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TRENDS IN PHARMACEUTICAL AND HEALTH SCIENCE RESEARCH VOLUME I

Editors:
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Trends in Pharmaceutical and Health Science Research Volume I

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PREFACE

The pharmaceutical and health science industries are at the forefront of innovation, continuously evolving to address global health challenges, from infectious diseases to chronic conditions and emerging therapeutic needs. Trends in Pharmaceutical and Health Science Research is a timely compilation of cutting-edge advancements, research methodologies, and transformative technologies that are reshaping modern medicine and healthcare delivery.

This book serves as a comprehensive resource for researchers, academicians, healthcare professionals, and industry experts by presenting the latest trends in drug discovery, biotechnology, nanomedicine, pharmacogenomics, and digital health. With contributions from leading scientists and practitioners, it explores groundbreaking developments such as AI-driven drug design, CRISPR-based therapies, personalized medicine, and sustainable pharmaceutical practices. Additionally, it highlights the integration of big data analytics, telemedicine, and wearable technologies in enhancing patient care and treatment outcomes.

The global healthcare landscape has witnessed unprecedented challenges, including pandemics, antimicrobial resistance, and the rising burden of non-communicable diseases. In response, this book emphasizes interdisciplinary research, evidence-based practices, and innovative solutions that bridge the gap between laboratory discoveries and clinical applications. Each chapter provides a critical analysis of current trends while discussing future directions, regulatory challenges, and ethical considerations in pharmaceutical and health science research.

We extend our sincere gratitude to the distinguished contributors who have shared their expertise, making this book a valuable reference for advancing knowledge in the field. We also acknowledge the relentless efforts of researchers, policymakers, and healthcare providers who strive to improve global health outcomes through scientific innovation.

As the boundaries of medical science expand, we hope this book inspires further research, collaboration, and technological integration to meet the ever-changing demands of healthcare. It is our belief that this compilation will serve as a catalyst for progress, fostering a deeper understanding of the trends that will define the future of pharmaceuticals and health sciences.

- Editors

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SURFACE FUNCTIONALIZATION, MODIFICATION, AND APPLICATIONS OF NANOMATERIALS

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ABSTRACT:

Nanomaterials have at least one dimension between 1 and 100 nm, exhibiting unique optical, electromagnetic, and piezoelectric properties due to their high surface area and nanoscale effects. These characteristics make them valuable in fields such as wastewater treatment, energy storage, biomedicine, and diagnostics. Despite their advantages, nanomaterials often suffer from limited surface reactivity, which can restrict their applications. To overcome this limitation, surface modifications are necessary to enhance biomolecular adsorption and overall performance. Functionalization improves stability, compatibility, and efficiency, making nanomaterials more effective in biomedical applications, including diagnostics and targeted drug delivery. Various techniques, such as chemical coatings, polymeric functionalization, and self-assembly, contribute to their adaptability for specific applications. In addition to biomedical uses, surface modifications also enhance their effectiveness in catalysis, environmental remediation, and electronic applications. This chapter discusses different methods of nanomaterial surface modification, including metallic nanoparticles, carbon-based nanomaterials, nanoceramics, and self-assembled structures, with a focus on biomedical advancements and broader technological applications.

Keywords: Biomedical Applications, Functionalization, Nanomaterials, Surface Modification

INTRODUCTION:

Recent advancements in fabrication and characterization techniques have enabled the precise synthesis of nanomaterials, offering superior properties compared to their bulk counterparts. Their enhanced surface-to-volume ratio and quantum confinement effects impart unique optical, electrical, and magnetic characteristics, making them highly suitable for various applications, including biotechnology, energy storage, catalysis, and drug delivery. These distinctive properties allow nanomaterials to play a crucial role in improving diagnostic tools, targeted drug delivery, and the development of next-generation medical devices [1]. Surface modification techniques have become essential for stabilizing nanomaterials, preventing

aggregation, and improving their solubility and biocompatibility. Functionalization using chemical ligands, polymeric coatings, and surface grafting enhances their applicability in different environments, particularly in biomedical fields [2]. Modified nanoparticles optimize imaging techniques such as MRI, PET, and CT, facilitating early disease detection and precise treatment. Additionally, metal nanoparticles, including gold, silver, and iron oxide, contribute significantly to diagnostic and therapeutic applications, improving drug targeting efficiency and reducing side effects [3,4].

Beyond biomedical applications, surface-modified nanomaterials have revolutionized fields such as environmental science, catalysis, and electronics. They enhance pollutant degradation, energy conversion processes, and advanced material fabrication. Self-assembly techniques further enable the formation of functional nanostructures, allowing cost-effective and scalable production of nanomaterials tailored for specific industrial applications [5]. The continuous evolution of surface modification strategies underscores the significance of nanomaterials in modern science, highlighting their indispensable role in advancing technology and healthcare [6,7].

Surface modification is a fundamental approach to stabilizing nanomaterials, preventing agglomeration, and improving phase compatibility. Functionalization with chemical ligands or polymeric coatings enhances their reactivity, solubility, and biocompatibility for specialized applications [8]. In biomedical fields, surface-modified nanoparticles optimize imaging techniques such as MRI, PET, and CT while enhancing targeted therapy effectiveness. Additionally, metal nanoparticles like gold, silver, and iron oxide play an essential role in diagnostic and therapeutic applications [9]. Self-assembly techniques further facilitate the organization of nanoparticles into functional structures, offering scalable and cost-effective fabrication methods. These developments have expanded nanomaterials' utility across industries such as electronics, robotics, and environmental science. The ability to modify and functionalize their surfaces has solidified nanomaterials as key components in modern technological and biomedical advancements [10].

SELF-ASSEMBLING OF NANOMATERIALS

In bioengineering, self-assembly techniques have emerged as an effective alternative to traditional cross-linked polymers, rubbers, and metallic nanoparticles. Molecular self-assembly provides a pathway to supramolecular structures, which form through noncovalent interactions that drive their organization. Many self-assembling molecules exhibit amphiphilic properties, containing both hydrophobic and hydrophilic domains [11]. Under aqueous conditions, these molecules organize into structures such as fibrils, tubules, or micelles due to weak noncovalent interactions, with their morphology being influenced by temperature, pH, ionic strength, and monomer concentration. The ability to trigger or reverse self-assembly through external stimuli

enhances its potential in drug delivery applications, allowing controlled disassembly at target sites [12]. Additionally, self-assembled structures impact soft material properties, influencing amphiphilic colloids, polymers, and other biomaterials. Researchers continue to explore fabrication strategies for precise control over nanoparticle shape, size, and functionality. Metal nanoparticles can be surface-patterned through self-organization techniques, including block copolymer-assisted assembly or selective wetting methods. These advancements have significantly improved drug bioavailability, blood circulation, tissue engineering, and targeted delivery. Their unique physicochemical properties make self-assembled nanomaterials highly desirable for bioapplications such as drug delivery, biosensing, and in vivo diagnostics [13].

This chapter explores the critical aspects of nanomaterial self-assembly, focusing on its applications in biomedical science and various surface modifications, including metallic nanoparticles, carbon nanomaterials, and nanoceramics. The classification of soft materials into synthetic and biological categories further illustrates their fabrication methodologies and impact across scientific and industrial domains.

Development of synthetic nanomaterials

The development of synthetic soft materials at the nanoscale relies on key components such as polymers, surfactants, lipids, colloids, and liquid crystals. These materials serve as fundamental building blocks for nanotechnology, particularly in the formation of nanostructures. One of the primary approaches for creating such structures is microphase separation of block copolymers, which facilitates the design of nanoscale architectures [14]. Surfactants, also known as surface-active agents, are widely used in the synthesis of nanomaterials. These molecules exhibit an amphiphilic nature, possessing both hydrophilic and hydrophobic segments. This unique property allows them to preferentially segregate at the interface of nanoparticles, influencing their stability and self-assembly. A common example of a surfactant is detergent, which demonstrates surface activity by reducing interfacial tension and promoting molecular organization. Lipids, which are biological amphiphiles, naturally self-assemble in aqueous environments, forming various nanostructures. This self-assembly minimizes the interaction between the hydrophobic segments of lipids and surrounding water molecules, leading to the formation of micelles and vesicles [15,16]. Micelles can adopt spherical or cylindrical morphologies, with hydrophobic cores shielded by hydrophilic coronas in aqueous environments. In contrast to micelles, vesicles possess a hollow spherical shape, where the outer surface consists of layers of surfactant molecules, creating a stable bilayer structure. Colloids are microscopic particles evenly dispersed in another medium, with sizes typically ranging from 1 nm to 1 μm. These systems exhibit heterogeneous properties, consisting of two distinct phases: the dispersed phase and the continuous phase. The interaction between these phases enables self-organization, leading to stable colloidal systems. Common types of colloidal materials include

aerosols (e.g., fog, smoke), foams (e.g., shaving cream, whipped cream), and emulsions (e.g., milk, mayonnaise) [17]. Liquid crystals belong to the category of soft materials and consist of moderate-sized organic molecules exhibiting ordered molecular arrangements. They exist in an intermediate state between liquids and crystalline solids and are classified based on their phase behavior. Thermotropic liquid crystals are formed in the absence of solvents, with phase transitions dependent on temperature changes. Lyotropic liquid crystals, composed of amphiphilic molecules, self-assemble in solvent-based solutions, forming well-organized nanostructures. Liquid crystals exhibit distinct phase orientations, such as the nematic phase, which is characterized by short-range positional order with molecules aligning in an average direction, and the smectic phase, which exhibits long-range translational order, where molecules form layered structures with higher viscosity compared to the nematic phase. These properties make liquid crystals valuable in various technological applications, including display technologies, drug delivery systems, and sensors [18,19].

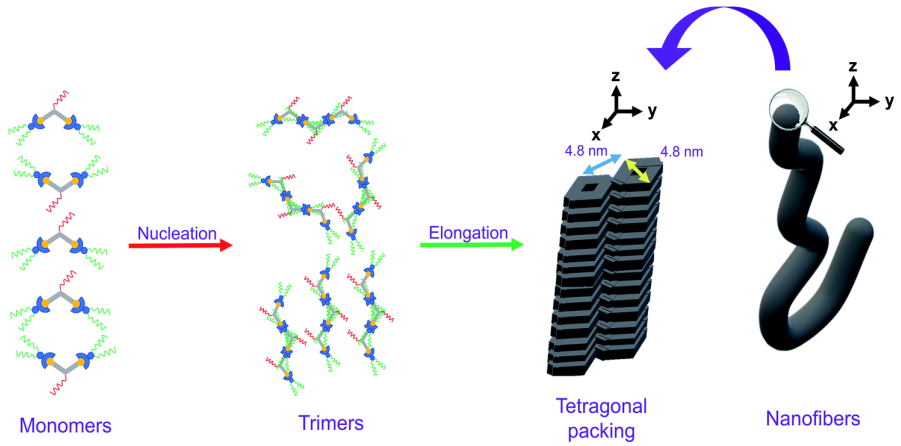

Figure 1: Schematic representation of Self-assembly of nanomaterials [20]

Development of biological nanomaterials

Biological self-assembly plays a fundamental role in the formation of soft materials, offering significant advantages over artificially synthesized counterparts. Various naturally occurring biological structures, including silk, collagen, proteins, DNA, microtubules, and viruses, exhibit intrinsic self-organizing properties that contribute to their specialized functions.

Silk is primarily composed of fibroin protein, which adopts an antiparallel β-sheet conformation. The peptide chains within silk are interconnected by intermolecular hydrogen bonds, facilitating the formation of β-sheet structures. The alignment of polypeptide chains along these sheets imparts high tensile strength, while the inter-sheet forces allow for structural flexibility [21,22]. Collagen, a structural protein ubiquitous in living organisms, self-assembles into cross-linked fibrillar networks that provide mechanical support to connective tissues. When exposed to heat or chemical treatment, collagen undergoes denaturation, leading to the formation of gelatin. Similarly, keratin, a naturally occurring fibrous protein, contributes to the formation

of hair, nails, wool, horns, and feathers. Keratin molecules establish intermolecular hydrogen bonds, resulting in fibrillary arrangements that enhance strength and resilience [23].

Beyond protein-based materials, DNA fragments exhibit self-assembling behavior, leading to the formation of lyotropic liquid crystals in solution. Short DNA segments behave as rigid rod-like structures, facilitating the development of an ordered liquid crystalline phase. As the concentration of DNA increases, the system undergoes self-organization into distinct liquid crystal phases, such as nematic cholesteric twists and hexagonal columnar assemblies [24]. Microtubules, which are essential components in cellular processes and nanotechnology, are formed by tubulin protein subunits. These cylindrical nanostructures play a crucial role in intracellular transport, acting as biological nanochannels that regulate molecular movement. Microtubules also form the structural basis of cilia, which are hair-like projections responsible for fluid transport across cellular surfaces. Viruses serve as another example of biological self-organization. As obligate intracellular parasites, viruses lack autonomous replication ability and instead rely on host cells for reproduction. Structurally, a virus consists of a core genetic material (DNA or RNA) enclosed within a protective protein shell, termed the capsid. Capsid structures vary, ranging from icosahedral and helical to more complex morphologies. For instance, herpes simplex virus (HSV-1) forms a self-assembled icosahedral capsid, whereas the tobacco mosaic virus (TMV) exhibits a self-organized helical arrangement, measuring approximately 300 nm in length and 18 nm in diameter [25,26].

The natural ability of biological molecules to self-organize into highly ordered structures has profound implications for nanotechnology, biomaterials science, and biomedical engineering. Understanding these self-assembling processes provides valuable insights into designing bioinspired materials for diverse scientific and technological applications.

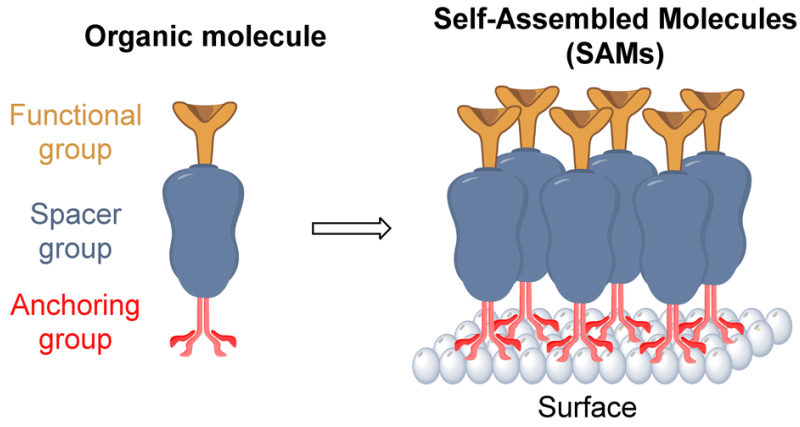

Figure 2: Self-assembly of a molecule to form a single layer [27].

METALLIC NANOPARTICLES

Metal nanoparticles, particularly gold and silver, have been extensively studied, establishing their significance in nanotechnology. With continuous advancements, a wide range of nanomaterials and nanoparticles have been developed for diverse applications, particularly in

chemical sensing, bio-labeling, and photonics. In various biochemical processes, these nanoparticles also function as catalysts. Their antioxidant properties make them particularly suitable for biomedical applications [28]. The synthesis of gold and silver nanoparticles can be efficiently achieved through chemical and green synthesis approaches, offering advantages over other nanomaterials. Additionally, their distinct optical properties further increase their application potential. Functionalizing these nanoparticles with appropriate ligands improves biocompatibility, expanding their range of applications. For example, gold nanoparticles have been combined with magnetic iron nanoparticles, allowing them to act as biological transporters for molecular tracers. Furthermore, when exposed to specific wavelengths of light, they demonstrate high absorbance and light-scattering properties, making them valuable in plasmonic applications [29].

Surface modification of noble metal nanoparticles is commonly performed through chemical attachment of ligands, such as thiols, disulfides, amines, nitriles, carboxylic acids, and phosphines. However, ensuring colloidal stability during functionalization remains a challenge. The effectiveness of chemical ligand exchange depends largely on the nanoparticle's composition and the chemical nature of the ligand. Because nanoparticles exhibit varied surface affinities, researchers have developed several strategies to enhance ligand attachment. Among noble metals, gold, silver, copper, platinum, mercury, and iron have a high tendency to form organo-sulfur bonds, due to their strong chemical interactions with thiols and amines. This affinity enables the formation of stable coordinate bonds, facilitating the immobilization of thiol groups on the nanoparticle surface and enhancing their adsorption capabilities [30]. However, oxidation of thiol groups reduces their binding efficiency, leading to the formation of sulfates or sulfonates. Surface modification using thiol- or disulfide-capping can be achieved through two key approaches. The first method involves ligand exchange, where pre-synthesized noble metal nanoparticles undergo surface modification by replacing existing capping agents with sulfur-based ligands. The second approach involves synthesizing nanoparticles under an inert environment with residual surface charges, enabling efficient ligand grafting using inductively coupled plasma techniques. Additionally, a one-step wet chemistry approach allows for simultaneous metal precursor nucleation and ligand capping, ensuring direct synthesis of organo-sulfur capped nanoparticles [31].

As an alternative to chemical and physical synthesis methods, biosynthesis using plant extracts has emerged as a promising and eco-friendly approach, particularly for applications in nanomedicine. Gold nanoparticles exhibit exceptional properties such as high surface plasmon resonance, chemical stability, biocompatibility, low toxicity, and a high surface-to-volume ratio, making them ideal for cancer diagnostics and therapy [32]. Studies conducted by T.S. Santra *et al.* have explored various biosynthetic approaches for fabricating gold and silver nanoparticles,

emphasizing their potential across multiple scientific domains. The focus of future research should be on stabilizing and functionalizing nanoparticles, ensuring their adaptability for biomedical applications, and developing multifunctional, externally tunable nanodevices. A particularly innovative application in this field is nanosecond pulsed photoporation, which involves the use of nano-corrugated, mushroom-shaped gold-coated polystyrene nanoparticles (nm-AuPNPs) for intracellular molecular delivery. When subjected to a pulsed laser at a plasmonic peak of 945 nm, these nanoparticles generate nano-bubbles, which expand and induce temporary membrane pores, enabling the transfection of molecules into cells. Fine-tuning key parameters, such as laser exposure time, nanoparticle concentration, and molecular size, has been shown to optimize results. This technique represents a significant advancement in therapeutic medical applications, offering a promising strategy for targeted molecular delivery.

Advantages of Metallic Nanoparticles

- Enhanced Rayleigh Scattering: Metallic nanoparticles exhibit strong Rayleigh scattering, improving their applicability in optical sensing and imaging.
- Surface-Enhanced Raman Scattering (SERS): These nanoparticles significantly amplify Raman signals, enabling highly sensitive molecular detection.
- Strong Plasmon Absorption: Their localized surface plasmon resonance (LSPR) properties enhance light absorption, making them valuable in optoelectronic applications.
- Biomedical Imaging: Metallic nanoparticles facilitate high-resolution imaging in biological systems, aiding in disease diagnosis and cellular tracking.
- Chemical Sensing: They provide precise chemical characterization at the nanoscale by acting as substrates for detecting molecular interactions.

Disadvantages of Metallic Nanoparticles

- Particle Instability: Due to their high surface energy, metallic nanoparticles are thermodynamically unstable and prone to aggregation, structural degradation, and reduced corrosion resistance.
- Impurity Formation: The synthesis process is susceptible to contamination from nitrides and oxides due to their reactive nature. Ensuring high purity during synthesis remains a significant challenge, especially in solution-based nanoparticle fabrication.
- Potential Toxicity: Some nanomaterials exhibit cytotoxic and carcinogenic properties, which may induce cell damage or apoptosis, raising concerns regarding their biocompatibility.
- Synthesis Challenges: Maintaining size stability in solution form is particularly difficult, requiring precise encapsulation techniques to prevent uncontrolled agglomeration during synthesis.

Characteristics of Metallic Nanoparticles

- High Surface Energy: Due to their nanoscale dimensions, metallic nanoparticles exhibit significantly high surface energy, influencing their reactivity and stability.
- Large Surface Area-to-Volume Ratio: Compared to bulk materials, nanoparticles possess a greater surface area-to-volume ratio, enhancing their chemical and catalytic efficiency.
- Quantum Confinement: The electronic properties of nanoparticles are governed by quantum effects, which impact their optical, electronic, and magnetic behaviors.
- Plasmon Excitation: Surface plasmon resonance (SPR) is a key characteristic that allows metallic nanoparticles to interact with light, leading to enhanced optical properties.
- Increased Number of Surface Defects (Kinks): The high density of surface kinks and edges enhances their adsorption capabilities and catalytic activity.

General Applications of Metallic Nanoparticles

Optical Function

The optical properties of metallic nanoparticles depend on factors such as size, shape, surface characteristics, doping, and environmental interactions [33]. These nanoparticles are widely used in:

- Imaging sensors
- Solar cells
- Displays
- Biomedical applications
- Optical detectors
- Photocatalysis

Thermal Function

The thermal properties of metallic nanoparticles are influenced by their size. For instance, nanoparticles with diameters below 10 nm exhibit a lower melting point compared to their bulk counterparts. This phenomenon is particularly useful in thermal energy storage and heat transfer applications [34].

Mechanical Function

The mechanical properties of nanoparticles can be enhanced through various approaches [35]:

- Polymer Integration: Coating or embedding nanoparticles within polymers improves their strength, elasticity, and durability.
- Ceramic-Nanoparticle Composites: Mixing metallic nanoparticles with ceramics enhances mechanical robustness, making them suitable for structural and industrial applications.

Magnetic Function

At the nanoscale, certain noble metals such as platinum and gold exhibit magnetic properties, even though they behave as non-magnetic in their bulk form. This phenomenon arises due to quantum confinement effects at the nanoscale. The physical and chemical properties of nanoparticles can be modulated by surface functionalization and capping agents, which enhance their interaction with other chemical species [35].

Catalysis

Metallic nanoparticles serve as highly efficient catalysts due to their large surface area and high reactivity. They are known for their selectivity, long-term stability, and enhanced catalytic activity across various chemical reactions [36]. There are two primary types of nanoparticle-based catalysts:

- Heterogeneous Catalysts: Immobilized on inorganic supports, these catalysts facilitate surface-driven reactions and are widely used in industrial applications.
- Homogeneous Catalysts: Metallic nanoparticles surrounded by stabilizers that enable reactions in solution-based systems with high selectivity and efficiency.

Fuel Cell Catalysts

Fuel cells are energy conversion devices that generate electricity by harnessing the chemical energy of hydrogen and oxygen. In a proton exchange membrane (PEM) fuel cell, hydrogen is supplied to the anode, while oxygen (O_2) is delivered to the cathode through ambient air [37]. The key components of a PEM fuel cell include:

- Proton exchange membrane (PEM)
- Catalyst layers (typically platinum-based nanoparticles)
- Gas diffusion layers (GDLs)

Nanoparticle-based catalysts enhance reaction efficiency by improving electron transfer rates, leading to higher energy output and reduced fuel consumption. The primary byproducts of this reaction are electricity, heat, and water, making fuel cells an environmentally friendly energy source.

