAPI-04 has been particularly prominent in sarcoma, NSCLC, breast, and esophageal cancers, whereas relatively lower uptake has been reported in renal cell carcinoma, differentiated thyroid carcinoma, and gastric cancer.[20] Nevertheless, increased FAP expression has also been observed in certain non-malignant conditions such as inflammation, fibrosis, and post-traumatic tissue remodelling, presenting a potential diagnostic confounder for oncologic theragnostic but also suggesting utility in non-oncologic imaging applications.[21]

Soft tissue sarcoma (STS) represents a particularly attractive indication for FAP-targeted radiopharmaceutical therapy, given the heterogeneity inherent to this disease group and the potential for sufficient radiopharmaceutical accumulation to overcome intrinsic radio resistance. The use of DOTA-chelated FAP ligands enhances their versatility by enabling labelling not only with ^{68}Ga for diagnostic imaging, but also with therapeutic isotopes such as ^{177}Lu, ^{90}Y, and ^{225}Ac, facilitating their application in theragnostic regimens.[22]

Several FAP-targeting compounds are currently under clinical investigation. Among the most well-characterized are ^{68}Ga-FAPI-04 (developed by the University of Heidelberg and licensed to SOFIE Biosciences) and the theragnostic pair FAPI-2286, radiolabelled with either ^{68}Ga or ^{177}Lu (licensed to Novartis Pharmaceuticals).[23] While early clinical findings have been promising, the available efficacy data remain preliminary and, at times, heterogeneous. In a Phase I study by Baum et al., FAPI-2286—which exhibits superior tumour retention compared to earlier generations such as FAPI-02 and FAPI-04—was administered at 5.8 GBq per cycle for up to three treatment cycles in 11 patients with advanced pancreatic, breast, rectal, or ovarian cancers. The mean tumour-absorbed dose was approximately 3 Gy/GBq, and the treatment was well-tolerated with minimal high-grade toxicity. Two patients achieved stable disease at 6–8 weeks post-therapy, supporting further clinical development. This has led to the ongoing Phase 1/2 LuMIERE trial (NCT04939610), evaluating ^{177}Lu-FAPI-2286 in a broader cohort of patients with advanced solid tumours.[24]

Another investigational agent, PNT6555 (developed by Point Biopharma), is being evaluated in the FRONTIER clinical trial (NCT05432193). This molecule consists of a DOTA-chelated FAP-targeting moiety (Bz-D-Ala-boroPro) linked via an aminomethyl spacer. Although preclinical data demonstrated robust tumour uptake and therapeutic efficacy with a favourable toxicity profile, the Phase I study revealed insufficient tumour accumulation in human subjects to warrant progression to Phase II efficacy trials.[25]

These findings collectively underscore both the tremendous potential and ongoing challenges in FAP-targeted radiopharmaceutical development. While current FAP-based agents exhibit strong diagnostic capabilities, improvements in molecular design—particularly in enhancing tumour retention and absorbed radiation dose—are imperative to fully realize their therapeutic potential and establish FAP-targeted RPT as a cornerstone of tumour-agnostic cancer care.[26]

GRPr:

Gastrin-releasing peptide (GRP), a mammalian analogue of bombesin, exerts its biological effects through the gastrin-releasing peptide receptor (GRPr), which is expressed predominantly in the central nervous system and gastrointestinal tract. GRPr, a G-protein-coupled receptor localized on the cell surface, is notably overexpressed in several malignancies, most prominently in prostate and breast cancers, and is implicated in processes related to tumorigenesis and

cellular motility.[27] In contrast, its expression in healthy adult tissues is relatively low, with the exception of certain lymphoid structures and select enteric tissues, such as the pancreas. Importantly, GRPr antagonists have demonstrated more favourable tolerability profiles than agonists, prompting their preferential development, primarily in the form of radiolabelled peptides.[28]

Given GRPr's elevated expression in various tumours, low physiological distribution in non-malignant tissues, and the feasibility of peptide-based targeting via DOTA-chelated theragnostic pairs, GRPr-directed molecular imaging and therapy has emerged as a highly promising strategy. These peptides are particularly attractive due to their rapid tumour uptake and clearance, low immunogenic potential, and streamlined synthetic and radiolabelling protocols.[29]

The clinical utility of GRPr-targeting agents is particularly relevant in the context of tumour heterogeneity. For instance, approximately 15–20% of patients with metastatic castration-resistant prostate cancer (mCRPC) do not express prostate-specific membrane antigen (PSMA), creating a compelling rationale for complementary targets such as GRPr. Multiple imaging studies have affirmed the diagnostic potential of GRPr-targeting radioligands, especially in prostate cancer. Notably, Touijer *et al.* conducted a prospective clinical trial in patients with untreated localized prostate cancer undergoing radical prostatectomy, where ^{68}Ga-RM2 PET/MRI demonstrated an 89% concordance with final histopathologic analysis.[30]

In breast cancer, GRPr expression correlates strongly with hormone receptor–positive (HR^+) subtypes, with reported positivity rates ranging between 93% and 100% in certain cohorts. These findings have spurred the initiation of multiple tumour-specific and basket-design theranostic trials to exploit GRPr overexpression. Among these is the NeoRay trial, a multi-center, open-label Phase I/II study evaluating the safety and antitumor activity of ^{177}Lu-NeoB, a GRPr-targeted peptide developed by Advanced Accelerator Applications (Novartis), administered at six-week intervals in patients with advanced solid tumours (NCT03872778). The agent demonstrated primarily renal clearance, minimal uptake in radiosensitive organs like the pancreas and bone marrow, and favourable toxicity profiles at doses of 150–250 MBq per administration. At the highest tested cumulative dose (11.1 GBq over 6 cycles), the renal absorbed dose was approximately 7.8 Gy, with a tumour dose exceeding 56 Gy, underscoring its therapeutic promise.

In breast cancer, ^{177}Lu-NeoB is also being assessed in a Phase Ib trial (NCT05870579) in combination with ribociclib (a CDK4/6 inhibitor) and fulvestrant (an anti-estrogen agent), with dose escalation ranging from 100 to 250 mCi per cycle. For mCRPC patients who are ineligible for ^{177}Lu-PSMA-617 therapy, the COMBAT trial (NCT05633160) is investigating a theranostic pair, ^{64}Cu-SAR-BBN/^{67}Cu-SAR-BBN, developed by Clarity Pharmaceuticals, as a potential therapeutic alternative.

Beyond β-emitters like ^{177}Lu, α-emitting GRPr ligands are also under active investigation. One such agent, ^{212}Pb-DOTAM-GRPR1, is being evaluated in a Phase I dose-escalation study (NCT05283330) in patients with GRPr-expressing advanced or recurrent solid tumours, including mCRPC, HR^+ breast cancer, colorectal cancer, cervical cancer, cutaneous melanoma, and NSCLC. In this study, patients are being administered 5.5 mCi per cycle, with a total cumulative dose of up to 24 mCi across four cycles. Preliminary safety and biodistribution data are awaited to determine clinical progression.