Applications in Materials Science

Nickel nanoparticles are employed in electrically conductive pastes and battery materials, enhancing energy storage capabilities [37]. Silver and gold nanoparticles contribute to the development of highly conductive coatings and inks used in flexible electronics and sensors.

Medical Applications

Gold nanoparticles (AuNPs) can be functionalized with antibodies, allowing for the selective identification and differentiation of healthy cells from cancerous cells. This approach is used in nanoparticle-based imaging, targeted therapy, and photothermal treatments [38].

CONCLUSION:

In recent years, the rapid advancement of nanotechnology has led to the development of a diverse range of nanomaterials for applications in biomedicine, cancer diagnosis and therapy, environmental remediation, particle separation, and water purification. This chapter has provided an overview of the surface modification strategies of metallic nanoparticles, carbon-based nanomaterials (CNMs), nano-ceramics, and self-assembled materials, highlighting their ability to enhance molecular interactions, improve targeting efficiency, and expand their applicability across various fields.

Modified nanomaterials have shown great promise in healthcare diagnostics, offering cost-effective, rapid, and simplified operational procedures compared to conventional diagnostic systems. However, several challenges remain, particularly in ensuring their biocompatibility, targeted efficiency, and large-scale cost-effective production. Additionally, the potential toxicity and environmental impact of nanomaterials must be thoroughly evaluated to establish specific regulatory frameworks for their clinical and industrial applications. Recent studies have demonstrated that self-assembled nanostructures, including nanovesicles, nanotubes, 3D peptide matrices, and nanofibers, have immense potential in tissue engineering, bio-nanotechnology, regenerative medicine, and dentistry. Among various techniques, self-assembly approaches have proven to be energy-efficient, cost-effective, and versatile for fabricating complex nanostructures with controlled morphologies and chemical functionalities. However, further research is needed to enhance their structural precision and functional properties for advanced applications.

As nanotechnology continues to evolve, the synthesis and application of self-assembled nanostructures in drug delivery, nanomotors, nanopatterning, and biomineralization will witness tremendous growth. While these advancements hold transformative potential for various industries, their societal and environmental impacts must be carefully assessed. The integration of nanotechnology into mainstream applications is expected to reshape scientific innovation and human lifestyles, presenting both opportunities and challenges in the coming decades.

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NATURAL POLYMERS IN DRUG DELIVERY SYSTEM

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ABSTRACT:

Natural polymers have gained significant attention in drug delivery systems due to their biocompatibility, biodegradability, and non-toxic nature. Derived from plant, animal, microbial, and marine sources, these polymers serve as efficient carriers for controlled and targeted drug delivery. Examples include polysaccharides (e.g., chitosan, alginate, cellulose), proteins (e.g., gelatin, collagen), and nucleic acids. Their unique physicochemical properties allow for the formulation of hydrogels, nanoparticles, microspheres, and films, enhancing drug stability and bioavailability. Natural polymers offer advantages such as sustained drug release, improved solubility of hydrophobic drugs, and reduced side effects. Polysaccharides like chitosan possess mucoadhesive properties, making them suitable for oral and nasal drug delivery. Alginate-based hydrogels provide controlled drug release, while proteins like gelatin are used in wound healing and tissue engineering applications. The biodegradability of these polymers ensures minimal toxicity, making them ideal for pharmaceutical applications. Challenges such as batch variability, limited mechanical strength, and susceptibility to enzymatic degradation require further research. Strategies like chemical modifications, cross-linking, and blending with synthetic polymers are being explored to enhance their stability and functionality. The growing demand for eco-friendly and sustainable drug delivery systems continues to drive research in natural polymers. With advancements in nanotechnology and polymer engineering, natural polymer-based drug delivery systems hold promise for improved therapeutic outcomes in various medical fields, including cancer treatment, gene therapy, and regenerative medicine.

Keywords: Biodegradability, Controlled Release, Biocompatibility, Polysaccharides, Nanocarriers

INTRODUCTION:

Natural polymers have emerged as vital components in modern drug delivery systems due to their biocompatibility, biodegradability, and ability to enhance drug stability and efficacy. These polymers, derived from plant, animal, microbial, and marine sources, provide an eco-friendly and sustainable alternative to synthetic materials. Their unique structural and functional properties make them highly adaptable for various pharmaceutical applications, including controlled release, targeted drug delivery, and improved bioavailability.

Natural polymers can be classified into several categories, including polysaccharides (e.g., chitosan, alginate, cellulose, starch), proteins (e.g., gelatin, collagen, albumin), and nucleic acids. These materials play a crucial role in the formulation of different drug delivery systems, such as hydrogels, nanoparticles, microspheres, liposomes, and films. Their ability to form stable matrices allows for the encapsulation of drugs, protecting them from degradation and ensuring a sustained and controlled release. For instance, chitosan, a polysaccharide derived from chitin, is widely used due to its mucoadhesive properties, which enhance drug absorption in oral and nasal delivery. Alginate-based hydrogels are known for their ability to provide controlled drug release, while gelatin is commonly used in wound healing and tissue engineering.

1. Role of Natural Polymers in Drug Delivery

Natural polymers play a crucial role in drug delivery systems due to their biocompatibility, biodegradability, and ability to enhance drug stability and efficacy. These polymers serve as carriers that control drug release, improve solubility, and enhance bioavailability while minimizing side effects. Derived from polysaccharides (e.g., chitosan, alginate, cellulose), proteins (e.g., gelatin, collagen, albumin), and nucleic acids, natural polymers offer diverse functionalities in pharmaceutical formulations. Hydrogels, nanoparticles, and microspheres made from natural polymers ensure prolonged drug release, reducing the frequency of administration. Polymers like chitosan exhibit mucoadhesive properties, enhancing drug absorption in oral and nasal delivery. Alginate-based formulations provide pH-sensitive drug release, making them ideal for gastrointestinal targeting. Natural polymers improve drug encapsulation and protection from enzymatic degradation, ensuring stability during transport in the body. They are also widely used in targeted drug delivery, particularly in cancer therapy, where polymer-based nanocarriers enhance drug accumulation at tumor sites.

2. Advantages of Natural Polymers over Synthetic Polymers

Natural polymers offer several advantages over synthetic polymers in drug delivery systems. They are biodegradable, ensuring safe elimination from the body without harmful residues. Their biocompatibility reduces toxicity and immune reactions, making them safer for pharmaceutical applications. Natural polymers also provide and controlled drug release**,** enhancing therapeutic efficacy while minimizing side effects. Their mucoadhesive and bioadhesive properties improve drug absorption and retention. Additionally, they are eco-friendly and renewable, making them a sustainable alternative. Unlike synthetic polymers, natural polymers often have lower processing costs and require fewer chemical modifications, making them highly suitable for advanced drug delivery applications.

CLASSIFICATION OF NATURAL POLYMERS

1. Polysaccharides

- Chitosan

- Alginate
- Cellulose and Its Derivatives
- Starch-Based Polymers
- Hyaluronic Acid

2. Proteins

- Gelatin
- Collagen
- Albumin
- Silk
- Fibroin

3. Nucleic Acids

- DNA and RNA-Based Polymers

4. Marine-Derived Polymers

- Carrageenan
- Fucoidan
- Chitin and Chitosan

5. Microbial-Derived Polymers

- Xanthan Gum
- Polyhydroxyalkanoates (PHA)

MECHANISMS OF DRUG DELIVERY USING NATURAL POLYMERS

Natural polymers facilitate drug delivery through various mechanisms, ensuring controlled and sustained release. Diffusion-controlled release allows the gradual movement of drugs from polymer matrices. Swelling-controlled systems regulate drug release based on polymer hydration and expansion. Enzyme-responsive delivery ensures targeted release in specific biological environments. pH-sensitive systems release drugs at desired pH levels, useful for gastrointestinal targeting. Temperature-sensitive polymers respond to body temperature changes for site-specific drug delivery. Additionally, biodegradable systems degrade naturally, releasing drugs over time. These mechanisms enhance bioavailability, improve therapeutic efficacy, and reduce dosing frequency in pharmaceutical applications.

1. Diffusion-Controlled Drug Release

Diffusion-controlled drug release is a widely used mechanism in drug delivery systems, where the drug diffuses from a polymeric matrix or reservoir at a controlled rate. This method ensures a sustained and predictable drug release, enhancing therapeutic efficacy while minimizing side effects. Natural polymers such as chitosan, alginate, cellulose derivatives, and gelatin are commonly used in diffusion-controlled drug delivery due to their biocompatibility and tunable properties. There are two primary types of diffusion-controlled systems: matrix

systems and reservoir systems. In matrix systems, the drug is uniformly dispersed within the polymer, and its release occurs as the drug molecules diffuse through the hydrated polymer network. The rate of drug release depends on the polymer's porosity, swelling capacity, and degradation profile. Reservoir systems, on the other hand, consist of a core containing the drug, surrounded by a polymeric membrane. The drug diffuses through this membrane at a controlled rate, which is influenced by the polymer thickness and permeability.

Diffusion-controlled drug release is advantageous for maintaining consistent drug levels in the body, reducing dosing frequency, and improving patient compliance. It is widely applied in transdermal patches, hydrogels, microspheres, and implants for the sustained delivery of various drugs, including antibiotics, anticancer agents, and hormones.

2. Swelling-Controlled Drug Release

Swelling-controlled drug release is a mechanism in which drug release is governed by the hydration and expansion of a polymer matrix. When exposed to biological fluids, the natural polymer absorbs water, swells, and forms a gel-like structure. This swelling increases polymer permeability, allowing the encapsulated drug to diffuse out gradually. Natural polymers such as chitosan, alginate, starch, and cellulose derivatives are commonly used in swelling-controlled drug delivery systems due to their excellent water-absorbing capacity and biocompatibility. The release rate in swelling-controlled systems depends on factors such as polymer composition, cross-linking density, and environmental conditions like pH and temperature. The process typically follows two stages: polymer hydration and swelling, which controls the rate of water penetration, and drug diffusion, where the swollen matrix facilitates the release of the drug into surrounding tissues. Swelling-controlled drug release is particularly useful for oral drug delivery, where pH-sensitive polymers can release drugs at specific locations in the gastrointestinal tract. It is also employed in transdermal patches, hydrogels, and injectable formulations to achieve sustained and site-specific drug delivery. This method enhances bioavailability, reduces dosing frequency, and minimizes systemic side effects, making it an essential approach in controlled drug delivery systems.

3. Enzyme-Responsive Drug Delivery

Enzyme-responsive drug delivery systems utilize natural polymers that degrade in the presence of specific enzymes, ensuring targeted and controlled drug release. These systems are particularly useful for site-specific drug delivery, where enzymes present in specific tissues or diseased areas (e.g., tumors, inflamed tissues) trigger drug release. Natural polymers such as chitosan, alginate, dextran, hyaluronic acid, and gelatin are commonly used due to their biodegradability and responsiveness to enzymatic activity. The mechanism of enzyme-responsive drug delivery involves the breakdown of polymeric carriers by enzymes such as proteases, glycosidases, lipases, and esterases. For example, gelatin-based drug carriers degrade

in the presence of matrix metalloproteinases (MMPs), which are overexpressed in cancerous tissues, enabling targeted chemotherapy. Similarly, chitosan-based systems degrade under lysozyme action, making them ideal for ocular, nasal, and wound healing applications.

This approach ensures precise drug release, minimizing systemic toxicity and enhancing therapeutic efficacy. Enzyme-responsive systems are widely applied in cancer therapy, inflammatory disease treatment, and tissue engineering. Advances in polymer engineering have further improved enzyme sensitivity, leading to smart drug delivery systems capable of responding dynamically to disease-specific enzyme levels for more effective treatment strategies.

4. pH-Sensitive Drug Delivery

pH-sensitive drug delivery systems utilize natural polymers that respond to pH variations in the body, enabling controlled and site-specific drug release. These systems are particularly effective for oral, tumor-targeted, and intracellular drug delivery, as different organs and diseased tissues exhibit distinct pH levels. Natural polymers such as chitosan, alginate, pectin, hyaluronic acid, and cellulose derivatives are commonly used due to their ability to undergo structural changes in response to pH variations. The mechanism involves protonation or deprotonation of functional groups within the polymer, altering solubility, swelling behavior, or degradation rate. For example, chitosan remains insoluble at neutral pH but dissolves in acidic conditions, making it useful for gastric drug delivery. Conversely, enteric-coated polymers like alginate and pectin remain intact in the acidic stomach but dissolve in the alkaline intestines, ensuring targeted drug release in the small intestine.

pH-sensitive drug delivery is widely applied in gastrointestinal-targeted therapies, cancer treatments, and controlled-release formulations. In cancer therapy, acidic tumor environments trigger drug release specifically at the tumor site, minimizing systemic side effects. This smart drug delivery approach enhances bioavailability, prolongs drug activity, and improves therapeutic outcomes, making it a crucial advancement in pharmaceutical sciences.

5. Temperature-Sensitive Drug Delivery

Temperature-sensitive drug delivery systems utilize natural polymers that undergo phase transitions or structural changes in response to temperature variations, enabling controlled and site-specific drug release. These systems are particularly beneficial for targeted therapy, cancer treatment, and localized drug delivery, as diseased tissues, such as tumors and inflamed areas, often exhibit higher temperatures than healthy tissues.Natural polymers like gelatin, chitosan, carrageenan, and elastin-like polypeptides (ELPs) exhibit thermoresponsive behavior, allowing them to act as smart carriers for temperature-sensitive drug release. These polymers can be classified into positive and negative thermoresponsive systems. Positive thermoresponsive polymers remain soluble at lower temperatures but form a gel-like structure when heated, trapping the drug and releasing it gradually (e.g., Pluronic-based hydrogels). Negative

thermoresponsive polymers dissolve at higher temperatures but precipitate at lower temperatures, making them useful for injectable formulations.

This approach is widely used in tumor-targeted drug delivery, where localized hyperthermia (above 37°C) triggers drug release at the cancer site, minimizing systemic side effects. Temperature-sensitive hydrogels and nanoparticles are also utilized in wound healing, transdermal patches, and post-surgical drug administration. These smart drug delivery systems improve treatment precision, enhance bioavailability, and optimize patient compliance by reducing dosing frequency.

6. Biodegradable and Stimuli-Responsive Systems

Biodegradable and stimuli-responsive drug delivery systems utilize natural polymers that degrade safely in the body while responding to specific biological or environmental triggers to control drug release. These systems enhance drug stability, improve therapeutic efficacy, and minimize side effects by ensuring targeted and sustained drug delivery. Biodegradable systems are composed of natural polymers such as chitosan, alginate, gelatin, collagen, and hyaluronic acid, which break down into non-toxic byproducts through enzymatic or hydrolytic degradation. This ensures a controlled release of drugs without the need for surgical removal of the carrier, making them ideal for implants, nanoparticles, and hydrogels.

Stimuli-responsive systems release drugs in response to specific triggers such as pH, temperature, enzymes, light, or magnetic fields. For example, pH-sensitive polymers release drugs in acidic tumor environments or the gastrointestinal tract, while thermoresponsive hydrogels deliver drugs when exposed to increased temperatures at inflamed or cancerous sites. Enzyme-responsive polymers degrade selectively in diseased tissues, ensuring targeted therapy.These smart drug delivery systems are widely applied in cancer therapy, wound healing, and regenerative medicine. By combining biodegradability with stimuli-responsiveness, they offer precise, efficient, and patient-friendly drug administration, advancing modern pharmaceutical and biomedical applications.

APPLICATIONS OF NATURAL POLYMERS IN DRUG DELIVERY

1. Oral Drug Delivery

Natural polymers like chitosan, alginate, pectin, and cellulose derivatives enhance oral drug delivery by improving bioavailability, mucoadhesion, and controlled release. They protect drugs from degradation, ensure targeted intestinal release, and enable sustained drug absorption, making them ideal for gastrointestinal therapies, sustained-release tablets, and encapsulated probiotic formulations. Natural polymers such as chitosan, alginate, pectin, and cellulose derivatives are widely used in oral drug delivery due to their biocompatibility, biodegradability, and ability to enhance drug stability. These polymers enable controlled release and targeted drug delivery within the gastrointestinal tract. Chitosan and alginate are particularly effective for

enhancing bioavailability and intestinal absorption, while pectin-based systems facilitate sustained release. Additionally, natural polymers are utilized in tablet formulations, microcapsules, and hydrogels to improve drug solubility, protect active ingredients from degradation, and provide localized therapy for conditions like inflammatory bowel disease.

2. Ocular Drug Delivery:

Natural polymers play a crucial role in ocular drug delivery by improving drug retention, bioavailability, and controlled release. Polymers like chitosan, hyaluronic acid, alginate, gelatin, and cellulose derivatives are commonly used in eye drops, in situ gels, nanoparticles, and ocular inserts.These polymers enhance mucoadhesion, prolonging drug contact with the corneal surface for better absorption. Chitosan-based nanoparticles improve drug penetration into ocular tissues, while hyaluronic acid hydrogels provide sustained drug release for dry eye and glaucoma treatment. Alginate and gelatin-based inserts enable long-lasting drug delivery, reducing dosing frequency.Such polymer-based systems enhance therapeutic efficacy and improve patient compliance in ophthalmic treatments.

3. Nasal and Pulmonary Drug Delivery

Natural polymers like chitosan, alginate, hyaluronic acid, and starch enhance nasal and pulmonary drug delivery by improving mucoadhesion, bioavailability, and controlled release. They are used in nasal sprays, microspheres, and inhalable nanoparticles for treating respiratory diseases, allergies, and vaccine delivery, ensuring efficient absorption and prolonged drug action. Natural polymers such as chitosan, alginate, hyaluronic acid, and dextran are increasingly used in nasal and pulmonary drug delivery due to their mucoadhesive properties, biocompatibility, and ability to improve drug absorption. These polymers enhance the retention time of drugs in nasal and lung tissues, improving bioavailability and therapeutic efficacy. In nasal sprays and inhalable formulations, they enable controlled release and targeted delivery for conditions such as respiratory infections, asthma, and systemic drug delivery. Additionally, natural polymers help protect fragile biologics like vaccines and proteins from enzymatic degradation during delivery.

4. Transdermal and Topical Drug Delivery

Natural polymers like chitosan, gelatin, alginate, and hyaluronic acid enhance skin penetration, drug retention, and controlled release in transdermal and topical drug delivery. Used in gels, patches, films, and creams, they provide sustained drug release, improve wound healing, and treat skin infections, pain management, and dermatological conditions effectively.

5. Parenteral and Injectable Drug Delivery

Natural polymers like chitosan, alginate, gelatin, and hyaluronic acid enhance biocompatibility, biodegradability, and sustained drug release in parenteral and injectable formulations. They are used in nanoparticles, hydrogels, and microspheres for cancer therapy,

controlled protein delivery, and regenerative medicine, ensuring targeted, prolonged, and efficient drug action with minimal side effects.

6. Gene and Vaccine Delivery

Natural polymers like chitosan, alginate, hyaluronic acid, and dextran enhance gene and vaccine delivery by improving stability, cellular uptake, and controlled release. Used in nanoparticles, hydrogels, and microspheres, they protect genetic material, facilitate targeted delivery, and enhance immune responses, ensuring efficient DNA/RNA vaccine administration and gene therapy applications.

7. Cancer and Targeted Drug Delivery

Natural polymers like chitosan, alginate, hyaluronic acid, and gelatin enhance targeted drug delivery in cancer therapy by ensuring tumor-specific drug release, biodegradability, and prolonged circulation. Used in nanoparticles, hydrogels, and micelles, they improve drug accumulation at tumor sites, reducing systemic toxicity and enhancing chemotherapy and immunotherapy efficacy. Natural polymers like chitosan, alginate, and hyaluronic acid are utilized in targeted cancer drug delivery to improve tumor-specific release and reduce systemic toxicity. Used in nanoparticles, micelles, and hydrogels, these polymers enhance drug accumulation at cancer sites, improve efficacy, and enable personalized cancer therapies.

8. Wound Healing and Regenerative Medicine

Natural polymers like collagen, chitosan, alginate, and hyaluronic acid promote wound healing by providing moisture retention, antibacterial properties, and controlled drug release. Used in dressings, hydrogels, and scaffolds, they support tissue regeneration, accelerate healing, and enhance cell proliferation, making them ideal for skin regeneration and tissue repair.

FUTURE PERSPECTIVES AND ADVANCEMENTS

The future of natural polymers in drug delivery systems holds significant promise due to their sustainable, biocompatible, and biodegradable nature. As the demand for personalized and efficient therapies grows, natural polymers are poised to play an even more vital role in addressing complex medical challenges. Advances in Polymer Engineering and Synthesis: One of the most exciting areas of development is the modification of natural polymers to enhance their properties. Chemical modifications, such as grafting or crosslinking, can improve their mechanical strength, stability, and control over drug release. Additionally, biopolymer blending with synthetic polymers can create hybrid systems that combine the advantages of both materials, offering improved performance in drug delivery. Nanotechnology Integration: The integration of nanotechnology with natural polymers is revolutionizing the drug delivery landscape. Polymeric nanoparticles, micelles, and nanogels provide excellent platforms for targeted and controlled drug release. These nano-sized carriers can be engineered to enhance drug solubility, protect sensitive drugs, and improve bioavailability. Furthermore, the ability to

target specific tissues or cells through active targeting (e.g., receptor-mediated targeting) makes them ideal for applications in cancer therapy and gene delivery.

Smart and Stimuli-Responsive Systems: Future drug delivery systems will be more intelligent, responding dynamically to changes in the body's internal environment. Stimuli-responsive systems, such as pH-sensitive, temperature-sensitive, and enzyme-triggered carriers, are gaining attention for their ability to release drugs in a controlled and site-specific manner. These smart systems will provide patient-centric solutions by delivering drugs only when needed, minimizing side effects, and improving therapeutic outcomes. Sustainable and Eco-friendly Approaches: With increasing environmental concerns, the future of natural polymers in drug delivery systems will focus on creating eco-friendly, renewable, and biodegradable systems that align with the global push for sustainability in pharmaceutical practices.