Collectively, these investigations highlight the expanding therapeutic landscape of GRPr-targeted theragnostic. While clinical results are still emerging, these agents represent a valuable option for patients whose tumours lack PSMA expression or who are not eligible for existing molecular radiotherapies. Notably, GRPr-targeting agents do not significantly accumulate in salivary glands, a distinct advantage over PSMA-targeted α-emitters, which are often limited by dose-dependent xerostomia, thus enhancing their suitability for long-term therapeutic use.

CA-IX:

Carbonic anhydrase IX (CA-IX) is a transmembrane glycoprotein whose expression is markedly upregulated in response to hypoxic tumour microenvironments, where it plays a critical role in pH regulation through modulation of extracellular acidity. Its activity is closely linked to the hypoxia-inducible factor 1-alpha (HIF-1α) signalling axis, and CA-IX expression has been shown to enhance tumour growth, invasion, and metastatic potential, in part through its influence on cancer stem cell biology. While CA-IX expression is generally restricted to the small intestine under physiological conditions, it is aberrantly overexpressed in a wide range of malignancies, including renal cell carcinoma (RCC), breast, colon, lung, cervical, and head and neck cancers.[31]

A notable exception to its hypoxia-dependent expression is observed in clear cell RCC, where CA-IX upregulation occurs via HIF-1α stabilization resulting from inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene, independent of classical hypoxic stimuli. This tumour-specific regulatory mechanism renders CA-IX a particularly attractive target for theranostic strategies in clear cell RCC. Moreover, CA-IX-directed therapies may yield enhanced therapeutic outcomes when combined with cytotoxic or immune-based agents, especially in cancers where CA-IX expression is limited to hypoxic tumour niches.

Among the most extensively studied CA-IX-targeting agents is girentuximab (cG250), a monoclonal antibody with high affinity for the CA-IX epitope. Early clinical characterization utilized ^{124}I-girentuximab as a PET radiotracer to quantify uptake in renal tumors. In a Phase II clinical trial, Muselaers *et al.* evaluated ^{177}Lu-girentuximab in patients with advanced metastatic clear cell RCC, administering an initial dose of 2405 MBq/m², with a second reduced dose contingent on tolerance and disease stability. Stable disease was observed in 9 of 14 patients,

although the majority experienced Grade 3–4 myelotoxicity, underscoring the need for further optimization of therapeutic regimens.[26]

Ongoing clinical trials continue to investigate the therapeutic potential of CA-IX-targeted radionuclide therapies, including combinatorial regimens. The STARLITE-1 (NCT05663710) and STARLITE-2 (NCT05239533) trials are evaluating ^{177}Lu-girentuximab in combination with cabozantinib and nivolumab, and nivolumab alone, respectively, in patients with CA-IX-positive RCC. Additionally, the Phase Ib STARSTRUCK trial (NCT05868174) explores synergy between ^{177}Lu-girentuximab and peposertib, a DNA-dependent protein kinase (DNA-PK) inhibitor, which may potentiate DNA damage induced by radiotherapy.

Beyond antibody-based approaches, small-molecule and peptidomimetic agents are also under active investigation. The GaLuCi trial (Phase 1b/2, NCT05706129) is assessing the safety and efficacy of a novel peptidomimetic CA-IX-targeted theranostic pair, ^{177}Lu/^{68}Ga-DPI-4452. Preliminary imaging data demonstrated exceptionally high tumour-to-background uptake ratios in patients with clear cell RCC, with mean SUVmax values reaching 64.6, and 17 out of 36 metastatic lesions detected by ^{68}Ga-DPI-4452 PET that were missed on conventional contrast-enhanced CT, highlighting its diagnostic superiority and significant potential for therapeutic translation.[31]

Alpha Therapies

While the majority of currently approved radiopharmaceutical therapies (RPTs) utilize β-emitting radionuclides, there is growing interest in the application of α-particle emitters, driven by their unique radiobiological and physical properties. Alpha emitters are particularly attractive due to their exceptionally high linear energy transfer (LET)—ranging from 50 to 230 keV/μm—which facilitates the induction of clustered, irreparable double-strand DNA breaks, thereby enhancing cytotoxic efficacy. Their extremely short tissue penetration range (approximately 50–100 μm) also offers a significant advantage in minimizing off-target damage to adjacent healthy tissues.

In contrast, β-particles have a significantly lower LET (~0.2 keV/μm), produce primarily single-strand DNA breaks (which are often repairable), and exhibit longer path lengths (1,000–10,000 μm), making them more suitable for treating larger or less well-targeted tumours through the crossfire effect—a phenomenon whereby ionizing radiation reaches adjacent, antigen-negative tumour cells. This contributes to the therapeutic effectiveness of β-emitting agents in heterogeneous tumour environments.

Importantly, α-emitters may exhibit enhanced bystander and immunomodulatory effects, potentially activating immune pathways that contribute to tumour eradication. Their cytotoxic efficacy under hypoxic conditions is also advantageous, as the DNA damage induced by α

particles is less reliant on reactive oxygen species, rendering them less sensitive to the hypoxic microenvironments that often confer resistance to other modalities.

Additionally, some α-emitting radionuclides serve as in vivo α-particle generators through multi-step decay chains that release multiple α particles. For instance, ^{225}Ac (Actinium-225) emits four α particles during its decay to stable ^{209}Pb, offering substantial therapeutic payload per decay event.[27] However, this decay cascade also raises concerns regarding the redistribution of daughter radionuclides, which may result in unintended radiotoxicity to non-target organs. Consequently, strategies to retain radioactive daughters within the tumour microenvironment or minimize their systemic dissemination are essential for optimizing the therapeutic index of α-based therapies.

Conclusion:

The field of radiopharmaceutical therapy (RPT) is undergoing rapid evolution, with the emergence of novel molecular targets and innovative radionuclides aimed at optimizing the therapeutic index. While demonstrating the clinical efficacy of these next-generation agents remains an immediate priority, substantial opportunities also exist to enhance the effectiveness of currently approved therapies through more refined approaches. Recent approvals such as ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 have been based on fixed-activity dosing regimens, administered irrespective of individual tumour burden, lesion-specific absorbed dose, or intrinsic radiosensitivity. Although operationally straightforward, this uniform dosing model neglects the rich information provided by diagnostic theragnostic imaging, which could be leveraged to personalize therapy. Specifically, radiotracer uptake data can inform tumour dosimetry and guide treatment adaptation based on biological heterogeneity and responsiveness.