CONCLUSION:

Natural polymers have emerged as a transformative class of materials in drug delivery systems, offering numerous advantages in terms of biocompatibility, biodegradability, and sustainability. Their inherent properties make them highly suitable for a range of pharmaceutical applications, from controlled and targeted drug delivery to gene therapy and tissue regeneration. One of the key strengths of natural polymers is their ability to enhance drug stability, bioavailability, and controlled release, which are essential for improving therapeutic outcomes while minimizing side effects. Polymers like chitosan, alginate, hyaluronic acid, and gelatin offer versatility, with specific functions such as mucoadhesion, enzyme-responsiveness, and pH-sensitivity, making them ideal for applications in oral, ocular, transdermal, injectable, and pulmonary drug delivery. The incorporation of advanced technologies such as nanotechnology, 3D printing, and smart drug delivery systems has further expanded the potential of natural polymers. These innovations enable site-specific drug release, improving drug accumulation at target sites like tumors and inflammatory tissues, while reducing systemic toxicity. Natural polymers' ability to degrade into non-toxic byproducts also ensures safety, which is crucial for both short- and long-term drug delivery applications.

Despite their advantages, challenges such as batch-to-batch variability, mechanical strength, and processing limitations remain. However, ongoing research into polymer modification, blending, and engineering is addressing these challenges, paving the way for more efficient and patient-friendly formulations. The future of natural polymers in drug delivery systems holds great promise. With continued advancements in polymer engineering, targeted therapies, and sustainable practices, natural polymers will play a pivotal role in shaping the future of precision medicine, making treatments more effective, safer, and tailored to individual patient needs.

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THE ROLE OF PROBIOTICS IN HUMAN HEALTH AND DISEASE MANAGEMENT

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ABSTRACT:

Probiotics are live microorganisms that, when consumed in appropriate amounts, offer various health benefits to the host. In recent years, extensive scientific research has highlighted their crucial role in promoting human health and managing diseases. They contribute to maintaining gut microbiota balance, strengthening immune function, and preventing gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and antibiotic-associated diarrhea. Furthermore, emerging studies suggest that probiotics have broader systemic effects, including regulating metabolic disorders, reducing inflammation, and supporting mental health through the gut-brain axis. This chapter delves into the mechanisms by which probiotics exert their beneficial effects, including pathogen inhibition, immune system modulation, and the production of bioactive compounds. It also explores the selection of probiotic strains, their safety considerations, and the challenges related to their formulation and stability. Additionally, the potential of probiotics in preventing and managing various health conditions such as obesity, diabetes, cardiovascular diseases, and neurodegenerative disorders will be critically examined. With advancements in biotechnology and growing consumer interest, probiotic-based therapies are gaining recognition in the field of personalized medicine. However, despite their promising applications, challenges such as regulatory hurdles and inconsistencies in clinical outcomes hinder their widespread adoption. The chapter will conclude with future directions in probiotic research, including the development of next-generation probiotics, synbiotics, and postbiotics, and their potential impact on public health. By providing a comprehensive overview of probiotics in health and disease management, this chapter aims to serve as a valuable resource for researchers, healthcare professionals, and industry experts in the pharmaceutical and nutraceutical sectors.

Keywords: Probiotics, Gut Microbiota, Gut Dysbiosis, Synbiotics, Postbiotics

INTRODUCTION:

Probiotics are defined as live microorganisms that, when consumed in adequate amounts, provide health benefits to the host. The term ‘probiotic’ is derived from the Greek words *pro* (for) and *bios* (life), which reflects their essential role in supporting health and well-being. These

beneficial microbes, primarily consisting of bacteria and some yeasts, are naturally present in the human gut and various fermented foods. They play a crucial role in maintaining microbial balance, enhancing digestion, boosting immune function, and preventing pathogenic infections. The concept of probiotics has existed for centuries, but their scientific exploration began in the early 20th century [1]. The Russian microbiologist and Nobel laureate 'Élie Metchnikoff' is credited as one of the pioneers in probiotic research. He proposed that consuming fermented dairy products rich in beneficial bacteria, such as yogurt, could help improve gut health and increase longevity. Metchnikoff's observations were based on studies of Bulgarian peasants who consumed large amounts of fermented milk and displayed remarkable health and longevity. Following Metchnikoff's discoveries, research on probiotics gained momentum, leading to the identification of specific bacterial strains with health benefits [2]. Early studies primarily focused on Lactobacillus and Bifidobacterium species, which are now widely recognized as the most common probiotics. The discovery of *Lactobacillus acidophilus* in the human intestine and *Bifidobacterium bifidum* in infants further strengthened the understanding of the role these microorganisms play in gut health.

During the mid-20th century, advancements in microbiology allowed for the isolation and characterization of probiotic strains with targeted health benefits. This led to the commercial production of probiotic supplements and fortified foods. Today, probiotics are extensively studied for their therapeutic potential in treating various diseases, including gastrointestinal disorders, metabolic syndromes, cardiovascular diseases, and neurodegenerative conditions. The emergence of next-generation probiotics, such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, highlights the ongoing advancements in probiotic research [3]. These novel strains are being explored for their potential in personalized medicine, offering targeted solutions for specific health conditions. The evolution of probiotics from traditional fermented foods to clinically validated therapeutic agents showcases their growing importance in modern healthcare.

Importance of Gut Microbiota in Human Health

The gut microbiota is a vast and several groups of bacteria found in the human gastrointestinal system. This environment contains billions of bacteria, viruses, fungus, and archaea. It is also known as the 'forgotten organ', is important in a variety of physiological functions such as digestion, metabolism, immunological function, and even brain health. Maintaining a healthy gut microbiota is critical for general health because it helps with the breakdown of complex carbohydrates, the fermentation of dietary fibres, and the production of key nutrients such short-chain fatty acids (SCFAs), vitamins (B12, K), and amino acids. SCFAs, which include butyrate, acetate, and propionate, provide energy to intestinal cells, build the gut barrier, and assist control inflammation. Beneficial bacteria help to produce anti-inflammatory

cytokines while limiting excessive immune activation, which reduces the risk of autoimmune and inflammatory illnesses including Crohn's disease, ulcerative colitis, and rheumatoid arthritis [4]. Dysbiosis has been related to a number of health problems, including digestive disorders, metabolic illnesses, and weakened immunity. Understanding the function of gut microbiota in health and illness is critical for developing targeted treatment methods, such as probiotics, prebiotics, and dietary therapies that restore microbial equilibrium.

Dysbiosis is linked to various health problems, including:

- *Gastrointestinal disorders:* Dysbiosis is a major factor in conditions like IBS, IBD, constipation, and diarrhea.
- *Obesity and metabolic disorders:* Research shows that gut microbiota influences fat storage, insulin sensitivity, and appetite regulation. People with obesity often have a higher ratio of Firmicutes to Bacteroidetes, leading to increased calorie absorption.
- *Mental health and the gut-brain axis:* The gut microbiota communicates with the brain through the vagus nerve, neurotransmitters, and immune signaling molecules. Imbalances in gut bacteria have been linked to anxiety, depression, and neurodegenerative diseases like Alzheimer’s and Parkinson’s.
- Cardiovascular diseases: Certain gut bacteria contribute to cholesterol metabolism and blood pressure regulation, impacting heart health.
- *Autoimmune diseases:* Dysbiosis has been associated with autoimmune disorders like type 1 diabetes, multiple sclerosis, and lupus.

Probiotics help restore microbial balance by introducing beneficial bacteria that outcompete harmful microbes, reinforce the gut barrier, and produce bioactive compounds that enhance health. They can modulate immune responses, regulate inflammation, and improve metabolic function, making them valuable tools in preventive and therapeutic healthcare. Antibiotics, while essential for treating infections, can eliminate beneficial bacteria along with harmful pathogens, further contributing to dysbiosis. Regular consumption of probiotics through fermented foods (e.g., yogurt, kefir, kimchi, miso, and kombucha) or probiotic supplements can help restore gut microbiota balance and promote long-term health [5].

MECHANISMS OF ACTION FOR PROBIOTICS

1. Modulation of gut microbiota

The gut microbiota is a dynamic and intricate ecology that comprises billions of species, including viruses, fungus, bacteria, and archaea. However, several factors, including unhealthy dietary patterns, chronic stress, infections, and excessive antibiotic use, can disrupt this delicate microbial balance. This disruption, known as dysbiosis, occurs when there is an imbalance between beneficial and harmful microorganisms, potentially leading to various health complications. Probiotics are essential for repairing and controlling the gut microbiota because

they encourage the development of good bacteria while inhibiting the spread of harmful ones. One of the most critical aspects of gut health is the balance between the two dominant bacterial phyla, *Firmicutes* and *Bacteroidetes*, which are crucial for metabolic and immune homeostasis. Research indicates that an altered Firmicutes-to-Bacteroidetes ratio is linked to conditions such as obesity, inflammatory bowel disease (IBD), and metabolic disorders. Probiotic strains, particularly those belonging to the *Lactobacillus* and *Bifidobacterium* genera, support microbial balance by increasing bacterial diversity and stimulating the production of beneficial metabolites. Additionally, probiotics enhance microbial resilience, enabling the gut microbiota to recover more efficiently from disturbances. They strengthen colonization resistance, a process in which beneficial microbes outcompete pathogenic bacteria, preventing their establishment in the gut. This protective function is fundamental for maintaining gut health and highlights the long-term advantages of probiotic supplementation in sustaining a well-balanced microbiome [6,7].

2. Immune system regulation

The gut microbiota is essential for sustaining the immune system, ensuring proper immune function and defense against infections. The gut-associated lymphoid tissue (GALT), which accounts for approximately 70% of the body's immune system, is essential for immune surveillance and response. Probiotics contribute to immune regulation by interacting directly and indirectly with GALT, enhancing immune function. One of the key ways probiotics support immune health is by stimulating the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). These cytokines help maintain immune tolerance and prevent excessive inflammatory responses that could lead to autoimmune disorders and chronic inflammatory diseases like rheumatoid arthritis and Crohn's disease. Simultaneously, probiotics help lower the levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are often elevated in conditions like IBS and IBD. By modulating these inflammatory markers, probiotics help promote a balanced immune response, reducing the risk of chronic inflammation. Moreover, probiotics enhance the activity of key immune cells, including natural killer (NK) cells, macrophages, and dendritic cells, which are critical components of the innate immune system [8]. They also boost the production of immunoglobulin A (IgA), an essential antibody that reinforces mucosal immunity and neutralizes harmful pathogens before they enter the bloodstream. Through these mechanisms, probiotics act as natural immune modulators, strengthening the body's defense against infections, reducing inflammation, and preventing autoimmune reactions, ultimately supporting overall immune system balance.

3. Competitive exclusion of pathogens

One of the most effective ways probiotics contribute to gut health is through competitive exclusion, a natural process where beneficial bacteria inhibit the colonization and proliferation of

harmful pathogens. This occurs through multiple mechanisms, ensuring that pathogenic bacteria are unable to establish themselves within the gut environment. A key aspect of competitive exclusion is adhesion site competition. The intestinal mucosa contains numerous attachment sites that bacteria use to anchor themselves and form colonies. By occupying these sites, probiotics physically block pathogens from binding to the intestinal lining, thereby preventing infection and inflammation [9]. Strains such as *Lactobacillus rhamnosus* and *Bifidobacterium bifidum* have been particularly effective in displacing harmful bacteria like *Escherichia coli, Salmonella,* and *Clostridium difficile*. Probiotics produce antimicrobial compounds, including bacteriocins, hydrogen peroxide, and organic acids, which create an inhospitable environment for pathogens. Bacteriocins are small protein-based toxins that selectively target and kill pathogenic bacteria without harming beneficial microbes. Organic acids, such as lactic acid and acetic acid, lower the pH of gut, making it difficult for harmful bacteria to survive. Probiotics also contribute to nutrient competition, depriving pathogens of essential resources needed for their growth. By efficiently utilizing available nutrients, probiotics ensure that pathogenic microorganisms are unable to thrive, further reinforcing the body's natural defense mechanisms [10].

4. Production of bioactive compounds

Probiotics are not just passive inhabitants of the gut; they actively produce a wide range of bioactive compounds that contribute to human health. These compounds include short-chain fatty acids (SCFAs), vitamins, antimicrobial peptides, and neurotransmitters, all of which play vital roles in maintaining gut integrity, metabolism, and overall well-being [11]. One of the most important categories of bioactive compounds produced by probiotics is SCFAs, including butyrate, acetate, and propionate. CFAs serve multiple functions:

- *Gut barrier integrity:* Butyrate strengthens the intestinal lining by promoting mucus production and enhancing the function of tight junctions between epithelial cells, preventing leaky gut syndrome.
- *Immune regulation:* SCFAs regulate immune responses by modulating the activity of regulatory T cells (Tregs), which help control excessive immune reactions and prevent autoimmune diseases.
- *Metabolic health:* SCFAs influence insulin sensitivity, appetite regulation, and fat metabolism, reducing the risk of obesity and type 2 diabetes [12].

In addition to SCFAs, probiotics produce vitamin K and the vital B vitamins (B2, B6, and B12), which are required for blood coagulation, red blood cell formation, and energy metabolism. Because of their involvement in vitamin synthesis, they are especially advantageous to people who have nutritional shortages or have diseases that impair nutrient absorption. Probiotics also improve gut health by creating neurotransmitters and neuroactive chemicals such gamma-aminobutyric acid (GABA), serotonin, and dopamine. These chemicals play an

important role in mood regulation, stress reduction, and cognitive function, emphasising the gut-brain axis as a vital area of probiotic study 13[].

PROBIOTICS AND GASTROINTESTINAL HEALTH

1. Role in Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD)

Irritable Bowel Syndrome (IBS)

IBS is a prevalent functional gastrointestinal illness characterised by stomach discomfort, bloating, diarrhoea, constipation, and irregular bowel movements. Although the exact cause of IBS is unclear, several factors contribute to its development, including gut dysbiosis, low-grade inflammation, visceral hypersensitivity, and abnormal gut-brain interactions [14]. Probiotics shows a beneficial role in IBS by:

- *Restoring gut microbiota balance*: IBS patients often have an altered microbial composition, with decreased levels of useful bacteria like *Lactobacillus* and *Bifidobacterium* and an overgrowth of harmful species. Probiotic supplementation helps reintroduce beneficial strains, improving microbial diversity.
- *Reducing inflammation:* Certain probiotic strains, such as *Lactobacillus plantarum* and *Bifidobacterium infantis*, have been shown to lower inflammatory markers in IBS patients, alleviating symptoms.
- *Improving gut motility:* Probiotics regulate intestinal transit time, helping to relieve constipation in IBS-C (constipation-predominant IBS) and reducing diarrhea in IBS-D (diarrhea-predominant IBS).
- *Modulating gut-brain signaling:* The gut microbiota influences the gut-brain axis, and probiotics can help regulate neurotransmitters like serotonin, which affects mood and gut motility [15].

Inflammatory Bowel Disease (IBD)

It refers to chronic inflammatory disorders of gastrointestinal system, which include Crohn's disease (CD) and ulcerative colitis (UC). Unlike IBS, which is a functional disorder, IBD involves immune system dysregulation, chronic inflammation, and intestinal tissue damage. Probiotics help in managing IBD by:

- *Regulating immune responses:* Probiotics promote anti-inflammatory cytokines (IL-10, TGF-β) while suppressing pro-inflammatory cytokines (TNF-α, IL-6), reducing intestinal inflammation.
- *Enhancing intestinal barrier function*: Certain strains, like *Lactobacillus rhamnosus GG* and *Escherichia coli Nissle* 1917, strengthen the gut lining by increasing mucin production and tight junction integrity, preventing intestinal permeability 'leaky gut'.

- *Reducing flare-ups:* Clinical trials indicate that probiotics, especially VSL#3 (a multi-strain probiotic formulation), can help maintain remission in mild-to-moderate ulcerative colitis and pouchitis (a complication after colectomy) [16,17].

2. Management of antibiotic-associated diarrhea (AAD)

Antibiotic use is essential for treating bacterial infections, but it often disrupts the gut microbiota by killing beneficial bacteria along with harmful pathogens. This imbalance can lead to AAD, a condition affecting up to 30% of patients taking antibiotics. AAD symptoms range from mild diarrhea to severe cases involving Clostridium difficile infections (CDI), which can cause life-threatening colitis [18]. Probiotics help prevent and manage AAD by:

- *Replenishing beneficial gut bacteria:* Antibiotics reduce microbial diversity, allowing harmful bacteria like *Clostridium difficile* to overgrow. Probiotics, particularly *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii*, help restore balance and prevent dysbiosis.
- *Producing antimicrobial substances:* Probiotics release bacteriocins and organic acids that inhibit the growth of opportunistic pathogens, reducing the risk of CDI.
- *Enhancing gut barrier integrity:* Probiotics strengthen the intestinal lining, reducing permeability and preventing toxins from triggering inflammation.
- *Modulating immune responses*: They promote the production of IgA antibodies, enhancing mucosal immunity and reducing antibiotic-induced gut inflammation [19].

3. Impact on gut dysbiosis

Gut dysbiosis is characterised by reduced microbial diversity, loss of helpful bacteria, and expansion of dangerous pathogens. Probiotics help correct dysbiosis by:

- *Restoring microbial diversity:* Multi-strain probiotics reintroduce beneficial species, improving the overall balance of gut flora.
- *Outcompeting harmful microbes*: Probiotics produce antimicrobial peptides and organic acids that inhibit pathogenic bacteria and restore microbial equilibrium.
- *Fermenting dietary fibers into SCFAs:* SCFAs like butyrate, acetate, and propionate enhance gut health, regulate inflammation, and support metabolic function.
- *Reducing endotoxin production*: Dysbiosis often leads to an increase in lipopolysaccharides (LPS), which trigger systemic inflammation. Probiotics help lower LPS levels, reducing inflammation-related diseases [20].

THERAPEUTIC AND FUTURE PERSPECTIVE OF PROBIOTICS

1. Next-generation probiotics and synbiotics

Next-generation probiotics (NGPs) are traditional probiotics primarily consist of well-characterized *Lactobacillus* and *Bifidobacterium* species. However, recent discoveries have

identified NGPs, which include emerging gut-resident bacterial strains with enhanced therapeutic potential. These include:

- *Akkermansia muciniphila*: Known for its role in gut barrier integrity, obesity prevention, and metabolic health.
- *Faecalibacterium prausnitzii*: A potent anti-inflammatory bacterium linked to gut homeostasis and inflammatory bowel disease (IBD) relief.
- *Clostridium butyricum:* A producer of butyrate, a short-chain fatty acid (SCFA) that supports gut health and reduces inflammation [21].

Synbiotics

It refers to a combination of probiotics and prebiotics, designed to improve the survival, growth, and functionality of useful bacteria in the gut. Prebiotics, such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), act as nutritional substrates that selectively fuel probiotic bacteria, maximizing their effectiveness. Types of synbiotics:

- *Complementary synbiotics*: Probiotics and prebiotics both are independently beneficial for gut health.
- *Synergistic synbiotics*: A prebiotic specifically selected to promote the growth of a paired probiotic strain, ensuring enhanced microbial activity [22].

2. Postbiotics and their potential benefits

What are postbiotics?

Postbiotics are bioactive compounds produced by probiotics during fermentation. Unlike live probiotics, postbiotics do not require colonization or survival in the gut, making them more stable and easier to incorporate into pharmaceutical and nutraceutical formulations. Common postbiotic compounds include:

- *Short-chain fatty acids*: Improve gut barrier function, regulate inflammation, and support metabolic health.
- *Peptides and proteins*: Exhibit antimicrobial and immunomodulatory properties.
- *Exopolysaccharides (EPS)*: Enhance gut microbiota balance and immune function.
- *Enzymes and vitamins (e.g., vit B, K)*: Play crucial roles in cellular metabolism and overall health [23].

Potential benefits of postbiotics

- *More stability and longer shelf life:* Unlike probiotics, which require live cultures, postbiotics can be stored without refrigeration, making them ideal for pharmaceutical and food industries.
- *Stronger immunomodulation:* Postbiotics influence the immune system without the risks associated with live bacteria, reducing concerns about infections in immunocompromised individuals.

- *Better tolerance and safety:* Postbiotics are less likely to cause adverse effects, making them suitable for infants, elderly individuals, and critically ill patients.
- *Potential for precision medicine:* Since postbiotics have well-defined molecular properties, they can be tailored for specific health conditions, such as colitis, metabolic syndrome, and neurological disorders [24,25].

PERSONALIZED PROBIOTIC THERAPY AND FUTURE RESEARCH DIRECTIONS

The concept of personalized medicine has gained momentum, and probiotics are no exception. With advances in microbiome sequencing and artificial intelligence (AI)-driven analysis, scientists can now identify an individual's gut microbiota composition and recommend customized probiotic formulations. Key aspects of personalized probiotic therapy include:

- *Microbiome profiling*: Analyzing an individual's gut microbiota to determine specific imbalances and deficiencies.
- *Strain-specific probiotics*: Instead of generic probiotic supplements, tailor-made formulations are designed to address specific gut health needs.
- *Diet and lifestyle integration*: Personalized probiotics work best when combined with dietary and lifestyle adjustments, ensuring optimal microbiome restoration.
- *Targeted disease management*: Emerging research explores probiotics for obesity, diabetes, mental health disorders (via the gut-brain axis), and autoimmune diseases [26,27].

1. The role of artificial intelligence in probiotic research

Artificial Intelligence (AI) is transforming probiotic research by enabling large-scale microbiome data analysis, predicting probiotic effectiveness, and developing personalized therapies. Traditionally reliant on trial-and-error methods, probiotic research now benefits from AI-driven machine learning, big data analytics, and bioinformatics, which enhance our understanding of gut microbiota interactions. AI identifies microbial signatures linked to health and disease, predicts probiotic responses, and optimizes strain selection, dosage, and delivery methods. Additionally, AI accelerates drug discovery by identifying bioactive postbiotics, engineering Live Biotherapeutic Products (LBPs), and developing antibiotic alternatives. Companies like BiomeSense, Viome, and Ginkgo Bioworks leverage AI to create precision probiotics for conditions such as IBS, IBD, metabolic disorders, and mental health [28,29]. Looking ahead, AI-powered real-time microbiome monitoring and predictive health insights will further personalize probiotic therapy. However, challenges such as data standardization, regulatory approvals, and privacy concerns must be addressed to unlock AI's full potential in microbiome-based medicine [30].

CONCLUSION AND FUTURE DIRECTIONS

Probiotics have emerged as a promising tool for promoting human health and managing various diseases, particularly those related to gut microbiota imbalance. Advances in microbiome research have deepened our understanding of the complex interactions between probiotics and host physiology, highlighting their potential in gastrointestinal health, immune regulation, metabolic disorders, and even neurological conditions. With growing scientific evidence supporting their benefits, probiotics are increasingly being integrated into mainstream healthcare and personalized medicine. However, despite their proven therapeutic potential, challenges such as strain-specific efficacy, variability in individual responses, and regulatory considerations remain key hurdles in their widespread clinical adoption. The future of probiotic research is being shaped by cutting-edge technologies, particularly AI, bioinformatics, and next-generation sequencing, which are revolutionizing microbiome analysis and probiotic strain selection. AI-driven models are helping scientists design personalized probiotic therapies, optimize strain combinations, and develop microbiome-targeted therapeutics such as postbiotics and LBPs). Additionally, the emergence of synbiotics combinations of probiotics and prebiotics is paving the way for more effective gut microbiota modulation. Further large-scale clinical trials, standardized protocols, and regulatory frameworks are needed to validate the safety, efficacy, and long-term impact of probiotic interventions. Personalized probiotic therapies, based on an individual's genetic makeup, microbiome composition, and lifestyle factors, will likely define the next era of probiotic applications. Moreover, collaborations between researchers, healthcare providers, and biotech industries will be crucial in translating probiotic research into real-world therapeutic solutions.