Early intervention with theranostic agents—prior to tumour dedifferentiation or the development of clonal resistance—may yield superior outcomes, particularly when tumour biology is still conducive to radioligand binding. Additionally, combination strategies involving RPT and complementary therapeutic modalities such as DNA damage response inhibitors (e.g., PARP inhibitors), immune checkpoint inhibitors, cytotoxic chemotherapy, external beam radiation, or agents modulating target expression, hold promise in amplifying cytotoxic effects. These combinations can enhance efficacy either by increasing target density, altering radiosensitivity, or stimulating immunologic priming of the tumour microenvironment. It is important to underscore that, while there is conceptual overlap between RPT and external beam radiotherapy, the two modalities are governed by distinct biological and pharmacokinetic principles. RPT is influenced by factors such as ligand pharmacodynamics, biological half-life, and tumour-specific uptake kinetics, necessitating a separate framework for optimization and study. For instance, preclinical evidence suggests that low-dose RPT may convert immunologically “cold” tumours into immunogenic phenotypes, thereby sensitizing them to immunotherapy.

The implementation of personalized dosimetry represents a transformative advancement, enabling dose escalation for refractory tumours or dose de-escalation in sensitive malignancies, potentially minimizing toxicity. However, robust clinical data are still required to validate this approach, standardize protocols, and facilitate its integration into routine clinical practice.

References:

1. Ballal S, Yadav MP, Bal C, Sahoo RK, Tripathi M. Broadening horizons with 225Ac-DOTATATE targeted alpha therapy for gastroenteropancreatic neuroendocrine tumour patients stable or refractory to 177Lu-DOTATATE PRRT: first clinical experience on the efficacy and safety. Eur J Nucl Med Mol Imaging 2020;47(4):934–46.
2. Baum RP, Schuchardt C, Singh A, *et al.* Feasibility, Biodistribution, and Preliminary Dosimetry in Peptide-Targeted Radionuclide Therapy of Diverse Adenocarcinomas Using ¹⁷⁷Lu-FAP-2286: First-in-Humans Results. Journal of Nuclear Medicine 2022;63(3):415.
3. Bodei L, Herrmann K, Schöder H, Scott AM, Lewis JS. Radiotheranostics in oncology: current challenges and emerging opportunities. Nat Rev Clin Oncol 2022;19(8):534–50.
4. Bodei L, Kavan P, Liberman M, *et al.* Frontier: FAPi radioligand open-label, phase 1 study to evaluate safety, tolerability and dosimetry of [Lu-177]-PNT6555—A dose escalation study for treatment of patients with select solid tumors. Journal of Clinical Oncology 2023;41(16_suppl):TPS3161–TPS3161.
5. Bodei L, Michael Tuttle R, Grewal RK, *et al.* Toward individualized dosimetry for radiopharmaceutical therapy in day-to-day clinical practice of nuclear oncology: overcoming heterogeneity of radiation-absorbed dose to tumor and critical organs. Eur J Nucl Med Mol Imaging 2024;51(2):325–9.
6. Bodei L, Raj N, Do RK, *et al.* Interim Analysis of a Prospective Validation of 2 Blood-Based Genomic Assessments (PPQ and NETest) to Determine the Clinical Efficacy of ¹⁷⁷Lu-DOTATATE in Neuroendocrine Tumors. Journal of Nuclear Medicine 2023;64(4):567.
7. Brugarolas P, Comstock J, Dick DW, *et al.* Fifty Years of Radiopharmaceuticals. J Nucl Med Technol 2020;48(Supplement 1):34S.
8. D'Onofrio A, Engelbrecht S, Läppchen T, Rominger A, Gourni E. GRPR-targeting radiotheranostics for breast cancer management. Front Med (Lausanne) 2023;10.
9. Davidson B, Goldberg I, Kopolovic J. Inflammatory Response in CervicalIntraepithelial Neoplasia and Squamous Cell Carcinoma of the Uterine Cervix. Pathol Res Pract 1997;193(7):491–5.

10. Dumont RA, Tamma M, Braun F, *et al.* Targeted Radiotherapy of Prostate Cancer with a Gastrin-Releasing Peptide Receptor Antagonist Is Effective as Monotherapy and in Combination with Rapamycin. Journal of Nuclear Medicine 2013;jnumed.112.112169.
11. Feuerecker B, Tauber R, Knorr K, *et al.* Activity and Adverse Events of Actinium-225-PSMA-617 in Advanced Metastatic Castration-resistant Prostate Cancer After Failure of Lutetium-177-PSMA. Eur Urol 2021;79(3):343–50.
12. King AP, Lin FI, Escorcia FE. Why bother with alpha particles? Eur J Nucl Med Mol Imaging 2021;49(1):7–17.
13. Kratochwil C, Flechsig P, Lindner T, *et al.* ⁶⁸Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. Journal of Nuclear Medicine 2019;60(6):801.
14. Lai LT, *et al.* Tumor Therapy with Targeted Atomic Nanogenerators. Science (1979) 2001;294(5546):1537–40.
15. Lau J, Lin K-S, Bénard F. Past, Present, and Future: Development of Theranostic Agents Targeting Carbonic Anhydrase IX. Theranostics 2017;7(17):4322–39.
16. McDevitt MR, Finn RD, Ma D, Larson SM, Scheinberg DA. Preparation of α-Emitting ²¹³Bi-Labeled Antibody Constructs for Clinical Use. Journal of Nuclear Medicine 1999;40(10):1722.
17. Muselaers CHJ, Boers-Sonderen MJ, van Oostenbrugge TJ, *et al.* Phase 2 Study of Lutetium 177–Labeled Anti–Carbonic Anhydrase IX Monoclonal Antibody Girentuximab in Patients with Advanced Renal Cell Carcinoma. Eur Urol 2016;69(5):767–70.
18. Nakaya A, Qiu H, Santos EB, *et al.* Addition of Astatine-211-Labeled Anti-CD45 Antibody to TBI as Conditioning for DLA-Identical Marrow Transplantation: A Novel Strategy to Overcome Graft Rejection in a Canine Presensitization Model: "Radioimmunotherapy to Overcome Transfusion-Induced Sensitization". Transplant Cell Ther 2021;27(6):476.e1–476.e7.
19. Ostuni E, Taylor MRG. Commercial and business aspects of alpha radioligand therapeutics. Front Med (Lausanne) 2023;9.
20. Pallares RM, Abergel RJ. Development of radiopharmaceuticals for targeted alpha therapy: Where do we stand? Front Med (Lausanne) 2022;9.
21. Parker C, Nilsson S, Heinrich D, *et al.* Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. New England Journal of Medicine 2013;369(3):213–23.
22. Pryma DA, O'Donoghue JA, Humm JL, *et al.* Correlation of in vivo and in vitro measures of carbonic anhydrase IX antigen expression in renal masses using antibody 124I-cG250. J Nucl Med 2011;52(4):535–40.