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TRENDS OF HERBAL MEDICINES IN COSMECEUTICALS

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ABSTRACT:

The growing demand for natural and sustainable skincare solutions has led to the increasing incorporation of herbal medicine into cosmeceuticals. This chapter explores the latest trends in herbal-based cosmeceuticals, highlighting the benefits, scientific advancements, and consumer preferences driving this market shift. Key botanical ingredients such as aloevera, green tea, turmeric, and ginseng are examined for their bioactive compounds that promote skin health, anti-aging, and protection against environmental stressors. The role of phytochemicals, antioxidants, and essential oils in enhancing skin rejuvenation is also discussed. Additionally, emerging technologies in herbal extraction, formulation innovations, and regulatory considerations are explored to ensure efficacy and safety. The chapter further addresses the challenges and future prospects of herbal medicine in cosmeceuticals, emphasizing the balance between traditional knowledge and modern scientific validation. This evolving trend signifies a shift towards holistic beauty solutions, aligning with consumer preferences for natural and effective skincare products.

Keywords: Herbal Medicines, Cosmeceuticals, Holistic Approach, Consumer Compliance

INTRODUCTION:

Cosmeceuticals are a hybrid category of products that combine the benefits of cosmetics and pharmaceuticals. Unlike regular cosmetics, which primarily focus on enhancing appearance, cosmeceuticals contain bioactive ingredients that provide therapeutic effects on the skin. These products aim to improve skin health, treat specific dermatological conditions, and offer anti-aging, anti-inflammatory, or skin-repairing properties.

The term "cosmeceutical" was popularized by Dr. Albert Kligman in the 1980s to describe skincare products with biologically active compounds that influence skin function. While cosmeceuticals are not classified as drugs, they go beyond traditional cosmetics by delivering scientifically backed benefits. Examples include anti-aging creams with retinoids, serums infused with herbal extracts, and sunscreens with antioxidant-rich formulations.

Herbal cosmeceuticals, in particular, utilize plant-derived ingredients such as aloe vera, green tea, turmeric, and ginseng, offering natural and holistic skincare solutions. The increasing

demand for these products is driven by consumer preferences for organic, sustainable, and effective skincare options [1,2].

EVOLUTION OF HERBAL MEDICINE IN SKINCARE

The use of herbal medicine in skincare dates back thousands of years, with civilizations across the world incorporating plant-based remedies for beauty and dermatological care. Over time, the evolution of herbal skincare has been shaped by traditional practices, scientific advancements, and consumer demand for natural products[3-5].

1. Ancient Herbal Skincare Practices

- **Egyptian Civilization (3000 BCE)** – The Egyptians used aloe vera, honey, and essential oils for skin hydration and anti-aging. Cleopatra reportedly used milk and rosewater in her beauty regimen.
- **Traditional Chinese Medicine (TCM)** – Herbs like ginseng, green tea, and goji berries were used for skin rejuvenation, detoxification, and anti-aging benefits.
- **Ayurveda (India, 5000 BCE)** – Herbal preparations, including turmeric, sandalwood, neem, and saffron, were widely used for treating skin ailments and enhancing complexion.
- **Greek and Roman Eras** – Olive oil, myrrh, and herbal baths were popular for nourishing and protecting the skin.

2. Middle Ages to Renaissance (5th–17th Century)

- Herbal medicine was refined with the development of distillation techniques, leading to essential oils for skincare.
- European apothecaries used plant extracts like chamomile and rosemary in ointments for skin healing.

3. Industrial Revolution & 20th Century

- The rise of synthetic cosmetics in the 19th and 20th centuries led to a decline in traditional herbal remedies.
- However, concerns over chemical ingredients and their side effects sparked renewed interest in natural and herbal skincare.

4. Modern Herbal Cosmeceuticals (21st Century & Beyond)

- Advances in biotechnology and phytochemistry have validated the effectiveness of plant-based ingredients.
- Nanoencapsulation and green chemistry have improved the stability and absorption of herbal extracts.
- The rise of organic, vegan, and sustainable skincare has driven the growth of herbal cosmeceuticals in the global market.

The evolution of herbal medicine in skincare reflects a fusion of ancient wisdom and modern science, offering safe and effective solutions that align with the growing demand for natural beauty.

RISING CONSUMER PREFERENCE FOR NATURAL PRODUCTS

In recent years, there has been a significant shift in consumer preferences toward natural and herbal-based skincare products. This trend is driven by growing awareness of the potential risks associated with synthetic chemicals, environmental concerns, and a desire for safer, sustainable, and effective skincare solutions[6-9].

1. Awareness of Chemical-Free Skincare

- Consumers are becoming more informed about harmful ingredients like parabens, sulfates, and synthetic fragrances, leading to a preference for plant-based alternatives.
- Social media and digital marketing have amplified discussions on clean beauty, encouraging brands to adopt transparency in ingredient sourcing.

2. Demand for Organic and Sustainable Beauty

- The rise of eco-conscious consumers has fueled the demand for ethically sourced and environmentally friendly skincare products.
- Brands are incorporating biodegradable packaging, cruelty-free testing, and sustainable harvesting practices to align with consumer values.

3. Influence of Wellness and Holistic Lifestyles

- The popularity of Ayurveda, Traditional Chinese Medicine (TCM), and holistic wellness practices has increased interest in herbal cosmeceuticals.
- Consumers seek products with multifunctional benefits, such as turmeric for anti-inflammatory properties or aloe vera for hydration and healing.

4. Effectiveness and Scientific Validation

- Advances in research have confirmed the efficacy of herbal ingredients, reinforcing consumer trust in natural formulations.
- Innovations in biotechnology, such as nanoencapsulation of herbal extracts, have enhanced the stability and absorption of active compounds.

5. Growth of the Natural Beauty Market

- The global natural skincare industry has witnessed rapid growth, with many mainstream brands integrating herbal ingredients into their formulations.
- Independent and niche brands focusing on botanical skincare are gaining popularity, often marketed as "clean beauty" or "green beauty" products.

HERBAL INGREDIENTS IN COSMECEUTICALS

Herbal cosmeceuticals harness the power of plant-based ingredients to promote skin health, offering benefits such as anti-aging, hydration, skin brightening, and protection against

environmental damage. Below are some of the most commonly used and scientifically recognized herbal ingredients in cosmeceuticals[10-12].

1. Aloe Vera (*Aloe barbadensis* miller)

- **Benefits:** Hydrating, soothing, and anti-inflammatory properties
- **Uses:** Found in moisturizers, sunscreens, and after-sun gels for calming irritated skin
- **Key Compounds:** Polysaccharides, vitamins, and antioxidants that promote skin healing

2. Green Tea (*Camellia sinensis*)

- **Benefits:** Rich in antioxidants, anti-aging, and UV protection
- **Uses:** Included in serums, creams, and face masks for reducing fine lines and protecting against free radicals
- **Key Compounds:** Catechins (EGCG) that combat oxidative stress and inflammation

3. Turmeric (*Curcuma longa*)

- **Benefits:** Anti-inflammatory, skin-brightening, and antimicrobial
- **Uses:** Common in creams, masks, and acne treatments to even out skin tone and reduce blemishes
- **Key Compounds:** Curcumin, known for its powerful antioxidant and healing properties

4. Ginseng (*Panax ginseng*)

- **Benefits:** Improves skin elasticity, stimulates collagen production, and enhances radiance
- **Uses:** Present in anti-aging serums and revitalizing creams
- **Key Compounds:** Ginsenosides, which promote skin regeneration and reduce wrinkles

5. Neem (*Azadirachta indica*)

- **Benefits:** Antibacterial, anti-inflammatory, and acne-fighting properties
- **Uses:** Found in face washes, anti-acne creams, and scalp treatments
- **Key Compounds:** Nimbidin and azadirachtin, which help in treating acne and skin infections

6. Licorice Root (*Glycyrrhiza glabra*)

- **Benefits:** Skin brightening, anti-inflammatory, and pigmentation reduction
- **Uses:** Used in skin-lightening creams and serums for hyperpigmentation and dark spots
- **Key Compounds:** Glabridin, which inhibits melanin production and evens out skin tone

7. Rosehip Oil (*Rosa canina*)

- **Benefits:** Rich in vitamin C, promotes skin regeneration, and reduces scarring
- **Uses:** Added to facial oils, anti-aging serums, and scar treatment products
- **Key Compounds:** Essential fatty acids and retinoic acid, which boost skin renewal

8. Chamomile (*Matricaria chamomilla*)

- **Benefits:** Calming, anti-inflammatory, and skin-soothing properties
- **Uses:** Present in sensitive-skin formulations, including toners and moisturizers

- **Key Compounds:** Apigenin, which helps reduce redness and irritation

9. Essential Oils (Lavender, Tea Tree, Rose, etc.)

- **Benefits:** Various properties, including antibacterial, calming, and anti-aging effects
- **Uses:** Found in serums, face oils, and aromatherapy-based skincare
- **Key Compounds:** Terpenes and flavonoids that provide therapeutic benefits

These key herbal ingredients play a vital role in modern cosmeceuticals, offering natural alternatives to synthetic skincare solutions while enhancing efficacy through scientific research and advanced formulations.

SCIENTIFIC BASIS OF HERBAL COSMECEUTICALS

The effectiveness of herbal cosmeceuticals is supported by scientific research on the bioactive compounds found in plants. These compounds offer a range of skin benefits, including antioxidant protection, anti-inflammatory effects, collagen stimulation, and antimicrobial properties. The following key scientific principles explain the role of herbal ingredients in skincare[13-15]:

1. Role of Phytochemicals in Skin Health

Phytochemicals are natural bioactive compounds found in plants that contribute to their therapeutic effects. Some important classes include:

- **Flavonoids (e.g., Quercetin, Kaempferol)** – Found in green tea, chamomile, and citrus fruits; protect skin from oxidative stress and UV damage.
- **Polyphenols (e.g., Catechins, Resveratrol)** – Found in grape seeds, green tea, and berries; provide anti-aging and anti-inflammatory effects.
- **Alkaloids (e.g., Berberine, Caffeine)** – Found in coffee, neem, and goldenseal; help with skin detoxification and circulation.
- **Terpenoids (e.g., Carotenoids, Saponins)** – Found in turmeric, ginseng, and calendula; aid in wound healing and collagen synthesis.

2. Antioxidant Activity and Free Radical Protection

- Herbal ingredients such as green tea, ginseng, and rosemary contain high levels of antioxidants that neutralize free radicals.
- Free radicals cause oxidative stress, which leads to premature aging, fine lines, and skin damage.
- Polyphenols and flavonoids in herbal extracts help maintain skin elasticity and reduce the appearance of wrinkles.

3. Anti-Inflammatory and Skin-Calming Properties

- Many herbal cosmeceuticals reduce skin inflammation caused by environmental stressors, UV exposure, and skin disorders.

- **Turmeric (Curcumin), Aloe Vera, and Chamomile** contain potent anti-inflammatory agents that soothe irritated skin and reduce redness.
- These properties are beneficial in treating conditions like acne, eczema, and rosacea.

4. Herbal Extracts and Skin Penetration Technologies

- Traditional herbal formulations faced challenges in delivering active compounds deep into the skin.
- Advanced technologies such as **nanoencapsulation, liposomal delivery, and hydrogel formulations** enhance the bioavailability and absorption of herbal extracts.
- For example, **nano-sized curcumin and ginseng extracts** improve penetration and effectiveness in anti-aging treatments.

5. Herbal Ingredients and Collagen Synthesis

- Collagen is essential for maintaining skin structure and elasticity.
- **Ginseng, Gotu Kola (Centella Asiatica), and Rosehip Oil** are known to stimulate collagen production and improve skin firmness.
- These herbs promote fibroblast activity, leading to improved wound healing and reduced wrinkle formation.

6. Antimicrobial and Skin Protection Properties

- Many herbal extracts possess natural antibacterial and antifungal properties, making them effective in acne and skin infection treatments.
- **Neem, Tea Tree Oil, and Licorice Root** help combat acne-causing bacteria and reduce breakouts without harsh synthetic chemicals.
- **Sunscreen formulations** are also incorporating botanical UV protectants such as green tea and red algae to reduce photodamage.

7. Clinical Studies Supporting Herbal Cosmeceuticals

- Research has shown that **aloe vera** accelerates wound healing by increasing fibroblast activity.
- Studies on **green tea polyphenols** have demonstrated their role in reducing UV-induced skin damage and improving skin hydration.
- **Curcumin (turmeric)** has been clinically tested for its role in reducing hyperpigmentation and improving skin tone.

The scientific foundation of herbal cosmeceuticals lies in their bioactive compounds, which provide therapeutic skin benefits backed by modern research. Advances in formulation technologies have enhanced their efficacy, making them a key component in natural and effective skincare solutions.

FORMULATION TRENDS IN HERBAL COSMECEUTICALS

The increasing demand for herbal cosmeceuticals has led to advancements in formulation techniques to enhance the efficacy, stability, and delivery of bioactive compounds. Modern trends focus on sustainable, science-backed, and consumer-friendly innovations. Below are the key formulation trends shaping the herbal cosmeceutical industry[16-19].

1. Advanced Herbal Extraction Techniques

To maximize the potency of plant-based ingredients, modern extraction methods ensure higher concentrations of active compounds while preserving their bioavailability:

- **Supercritical CO_2 Extraction** – A solvent-free method used for essential oils and antioxidants (e.g., rosehip oil, green tea extracts).
- **Ultrasound-Assisted Extraction (UAE)** – Enhances the yield of bioactives such as flavonoids and polyphenols while reducing processing time.
- **Fermentation-Based Extraction** – Boosts the skin absorption of plant extracts (e.g., fermented ginseng and rice water) and enhances their probiotic benefits.

2. Nanoformulations for Enhanced Absorption

- **Nanocarriers (e.g., liposomes, nanospheres, solid lipid nanoparticles)** help increase the stability and penetration of herbal extracts into deeper skin layers.
- Example: **Nano-encapsulated curcumin** is used for hyperpigmentation treatments due to improved solubility and bioavailability.
- **Hydrogel-based herbal formulations** provide long-lasting hydration and targeted delivery of plant actives.

3. Green Chemistry and Sustainable Formulations

- The use of **biodegradable ingredients** and **plant-based emulsifiers** replaces synthetic stabilizers and preservatives.
- **Waterless formulations** (e.g., herbal-infused balms, solid cleansers, and powder-based masks) reduce the need for synthetic preservatives while minimizing environmental impact.
- **Upcycled ingredients** (e.g., fruit extracts from food industry byproducts) promote zero-waste skincare solutions.

4. Probiotics and Prebiotics in Herbal Skincare

- Fermented herbal extracts enhance the skin microbiome, improving barrier function and reducing inflammation.
- Examples include **fermented green tea**, **kombucha-based skincare**, and **probiotic-infused aloe vera formulations** to balance skin flora.

5. Multi-Functional and Minimalist Formulations

- Consumers prefer **all-in-one products** with multiple skin benefits, such as herbal serums that provide hydration, anti-aging, and sun protection.
- Example: **Turmeric-infused BB creams** combine skincare with makeup for natural coverage and skin healing properties.

6. Herbal Sunscreens and UV Protection Innovations

- Botanicals such as **green tea, red algae, and raspberry seed oil** are being integrated into sunscreens for natural SPF enhancement.
- **Hybrid sunscreens** combine mineral UV filters (zinc oxide) with antioxidant-rich herbal extracts for added skin defense.

7. Clean Label and Transparent Ingredient Sourcing

- Consumers demand **transparency in labeling**, favoring products with recognizable and traceable herbal ingredients.
- Formulations now avoid **parabens, sulfates, artificial fragrances, and synthetic dyes**, aligning with the "clean beauty" movement.

Herbal cosmeceuticals are evolving through scientific innovations, focusing on advanced extraction, sustainable practices, and high-performance formulations. These trends not only enhance the efficacy of herbal ingredients but also align with consumer preferences for clean, green, and effective skincare solutions.

MARKET TRENDS AND CONSUMER INSIGHTS

The herbal cosmeceutical industry has experienced significant growth due to increasing consumer awareness of natural skincare, sustainability concerns, and the demand for science-backed herbal ingredients. Below are key market trends and insights driving the industry[20-22].

1. Growth of the Herbal Cosmeceutical Market

- The global herbal cosmeceutical market is expanding rapidly, with an estimated CAGR of 8-10% over the next decade.
- The Asia-Pacific region, particularly India, China, and South Korea, dominates the market due to traditional herbal medicine (Ayurveda, TCM, and K-beauty).
- North America and Europe are experiencing a surge in demand for organic, cruelty-free, and clean beauty products.

2. Increasing Consumer Demand for Natural and Organic Skincare

- **Clean Beauty Movement** – Consumers prefer skincare products free from parabens, sulfates, synthetic fragrances, and artificial colors.
- **Organic Certifications Matter** – Brands with USDA Organic, Ecocert, and COSMOS certifications have a competitive advantage.

- **Vegan and Cruelty-Free Products** – Ethical concerns have led to a rise in plant-based formulations, avoiding animal-derived ingredients.

3. Rise of Ayurveda, Traditional Chinese Medicine (TCM), and K-Beauty

- **Ayurvedic and Herbal Beauty** – Indian brands are incorporating ingredients like turmeric, neem, and ashwagandha into skincare.
- **TCM Influence** – Chinese beauty brands use ginseng, goji berries, and licorice root for anti-aging and skin brightening.
- **K-Beauty Trend** – Korean brands integrate fermented herbal extracts, green tea, and centella asiatica into cosmeceuticals.

4. Growing Popularity of Functional and Multi-Benefit Products

- **Herbal-Infused Sunscreens** – Green tea, raspberry seed oil, and algae-based SPF products are trending.
- **Adaptogenic Skincare** – Herbs like holy basil (tulsi), reishi mushroom, and ginseng help skin adapt to stress and pollution.
- **Hybrid Skincare & Makeup** – BB creams, tinted moisturizers, and serums infused with herbal actives provide skincare benefits while offering coverage.

5. Influence of Social Media and Digital Marketing

- **Instagram & TikTok Trends** – Herbal skincare DIYs, product reviews, and before-after results drive consumer purchasing behavior.
- **Influencer & Celebrity Endorsements** – Brands collaborate with wellness influencers promoting clean and green beauty.
- **E-commerce Boom** – Online marketplaces like Amazon, Sephora, and niche herbal beauty platforms contribute to increased accessibility.

6. Shift Toward Sustainable and Eco-Friendly Packaging

- **Zero-Waste Packaging** – Recyclable, biodegradable, and refillable containers are gaining traction.
- **Waterless Formulations** – Solid skincare bars, powders, and concentrated serums reduce packaging waste and carbon footprint.
- **Upcycled Ingredients** – Brands utilize fruit extracts, plant residues, and herbal byproducts to minimize waste.

7. Challenges in the Herbal Cosmeceutical Market

- **Regulatory Hurdles** – Herbal products must comply with varying regulations (FDA, EU Cosmetic Regulation, etc.), affecting global expansion.
- **Standardization Issues** – Variability in herbal extract potency can impact product consistency.

- **Consumer Skepticism** – While demand is high, some consumers doubt the efficacy of herbal formulations compared to synthetic alternatives.

The herbal cosmeceutical market is experiencing strong growth, driven by consumer demand for natural, sustainable, and multifunctional skincare products. Brands that focus on scientific validation, eco-friendly practices, and digital engagement are more likely to succeed in this evolving landscape.

REGULATORY AND SAFETY CONSIDERATIONS

As the herbal cosmeceutical industry continues to grow, regulatory and safety considerations play a crucial role in ensuring product efficacy, consumer safety, and market compliance. Different countries have established guidelines for the formulation, labeling, and marketing of herbal cosmeceuticals. Below are key regulatory and safety factors governing this industry.

1. Regulatory Framework for Herbal Cosmeceuticals

Unlike pharmaceutical drugs, cosmeceuticals occupy a grey area between cosmetics and medicines. Various regulatory bodies oversee their safety and claims[23-24]:

a) United States (FDA – Food and Drug Administration)

- The FDA does not recognize "cosmeceuticals" as a separate category; products are classified as either cosmetics or drugs**.**
- Cosmetics (e.g., herbal face creams) do not require FDA approval but must be safe for consumer use.
- Drug-claim products (e.g., anti-acne creams with active herbal ingredients) must undergo New Drug Application (NDA) approval**.**
- The Federal Trade Commission (FTC) monitors misleading herbal product claims.

b) European Union (EU Cosmetic Regulation 1223/2009)

- Requires herbal cosmeceuticals to be dermatologically tested for safety and efficacy.
- Restricted ingredients list (Annex II & III) outlines banned or limited-use herbal extracts.
- Cosmetic Product Safety Report (CPSR) must be submitted before market approval.
- Requires Good Manufacturing Practices (GMP) certification for manufacturers.

c) India (AYUSH & CDSCO)

- Governed by the Ministry of AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy) and Central Drugs Standard Control Organization (CDSCO)**.**
- Herbal cosmetics follow BIS (Bureau of Indian Standards) guidelines, ensuring they comply with Ayurvedic principles.
- Products with medicinal claims must undergo clinical validation.

d) China (National Medical Products Administration – NMPA)

- Stricter regulatory process for herbal skincare under Special Use Cosmetics.

- Requires animal testing for imported herbal products (except for exempted categories).
- Traditional Chinese Medicine (TCM)-based cosmeceuticals follow additional herbal product safety evaluations.

e) Other Global Regulatory Bodies

- **Japan (PMDA)** – Requires safety validation for Kampo-based herbal formulations.
- **South Korea (MFDS)** – Strict rules for K-beauty herbal formulations, requiring efficacy studies.
- **Australia (TGA)** – Herbal cosmeceuticals are regulated under the **Therapeutic** Goods Administration (TGA) if they claim medical benefits.

2. Labeling and Marketing Compliance

- Ingredient Transparency – Herbal cosmeceuticals must list INCI (International Nomenclature of Cosmetic Ingredients) names.
- Avoiding False Claims **–** Terms like "100% herbal" or "chemical-free" are regulated to prevent misleading advertising.
- Patch Testing & Allergy Warnings – Must indicate potential allergens like essential oils, plant extracts, and preservatives**.**

3. Safety and Toxicological Assessments

- Microbial Testing – Ensures herbal extracts are free from bacterial contamination.
- Heavy Metal Testing – Some plant-based ingredients may contain traces of lead, mercury, or arsenic, requiring strict safety screening.
- Stability Testing – Confirms the shelf life and effectiveness of herbal actives over time.
- Clinical Trials & Dermatological Testing – Increasingly necessary to verify claims of herbal ingredients for skin benefits.

4. Challenges in Herbal Cosmeceutical Regulations

- Lack of Standardization – Variation in herbal extract concentrations can lead to inconsistent product performance.
- Cross-Border Regulatory Differences – A product approved in India or China may require reformulation for EU or US markets.
- Consumer Perception & Safety Concerns – Despite being "natural," some herbal extracts (e.g., citrus oils, neem) can cause skin irritation or photosensitivity**.**

5. Future Trends in Herbal Cosmeceutical Regulation

- Harmonization of global herbal regulations to streamline approvals.
- Ban on animal testing leading to alternative safety assessment methods.
- Blockchain & AI-based ingredient tracking for improved transparency in herbal sourcing.
- More rigorous clinical validation for cosmeceutical claims (e.g., proving turmeric’s skin-brightening effects through trials).

Regulatory and safety considerations ensure that herbal cosmeceuticals are safe, effective, and legally compliant. While the market is rapidly expanding, adherence to global regulatory standards, scientific validation, and ethical marketing is critical for brand success.

CHALLENGES AND FUTURE PERSPECTIVES:

The herbal cosmeceutical industry is witnessing rapid growth, driven by consumer demand for natural, safe, and effective skincare solutions. However, despite its potential, the sector faces several challenges that impact product development, market acceptance, and regulatory compliance. At the same time, technological advancements and evolving consumer preferences are shaping the future of herbal cosmeceuticals. While herbal cosmeceuticals face challenges in standardization, regulation, and scientific validation, the future holds promising advancements in biotechnology, sustainable formulations, and personalized skincare. As consumer awareness grows and research evolves, the industry will continue to expand, offering innovative, safe, and effective herbal solutions for skincare.

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PREVALENCE OF DEPRESSION, ANXIETY AND STRESS AMONG PHYSIOTHERAPY STUDENTS DURING CLINICAL POSTINGS, POST COVID-19

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ABSTRACT:

BACKGROUND: Depression, Anxiety and Stress are well- known among youngsters. As the education proceed to higher level, the student experiences more stressful events.

A study in 2013 reported high level of stress among medical students, reported as 47.7 % anxiety and 35.1% depression. Due to Covid-19 breakdown, medical students were facing sudden change in their training routine, change in the teaching methods (online sessions), increased screen time[30] and increased time spent in social media and digital devices, leading to sleep disturbances[31], uncertainties about the future, fear of infection, altered living conditions, increased risk of contacting the infection, news about shortage of personal protective equipment, quarantine induced boredom, frustrations, lack of freedom, etc. These were also the main cause of Depression, Anxiety and Stress among medical students.

The level of Depression, Anxiety and Stress is reported in few literature articles. This study aims to find out the prevalence of Depression, Anxiety and Stress among Physiotherapy Students who are attending clinical postings, post COVID-19.

OBJECTIVES: The main objective of the study is to find out prevalence of Depression, Anxiety and Stress among physiotherapy students who are attending clinical postings, post covid-19. Another objective is to find out frequency of prevalence of stress, anxiety and depression among students of all the years who are attending clinical postings in wards, ICU or even in outpatient departments (OPD's).

METHODOLOGY: This is a cross-sectional observational study involving a total of 120 participants aged between 17 to 26 were selected according to the inclusion criteria. The Data was collected using the self-administered standardized DASS-42 (Depression, Anxiety and Stress scale).

RESULTS: The Prevalence of Depression, Anxiety, and Stress among Physiotherapy students who were attending clinical postings, post COVID-19 was found to be: Depression (83.4%), Anxiety (87.5%), Stress (65.9%). The prevalence of Depression was found to be higher than the prevalence of Anxiety and Stress among students.

CONCLUSION: In this study, it was concluded among Physiotherapy Students who were attending Clinical Postings post COVID-19 prevails Depression, Anxiety and Stress. Depression was reported higher than the other two (anxiety and stress). Also, it was concluded that irrespective of any area of posting (whether ICUs, wards, OPD), the frequency of Depression, Anxiety and Stress was noted amongst students. Wherein, the reports were higher for ICU's and OPD than wards.

KEYWORDS: Depression, Anxiety, Stress, DASS-42, Prevalence, COVID- 19.

INTRODUCTION:

HANS SELYE, the Canadian physiologist in 1936, first introduced the concept of stress in life sciences. It is a concept borrowed from the natural sciences, derived from Latin word "Stringere".[1] According to him "stress is defined as, the nonspecific response of the body to any demand or "our reaction to events, environmental or internal, that tax or exceed our adaptive resources".[1]

We have a certain number of coping resources, and when those coping resources are challenged or exceeded, the usual outcome is stress.[1] Stress reactions consist of both physical and emotional responses. Human beings deal with stress in our own unique way.[1]

University students experience a high prevalence of mental health problems and exacerbation of mental health difficulties including sleep disturbances and stress during their studies.2

The human body strives to maintain appropriate functioning at all times, a notion called homeostasis, which demands often called "stressful events". It has the effect of changing the balances of our body. When the body tries to keep functioning a particular way, it is known as "stress response". The stress response is a series of hormones released from the brain in order to help us overcome the stressful event.[4]

Stress is not always negative or problematic. Stress can be a motivator toward change and growth or a cause of impairment.[1]

Anxiety is one of the most common psychiatric disorders in general population. Anxiety is defined as "a distressing, unpleasant emotional state of nervousness and uneasiness". Anxiety can be anticipatory before a threat, persist after a threat has passed, or occur without an identifiable threat.[4]

CLASSIFICATION OF ANXIETY DISORDERS ACCORDING TO DSM-5 -

1) Generalized anxiety disorders - Lifetime Prevalence Estimate (LPE) - 5% of the population.
2) Panic disorders – LPE- 1%-2% of the population.
3) Phobias – LPE- 9%-24% of the population
4) Obsessive compulsive disorders- LPE- 1%-2.5% of the population

5) Posttraumatic stress disorders and acute stress disorders – LPE- 8% of the population.[2]

Depression is also one of the most prevalent mental disorders encountered by different age groups worldwide. Depression is characterized by persistent low mood and loss of interests/ pleasure. Prolonged depression is called as dysthymia.[2]

According to WHO, depression is a common mental disorder, characterized by sadness, loss of interest, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration.[5] Depression may be mild, moderate and severe and episodic, recurrent or chronic. It can be both a complication of medical condition or can be a cause of medical condition.[3]

Mental health among the undergraduate students represents an important and developing public health concern.[6]

Students with Depression, Anxiety and Stress are prone to academic difficulties, dropouts, relationship disturbances with friends and family members, failure to cope with anxious situation which results in advanced panic disorders. Currently mental health morbidities is an important public health problem and it is leading cause of disability worldwide.[5,7] Students encounter stressful situations including high workload, difficulty in evaluating patients and assessment of patient, pressure of clinical environment created anxiety among students.[9]

The Global prevalence of Depression, Anxiety and Stress was found out among health care professionals in the year 2021.[15] The prevalence was Depression was found out to be moderately high in hospital staff and the prevalence rates was reported to be about 26%. The Female workers aged between 29 and 35 among the hospital staff were at the higher risk of developing mental health problems during the pandemic.

Students in Asia seems to be suffering more for depression, anxiety, and stress. A study reported the percentage of university students in India, where more than half of the respondents were affected by depression (50.3%), Anxiety (66.9%), and Stress (53%).[5,8]

COVID -19 not only causes the physical health concerns, but also results in number of mental and psychological disorders.[5] COVID -19 pandemic has been associated with high levels of anxiety and panic, both in general population and particularly in health care settings. Post lockdown there was an abrupt swift to a new regimes and protocols which had a negative impact on their psychological well- being. Studies show the prevalence of depression, anxiety and stress in students was significantly high.[11] Due to the emergence of COVID-19, with its rapid spread, has exacerbated anxiety among populations globally, leading to mental health disorders among the individuals. Evidence suggests that individuals were experiencing psychosis, anxiety, trauma, suicidal thoughts, and panic attacks[16].

Students were having limited opportunities to practice interviewing and cultivate the necessary communication and empathy skills for interacting patients and their colleagues.[9,10]

Imposition of unfamiliar public health measures including social distancing and lockdown, social fear related to covid-19 closures of universities, fear of being infected by the SARS- Cov-2, anxiety for being unable to attend their clinical practice.

As there were no clinical postings, the students were away from the academic environment, where the students have the opportunity to gain experience with a different hospital, medical record system, faculty and patient population, due to this there was less recommendation of students and also had negative impact on their life.[11] Restricted access to clinical environment is a main obstacle to student's preparation for clinical practices, thus lowering their self-confidence.[11,12]

The recent studies have shown that COVID-19 affects mental health outcomes such as Depression, Anxiety and Stress. Due to their absence from clinical settings, medical students have limited personal exposure to positive role models and members of faculty, and this may influence career decisions and professional recognition.[12,13]

Due to Covid-19 breakdown, medical students were facing sudden change in their training routine, change in the teaching methods like assessment and explanation via online sessions, this leads to changes like increased screen time[30] and increased time spent in social media and digital devices which was the only way students used to cope with social isolation, which was associated with increased tendencies to develop sleep disturbances which may lead to altered sleep wake schedule, studies show that poor sleep quality and lack of sound sleep were also the main cause of Depression, Anxiety and Stress among medical students.[31]

The other challenges faced by the students during COVID-19 were, uncertainties about the future, fear of infection, altered living conditions, increased risk of contacting the infection, news about shortage of personal protective equipment, quarantine induced boredom, frustrations, lack of freedom, decreased contact with the patients and their peers, and also fears caused by the rumours and misleading from the social media etc. As student population were highly active in social media, which was filled with high amounts of misleading information added fear and affected the mental well- being of students causing increased prevalence of Depression, Anxiety and Stress.[31]

COVID-19 is novel and unexplored, and its rapid transmission, its high mortality rate and concerns about the future can be the causes of anxiety, due to the increased levels of anxiety, there are high chances of affecting the body's immune system and risk of increased stress and depression[16].

The Aim is to determine the prevalence of Depression, Anxiety and Stress among physiotherapy students during clinical postings after Covid-19.

METHODOLOGY

This was a Cross-sectional observational study targeting Physiotherapy students. After obtaining Ethical approval from Institutional Ethical Committee, students were informed about the purpose of study. Students willing to participate were selected and recruited for study based on Inclusion criteria. A total of 120 participants were taken for the study.

Inclusion criteria -

- Physiotherapy students of all the years who are attending clinical postings.
- Physiotherapy students who are attending the clinical postings, irrespective of wards ICU or OPD's.

Exclusion criteria -

- Physiotherapy students who are not attending the clinical postings.
- Other health care professionals (medical and paramedical).
- Study subjects must not have any prior history of any mental illnesses i.e, Depression, Anxiety, or Stress.
- The study subjects must not be taking any medications related to the above illnesses.
- Subjects who agree to participate in the study with or without physical illness and this physical illness must not disturb their mental health.
- The study subjects must declare himself as apparently healthy to participate in the study.

The Procedure began with collecting the Demographic data from the participants, then the participants were provided with the questionnaire in presence of the researcher, the questionnaires were filled by the subjects. The Data was collected by using the (DASS-42) Depression, Anxiety and Stress - 42 item self report scale.

All the data was recorded in the MS Excel and was analysed using SPSS software (SPSS Inc; Chicago, IL) version 26.0.

The collected Data was summarized by using the Descriptive Statistics: frequency, percentage, mean, and Standard Deviation. The Independent sample "t" test was used to compare Age according to gender. The Likelihood Ratio test was used to compare between gender, area of posting, Depression, Anxiety and Stress. The One way ANOVA test was used to compare age according to Depression, Anxiety and Stress. The p value < 0.05 was considered as significant.

RESULTS:

Table 1: Frequency of age

(n = 120)	Range	Mean	S.D.
Age (Years)	19 to 27	22.5	1.8

Table 2: Frequency distribution among gender and area of posting

(n = 120)		**Frequency**	**%**
Gender	**Male**	**24**	**20**
	Female	**96**	**80**
Area of posting	Abalashram	3	2.5
	Brains, Super Specialty hospital	1	0.8
	CDSIMER	2	1.7
	Kanteerva stadium (CSK)	1	0.8
	Motherhood hospitals	1	0.8
	N.R colony, Maternity hospital	35	29.2
	OPD, DSU	48	40
	Sagar hospitals, Bangalore	29	24.2

Table 3: Comparison of age according to gender

		Mean	S.D.	"t"	p value
Age (Years)	Male	22.7	1.9	0.61	0.544
	Female	22.5	1.8		

Table 4: Assessment of dass

DASS	**Never**		**Sometimes**		**Often**		**Almost always**	
	n	%	n	%	n	%	n	%
I found myself getting upset by quite trivial things	38	31.7	68	56.7	8	6.7	6	5
I was aware of dryness of my mouth	58	48.3	50	41.7	8	6.7	4	3.3
I couldn't seem to experience any positive feeling at all	58	48.3	45	37.4	15	12.5	2	1.7
I experienced breathing difficulty (eg, excessively raid breathing, breathlessness in the absence of physical exertion)	77	64.2	28	23.3	15	12.5	0	0
I just couldn't seem to get going	64	53.3	44	36.7	8	6.7	4	3.3
I tended to over- react to situations	40	33.3	56	46.7	13	10.8	11	9.2
I had a feeling of shakiness (eg, legs going to give way)	70	58.3	47	39.2	3	2.5	0	0
I found it difficult to relax	55	45.8	49	40.8	11	9.2	5	4.2
I found myself in situations that made me so anxious I was most relieved when they ended	52	43.3	50	41.6	11	9.2	7	5.8

I felt that I had nothing to look forward to	70	58.3	40	33.3	7	5.8	3	2.5
I found myself getting upset rather easily	41	34.2	58	48.3	18	15	3	2.5
I felt that I was using a lot of nervous energy	61	50.8	47	39.2	8	6.7	4	3.3
I felt sad and depressed	45	37.5	62	51.7	11	9.2	2	1.7
I found myself getting impatient when I was delayed in any way (eg, lifts, traffic lights, being kept waiting)	41	34.2	53	44.2	24	20	2	1.7
I had a feeling of faintness	76	63.3	30	25	9	7.5	5	4.2
I felt that I had lost interest in just about everything	55	45.8	45	37.5	16	13.3	4	3.3
I felt wasn't worth much as a person	77	64.2	33	27.5	7	5.8	3	2.5
I felt that I was rather touchy	91	75.8	23	19.2	4	3.3	2	1.7
I perspired noticeably (eg, hands sweaty) in the absence of high temperatures or physical exertion	66	55	45	37.5	4	3.3	5	4.2
I felt scared without any reason	73	60.8	39	32.5	5	4.2	3	2.5
I felt that life wasn't worthwhile	80	66.7	30	25	6	5	4	3.3
I felt it hard to wind down	76	63.3	35	29.2	7	5.8	2	1.7
I had difficulty in swallowing	99	82.5	19	15.8	2	1.7	0	0
I couldn't seem to get any enjoyment out of the things I did	67	55.8	46	38.3	5	4.2	2	1.7
I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase , heart missing a beat)	57	47.5	52	43.3	11	9.2	0	0
I felt down-hearted and blue	71	59.2	40	33.3	7	5.8	2	1.7
I found that I was very irritable	59	49.2	41	34.2	17	14.2	3	2.5
I felt I was close to panic	60	50	46	38.3	13	10.8	1	0.8
I found it hard to calm down after something upset me	52	43.3	47	39.2	14	11.7	7	5.8
I feared that I would be "thrown" by some trivial but un familiar task	73	60.8	37	30.8	7	5.8	3	2.5
I was unable to become enthusiastic about anything	69	57.5	34	28.3	15	12.5	2	1.7
I found it difficult to tolerate interruptions to what I was doing	58	48.3	45	37.5	12	10	5	4.2

I was in a state of nervous tension	63	52.5	49	40.8	7	5.8	1	0.8
I felt I was pretty worthless	75	62.5	36	30	8	6.7	1	0.8
I was intolerant of anything that kept me from getting on with what I was doing	65	54.2	45	37.5	8	6.7	2	1.7
I felt terrified	77	64.2	34	28.3	7	5.8	2	1.7
I could see nothing in the future to be hopeful about	74	61.7	29	24.2	13	10.8	4	3.3
I felt that life was meaningless	83	69.2	23	19.2	12	10	2	1.7
I found myself getting agitated	65	54.2	41	34.2	9	7.5	5	4.2
I was worried about situations in which I might panic and make fool of myself	51	42.5	54	45	11	9.2	4	3.3
I experienced trembling (eg, in hands)	72	60	42	35	6	5	0	0
I found it difficult to work up the initiative to do things	56	46.7	50	41.7	9	7.5	5	4.2

Table 5: Frequency of depression

Depression	Frequency	%
Normal	20	16.7
Mild	20	16.7
Moderate	17	14.2
Severe	19	15.8
Extremely severe	44	36.7

Table 6: Frequency of anxiety

Anxiety	Frequency	%
Normal	15	12.5
Mild	1	0.8
Moderate	27	22.5
Severe	11	9.2
Extremely severe	66	55

Table 7: Frequency of stress

Stress	Frequency	%
Normal	41	34.2
Mild	9	7.5
Moderate	20	16.7
Severe	14	11.7
Extremely severe	36	30

Table 8: Comparison of depression, anxiety and stress according to gender

		Gender				Likelihood ratio	p value
		Male		Female			
		n	%	n	%		
Depression	Normal	8	33.3	12	12.5	6.958	0.138
	Mild	2	8.3	18	18.8		
	Moderate	3	12.5	14	14.6		
	Severe	2	8.3	17	17.7		
	Extremely severe	9	37.5	35	36.5		
Anxiety	Normal	6	25.0	9	9.4	5.126	0.275
	Mild	0	0.0	1	1.0		
	Moderate	6	25.0	21	21.9		
	Severe	1	4.2	10	10.4		
	Extremely severe	11	45.8	55	57.3		
Stress	Normal	11	45.8	30	31.3	3.111	0.539
	Mild	1	4.2	8	8.3		
	Moderate	2	8.3	18	18.8		
	Severe	3	12.5	11	11.5		
	Extremely severe	7	29.2	29	30.2		

Table 9: Association between depression and anxiety

Depression	Anxiety										Likelihood Ratio	p value
	Normal		Mild		Moderate		Severe		Extremely severe			
	n	%	n	%	n	%	n	%	n	%		
Normal	15	100	1	100	4	14.8	0	0	0	0	198.07	< 0.001*
Mild	0	0	0	0	18	66.7	2	18.2	0	0		
Moderate	0	0	0	0	5	18.5	8	72.7	4	6.1		
Severe	0	0	0	0	0	0	0	0	19	28.8		
Extremely severe	0	0	0	0	0	0	1	9.1	43	65.2		

Table 10: Association between depression and stress.

	Normal		**Mild**		**Moderate**		**Severe**		**Extremely severe**		**Likelihood Ratio**	**p value**
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
Normal	20	48.8	0	0	0	0	0	0	0	0	238.83	< 0.001*
Mild	18	43.9	1	11.1	0	0	1	7.1	0	0		
Moderate	3	7.3	8	88.9	6	30	0	0	0	0		
Severe	0	0	0	0	14	70	5	35.7	0	0		
Extremely severe	0	0	0	0	0	0	8	57.1	36	100		

Table 11: Association between anxiety and stress

	Normal		**Mild**		**Moderate**		**Severe**		**Extremely severe**		**Likelihood Ratio**	**p value**
	n	%	n	%	n	%	n	%	n	%		
Normal	15	36.6	0	0	0	0	0	0	0	0	188.13	< 0.001*
Mild	1	2.4	0	0	0	0	0	0	0	0		
Moderate	25	61.0	1	11.1	1	5	0	0	0	0		
Severe	0	0	8	88.9	1	5	2	14.3	0	0		
Extremely severe	0	0	0	0	18	90	12	85.7	36	100		

Table 12: Frequency of area of posting (ICU's) and depression

Area of posting	**Depression**			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
Brains Superspeciality Hospital	0	0	5.3	0
Sagar Hospitals	35	23.5	10.5	20.5
	35	**23.5**	**15.8**	**20.5**

Table 13: Frequency of area of posting (wards) and depression

Area of posting	**Depression**			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
CDSIMER	10	0	0	0
Motherhood Hospitals	5	0	0	0
	15	**0**	**0**	**0**

Table 14: Frequency of area of posting (opd's) and depression

Area of posting	Depression			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
Abhalashrama	10	0	0	2.3
Kanteerva Stadium	5	0	0	0
NR colony - BBMP	15	41.2	47.4	27.3
OPD- DSU	20	35.3	36.8	50
	50	**76.5**	**84.2**	**77.3**

Table 15: Frequency of area of posting (ICU's) and anxiety

Area of posting	Anxiety			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
Brains Superspeciality Hospital	0	0	0	1.5
Sagar Hospitals	100	29.6	45.5	16.7
	100	**29.6**	**45.5**	**18.2**

Table 16: Frequency of area of posting (wards) and anxiety

Area of posting	Anxiety			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
CDSIMER	0	7.4	0	0
Motherhood Hospitals	0	3.7	0	0
	0	**11.1**	**0**	**0**

Table 17: Frequency of area of posting (OPD's) and anxiety

Area of posting	Anxiety			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
Abhalashrama	0	7.4	0	1.5
Kanteerva Stadium	0	3.7	0	0
NR colony - BBMP	0	29.6	9.1	36.4
OPD- DSU	0	18.5	45.5	43.9
	0	**59.2**	**54.6**	**81.8**

Table 18: Frequency of area of posting (ICU's) and stress

Area of posting	Stress			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
Brains Superspeciality Hospital	0	5	0	0
Sagar Hospitals	44.4	5	35.7	16.7
	44.4	**10**	**35.7**	**16.7**

Table 19: Frequency of area of posting (wards) and stress

Area of posting	Stress			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
CDSIMER	0	0	0	0
Motherhood Hospitals	0	0	0	0
	0	**0**	**0**	**0**

Table 20: frequency of area of posting (OPD's) and stress

Area of posting	Stress			
	Mild	**Moderate**	**Severe**	**Extremely Severe**
Abhalashrama	0	0	0	2.8
Kanteerva Stadium	0	0	0	0
NR colony - BBMP	11.1	50	21.4	30.6
OPD- DSU	44.4	40	42.9	50
	55.5	**90**	**64.3**	**80.6**

DISCUSSION:

In this study, a total of 120 subjects were selected. All subjects were physiotherapy students which attends clinical postings. Their age ranged between 19 to 25. Mean age was found to be 22.5 ± 1.8 years (Table 1). Both male and female participants were taken, who are attending clinical postings post COVID- 19. The Male to Female ratio in this study was 1:4.