23. Puré E, Blomberg R. Pro-tumorigenic roles of fibroblast activation protein in cancer: back to the basics. Oncogene 2018;37(32):4343–57.
24. Robertsa. Radioactive Iodine in the Study of Thyroid Physiology: VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism. J Am Med Assoc 1946;131(2):81–6.
25. Rugo HS, Van Poznak CH, Neven P, *et al.* Radium-223 in women with hormone receptor-positive bone-metastatic breast cancer receiving endocrine therapy: pooled analysis of two international, phase 2, randomized, double-blind, placebo-controlled trials. Breast Cancer Res Treat 2023;
26. Salerno KE, Roy S, Ribaudo C, *et al.* A Primer on Radiopharmaceutical Therapy. International Journal of Radiation Oncology*Biology*Physics 2023;115(1):48–59.
27. Sartor O, de Bono J, Chi KN, *et al.* Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. New England Journal of Medicine 2021;385(12):1091–103.
28. Sidrak MMA, De Feo MS, Corica F, *et al.* Fibroblast Activation Protein Inhibitor (FAPI)-Based Theranostics-Where We Are at and Where We Are Heading: A Systematic Review. Int J Mol Sci 2023;24(4).
29. Stoykow C, Erbes T, Maecke HR, *et al.* Gastrin-releasing Peptide Receptor Imaging in Breast Cancer Using the Receptor Antagonist ^{68}Ga-RM2 And PET. Theranostics 2016;6(10):1641–50.
30. Strosberg J, El-Haddad G, Wolin E, *et al.* Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. New England Journal of Medicine 2017;376(2):125–35.
31. Touijer KA, Michaud L, Alvarez HAV, *et al.* Prospective Study of the Radiolabeled GRPR Antagonist BAY86-7548 for Positron Emission Tomography/Computed Tomography Imaging of Newly Diagnosed Prostate Cancer. Eur Urol Oncol 2019;2(2):166–73.
32. Zalutsky MR, Reardon DA, Akabani G, *et al.* Clinical experience with alpha-particle emitting 211At: treatment of recurrent brain tumor patients with 211At-labeled chimeric antitenascin monoclonal antibody 81C6. J Nucl Med 2008;49(1):30–8.
33. Zhang J, Wang H, Jacobson O, *et al.* Safety, Pharmacokinetics, and Dosimetry of a Long-Acting Radiolabeled Somatostatin Analog DOTA-EB-TATE in Patients with Advanced Metastatic Neuroendocrine Tumors. Journal of Nuclear Medicine 2018;59(11):1699.
34. Zhao L, Chen J, Pang Y, *et al.* Fibroblast activation protein-based theranostics in cancer research: A state-of-the-art review. Theranostics 2022;12(4):1557–69.

HERBAL PLANTS AND THEIR ROLE IN PREVENTING RHEUMATOID ARTHRITIS

Sunil Kardani*, Ghanshyam Parmar, Sunil Baile, Hadia Rajesh
Department of Pharmacy,
Sumandeep Vidyapeeth Deemed to be University, Vadodara-391760, Gujarat
*Corresponding author E-mail: sunilkardani@yahoo.co.in

Abstract:
Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder that primarily affects the joints, leading to pain, stiffness, and progressive joint damage. Despite advances in disease-modifying antirheumatic drugs (DMARDs) and biologics, many patients experience inadequate responses or adverse effects. Herbal medicines have long been used in traditional systems to alleviate arthritis symptoms. This review summarizes scientific evidence for seven herbal plants-ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), *Boswellia serrata*, willow bark (*Salix alba*), *Commiphora mukul*, devil's claw (*Harpagophytum procumbens*), and feverfew (*Tanacetum parthenium*)-highlighting their phytochemistry, mechanisms of action, preclinical and clinical evidence in RA management. These herbs demonstrate anti-inflammatory, antioxidant, and immunomodulatory effects, suggesting their potential as adjuncts to conventional therapies.

Keywords: Rheumatoid Arthritis, Herbal Medicines, Anti-Inflammatory

Introduction:

Rheumatoid arthritis (RA) is an autoimmune, systemic inflammatory disease characterized by synovial hyperplasia, joint destruction, and systemic complications. It affects about 0.5–1% of adults globally, with a higher prevalence in women. The pathogenesis of RA involves activation of immune cells, release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), and production of reactive oxygen species (ROS), leading to chronic inflammation and joint erosion.

Current pharmacological treatments include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic DMARDs (like methotrexate), and biologic agents (e.g., TNF inhibitors). While effective, these drugs are associated with significant side effects, including immunosuppression, liver toxicity, and increased infection risk.

Consequently, there is growing interest in complementary and alternative therapies, particularly herbal remedies, which have been used for centuries in Ayurvedic, Chinese, and Western herbal medicine to treat arthritis and related disorders. This review evaluates the scientific evidence supporting the efficacy of seven herbs commonly used for RA.

1. Ginger (*Zingiber officinale*)

Ginger, derived from the rhizome of *Zingiber officinale*, has been used for centuries in traditional medicine to treat inflammatory conditions, including arthritis. The bioactive compounds responsible for its therapeutic effects include gingerols, shogaols, paradols, and zingerone. These phytochemicals exhibit anti-inflammatory, antioxidant, and immunomodulatory activities that may alleviate RA symptoms.

Ginger's anti-arthritic activity is attributed to its ability to inhibit inflammatory pathways:

- Suppression of nuclear factor-kappa B (NF-κB), thereby reducing transcription of pro-inflammatory genes [1].
- Inhibition of cyclooxygenase (COX-1 and COX-2) and lipoxygenase (LOX), which decreases prostaglandin and leukotriene production [2].
- Reduction in production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [3].
- Scavenging reactive oxygen species (ROS) and enhancing antioxidant defenses [4].

These actions collectively reduce synovial inflammation, cartilage degradation, and pain associated with RA.

In experimental arthritis models, ginger has shown promising results.

- Funk et al. reported that ginger extract reduced paw swelling, decreased leukocyte infiltration, and preserved cartilage in collagen-induced arthritis in rats [5].
- Grzanna et al. demonstrated suppression of prostaglandin E2 production and inhibition of synoviocyte proliferation in vitro [6].

Several clinical trials and meta-analyses have investigated ginger's effects on joint diseases, including RA and osteoarthritis.

- Bartels et al. conducted a meta-analysis of randomized controlled trials (RCTs) and found ginger significantly reduced pain and disability in osteoarthritis [7].
- Another trial in RA patients by Srivastava and Mustafa found significant reductions in joint swelling and pain after 3 months of ginger supplementation [8].
- Daily *et al.* reported that ginger alleviated symptoms of primary osteoarthritis, suggesting its utility as an adjunct therapy [9].

Ginger exhibits strong anti-inflammatory, antioxidant, and immunomodulatory activities that mitigate joint inflammation and pain in RA. Preclinical and clinical evidence suggests it may serve as an effective complementary therapy in RA management.

2. Turmeric (*Curcuma longa*)

Turmeric, the rhizome of *Curcuma longa*, is a prominent spice and medicinal herb used widely in Ayurveda and Traditional Chinese Medicine. Its therapeutic properties are primarily attributed to its polyphenolic compound curcumin, which constitutes 2–5% of turmeric powder. Curcumin

has potent anti-inflammatory, antioxidant, and immunomodulatory properties relevant to the management of RA.

Curcumin mitigates RA-related inflammation by targeting multiple molecular pathways:

- Inhibition of nuclear factor-kappa B (NF-κB), reducing transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) [10].
- Downregulation of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), lowering prostaglandins and nitric oxide [11].
- Suppression of Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, which contributes to RA pathogenesis [12].
- Antioxidant effects via neutralization of reactive oxygen species (ROS) and induction of endogenous antioxidant enzymes [13].

These mechanisms lead to reduced synovial inflammation, cartilage destruction, and bone erosion.

Numerous animal studies have supported the use of curcumin in arthritis models:

- Funk *et al.* demonstrated that curcumin significantly suppressed joint inflammation, decreased pannus formation, and prevented bone destruction in collagen-induced arthritis (CIA) mice [14].
- Another study showed curcumin attenuated serum cytokine levels and prevented cartilage damage in adjuvant-induced arthritis rats [15].

Clinical trials and meta-analyses have corroborated preclinical findings:

- Chandran & Goel conducted a pilot randomized controlled trial (RCT) comparing curcumin (500 mg twice daily), diclofenac, and their combination in RA patients. The curcumin-only group had the greatest reduction in Disease Activity Score (DAS28) and was well tolerated [16].
- Daily *et al.* performed a systematic review and meta-analysis of RCTs, concluding that turmeric extracts and curcumin significantly reduced pain and improved joint function in arthritis [17].
- A study by Amalraj *et al.* demonstrated that bioavailable forms of curcumin improved clinical symptoms and reduced inflammatory markers in RA patients [18].

Curcumin effectively targets the molecular pathways underlying RA, providing pain relief, reducing inflammation, and improving joint function. It is well tolerated with a favorable safety profile, making it a promising adjunct therapy for RA management.

3. *Boswellia serrata*

Boswellia serrata, also known as Indian frankincense, is a tree native to India and the Middle East. The gum resin of *Boswellia serrata* has been used in Ayurvedic medicine for centuries to

treat inflammatory diseases such as arthritis. Its active constituents are boswellic acids, which exhibit potent anti-inflammatory and anti-arthritic effects.

Boswellic acids modulate inflammation and immune response through several pathways:

- Inhibition of 5-lipoxygenase (5-LOX) enzyme, thereby suppressing leukotriene synthesis, which contributes to joint inflammation in RA [19].
- Downregulation of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 [20].
- Prevention of matrix metalloproteinases (MMPs)-induced cartilage degradation [21].
- Reduction of oxidative stress and reactive oxygen species (ROS) in synovial tissues [22].

These effects result in decreased synovial hyperplasia, cartilage damage, and inflammatory cell infiltration.

Animal models have provided strong support for Boswellia's anti-arthritic activity:

- Sharma *et al.* demonstrated that Boswellia extract significantly reduced paw swelling, improved mobility, and suppressed inflammatory mediators in adjuvant-induced arthritis rats [23].
- In collagen-induced arthritis mice, boswellic acids reduced arthritis severity and protected joint integrity [24].

Numerous randomized controlled trials (RCTs) have evaluated *Boswellia serrata* in patients with arthritis:

- Kimmatkar *et al.* conducted an RCT in osteoarthritis patients, reporting significant improvement in knee pain, stiffness, and joint function after Boswellia extract (333 mg thrice daily) for 8 weeks, compared to placebo [25].
- Sengupta *et al.* tested a standardized extract of Boswellia (5-Loxin®) in osteoarthritis patients and observed reduced pain and improved physical function as early as 7 days, with a favorable safety profile [26].
- A review by Ammon highlighted that Boswellia also benefits RA patients by reducing synovitis and inflammatory markers [27].

Although most clinical studies focus on osteoarthritis, the mechanisms involved—particularly the inhibition of 5-LOX and cytokines—are highly relevant to RA.

Boswellia is generally well tolerated, with mild gastrointestinal side effects reported in a minority of patients. It has been proposed as a safer alternative or adjunct to NSAIDs in managing inflammatory joint diseases.

Boswellia serrata has significant anti-inflammatory and cartilage-protective effects that make it an attractive complementary therapy for RA. Its ability to inhibit leukotrienes and cytokines while preserving joint integrity is supported by both preclinical and clinical evidence.

4. Willow Bark (*Salix alba*)

Willow bark, derived from the bark of *Salix alba* and other *Salix* species, has been used since antiquity as a natural remedy for pain and inflammation. Its therapeutic effects are attributed to salicin, a β-glucoside of salicylic alcohol, which is metabolized in the body to salicylic acid — a precursor to aspirin. Other polyphenols and flavonoids in willow bark also contribute to its anti-inflammatory activity.

The anti-arthritic effects of willow bark are primarily mediated by:

- Inhibition of cyclooxygenase (COX-1 and COX-2) enzymes, leading to reduced prostaglandin synthesis and hence diminished inflammation and pain [28].
- Antioxidant activity through scavenging reactive oxygen species (ROS) and reducing oxidative stress in inflamed joints [29].
- Modulation of nuclear factor-kappa B (NF-κB) signaling, which downregulates pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [30].

Several animal studies support the use of willow bark in arthritis:

- Willow bark extract reduced paw edema and arthritis severity in carrageenan- and collagen-induced arthritis models [31].
- In vitro studies demonstrated inhibition of nitric oxide and prostaglandin E2 production by macrophages exposed to inflammatory stimuli [32].

Although most human trials have focused on osteoarthritis and back pain, their findings are relevant to RA because of overlapping inflammatory pathways:

- Chrubasik *et al.* conducted a double-blind RCT showing that 240 mg/day of salicin from willow bark extract significantly reduced osteoarthritis-related pain compared to placebo [33].
- Biegert *et al.* demonstrated comparable pain relief between willow bark extract and rofecoxib (a COX-2 inhibitor) in osteoarthritis patients [34].
- A systematic review by Vlachojannis *et al.* concluded that willow bark is effective in reducing musculoskeletal pain and has a favorable safety profile [35].

These findings suggest that willow bark could be beneficial as an adjunct therapy in RA to alleviate pain and inflammation.

Willow bark is generally well tolerated at recommended doses. Gastrointestinal discomfort and hypersensitivity reactions are rare but possible, especially in individuals allergic to aspirin. Unlike synthetic NSAIDs, willow bark seems to have a lower risk of gastric irritation.

Willow bark (*Salix alba*) is an effective natural anti-inflammatory and analgesic agent. By inhibiting COX enzymes and modulating inflammatory pathways, it can reduce pain and inflammation in arthritis, making it a potential complementary therapy for RA.

5. *Commiphora mukul* (Guggul)

Commiphora mukul, commonly known as guggul, is a resin extracted from the bark of the mukul myrrh tree, native to India. Guggul has been used for thousands of years in Ayurveda for its anti-inflammatory, analgesic, and lipid-lowering properties. The principal active components are guggulsterones, along with essential oils, diterpenes, and polysaccharides, which together confer its pharmacological activity [36].