According to our study the prevalence of Depression, Anxiety and Stress was found by using the DASS-42 item questionnaire. The data was interpreted under normal, mild, moderate, severe and extremely severe categories.

According to the study Mahmud, S. *et al.* (2021) the global prevalence of Depression among health care workers was found to be 37.12%[15]. According to the same study, the prevalence of depression in India was reported to be about 42.98% [15]. In our study, the prevalence of depression among physiotherapy students who were attending clinical postings, post COVID-19 was found out to be 83.4%. (Table 5)

Depression was recorded in following categories according to DASS-42 item Questionnaire as: Normal in 20 (16.7%), Mild in 20 (16.7%) Moderate in 17 (14.2%) Severe in 19 (15.8%) and Extremely Severe in 44 (36.7%). (Table 5)

A study conducted by Martin-Gill, et.al (2018) stated health care staff were discouraged to attend social gatherings, quality time with friends and family, etc. The fear of spreading SARS – CoV to friend, family and/or relatives were constantly a reason of depression among health care professionals [23]. According to the study conducted by Bourbon, A et.al (2019), the health risk behaviours like, insufficient physical activity and sleep reduction are associated with increased risk of depression in health care workers[22].

According to the study Mahmud, S. *et al.* (2021) the global prevalence of anxiety was found out to be 41.42%.[15] According to the same study, the prevalence of Anxiety in India was reported as 50.28%.[15] According to our study, the prevalence of anxiety among physiotherapy students who are attending clinical postings post COVID-19 was found out to be 87.5% (Table 6).

Anxiety in different categories was found as mild in 1(0.8%) moderate in 27 (22.5%) severe in 11(9.2%) extremely severe in 66 (55%) (Table 6). Anxiety was not found among 15(12.5%) as they were normal.

This study Zheng , R. *Et al.* (2021) found out that there were challenges in accessing appropriate supplies of equipment, job stress due to increased work demands and lack of effective treatment, working under rapidly changing COVID-19 protocols, risk of being infected and infecting their family members, treating and comforting patients and decline in their immunity due to physical and mental exhaustion or underlying health conditions resulted in increased prevalence of Anxiety among health care workers.[25]

Similarly, according to the study Cheng, W.-J. and Cheng, Y. (2017) it was found that the higher rates of anxiety among health care professionals was associated with their working conditions and overload working environment. This increased the rates of mortality too.[26] According to the study Batra, K. *Et al.* (2020) it was found that as anxiety increased among the general population, at the frontline the health care workers also experienced increased emotional responses as they were more frequently exposed to the virus.[24]

According to the study Mahmud, S. *et al.* (2021) the global prevalence of Stress was found to be 44. 86%.[15]The same study reported the prevalence of Stress in India as 52.76%.[15]

According to our study, the prevalence of stress among physiotherapy students who are attending clinical postings post COVID-19 was found out to be about 65.9% (Table 7).

In our study, stress was found out to be normal among 41 (34.2%). Students who were mildly involved were 9 (7.5 %) moderate was 20 (16.7%) severe was 14 (11.7%) and the students who were extremely involved were 36(30%) (Table 7).

According to the study Nyashanu, M., Pfende, F. and Ekpenyong, M.S. (2020) One of the main stressors among health care professionals was found to be the fear of contagion and transmission.[27] These results coincide with many studies that health care workers find difficulty due to lack of vaccine availability and also with poor protective materials, this describes the fear of contagion among them.

According to the study Herraiz-Recuenco, L. *et al.* (2022) fear of spreading the disease in the immediate environment, changes introduced during the pandemic in work procedures and organisations, and perceived social stigma of working in direct contact with people with COVID-19 contribute to high levels of stress among medical staff.[28]

According to the study Hummel, S. *et al.* (2021) the lack of the personnel available during sick leave or vacations, which also had to be deferred or cancelled during the pandemic. Postponing vacations added to another main reason for stress which took away their major means to recover from the periods of stress.[29]

Above reasons were responsible for prevalence of Depression, Anxiety and Stress amongst healthcare workers. But the rules and restrictions and application of modified protocols as per the new norms after lockdown was resurfaced, remained same. This led to prevalence amongst the physiotherapy students.

According to our present study, it was also found out that there was increased prevalence of Depression, Anxiety and Stress among females than males (Table 2). The percentage of frequency of Depression, Anxiety and Stress was found to be 20% in males and 80% in females (Table 2). Similarly, according to the study Rezaei, S. *et al.* (2022) the prevalence of Depression was reported higher among females 32% compared to males which was 23 %.[16]

The results of some epidemiological studies show that women are at a higher risk of Depression. Women are more vulnerable to stress and post-traumatic stress than men. It was found that this difference among females can be due to cultural constraints, socioeconomic disadvantage, family constraints etc. Women are more likely to express mental health problems than men.[17]

Evidence also suggests that there is increased Prevalence of Depression, Anxiety and Stress among females due to the role of sex hormones.[18] According to the study Kaspi SP et.al it is also evident that fluctuating levels of sex hormones like oestradiol and progesterone, play a

significant role in causing increased prevalence of depression, anxiety and stress among women.[18]

Several studies also reported that sex differences in anxiety emerge at puberty and womem also have an elevated risk of development of anxiety disorders, or exacerbation of current anxiety symptoms, during the phases of their reproductive cycles due to reduced hormone levels.[18]

Due to the emergence of COVID-19, with its rapid spread, has exacerbated anxiety among populations globally, leading to mental health disorders among the individuals.

Evidence suggests that individuals were experiencing psychosis, anxiety, trauma, suicidal thoughts, and panic attacks.[16]

The prevalence of Depression among physiotherapy students who are attending clinical postings, post COVID-19 in ICU's was found to be 94.8% (Table 12), in wards was found to be 15% (Table 13), in OPD's was found to be 288% (Table 14).

The prevalence of Anxiety among physiotherapy students who are attending clinical postings, post COVID-19 in ICU's was found to be 193.3% (Table 15), in Wards was found to be 11.1% (Table 16), in OPD's was found to be 95.6 % (Table 17).

The prevalence of Stress among physiotherapy students who are attending clinical postings, post COVID-19 in ICU's was found to be 106.8% (Table 18), in Wards was found to be 0% (Table 19), in OPD's was found to be 94.8%. (Table 20).

As found in our study, the prevalence of depression was higher than the prevalence of anxiety and stress amongst physiotherapy students, attending clinical postings post COVID-19. (Table 5). There was a significant association found between depression and stress (Table 10), and depression and anxiety (Table 9) and anxiety and stress (Table 11). The association between depression and stress was found much higher than the other components (Table 10).

CONCLUSION:

In our present study, it was concluded that Depression, Anxiety and Stress prevails among Physiotherapy Students who were attending clinical postings post COVID-19.

Also, it was concluded that irrespective of any area of posting (whether ICUs, wards, OPD), the frequency of Depression, Anxiety and Stress was noted amongst students. Wherein, the reports were higher for ICU's and OPD than wards.

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ETHOSOME A PROMISING CARRIER FOR DRUG DELIVERY

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INTRODUCTION:

The important part of the human body is skin and available route for systemic and topical drug administration. The outer most skin layer is stratum corneum, when the medicament is applied on the skin layer; it acts as strongest barrier against drug absorption and resists the drug bioavailability [Benson (2005)]. Drugs having 'first-pass metabolism' are used in 'Transdermal rout', it administers medications topically at a predetermined and controlled rate through patches designed for 'systemic effects' [Elsayed *et al.* (2007)]. The 'transdermal drug delivery system' (TDDS) advantages compared to standard techniques Reduction of 'side effects' in the 'gastrointestinal tract', painless drug delivery, less wear and tear sensitivity compared to tablets, no risk of forgetting doses once the device is applied to the skin surface. Ethosome is a modified version of liposome. It is having the lower size, lower efficacious and negative zeta potential. Ethosomes are prepared by phospholipids, isopropyl alcohol, ethanol, water, polyglycol or glycol, cholesterol, dye-rodamine and FITC, vehicle like carbopol is used. The water and phospholipids are used which helps to increased skin penetration and vesicular properties [Nayak *et al.* (2023)].

Ethosome Types: It is classified based on composition of ethanol compounds, Ethosome are three types, namely: classical, binary, and trans-ethosomes. Binary ethosomes have an additional alcohol group, either propylene glycol or isopropyl alcohol to the ethosome. Trans-ethosomes are prepared by extra compounds use as 'skin permeation enhancer' or an edge activator, besides the fundamental components of classical ethosomes [Narang and Sharma (2011)]

Function of ethosome: It can act in three ways like ethanol effect, ethosome effects and water-soluble effects. The Ethanol effect is associate with skin's lipid bilayers, present in Ethosome, it helps them more fluid and less dense. It allows the ethosomes to penetrate the stratum corneum. The Ethosomes effect, the medication can get into the skin more penetrate because the ethosomes merge with the layers of the skin. The water-soluble polymers which are hydrates with water molecules in the skin, increases the permeability and solubility of the drug.

Additives used in Ethosomes Preparation

Ingredients	Examples	Purpose
Alcohol	Isopropyl alcohol, ethanol	Permeation enhancer
Phospholipid	Dipalmithyl phosphatidylcholine, Egg phosphatidylcholine, Distearyl phosphatidylcholine	Formation of vesicles
Polyglycol	Transcutol, Propylene glycol	Skin penetration enhancer.
Cholesterol	Cholesterol	Stability of vesicle.
Dye	Rhodamine, 6-Carboxy fluorescine, fluorescine Isothiocynate, etc	Coloring agent
vehicle	Carbopol in different grad	Gel forming agent.

In ethosome function, vesicles, ethanol, and skin lipids work in concert. The dispersion of drug is improved over liposomes by ethosomes and skin lipids because they interact more effectively. Ethanol interacts with the lipid molecules in the polar head group region to lower the change temperature of the lipids in the stratum corneum. These increase a fluidity and lipid multilayer density decrease, which allows the medicine to enter the deep layers of the skin. Ethanol also gives vesicles flexibility and smoothness, which promotes penetration into the epidermal deeper layer [Rada and Yadav (2022)]

Preparation of Ethosome:

Hot method: In this process, heating to disperse phospholipid in water it in water bath at 40 ^{0}C until a colloidal solution forms. Propylene glycol and ethanol are mixed and heated to 40 °C in a different beaker. If both mixtures exceed 40^{0}C The organic phase gets combined with the aqueous phase. The drug dissolves in either water or ethanol, depending on its hydrophilic or hydrophobic characteristics. The ethosomal formulation's vesicle size can be lessen as much as desired by using the extrusion or probe sonication processes.

Cold method: There are two easy types in this method. In the first setup, at room temperature and with constant stirring the phospholipid and other lipid material is dissolved in ethanol with the Heidolph mixer with continuous addition of propylene glycol, with constant stirring, heating at 30^{0}C in water bath. In the second setup, water is heated at 30^{0}C in a vessel, both mixtures (obtained from first and second setup) are blended for 5 min. with continuous stirring in a covered vessel. Following sonication method, it is possible to lower the ethosomal formulation's vesicle size to the desired extent. Finally, the formulation is stored inside the refrigerator.

Classic mechanical dispersion method: In a round-bottom flask (RBF), phospholipid can be dissolved in an organic solvent or a mixture of organic solvents. creating a thin lipid coating on the RBF wall by removing the organic solvent using a rotating vacuum evaporator set above the lipid transition temperature; Any leftover using the vacuum the solvent should evaporated from the accumulated lipid film. At the proper temperature, to hydrate the lipid layer with the drug's

hydroethanol solution, spin the flask either with or without periodic sonication. Finally, let the ethosomal suspension to settle to room temperature. It is recommended that the mixture be kept refrigerated.

Ethanol injection–sonication method: The organic phase, which contains the phospholipid dissolved in ethanol, is introduced into the aqueous phase at a rate of 38 µl per minute using a 200-flow syringe device. The mixture is then homogenized for five minutes using an ultrasonic probe [Touitou *et al.* (2000)].

Characterization: Ethosomal vesicle production can be analyzed using photomicrographs, transmission electron microscopy (TEM), and scanning electron microscopy (SEM) micrographs. A zeta meter can be used to measure the zeta potential of the formulation. The amounts of phospholipid and ethanol can affect the mean vesicle diameter reduction. Using differential scanning calorimetry, the transition temperature of the vesicular lipid systems can be measured, a technique that can be followed to identify ethanol-skin phospholipid interaction, a characteristic linked to ethanol's fluidizing effect on phospholipid bilayers. The ultracentrifugation method can be used to assess the ethosomes' level of entrapment. The high degree of lamellarity and the presence of ethanol in the vesicles account for ethosomes' capacity to effectively entrap hydrophilic and lipophilic drugs. Furthermore, ethosomal formulations are more effective at trapping than liposomes [Abu-Huwaij *et al.* (2024)].

COMPOSITION OF ETHOSOMES

Ethanol: The effective penetration enhancer is ethanol. It is having an important function in ethosomal preparation by obtaining the vesicles special dimensional characteristics size, shape, prevention of clogging and increased permeability of the skin, stability. Concentrations of ethanol in ethosomal systems have been reported to be 10%– 50%. The concentration of ethanol is increased; the size of the ethosomes would decrease. When ethanol concentration is increased, causes the bilayer to be leaky, leading to a small increase in vesicular size and a significant decrease in the efficacy of trapping and would solubilize the vesicles by further raising the ethanol concentration [Moghassemi and Hadjizadeh (2018)]. Vesicular load is an important parameter which can affect vesicular properties such as stability and skin vesicle interaction. The high concentration of ethanol in ethosomes has moved the vesicular load from positive to negative. Ethanol serves as a negative charge supplier for ethosomal surfaces, thereby preventing accumulation of the vesicular network as a result of electrostatic repulsion. Ethanol also has a direct effect on the efficiency of trapping in ethosomal systems, and typically increasing concentrations in ethanol would increase the efficiency of trapping [Fang *et al.* (2019)].

Phospholipids: Phospholipids from different sources were used in formulation of the ethosomal scheme. The selection of phospholipid type and concentration for formulation are important factors during the production of ethosomal system since they will affect the scale, the effectiveness of the trapping, Potential vesicular properties, stability, and penetration. Highly

negatively charged vesicles were produced by the incorporation of DPPG (1,2-dipalmitoylsn-glycero-3-phosphatidylglycerol) in the ethosomal formulation, while cationic ethosomal vesicles were produced by using a cationic lipid, such as DOTAP (1,2- dioleoyl-3- trimethylammonium-propane [chloride salt]) [Mbah and Builders (2019)]. In general, in an ethosomal formulation, the concentration range of phospholipids is 0.5%–5%. Rising phospholipid concentration can increase vesicular size marginally or moderately, but will greatly improve the efficiency of trapping. The relationship, however, is only valid until there is a certain concentration.

Cholesterol: As a stable steroid molecule, cholesterol improves the stability and clogging efficacy of medications when it is incorporated into ethosomal structures. This prevents leakage and lowers vesicular fusion and permeability. 3% concentration is use in some formulation; it was used up to 70% of the total phospholipid concentration in the formulation. Several studies have recorded that the vesicular size of ethosomal systems increased with cholesterol [Mishra *et al.* (2018)]

Dicetyl phosphate: Dicetyl phosphate is used to increase formulation stability and prevent vesicle aggregation. In the ethosomal formulation, it is utilized at concentrations ranging from 8% to 20% of the total phospholipid concentration.

Stearylamine: Stearylamine is an agent with a positive charge. Stearylamine significantly increased vesicular size and decreased entrapment when added to the ethosomal formulation. Stearylamine's reduced molecular weight (296.5 Da) allows it to easily enter the skin.

Propylene glycol: One popular penetration enhancer is PG. It has been observed to affect the ethosomal properties such as size, trapping capacity, permeation, and stability when applied at concentrations between 5% and 20% in the formation of binary ethosomes. When PG is included into ethosomal systems, particle size will decrease more than in systems without PG. The particle size decreased significantly from 103.7±0.9 nm to 76.3±0.5 nm when the PG concentration was increased from 0% to 20% v/v. It is hypothesised that via improving the viscosity and antihydrolysis properties, PG improves ethosome stability.

Isopropyl alcohol: Dave *et al.* studied how IPA affected an ethosomal system loaded with diclofenac's effectiveness at entrapment and skin penetration. Three different formulations have been made: a vesicular system with 40% IPA, binary ethosomes with roughly 20% IPA and 20% ethanol, and classical ethosomes with 40% ethanol. It was discovered that the vesicular device with 40% IPA had better trapping performance (95%) than the binary ethosomes (83.8%).

Edge activators or penetration enhancers: Since they significantly alter the characteristics of the ethosomal system, choosing the right edge activator or penetration enhancer is an essential step in the creation of transethosomes [Pleguezuelos-Villa *et al.* (2020)].

Tweens and spans: In the ethosomal scheme, Tween 80 is used at concentrations of 10% -50% of the total phospholipid concentration. It has been stated that Tween 80 has been integrated in ethosomal systems to minimize vesicular size and improve the stability of the system and

skinpermeation properties. Mainly due to its solubilizing properties and the prevention of vesicle fusion, the impact of Tween 80 on the ethosomal system. Tween 20 formed an unstable formulation. Spans 80, 60, and 40 did not manage to generate homogeneous and stable transethosomes. Only Span 20 was used successfully in the preparation of transethosomes of caffeine and vitamin E.30 [Mohd *et al.* (2024)]

Oleic acid: By enhancing the fluidity of the stratum corneum, oleic acid influences vesicular scale and elasticity and skin-permeating qualities. Cremophor An assortment of nonionic polyethoxylated detergents are marketed under the Cremophor brand. Cremophor EL-35 was employed at 0.5%–1.5% w/w in an ethosomal system of testosterone propionate. It was discovered to decrease vesicular size and improve the drug's solubility and trapping effectiveness [Haq *et al.* (2021)]

Skin-penetrating and cell-entering peptide: After direct chemical conjugation, the skin-penetrating and cell-entering peptide (SPACE), a skin-penetration enhancer identified by phage display, has been demonstrated to carry streptavidin and short RNA (SiRNA) to the skin. To distribute hyaluronic acid, this penetration enhancer was added to transethosomes [Emanet and Ciofan (2023)].

Mechanism of penetration: The exact mechanism of ethosomal drug delivery is debated, but multiple factors contribute to its effectiveness. At physiological temperature, the stratum corneum lipid layers are tightly packed. Ethanol disrupts these lipid bilayers, allowing ethosomes to penetrate the stratum corneum. Its high ethanol content makes ethosomes more flexible than traditional vesicles, enabling them to pass through small openings. Ethanol also reduces lipid rigidity and increases membrane fluidity, enhancing permeability. Ethosomes interact directly with the stratum corneum barrier, improving drug absorption. Unlike classic liposomes, which keep drugs on the skin surface, ethosomes efficiently deliver drugs transdermally. Their stability and enhanced drug delivery potential make them a promising option for transdermal drug administration. [Niu *et al.* (2019)]

Ethanol Effect: Ethanol acts as a penetration enhancer through the skin. The process by which it improves penetration is widely understood. Ethanol enters intercellular lipids, increases their fluidity, and lowers the density of the lipid multilayer in the cell membrane [Verma and Pathak (2010)].

Ethosomes Effect The skin becomes more permeable as a result of ethosomal ethanol's enhanced lipid fluidity in the cell membrane. As a result, the ethosomes enter the deep layers of the skin very rapidly, fuse with the lipids in the skin, and release the medications into the deep blood layers [Dayan and Touitou (2000)].

Physicochemical characterization:

Vesicle morphology: Transmission electron microscopy (TEM) and scanning electron microscopy (SEM), which involves negative staining of the formulation with an aqueous

solution of agents like phosphotungstic acid, etc., can reveal the vesicular morphology of ethosomal systems [Barupal *et al.* (2010)]

Vesicle size and distribution: The ethosomal framework's vesicular size is managed by dynamic light scattering (DLS), and the size varies between nanometres to microns, relying on the formulation's composition [Touitou *et al.* (2000)].

Vesicular bilayer configuration: Exploring the most efficient bilayer formation is important since the ethosomal trapping system's efficacy heavily depends on its vesicle bilayer. Nuclear Magnetic Resonance (NMR) studies can be used to accomplish this [Touitou *et al.* (2000)].

Drug entrapment efficiency: Drug trapping efficiency Since it gives the ethosomal system sustained release properties, measuring the effectiveness of ethosome trapping becomes the next crucial characterization parameter after the investigative studies of the vesicular bilayer configuration of ethosomal systems are confirmed in the affirmative. Usually, two techniques are used to do this, as explained below [Li *et al.* (2023)].

Dialysis: For instance, polymers were used to make the bags used in this dialysis. After that, 500 milliliters of phosphate buffer saline (PBS) with a pH of 7.0 were added to the dialysis bag together with a measured amount of drug-loaded vesicles or free drug in aqueous solution. To ensure complete membrane wetting, cellulose acetate was soaked in a saline solution for an hour before dialysis. Using a magnetic stirrer, the receiver media were agitated. At specified times, aliquots of the same volume were removed from the receiver medium and replaced with equivalent volumes of PBS solution in order to maintain optimal sink conditions. The drug content samples were subsequently examined using HPLC methods [Li *et al.* (2023)].

Distinctiveness of penetration: It has long been believed that ethanol has the capacity to increase permeability. However, the permeation improvement from ethosomes was much better than what would be expected from ethanol alone. This suggests that ethanol, vesicles, and skin lipids work together in a way that makes ethosomes more flexible, which leads to better penetration for two reasons. (A) the "pressure effect"—a rise in thermodynamic activity brought on by ethanol evaporation and (B) the drug molecule's greater penetration as a result of ethanol's diminution of the subcutaneous tissue's barrier qualities [Touitou *et al.* (2000)].

Stability of the body: The freeze-drying process might have assured the stability of the ethosome suspension throughout long-term preservation. Freeze-dried ethosome cakes have been observed to be glassy, light, and characterized by low viscosity and efficient rehydration. However, the percentage of drug encapsulation within ethosome was partially dependent upon the storage time span, leading to about 10% drug leakage after rehydration. The lipid component of ethamomes is composed of either natural or synthesized phospholipids. It is well known that phospholipids, or unsaturated fats, may experience oxidative reactions. Byproducts of the process can change the permeability of the bilayer ethosomes. Antioxidants like α-tocopherol can lessen oxidative lipid breakdown in general by protecting the lipid preparation from light.