The anti-arthritic and anti-inflammatory effects of guggul are mediated through:

- Inhibition of nuclear factor-kappa B (NF-κB), reducing production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [37].
- Suppression of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, lowering prostaglandins and leukotrienes [38].
- Antioxidant activity by scavenging reactive oxygen species (ROS) and protecting joint tissues from oxidative damage [39].
- Modulation of lipid metabolism, which may indirectly reduce inflammation by decreasing low-density lipoprotein (LDL) levels [40].

Experimental studies have demonstrated significant anti-arthritic activity of guggul:

- Sharma *et al.* reported that guggul extract reduced paw swelling, improved mobility, and suppressed inflammatory cytokines in adjuvant-induced arthritis in rats [41].
- In collagen-induced arthritis models, guggul extract inhibited joint destruction and reduced serum levels of inflammatory mediators [42].

Clinical studies on guggul for arthritis are relatively limited but promising:

- Singh *et al.* conducted an open-label study on osteoarthritis patients, showing that 500 mg guggul extract thrice daily for one month led to significant reductions in pain, stiffness, and swelling, along with improved joint mobility [43].
- A review by Rastogi *et al.* highlighted its efficacy in treating chronic inflammatory diseases, including arthritis, with good tolerability [44].
- Though most trials focus on osteoarthritis, its mechanisms and preclinical data suggest potential benefits in RA.

Guggul is generally well tolerated at recommended doses, though mild gastrointestinal symptoms and skin rashes have been reported in some individuals [45]. Patients with thyroid disorders should use caution, as guggul can modulate thyroid hormone levels.

Commiphora mukul demonstrates anti-inflammatory, antioxidant, and lipid-lowering effects, making it a valuable adjunct in managing inflammatory joint diseases such as RA. Its historical use and emerging scientific evidence support its potential role in RA management.

6. Devil's Claw (*Harpagophytum procumbens*)

Devil's claw (*Harpagophytum procumbens*), a perennial plant native to southern Africa, derives its name from the hook-like projections on its fruit. The tuberous roots of the plant have been traditionally used to treat pain, fever, and inflammatory disorders. Its therapeutic effects are primarily attributed to iridoid glycosides, notably harpagoside, which exhibits potent anti-inflammatory and analgesic activities [46].

Devil's claw exerts its anti-arthritic effects through several pathways:

- Inhibition of cyclooxygenase (COX-2) and lipoxygenase (LOX), leading to decreased prostaglandin and leukotriene synthesis [47].
- Suppression of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) secretion, both key drivers of RA pathology [48].
- Inhibition of nitric oxide (NO) production in activated macrophages, reducing oxidative damage [49].
- Antioxidant activity that helps protect joint tissues from free radical-induced damage [50].

These actions reduce synovial inflammation, pain, and joint destruction.

Animal and in vitro studies have demonstrated the potential of devil's claw in inflammatory diseases:

- Harpagoside was shown to significantly reduce paw edema and inhibit inflammatory enzymes in carrageenan-induced arthritis models [51].
- In vitro, devil's claw extracts inhibited NO and PGE2 production in lipopolysaccharide-stimulated macrophages [52].

Several clinical trials and systematic reviews have assessed the efficacy of devil's claw in musculoskeletal pain and arthritis:

- Chrubasik *et al.* conducted a randomized controlled trial (RCT) in patients with osteoarthritis of the hip and knee, finding that 2,610 mg/day of devil's claw extract significantly reduced pain and improved mobility [53].
- Another study by Leblan *et al.* showed that devil's claw extract was as effective as diacerhein (an anti-inflammatory drug) in alleviating osteoarthritis symptoms with fewer side effects [54].
- A systematic review by Gagnier *et al.* concluded that there is moderate evidence supporting the use of devil's claw for osteoarthritis and low back pain [55].

While most human studies have focused on osteoarthritis, the anti-inflammatory mechanisms are equally relevant to RA.

Devil's claw is generally well tolerated, with mild gastrointestinal discomfort and allergic reactions reported in a small number of patients [8]. It is considered safer than conventional NSAIDs for long-term use.

Devil's claw (*Harpagophytum procumbens*) exhibits significant anti-inflammatory and analgesic effects by inhibiting inflammatory mediators, making it a promising adjunct in the management of RA. Its iridoid glycosides are particularly effective in suppressing joint inflammation and pain.

7. Feverfew (*Tanacetum parthenium*)

Feverfew (*Tanacetum parthenium*), also known as bachelor's button or featherfew, is a perennial plant from the Asteraceae family, native to southeastern Europe and now widely cultivated. Traditionally, it has been used for centuries to treat fevers, migraines, and inflammatory conditions. The main active constituents are parthenolide and related sesquiterpene lactones, which have demonstrated anti-inflammatory and immunomodulatory properties [56].

Feverfew exerts its anti-arthritic and anti-inflammatory effects by:

- Inhibiting nuclear factor-kappa B (NF-κB), reducing transcription of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [57].
- Blocking the release of arachidonic acid from cell membranes, thereby lowering prostaglandin and leukotriene synthesis [58].
- Inhibiting platelet aggregation, which may help reduce microvascular injury in inflamed joints [59].
- Reducing oxidative stress and protecting synovial and cartilage tissue from free radical damage [60].

These mechanisms collectively suppress the inflammatory response and joint destruction observed in RA.

Several in vitro and animal studies highlight feverfew's potential in inflammatory diseases:

- Rogers *et al.* demonstrated that parthenolide inhibited LPS-induced production of nitric oxide and cytokines in macrophages [61].
- Preclinical models of arthritis have shown that feverfew extract attenuates joint inflammation and protects cartilage from degradation [62].

While clinical studies of feverfew have largely focused on migraines, some evidence supports its role in inflammatory arthritis:

- A pilot study by Pattrick *et al.* explored feverfew in RA patients but reported inconclusive results, likely due to small sample size and variability in extract standardization [63].
- In vitro and animal data strongly suggest a therapeutic role, but more rigorous clinical trials are needed specifically in RA patients.

Nevertheless, its mechanisms of action overlap with those of standard anti-inflammatory drugs, making it a promising adjunctive therapy.

Feverfew is generally safe when used at recommended doses, though mild side effects such as oral ulcers, gastrointestinal discomfort, and allergic reactions have been reported [64]. Long-term use should be monitored, and abrupt discontinuation may cause withdrawal symptoms in some individuals [65].

Feverfew (*Tanacetum parthenium*) has notable anti-inflammatory and antioxidant properties that target key pathways involved in RA. Although high-quality clinical evidence in RA is still emerging, its ability to inhibit NF-κB, cytokine production, and oxidative damage makes it a potential complementary treatment for RA.