Furthermore, lipid hydrolysis results in the formation of lyso-PC. It is essential to reduce the amount of lyso-PC in a given preparation since its presence increases the permeability of ethosomes [Cortesi *et al.* (2010)].

Transition temperature: DSC can determine the vesicular lipid transition temperature (T) in duplicate by utilizing an aluminium pan and a continuous stream of nitrogen at a rate of 10°C per minute. Confocal laser scanning microscopy (CLSM). CSLM can be used for studying the depth and function of ethosomal preparation skin penetration. A confocal laser scanning microscope's z-axis can be used to visually scan the thickness of the skin in various increments [Chauhan *et al.* (2022)].

Content of drugs: Ethosome quality can be analysed with the UV spectrophotometer. A modern chromatographic high-performance liquid methodology can also be used to quantify it [Kako *et al*. (2024)]

Measurement of surface tension: The ring process in a Du Nouy ring tensiometer can be used to assess the drug surface tension activity in a water-based solution [Chauhan *et al.* (2022)].

Phospholipid-ethanol interaction :31P-NMR decoupled protons and calorimetry differential scanning were used to test the phospholipid-ethanol interaction [Chauhan *et al.* (2022)].

Level of Turbidity and Degradability: The ethosomal preparation's degree of deformability can be determined by the extrusion method, and a Nephelometer can be employed to assess the preparation's turbidity [Chauhan *et al.* (2022)].

Efficiency of drug entrapment: Anisotropy study of AVPC (a fluorescent analog of phosphatidylcholine) and differential calorimetry scanning thermograms indicated that the bilayers had a high degree of fluidity and that ethosomes had a lower Tm than regular liposomes. This gave the vesicles a soft, amiable touch. Godin and Touitou revealed that ethosomes may competently trap both hydrophobic and hydrophilic fluorescent materials by utilizing CLSM. When testing the trapping of several medicines using the ultracentrifugation method, similar results were observed. Using hydrophilic 6-carboxyfluorescein and hydrophobic Rhodamine 123 fluorescent markers, hydrophobic and hydrophilic medications have been reliably evaluated. The high level of lamellarity and the existence of ethanol in the vesicles account for ethosomes' potential to smoothly clog hydrophilic and lipophilic medicines. Moreover, liposomes are not as efficient at trapping as ethosomal formulations. Trihexyphenidyl hydrochloride trapping efficiency expanded from 36% for liposomes to 75% for ethosomes, based upon Dayan and Touitou's research [Chauhan *et al.* (2022)].

Assessment of Ethosomes:

Study of vesicle-skin interaction: Diverse visualization techniques, especially analyzing the process of expanded ethosomal formulation skin penetration. Fluorescence microscopy, laser microscopy confocal scanning(cslm), eosinhematoxl staining, and transmission electron microscopy were all employed. When combined, these imaging techniques

also improved knowledge of vesicle penetration approaches and structural modulation. Traditional liposomes barely penetrated the stratum corneum, the outermost protective layer of skin. The deep penetration of alcohol-free liposomes was almost insignificant. Comparatively, a superior dispersion of 6-CF and Rhodamine 123 in terms of depth and quantity (dermis-layer) has been found using the ethosomal carrier [Niu *et al.* (2022)].

1. Utilizing scanning electron microscopy to investigate the filter membrane-vesicle interaction: To do this, a 0.2 ml vesicle suspension is put on 50 nm-pore filter membranes, which are then put in diffusion cells. After an hour, we removed the filters and fixed them in Karnovsky's fixative at 4°C for the entire night. After that, ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% v/v in water) were used to dry them out so that they could be used for SEM analyses. While the lower side of the filter came into contact with a phosphate buffer saline solution (pH 6.5), the upper side was left open to the air.

2. Studies on skin penetration: A couple of scissors was used to cautiously eliminate the test animals' (rats') hair to less than 2 mm, and then a scalpel was used to cut the abdomen skin free of the connective tissue underneath. The removed skin was placed on aluminium foil, and the dermal side of the skin was carefully scraped off to remove any remaining fat and/or subcutaneous tissue. 1.0 cm^2 and 10 ml, respectively, were the effective diffusion cell and receptor cell volume penetration area. A temperature of 32°C ± 1°C was maintained. There was a saline solution with phosphate buffer (10 ml pH 6.5) in the receptor compartment. It positioned the removed skin between the receptor compartment and the donor. Ethosomal formulation (1.0 ml) was applied to the skin's epidermal surface. Using a high-performance liquid chromatography (HPLC) experiment, samples (0.5 ml) was taken out via the diffusion cell's sampling port at 1, 2, 4, 8, 12, 16, 20 and 24 hour durations [Pathan *et al.* (2016)].

3. Study of stability: When the vesicles were maintained at 4°C ± 0.5°C, their stability was assessed. After 180 days, calculated the zeta potential, vesicle size, and trapping effectiveness [Maniyar *et al.* (2022)].

4. Studies on drug uptake: 100 µl of RPMI media was inserted into 24-well plates (Corning Inc.) to facilitate drug absorption into MT-2 cells (1,1106 cells/ml). Drug absorption was determined by HPLC test assessment of the drug material after cells were treated with 100 µl of the drug solution in phosphate buffer saline solution (pH 7.4), ethosomal formulation, or marketed formulation [Pathan *et al.* (2016)].

5. HPLC test: The amount of drug that penetrated the receptor compartment in MT-2 cells and in vitro skin permeation tests was analysed using an HPLC assay with methanol as a mobile step, distilled water: acetonitrile combination (70:20:10 v/v) [Pathan *et al.* (2016)].

Use:

- Numerous studies have proven that ethosomes are a powerful remedy for microbial and viral skin infections. The bacitracin and erythromycin ethosomal systems have been created and assessed in animal models of deep skin infections.
- Ammonium glycyrrhizinate ethosomes were demonstrated to have an anti-inflammatory effect on human volunteer subjects' skin after manufacturing.
- Ethosomal patches have proven adequate advancement for treating menopausal symptoms in women and lack of androgen in men when tested in vivo on rabbits.
- Ethosomes may have analgesic, antipyretic, and effective effects on erectile dysfunction, according to research.

Additionally, studies have suggested that ethosomes could be intended to topically transport DNA molecules so that certain genes are expressed by skin cells.

Delivery of hormones: Multiple issues, especially poor oral bioavailability, high first-pass metabolism, and several dose-dependent adverse effects, are associated with oral hormonal medication. Furthermore, patient adherence to these side effects becomes crucial for oral hormonal formulations. Every missed dose is known for raising the possibility of treatment failure. By comparing the transdermal delivery of testosterone-loaded ethosomes (testosome) to transdermal testosterone patches (Testoderm patch) through rabbit pinna skin, Touitou *et al.* demonstrated the potential of ethosomes in hormonal delivery. They observed that the skin absorbed testosterone from the ethosomal formulation by about 30 times. Ethosomal formulation has been established to improve skin penetration and testosterone absorption in both in vitro and in vivo experiments [Touitou *et al.* (2000)].

Delivery through the cell: In ongoing clinical trials, ethosomes have proven beneficial effects as a carrier and penetration enhancer for the transcellular administration of a variety of therapeutic supplements. However, when integrated into conventional liposomes or a hydroethanolic solution, very little fluorescence was noticed. Each of the three examined probes' intracellular presence was detected after three minutes of incubation [Godin and Touitou (2003)].

Pilosebaceous targeting: Percutaneous medication allocation to sebaceous glands and hair follicles is becoming more frequently recognized as a potentially important ingredient. As depots for localized therapy, pilosebaceous units have attracted attention, especially for the treatment of follicle-related conditions like alopecia or acne. For systemic medication delivery, a lot of focus has also been placed on exploiting the follicles as transportation shunts [Godin and Touitou (2003)].

DNA delivery topically: Numerous environmental infections attempt to penetrate the body via the skin, which has transformed into an exceptional defense barrier that is both gene-expressing and immunologically active. Based on the preceding information, ethosomes are crucial for topical transport of DNA molecules that express genes in skin cells. Ethosomes have been

considered as potential carriers for gene therapy applications that call for temporary gene expression. The results also revealed that ethosomes may be used for effective transdermal vaccination. Consequently, increased ethosomal skin penetration capacity makes it possible to deliver immunization agents using these dosage forms [Godin and Touitou (2003)].

Delivery of a medication for arthritis: The difficulties associated with traditional oral therapy are fixed by topical distribution of anti-arthritis medication, which is an excellent alternative for site-specific delivery. Recently, a therapeutic candidate called cannabidol (CBD) came to light to treat rheumatoid arthritis. Numerous problems, including limited bioavailability, first pass metabolism, and GIT degradation, have been traced to his oral administration. The pharmacological anti-inflammatory effect of the CBD-ethosomal formulation was significantly enhanced when tested using the carrageenan-mediated rat paw edema model. Therefore, it was established that encapsulating CBD in ethosomes significantly enhanced its skin piercing, accumulation, and hence its biological activities [Lodzki *et al.* (2003)].

Antibiotic delivery: A safer manner to enhance the therapeutic effectiveness of those medications is by using topical administration of antibiotics. Many allergic reactions have been triggered by the side effects of conventional oral medications. The capacity to penetrate of conventional exterior formulations to the innermost layers of skin and subdermal tissues is poor. Ethosomes can circumvent this problem by adequately shipping antibiotics into the innermost layers of the skin. Ethosomes can effortlessly travel through the epidermis, transport an extensive amount of medications into the skin's innermost layers, and eradicate infections at their source. Conclusions of this investigation demonstrated that an antibiotic ethosomal formulation might be very effective to address the issues with traditional medications [Godin and Touitou (2003)].

Ethosome application in cosmetics: Applying ethosomes to cosmetics has combined advantages of boosting transdermal permeability, specifically for elastic categories, and improving the stability of cosmetic chemicals while minimizing skin irritation from irritating cosmetic chemicals. likewise, the main factors that must be considered to realize the beneficial effects of elastic vesicles for cosmetics are their compositions and sizes [Godin and Touitou (2003)].

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HEALTH-RELATED QUALITY OF LIFE IN CHILDREN WITH SICKLE CELL DISEASE

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ABSTRACT:

Sickle cell disease (SCD) significantly impairs the health-related quality of life (HRQoL) of affected children, influencing physical, psychosocial, familial, and academic domains. This systematic review synthesized evidence from studies exploring HRQoL in pediatric SCD populations, highlighting challenges such as pain, fatigue, social isolation, emotional distress, and educational setbacks. Factors impacting HRQoL include disease severity, socioeconomic challenges, coping mechanisms, and access to healthcare. Effective medical treatments like hydroxyurea and blood transfusions improve certain HRQoL aspects, but a holistic, multidisciplinary approach is necessary to optimize outcomes. Interventions addressing pain management, psychosocial support, family-centered care, and education are critical. Disparities in access to quality care exacerbate these challenges, underscoring the need for equity-focused strategies. Limitations of the review include geographic bias, study heterogeneity, and a lack of longitudinal data, emphasizing the importance of future research in addressing these gaps. Long-term and culturally tailored interventions, alongside the integration of HRQoL assessments into clinical care, are essential to improving outcomes for children with SCD and their families.

Keywords: Sickle Cell Disease, Health-Related Quality of Life, Pediatric, Psychosocial Support, Pain Management, Socioeconomic Factors, Family-Centered Care, Educational Interventions, Holistic Care, Equity in Healthcare.

INTRODUCTION:

This systematic review comprehensively examines the impact of sickle cell disease (SCD) on the health-related quality of life (HRQoL) of children and adolescents. SCD, an inherited and debilitating blood disorder, imposes a substantial burden on affected individuals and their families. It is characterized by recurrent painful vaso-occlusive crises, chronic organ damage, and frequent hospitalizations, all of which disrupt the normalcy of daily life and hinder childhood development [1,2]. The physical challenges posed by SCD are compounded by psychosocial and emotional strain, profoundly affecting children's well-being and life trajectory [3]. The unpredictable course of SCD and its complications introduce significant uncertainty and anxiety for both children and their caregivers, further exacerbating the impact on HRQoL [4].

For children, this can mean limitations in school attendance, physical activity, and peer relationships, while parents often face increased stress, financial burdens, and disruptions to family dynamics. Understanding these complexities is critical for tailoring interventions that address both the physical and emotional dimensions of SCD. This review synthesizes existing literature to elucidate the multifaceted nature of HRQoL impairment in pediatric SCD. It explores perspectives from both children and their parents, identifies factors associated with compromised HRQoL, and evaluates gaps in the current research. By doing so, the review aims to inform the development of targeted, evidence-based interventions to enhance the quality of life for children living with SCD and support their families in managing the disease.

METHODOLOGY:

A systematic literature search was conducted to identify and analyze studies examining health-related quality of life (HRQoL) in children with sickle cell disease (SCD). To ensure comprehensive coverage, multiple electronic databases, including MEDLINE, Scopus, CINAHL, Masader, and EBSCOhost, were searched extensively. These databases were selected due to their broad indexing of medical, nursing, and allied health literature, allowing for the retrieval of relevant studies across multiple disciplines [3]. The search aimed to encompass a diverse range of studies from various geographic regions to provide a comprehensive understanding of HRQoL in pediatric SCD patients. A structured search strategy was employed, incorporating keywords and Medical Subject Headings (MeSH) terms to enhance the accuracy and relevance of the search results. The primary search terms included “sickle cell disease,” “sickle cell anemia,” “health-related quality of life,” “HRQoL,” “children,” “adolescents,” and “pediatric”. Additionally, geographical terms were used to capture studies conducted in different regions, ensuring a global perspective on HRQoL in children with SCD. Boolean operators (AND, OR) and truncation techniques were applied to refine the search results, minimizing irrelevant studies and maximizing the retrieval of pertinent literature [5]. To ensure the selection of high-quality studies, specific inclusion criteria were established. Studies were eligible for inclusion if they: (1) focused on pediatric populations (children and adolescents) diagnosed with SCD; (2) utilized validated and reliable HRQoL instruments; (3) reported quantitative data on HRQoL outcomes; and (4) were published in peer-reviewed journals [6]. These criteria ensured that only studies providing robust, scientifically valid findings were considered for the review. Conversely, exclusion criteria were applied to eliminate studies that lacked methodological rigor. Studies that focused solely on adult populations were excluded, as the review aimed to examine HRQoL specifically in pediatric patients. Additionally, studies relying on non-validated HRQoL assessment tools or those based exclusively on qualitative data were excluded to maintain consistency in outcome measurement. Research with significant methodological limitations, such as inadequate sample sizes, lack of statistical analysis, or high risk of bias, was also excluded to

ensure the reliability of the findings [5]. To further enhance methodological rigor and minimize bias, a quality assessment of the included studies was performed using established critical appraisal tools. The Critical Appraisal Skills Programme (CASP) checklist and the Joanna Briggs Institute (JBI) critical appraisal tools were used to systematically evaluate study validity, reliability, and risk of bias. These tools facilitated a structured assessment of study design, sampling methods, statistical analysis, and overall credibility, ensuring that only high-quality evidence was synthesized [5]. The screening and selection process was conducted in multiple stages. Initially, titles and abstracts were reviewed to identify potentially relevant studies. Full-text articles were then assessed for eligibility based on the predefined inclusion and exclusion criteria. Once the final selection was made, data extraction was conducted using a standardized extraction form to ensure consistency in recording key study details, including study design, sample size, HRQoL assessment tools, main findings, and limitations [6]. This rigorous and systematic methodology provided a strong foundation for analyzing HRQoL in pediatric SCD patients. By focusing on high-quality evidence, the review aimed to generate meaningful insights into the impact of SCD on children's well-being and contribute to the development of targeted interventions to improve their HRQoL.

HRQOL DOMAINS AFFECTED IN PEDIATRIC SCD:

The findings from the included studies consistently reveal that children with sickle cell disease (SCD) experience significantly lower health-related quality of life (HRQoL) compared to their healthy peers [1,7,8,9,10,11]. This impairment spans multiple domains of a child's life, reflecting a complex interplay of challenges that significantly impact their overall well-being.

Physical Functioning: Pain is a hallmark of SCD, frequently presenting as acute painful vaso-occlusive crises, and it has a profound impact on physical functioning [1]. These painful episodes often lead to significant limitations in physical activities such as running, jumping, and engaging in sports, with children reporting substantial difficulties in these areas [1,7,8,12,13]. The intensity and frequency of pain episodes strongly correlate with reduced physical HRQoL scores, leading to diminished participation in physical activities and negatively impacting overall physical health [8,5,14]. Fatigue, another pervasive symptom in SCD, often results from anemia and chronic inflammation [12]. This fatigue further restricts children's physical activity, adversely affecting their ability to engage in school, social events, and other developmental activities crucial for their growth. Beyond simple activity limitations, the chronic nature of pain and fatigue undermines children's overall sense of well-being and has the potential to negatively influence long-term physical health outcomes.

Psychosocial Functioning: The chronic and unpredictable nature of sickle cell disease (SCD), coupled with its associated pain, has a profound impact on psychosocial functioning [3,8,4,9]. Children with SCD often face social isolation due to frequent school absences, limited

participation in physical activities, and the need for recurrent medical appointments [8,4]. This isolation can foster feelings of loneliness, exclusion, and difficulty forming or maintaining peer relationships, further amplifying the social challenges they encounter [8,4]. Additionally, the persistent pain and uncertainty associated with SCD contribute significantly to emotional distress, manifesting as anxiety, depression, and anger [1,7,9,15]. These emotional difficulties negatively influence self-esteem, self-concept, and overall psychological well-being, impairing children's ability to thrive in social and academic settings [7,15]. The cumulative emotional burden frequently necessitates access to specialized psychosocial support services to help children cope with the complexities of living with SCD. Addressing these psychosocial challenges is critical to improving the overall quality of life for children with SCD.

Family and Economic Impact: The impact of sickle cell disease (SCD) extends far beyond the affected child, profoundly influencing the emotional, social, and financial well-being of the entire family [7,8,15,16]. Parents and caregivers frequently face elevated stress levels, anxiety, and reduced health-related quality of life (HRQoL) due to the relentless demands of managing their child's condition. These demands include frequent hospital visits, administering medications, and managing pain episodes [17,18]. The financial burden associated with SCD care can be overwhelming. Families often incur substantial costs for medical care, medications, transportation, and, in many cases, experience a loss of work income due to caregiving responsibilities [3,16]. These financial strains compound the emotional challenges faced by families, who must balance caregiving with maintaining their own emotional well-being. The emotional toll on families is often underestimated, as caregivers navigate the complexities of providing care while managing the uncertainties and chronic nature of the disease. This ripple effect highlights the critical need for comprehensive family-centered interventions designed to address these multifaceted challenges. Such interventions should include psychosocial support, financial assistance, and resources to improve caregivers' overall quality of life, ultimately enhancing the well-being of both the child and their family.

Academic Functioning: The chronic nature of sickle cell disease (SCD) and its associated complications significantly affect academic functioning [3,12]. Frequent hospitalizations, pain episodes, and fatigue often result in school absenteeism, which can lead to academic setbacks and reduced educational attainment [3]. The unpredictable nature of SCD symptoms, including sudden pain crises and fatigue, makes it challenging for children to maintain consistent attendance and focus in the classroom, further hindering their learning and overall academic performance [3]. These academic challenges have the potential to create long-term consequences, including reduced career opportunities and socioeconomic mobility. Addressing these issues requires the implementation of robust school support systems and accommodations tailored to the unique needs of children with SCD. Interventions may include individualized

education plans (IEPs), flexible attendance policies, and proactive communication between schools and healthcare providers. These measures are essential to mitigate the impact of SCD on educational attainment and to support the holistic development of affected children.

Factors Associated with HRQoL in Pediatric SCD: The health-related quality of life (HRQoL) of children with sickle cell disease (SCD) is influenced by a complex interplay of factors that extend beyond the immediate effects of the disease itself. Understanding these factors is essential for designing targeted interventions to improve HRQoL and address the specific challenges faced by these children.

Disease Severity: The severity of SCD, particularly the frequency and intensity of pain crises, is a significant predictor of HRQoL [8,5,14,19,20]. Frequent and severe pain episodes are strongly associated with lower HRQoL scores across multiple domains, including physical, emotional, and social functioning [8,5,14]. Children who experience recurrent pain crises often report greater limitations in daily activities, lower participation in social and school events, and a diminished overall sense of well-being. Additionally, severe complications such as acute chest syndrome, stroke, or organ damage further exacerbate the negative impact of SCD on HRQoL [2,21]. These complications not only contribute to physical suffering but also increase emotional distress and the burden on families. Effective pain management strategies, including pharmacological interventions, psychosocial support, and multidisciplinary care, are critical for mitigating these challenges and enhancing HRQoL in children with SCD.

Socioeconomic Factors: Socioeconomic factors play a pivotal role in shaping the health-related quality of life (HRQoL) in children with sickle cell disease (SCD) [3,16,22,23]. Poverty and limited access to quality healthcare are consistently linked with lower HRQoL scores across multiple studies [3,16,22,23]. Financial hardships often limit families' ability to afford essential medications, secure reliable transportation to medical facilities, and access other necessary resources [3]. For many families, these economic constraints lead to delayed or suboptimal care, compounding the physical and psychosocial challenges experienced by children with SCD. Additionally, limited access to specialized care, including hematology clinics and psychosocial support services, further exacerbates the burden on children and their caregivers. This lack of access can result in inadequate disease management, higher complication rates, and a lower overall quality of life. Addressing these socioeconomic disparities is crucial for improving outcomes in children with SCD. Efforts should focus on implementing policies and programs to reduce financial barriers, expand access to specialized care, and provide targeted support for economically disadvantaged families. Such measures are essential to ensure equitable access to healthcare and to enhance the overall quality of life for all children living with SCD.

Psychosocial Factors: Psychosocial factors, including coping mechanisms and family support, play a critical role in shaping the health-related quality of life (HRQoL) in children with sickle cell disease (SCD) [15,4,24,25]. Adaptive coping strategies, such as problem-solving, seeking social support, and engaging in positive self-talk, are strongly associated with better HRQoL outcomes [15,4]. Conversely, maladaptive coping mechanisms, such as avoidance, denial, and emotional suppression, are linked to poorer HRQoL scores [15,14]. Strong family support systems act as a protective buffer against the challenges posed by SCD, fostering resilience and improving children's overall well-being [4,25]. Families that provide emotional, psychological, and logistical support enable children to navigate the complexities of their condition more effectively, thereby enhancing HRQoL. Interventions focused on promoting adaptive coping skills and reinforcing family support networks are essential to improving the psychosocial and overall health outcomes of children with SCD.