References:

1. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol. 2009;41(1):40-59.
2. Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. Med Hypotheses. 1989;29(1):25-28.
3. Thomson M, Al-Qattan KK, Al-Sawan SM, *et al.* The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostaglandins Leukot Essent Fatty Acids. 2002;67(6):475-478.
4. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): a review of recent research. Food Chem Toxicol. 2008;46(2):409-420.
5. Funk JL, Frye JB, Oyarzo JN, *et al.* Anti-arthritic effects and toxicity of the essential oils of turmeric (Curcuma longa L.) and ginger (Zingiber officinale Rosc.) in rats. J Agric Food Chem. 2010;58(16):842-849.
6. Grzanna R, Lindmark L, Frondoza CG. Ginger-an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005;8(2):125-132.
7. Bartels EM, Folmer VN, Bliddal H, *et al.* Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis Cartilage. 2015;23(1):13-21.
8. Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. Med Hypotheses. 1989;29(1):25–28.
9. Daily JW, Yang M, Park S. Efficacy of ginger for alleviating the symptoms of primary osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage. 2015;23(1):13–21. **2**

10. Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. Trends Pharmacol Sci. 2009;30(2):85–94.
11. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev. 2009;14(2):141–153.
12. Jagetia GC, Aggarwal BB. "Spicing up" of the immune system by curcumin. J Clin Immunol. 2007;27(1):19–35.
13. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol. 2007; 595:105–125.
14. Funk JL, Oyarzo JN, Frye JB, *et al.* Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis. J Nat Prod. 2006;69(3):351–355.
15. Banji D, Banji OJ, Dasaroju S, Annamalai AR. Investigation on the antiarthritic activity of curcumin in adjuvant-induced arthritic rats: behavioral and biochemical analysis. Asian Pac J Trop Biomed. 2011;1(2): S63–S69.
16. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res. 2012;26(11):1719–1725.
17. Daily JW, Yang M, Park S. Efficacy of turmeric extracts and curcumin for alleviating arthritis symptoms: a systematic review and meta-analysis. J Med Food. 2016;19(8):717–729.
18. Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives – A review. J Tradit Complement Med. 2017;7(2):205–233. 3
19. Safayhi H, Mack T, Sabieraj J, *et al.* Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. J Pharmacol Exp Ther. 1992;261(3):1143–1146.
20. Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. Curr Med Chem. 2006;13(28):3359–3369.
21. Sengupta K, Alluri KV, Satish AR, *et al.* A double-blind, randomized, placebo-controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. Arthritis Res Ther. 2008;10(4): R85.
22. Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med. 2006;72(12):1100–1116.
23. Sharma ML, Khajuria A, Kaul A, *et al.* Antiarthritic activity of boswellic acids in experimental arthritis. J Ethnopharmacol. 1989;27(1–2):45–55.
24. Gupta I, Gupta V, Parihar A, *et al.* Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, crossover study. Eur J Med Res. 1998;3(11):511–514.

25. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee – a randomized double-blind placebo-controlled trial. Phytomedicine. 2003;10(1):3–7.
26. Sengupta K, Alluri KV, Satish AR, *et al.* A double-blind, randomized, placebo-controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. Arthritis Res Ther. 2008;10(4): R85.
27. Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med. 2006;72(12):1100–1116. 4
28. Shara M, Stohs SJ. Efficacy and safety of white willow bark (*Salix alba*) extracts. Phytother Res. 2015;29(8):1112–1116.
29. Nahrstedt A, Schmidt M, Jäggi R, *et al.* Willow bark extract: the contribution of polyphenols to the overall effect. Wien Med Wochenschr. 2007;157(13–14):348–351.
30. Bittner C, Eichner M, Wölfle U, Schempp CM. Anti-inflammatory effects of willow bark extract in human keratinocytes are associated with suppression of the nuclear factor-kappa B signaling pathway. Acta Derm Venereol. 2014;94(5):537–541.
31. Meier B, Sticher O, Betts TJ. Anti-inflammatory activities of *Salix alba* and *Populus* tremula: an in vitro study. Planta Med. 1989;55(6):577–578.
32. Majeed M, Nagabhushanam K, Gowda S, *et al.* Polyphenolic fraction of willow bark extract exhibits anti-inflammatory effects by inhibiting pro-inflammatory mediators and oxidative stress markers. Mol Cell Biochem. 2015;403(1–2):77–86.
33. Chrubasik S, Eisenberg E, Balan E, *et al.* Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med. 2000;109(1):9–14.
34. Biegert C, Wagner I, Ludtke R, *et al.* Efficacy and safety of willow bark extract in osteoarthritis and rheumatoid arthritis patients: results of a randomized, placebo-controlled, double-blind study. Phytomedicine. 2004;11(6):498–507.
35. Vlachojannis JE, Cameron M, Chrubasik S. A systematic review on the effectiveness of willow bark for musculoskeletal pain. Phytother Res. 2009;23(7):897–900. 5
36. Urizar NL, Moore DD. Guggulsterone: a promising anti-inflammatory and cholesterol-lowering agent. Curr Opin Investig Drugs. 2003;4(10):1108–1112.
37. Sharma JN, Srivastava KC, Gan EK. Suppressive effects of eugenol and guggulsterone on leukotriene and prostaglandin biosynthesis in rat peritoneal macrophages. Prostaglandins Leukot Essent Fatty Acids. 1997;57(4–5):293–299.
38. Szapary PO, Wolfe ML, Bloedon LT, *et al.* Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. JAMA. 2003;290(6):765–772.
39. Satyavati GV, Gupta AK, Tandon N. Medicinal plants of India: Vol. 2. New Delhi: ICMR; 1987.

40. Satyavati GV. Gum guggul (*Commiphora mukul*)—the success of an ancient insight leading to a modern discovery. Indian J Med Res. 1988; 87:327–335.
41. Sharma JN, Bani S, Singh GB. Anti-inflammatory effects of guggulipid—a new non-steroidal agent. Indian J Med Res. 1977;65(4):653–662.
42. Beg S, Javed S, Kohli K, *et al.* Anti-inflammatory and antiarthritic potential of *Commiphora mukul*: an ancient herb. Curr Med Chem. 2011;18(11):1592–1601.
43. Singh BB, Mishra LC, Vinjamury SP, *et al.* The effectiveness of *Commiphora mukul* for osteoarthritis of the knee: an outcomes study. Altern Ther Health Med. 2003;9(3):74–79.
44. Rastogi S, Pandey MM, Rawat AK. Medicinal plants of the genus *Commiphora*: a review of their traditional uses, phytochemistry and pharmacology. Afr J Tradit Complement Altern Med. 2011;8(2):95–111.
45. Tripathi YB, Malhotra OP, Tripathi SN. Thyroid stimulating action of *Z-guggulsterone* obtained from *Commiphora mukul*. Planta Med. 1984;50(1):78–80. 6
46. Blumenthal M, Goldberg A, Brinckmann J, editors. Herbal Medicine: Expanded Commission E Monographs. Boston: Integrative Medicine Communications; 2000.
47. Schulze-Tanzil G, De Souza P, Behnke B, *et al.* Effects of harpagoside on cytokine expression in human osteoarthritic synovial fibroblasts and cartilage explants. Phytomedicine. 2010;17(5):358–363.
48. Fiebich BL, Heinrich M, Hiller K, Kammler T. Inhibition of TNF-α synthesis in LPS-stimulated PBMC by an extract of *Harpagophytum procumbens* (devil's claw). Phytother Res. 2001;15(8):640–642.
49. Lanhers MC, Fleurentin J, Cabalion P, *et al.* Analgesic and anti-inflammatory effects of an aqueous extract of *Harpagophytum procumbens*. Planta Med. 1992;58(2):117–123.
50. Mncwangi N, Finnie JF, Van Staden J. Devil's claw—A review of the ethnobotany, phytochemistry and pharmacology of *Harpagophytum procumbens*. J Ethnopharmacol. 2012;143(3):755–771.
51. Wegener T, Lupke NP. Treatment of patients with arthrosis of hip or knee with an aqueous extract of devil's claw (*Harpagophytum procumbens* DC.). Phytother Res. 2003;17(10):1165–1172.
52. Loew D, Rietbrock N. Phytopharmaceuticals: Drugs of plant origin: Their pharmacology and therapeutic use. Stuttgart: CRC Press; 1996.
53. Chrubasik S, Conradt C, Oberbaum M, *et al.* Efficacy and safety of *Harpagophytum procumbens* in osteoarthritis and low back pain. Phytomedicine. 1996;3(1):1–10.
54. Leblan D, Leclerc P, Pelletier JP, *et al.* Diacerhein and *Harpagophytum procumbens*: comparative effects on osteoarthritic chondrocytes. Phytomedicine. 2000;7(6):397–402.

55. Gagnier JJ, Chrubasik S, Manheimer E. Harpagophytum procumbens for osteoarthritis and low back pain: a systematic review. BMC Complement Altern Med. 2004; 4:13. 7
56. Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. BMJ. 1985;291(6495):569–573.
57. Hehner SP, Heinrich M, Bork PM, *et al.* Sesquiterpene lactones specifically inhibit the NF-κB pathway by targeting the IκB-kinase complex. J Biol Chem. 1999;274(41): 32094–32103.
58. Groenewegen WA, Heptinstall S. Studies on the pharmacological activities of parthenolide, the principal extract from feverfew (*Tanacetum parthenium*). J Pharm Pharmacol. 1990;42(8):553–559.
59. Sumner H, Salan U, Knight DW, Hoult JR. Inhibition of 5-lipoxygenase and cyclooxygenase in leukocytes by parthenolide, a germacranolide sesquiterpene lactone from feverfew (*Chrysanthemum parthenium*). Biochem Pharmacol. 1992;43(11):2313–2320.
60. Williams CA, Harborne JB, Geiger H, Hoult JR. The flavonoids of *Tanacetum parthenium* and T. vulgare and their anti-inflammatory properties. Phytochemistry. 1999;51(3):417–423.
61. Rogers NC, Guschin D, Briscoe J, *et al.* Inhibition of IκB kinase by parthenolide and BAY 11-7082: differential effects on NF-κB activation and cytokine production in T lymphocytes and macrophages. J Immunol. 2001;167(9): 5221–5227.
62. Sumner H, Salan U, Knight DW, Hoult JR. Inhibition of eicosanoid biosynthesis by the extract of feverfew and parthenolide. Biochem Pharmacol. 1992;43(11):2313–2320.
63. Pattrick M, Kinsey M, Hughes GR. Clinical experience with feverfew (*Tanacetum parthenium*) in rheumatoid arthritis. Ann Rheum Dis. 1989;48(8):547–549.
64. Ernst E, Pittler MH, Stevinson C. Feverfew for preventing migraine. Cochrane Database Syst Rev. 2004;(1):CD002286.
65. Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. Lancet. 1988;2(8604):189–192.

Progressive Trends in Pharmaceutical, Chemical and Biological Sciences Volume II
ISBN: 978-81-989981-3-2

About Editors

Dr. Ghanshyam R. Parmar is a Professor and Head of Pharmacognosy at the Department of Pharmacy, Sumandeep Vidyapeeth, Vadodara, Gujarat, with over 17 years of academic and research experience. He holds a Ph.D. in Pharmaceutical Sciences, specializing in anticancer drug discovery from phytoconstituents by integrating molecular pharmacology, computer-aided drug design (CADD), and in vitro–in vivo approaches. He also serves as In-charge of the Sumandeep Vidyapeeth Incubation and Innovation Centre and as the SSIP Coordinator of the University. Dr. Parmar has guided numerous postgraduate and doctoral scholars, published extensively in reputed peer-reviewed journals, and holds multiple patents. He actively contributes to the scientific community as an editor, reviewer, and resource person in various national and international conferences, workshops, and forums, advancing pharmacognosy and drug discovery research.

Dr. Ganesh D. Satpute, M.Sc. (Chemistry), NET, Ph.D., is currently serving as Assistant Professor and Head of the Department of Chemistry at Shri Govindrao Munghate Arts and Science College, Kurkheda, affiliated to Gondwana University, Gadchiroli, since 2012. He has 13 years of teaching experience at both undergraduate and postgraduate levels. Dr. Satpute has published more than 20 research articles in reputed national and international journals and authored two books. Recognised as a Ph.D. Supervisor by Gondwana University, Gadchiroli since 2021, he is presently guiding three research scholars at IHLR & SS Government Science College, Gadchiroli. His areas of academic interest include advanced chemical sciences and interdisciplinary research. He actively contributes to academic growth through teaching, research, and guidance, nurturing future chemists and researchers under his mentorship.

Dr. Rakhi B. Shambharkar, M.Sc. (Botany), M.Phil., NET, GET, Ph.D., is currently working as Assistant Professor in the Department of Botany at Shri Govindrao Munghate Arts and Science College, Kurkheda, affiliated to Gondwana University, Gadchiroli, since 2012. She has 13 years of teaching experience at undergraduate and postgraduate levels. Dr. Shambharkar has published over 30 research articles in reputed national and international journals and authored two books. She has completed a minor research project funded by the National Innovation Foundation, Gujarat. Recognised as a Ph.D. Supervisor by Gondwana University since 2021, she is guiding two research scholars at IHLR & SS NS College, Bhadrawati. She has been nominated as a Master Trainer by UGC-UBA for CBPR syllabus implementation under NEP 2020, contributing significantly to research, teaching, and academic development.

Dr. N. Jyothi is an Assistant Professor of Chemistry with a Ph.D. in Organic Chemistry from Osmania University, Hyderabad. Her research interests include green chemistry, Schiff base metal complexes, and the development of sustainable chemical processes. She has published more than three research papers in reputed journals such as Molecular Structure (Elsevier) and the Journal of Organic Chemistry. Dr. Jyothi received the Best Paper Award at the National Conference on Sustainable Chemistry in 2023. Her contributions to curriculum development and academic outreach are widely recognized. She actively participates in institutional activities, coordinating various fests and outreach programs. She has served as Magazine Convener and NSS Programme Officer. Her dedication to teaching, research, and student development continues to enrich the department, fostering an environment of academic excellence and innovation.

Bhumi Publishing

ISBN 978-81-989981-3-2
9 788198 998132