Treatment and Interventions: Treatment interventions, particularly hydroxyurea and blood transfusions, are instrumental in improving clinical outcomes and positively influencing HRQoL [26,13,27,28,29]. Hydroxyurea, a disease-modifying therapy, has demonstrated efficacy in reducing the frequency of pain crises, improving hemoglobin levels, and enhancing overall HRQoL [26,27]. Regular blood transfusions are also effective in alleviating symptoms, reducing complications such as stroke and acute chest syndrome, and improving physical functioning and pain management [29]. The effectiveness of these treatments, however, can vary depending on individual patient factors, including disease severity, genetic background, and adherence to treatment regimens. Optimal use of these therapies requires a patient-centered approach, involving careful consideration of individual needs, ongoing monitoring of clinical outcomes, and regular assessment of HRQoL to ensure sustained benefits.

Parental and Child Perspectives on HRQoL: Studies comparing parental and child self-reports on health-related quality of life (HRQoL) often reveal notable discrepancies [7,8,10,17]. Parents frequently report lower HRQoL scores than their children, particularly in domains related to physical functioning and behavior [7,10]. This divergence may stem from parents' broader concerns about their child's future, the long-term implications of sickle cell disease (SCD), and the overall impact of the disease on family life [7]. While children's reports often focus on their immediate experiences, such as current symptoms or limitations, parents tend to anticipate future challenges, including disease progression, potential complications, and the cumulative burden on the family. These differing perspectives highlight the multidimensional nature of HRQoL and underscore the importance of considering both parental and child inputs when evaluating the impact of SCD and the effectiveness of interventions. The integration of both child and parent perspectives provides a more comprehensive understanding of the challenges faced by children

with SCD and their families. It ensures that interventions are tailored to address both immediate needs and long-term concerns, enhancing their overall effectiveness in improving HRQoL.

Interventions to Improve HRQoL in Pediatric SCD: Improving health-related quality of life (HRQoL) in children with sickle cell disease (SCD) requires a comprehensive, multidisciplinary approach that addresses the multifaceted nature of the disease [3,1,8,20,30,25]. Effective interventions should incorporate medical, psychological, and social strategies.

Comprehensive Pain Management: Effective pain management is a cornerstone of improving HRQoL in children with SCD. This includes pharmacological approaches such as opioids and non-opioid analgesics, as well as non-pharmacological techniques, including cognitive behavioral therapy (CBT), relaxation strategies, and physical therapy [31]. A multi-modal approach is often necessary to achieve optimal pain control.

Psychosocial Support: Addressing the psychosocial needs of children with SCD is essential. Interventions should focus on building coping skills, reducing anxiety and depression, and promoting emotional well-being [31,15,14]. Individual and group therapy, support groups, and educational programs can effectively enhance psychological resilience.

Strengthening Family Support: Family-centered interventions play a crucial role in improving HRQoL. Providing education and support to families enhances their ability to manage their child's condition, reduces parental stress, and improves family dynamics [26,32,33].

Educational Interventions: Educational programs that empower families with knowledge about SCD management, treatment options, and available resources are critical. These programs improve parental confidence and reduce feelings of helplessness [26,32,33]. The integration of technology, such as smartphone applications, can facilitate access to information and support.

Early Intervention and Prevention: Early diagnosis and timely intervention are crucial for preventing long-term complications and improving HRQoL [2,34]. Proactive measures such as hydroxyurea therapy or regular blood transfusions initiated early can significantly improve outcomes.

Addressing Health Disparities: Efforts to reduce health disparities are fundamental to improving HRQoL for all children with SCD. Addressing socioeconomic barriers, improving access to specialized care, and culturally tailoring interventions are essential for promoting health equity [16,22,23].

LIMITATIONS AND FUTURE RESEARCH DIRECTIONS:

This systematic review has several limitations that warrant consideration. The number of eligible studies included was relatively small, particularly for specific geographical regions and age groups [5]. There was a notable geographic bias, with a concentration of studies in certain regions and underrepresentation from others, potentially limiting the generalizability of findings to diverse populations. Additionally, the heterogeneity of study designs and health-related

quality of life (HRQoL) measures used complicated the ability to perform meta-analyses and draw consistent conclusions across studies. To address these limitations, future research should focus on the following:

Longitudinal Studies: There is a critical need for longitudinal studies to track HRQoL trajectories over time and assess the long-term impact of sickle cell disease (SCD) and interventions [12]. Such studies would provide valuable insights into disease progression and the sustained effects of various treatments and support strategies.

Intervention Studies: Well-designed randomized controlled trials (RCTs) are essential for evaluating the effectiveness of specific interventions, such as advanced pain management strategies, psychosocial interventions, and family support programs, on HRQoL outcomes [30]. This robust evidence base would help refine clinical practice and improve outcomes for children with SCD.

Qualitative Research: Qualitative studies are needed to delve deeper into the lived experiences of children and families affected by SCD [4]. These insights will help develop more patient-centered interventions that address the unique challenges faced by individuals and families.

Addressing Health Disparities: Further research should focus on addressing health disparities and identifying culturally sensitive interventions effective across diverse populations [24]. This is crucial for ensuring equitable access to quality healthcare and improving HRQoL for all children with SCD.

Long-Term Effects: More studies are required to examine the long-term effects of SCD and its treatments on HRQoL [35]. Understanding these long-term consequences is essential for developing strategies to manage chronic health challenges and ensure sustained quality of life.

Younger Children: There is a significant gap in research on the HRQoL of younger children with SCD [34]. Collecting self-reported data from very young children is challenging, but proxy reports from parents can provide valuable information. Additionally, the development and validation of age-appropriate assessment tools are necessary for capturing HRQoL accurately in this population.

CONCLUSION:

This systematic review highlights the profound impact of sickle cell disease (SCD) on the health-related quality of life (HRQoL) of children and adolescents, with impairments across physical, psychosocial, familial, and academic domains. Influencing factors include disease severity, socioeconomic challenges, coping strategies, and healthcare access. While medical treatments improve some HRQoL aspects, a holistic, multidisciplinary approach is crucial, addressing both physical and psychosocial needs. Interventions should include effective pain management, psychosocial support, family-centered care, and educational programs. Future research should address current limitations, evaluate interventions, and promote health equity.

Integrating HRQoL assessments into clinical care is vital for guiding strategies and improving outcomes, focusing on a patient-centered approach that encompasses both the child's and family's well-being.

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MULTIFACETED THERAPEUTIC EFFECTS OF GLYCYRRHIZIN: A HIGHLIGHT

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ABSTRACT:

Liquorice has been recognized as an herbal remedy in ancient medical texts from China & India, and has been used for thousands of years. Glycyrrhizin the primary active compound in liquorice root, has been recognized in traditional medicine since ancient times. Glycyrrhizin is classified as a terpenoid. It is among the most promising naturally derived molecules due to its inherent pharmacological properties, including anti-arthritic, anti-inflammatory, anti-Alzheimer's, antimicrobial, and anticancer effects**.** It plays a key role in the pharmacological effects of liquorice. GA is known to possess a variety of therapeutic efficiency. At the molecular level, it exhibits effects such as reducing inflammation and blood glucose levels, decreasing the secretion of inflammatory mediators, enhancing insulin sensitivity, and promoting memory formation in the brain. GA also demonstrates the ability to induce cell cycle arrest and inhibit rapid cell growth, helping to mitigate cancer symptoms. GA lowers the levels of reactive oxygen species, which are responsible for numerous pathological conditions. This review highlights the pharmacological properties of GA, its beneficial effects on various health conditions, and its potential for the development of new pharmaceutical agents.

Keywords: Anti-Arthritic, Anti-Diabetic, Anti-Inflammatory, Anti-Alzheimer’s, Glycyrrhizin, Glycyrrhizic Acid, Therapeutic Agent.

INTRODUCTION:

For thousands of years, indigenous cultures worldwide have relied on traditional herbal medicine to address a wide range of ailments. Throughout history, plants have served as a valuable source of cost-effective natural compounds, particularly secondary metabolites. These compounds, known for their intricate structural complexity that often makes their synthesis challenging or currently unachievable, display a wide range of biological activities, including antitumor properties. Secondary metabolites are principally minor organic moiety produced by an organism that are noncrucial for its growth progression or replica. [1]

Nature provides a vast reservoir of therapeutic compounds, many of which have been utilized in modern medicine. In developing countries, traditional medicine is among the most readily available treatment options. In certain regions, approximately 80% of the global

population is believed to depend on traditional medicine to meet their primary healthcare needs. A significant number of pharmacologically active compounds and new drug innovations are derived from plants, as demonstrated by the prevalence of widely used medications that trace their origins to plant sources. At the start of the 21st century, the World Health Organization (WHO) reported that eleven percent of more than 250 essential medicines originated from flowering plants. [1, 2]

Though floras are evidently effective in providing nutrition and shelter, their standing as a source of medicine is regularly underestimated. Humanoid societies have rest on floras for nourishment, shelter, and medicinal uses for almost the same length of time. Phytochemicals encompass a wide range of compounds derived from plants and are thought to play a key role in preventing numerous diseases, often linked to diets abundant in fruits as well as vegetables, and also in florae-based brews. These compounds appear to work both individually and in combination, possibly together with vitamins and added nutrients, to prevent, interrupt, or slow the progression of illnesses. Henceforth, emphasizing the consumption of whole diets is essential rather than reliant on supplements. [3,4]

Throughout history, natural products have been utilized as medicines in various forms such as traditional remedies, potions, and oils, with many of these bioactive compounds yet to be identified. The primary source of knowledge about the medicinal uses of natural products from plants stems from centuries of human experimentation, involving trial and error through palatability tests or accidental fatalities, in the quest for food and remedies to treat diseases. The procedure through which an organism generates compounds recognized as 'secondary metabolites' (natural foods) is regularly unique to that organism or reflects the distinct characteristics of its species, a process referred to as "secondary metabolism." Secondary metabolites are typically not vital for an organism's growth, development, or reproduction. Instead, they are produced as adaptations to the surrounding environment or as potential defence mechanisms against predators, aiding the organism's existence. The biogenesis of secondary metabolites originates after core procedures such as photosynthesis, lysis of glycogen, and the Krebs cycle, which generate biosynthetic intermediates that ultimately lead to the production of secondary metabolites, also referred to as natural products. [4,5]

Phytochemicals are often concentrated in the pigments of fruits and vegetables, highlighting the benefits of including more vibrant-coloured varieties in the diet. However, many beneficial phytochemicals are also present in less colourful or pale fruits and vegetables, such as carrots and corn, which are rich in these compounds. The use and importance of natural substances as treatments for various illnesses have been well-established for centuries. Although natural products have a wide range of applications in medicine, further research in this area is still necessary. Naturally occurring compounds and their active constituents are widely available

and play a vital role as therapeutic agents. Ayurveda, which originated in ancient India, is one of the oldest scientific systems of medicine. It emphasizes natural healing for both the body and mind, promoting the use of natural remedies to treat a range of health conditions. This traditional medical approach is renowned for its minimal side effects. Ayurvedic treatments focus on addressing both the underlying cause and the symptoms of a condition. Ayurveda identifies three primary substances, known as dosha like Vata & Pitta as well as Kapha and emphasizes that maintaining their balance supports good health, while imbalances can result in illness. his ancient practice is rooted in classical Sanskrit literature and consists of eight core components. [6,7,8]

Phytochemicals are natural pharmacologically active complexes and originate in plants that provide medicinal properties and nutritional benefits to humans. These compounds protect plants from diseases and damage while also enriching their colour, aroma, and flavour. The chemicals in plants that protect them from environmental hazards such as contamination, strain, scarcity, UV radiation, and pathogens are commonly known as phytochemicals. Current studies have clearly revealed that these compounds perform a vital part in protecting human health, especially when consumed in significant amounts through the diet. [7,9]

Flora has long stayed an ironic basis of therapeutic agents, providing plentiful medicinal plants that give rise to treasured phytochemicals. Licorice, scientifically known as *Glycyrrhiza glabra*, (GG) belongs to the Leguminosae family. This is an Ayurvedic herb commonly used in ancient system of medicines. This medicinal plant is widely distributed across Asia and parts of Europe. is believed to have originated in Iraq. Licorice is among the most commercially significant plants worldwide, with diverse applications in tobacco & make-ups, the food industry as well as pharmaceuticals. In traditional system of Chinese medicine (TCM), *GG* is regarded as a "vital herbal medication." [8,10]

GG has been renowned in traditional medicine for centuries. In ancient Chinese pharmacopeia, it was regarded as a top-tier remedy, believed to possess rejuvenating properties when consumed over extended eras. Liquorice was extensively utilized in some countries like Egypt, Greece as well as Rome. Its continued use from that time to the present demonstrates its effectiveness. Indian, Chinese, Egyptian, Roman & Greek beliefs likewise used the rhizome in dried form and root as carminatives & expectorants. The official publication materia medica described it by way of being useful for conditions such as bronchitis, laryngitis and as an emollient as well as demulcent, diuretic, expectorant, and more. GG is used as a suppressant of cough, to relieve dryness of throat, and also as a tonic. Licorice enhances memory, acts as an antidepressant, and helps lower blood cholesterol levels. The Image 1a and 1b represent the plant and stem of GG. [11]

Figure 1a: Plant of GG

Figure 1b: Dry stem of GG

It is widely found and cultivated in Afghanistan, India, Pakistan as well as European & other North Asian countries. *Glycyrrhiza glabra* is known by different names depending on regional languages and areas, as listed below in table 1. Also, the biological classification of GG is presented in figure 2. [12]

Table 1: Common names of GG [12]

Language	**Common Name**
Hindi	Mulethi, Mulhatti
Gujarati	Jethimadhu
Sanskrit	Yashti-madhuh
Bengali	Jashtimadhu
Kannada	Yastimadhuka
English	Licorice or sweet wood

Classification of *Glycyrrhiza glabra* linn.

Kingdom: Plantae
Subkingdom: Tracheobionta-Vascular plants
Super division: Spermatophyta-Seed plants
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Fabales
Family: Fabaceae-Pea family
Genus: *Glycyrrhiza licorice*
Species: *Glycyrrhiza glabra Linn*

Figure 2: Describes the biological classification of GG. [12]

Numerous components have been extracted from liquorice roots, with water-soluble, biologically active compounds comprising 40-50% of the total dry weight of GG. The pharmacologically active composite includes asparagine, amino acids, essential oils, fats bitters, flavonoids, gums, glycosides, mucilage, mineral salts, proteins, polysaccharides, resins, starch, simple sugars, tannins, triterpene saponins, sterols, volatile oils, and various other complexes.[12, 13]

Glycyrrhizin:

The primary component of liquorice is glycyrrhizin, which exists in the plant in the form of potassium salt as well as calcium salts of glycyrrhizic acid (GA). It is never known as glycosidic compound because, upon hydrolysis, it produces one moiety of glycyrrhetic acid and two moieties of glycuronic acid, but not sugar. The second product Glycuronic acid is nearly linked to hexose sugars, while the first product glycyrrhetic acid exhibits properties of blood lysis similar to those of saponins. Its molecular weight is 822.92 g/mol, and its molecular formula is $C_{42}H6_2O_{16}$ as represented in figure 3.

Glycyrrhizin is said to be about 50 times sweeter than cane sugar, with its sweetness detectable even at a dilution of 1:15,000. Glycyrrhizin (also identified as glycyrrhizic acid) makes up 10-25% of the liquorice root extract. Glycyrrhizin, a compound of triterpenoid class, is responsible for the sweet taste of liquorice root. is a key compound responsible for the pharmacological and biological effects of liquorice. [14]

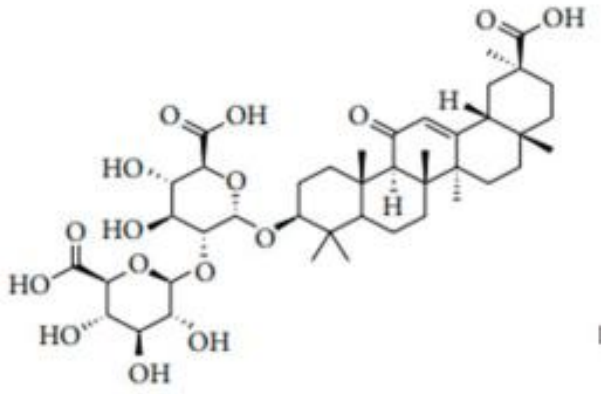

Figure 3: Molecular structure of GA.

It is absorbed as glycyrrhetic acid subsequently hydrolysis through enzymes by commensal microbiota. Thus, the pharmacological effects of GA are primarily those associated with glycyrrhetinic acid. [14] The glycyrrhizin possesses multiple pharmacological effects. Few best examples are described below.

1. **Anti-inflammatory activity:** Various clinical studies have demonstrated that GA is effective in treating multiple inflammatory diseases across different organs. Inflammation is a defensive mechanism aimed at eliminating primarily infectious agents and restoring

damaged tissues to their normal state of balance. Inflammation can be classified as acute or chronic, both of which share a similar underlying mechanism. When an induction is detected, the inflammatory cascade is initiated at the receptors of cell surface, to give rise to markers of inflammatory reactions and the employment of cells of inflammatory process. In the first instance, the procedure concludes once the trigger is removed or else resolved; however, in the second instance, the body is incapable to reparation the damage or else eliminate the induction. The inflammation process starts with increased blood vessel permeability, followed by immune cell infiltration, which eventually results in granuloma formation and tissue repair. Chronic inflammation is a long-lasting, low-level, and often symptomless condition that can result from factors for example obstinate infections, dormancy linked to corporal, overweightness, deprived diet, interrupted patterns of sleep, social seclusion, and strain. If not addressed, ongoing chronic inflammation can lead to severe conditions, including metabolic syndromes, neurodegenerative disorders, and immune system dysfunction diseases. Long term inflammatory diseases are responsible for 60% of all deaths globally. The anti-inflammatory effects of GA are attributed to its ability to inhibit the synthesis, generation, or action of TNF-α, as well as interleukins IL-1β & IL-6, also the activation of mitogen-activated protein kinases (MAPKs). Previous researchers also reported the effect of GA on NF-ƘB activation. [15]

2. **Anti-Cancer activity:** Cancer has affected multicellular organisms for over two hundred million ages, and the families of current creatures experienced cancer over a lakhs years before. Cancer is in second position for the foremost normal reason of death among children as well as adults, with apiece kind having a specific age array and method of incidence, varying in prevalence across diverse genders. Despite significant hard work to realize the derivation of cancer cells, the development of cancerous tissue, and the mechanism in arrears their spread and relapse, this illness continues to be an unidentified. An increasing amount of research indicates that shifts in cancer incidence rates may be driven by more subtle changes within the cellular pyramid. Cancer development likely follows three pathways:
   1) scattering start from the site of origin to neighbouring cellular structure.
   2) distribution from lymph nodes to nearby lymph nodes,
   3) dispersion to countless tissues and body part all over the body via circulation of blood.

   The primary molecular antitumor mechanism of GA, as reported in the literature, involves the suppression of rapid cell growth, metastasis, seizure of cell cycle, cell

death due to apoptosis, and the down-regulation of the transcription factor nuclear factor kappa beta (NF-κB). [16,17]

3. **Anti-diabetic activity:** Diabetes mellitus (DM) is a chronic disorder linked to metabolism process and characterized by obstinately higher levels of glucose in blood, known as hyperglycemia, which gradually causes severe and irreversible damage to various organs. The global population of individuals with DM is projected to rise to more than 640 million by 2030 as well as 780 million by the year 2045. T2DM arises from a amalgamation of two key issues: impaired secretion of insulin hormone by β-cells of pancreas and persistent resistance of insulin in insulin-sensitive tissues. A variety of hypoglycemic drugs for the treatment of T2DM are currently available on the market. However, many of these medications cause side effects such as nausea, inflating, diarrhoea, mass gain, stomach pain, hypoglycemia, and secondary therapy failure, which can impact patients' obedience to treatment. Furthermore, T2DM patients are at risk of becoming poorly controlled diabetics, which is strongly linked to the development of diabetic complications. The anti-diabetic properties of GA and its by-products stood validated through both in vitro as well as in vivo studies. The mechanism of action encompass enhancing tolerance as well as sensitivity of glucose molecule, regulation of glucose balance and metabolism of lipid, as well as promoting secretion of insulin. [15, 18]
4. **Anti-arthritic activity:** Rheumatoid Arthritis (RA) is recognized as a continuing disorder of immune system with a mysterious cause. Persistent synovitis is a key characteristic, often accompanied by involvement of multiple organs and the production of autoantibodies like rheumatoid factor and anti-citrullinated peptide protein antibodies. Joint dysfunction, particularly in the hands & wrists and also involves knees, and is a communal feature of RA. As the disorder advances, it impacts the joints and various other parts of the body, leading to premature death and numerous issues such as disability and a lower quality of life, particularly in developing countries. Long-lasting inflammation leads to body imbalance and joint damage, a common complaint among nearly all patients. Epidemiological data indicates that RA affects approximately one percent of adults. The condition is particularly prevalent among females and older adults. Approximately 40 new cases per 100,000 people are diagnosed with RA each year. Conferring to the Center for Disease Control and Prevention, key risk factors for developing RA include environmental influences such as overweightness, elderly, being smoker, being female, and hereditary predisposition. Previous studies have shown that glycyrrhizin significantly reduced the level of IL-1β- chiefly of nitric oxide (NO), prostaglandins chiefly E2 (PGE2), suppression of TNF-α, and interleukin-6 (IL-6), as

well as the generation of cyclooxygenase-2 (COX-2) with inducible nitric oxide synthase (iNOS), as well as metalloproteinase-3 (MMP3). The all given factors are key factors responsible for the arthritic disorders. [19,20]

5. **Anti-bacterial Activity:** Glycyrrhizin, an active component of the traditional Chinese medicine (TCM) liquorice, plays a significant role in protecting mammals against bacterial infections. Infections have historically remained a leading source of disease, with infections chiefly of bacterial one posing a severe menace to humanoid health, often resulting in substantial morbidity and mortality. Bacterial infections can lead to inflammation in various organs, such as glomerulonephritis caused by streptococcal and staphylococcal infections, many of which progress to chronic kidney disease or end-stage renal disease. Staphylococcus aureus is frequently associated with influenza-bacterial co-infections in individuals, which can exacerbate the disease and result in severe complications or even death. Manifold myeloma is more likely to occur with heightened susceptibility to bacterial infections. Pneumonia caused by *K pneumoniae*, infections of urinary tract resultant from gram-negative bacteria as well as acute infections linked to various bacteria can potentially progress to several myeloma. Highly effective drugs are urgently needed to treat bacterial infections, given the numerous limitations of antibiotics targeting -resistance against multidrug. Antibiotics continue to play a vital role in organ transplantation, other surgical procedures, and bacterial infections. However, the rise of drug resistance has led to a gradual reduction or complete loss of the inhibitory effects of antibiotics on certain pathogenic bacteria. Thus, there is a need to develop new therapeutic agents capable of effectively combating bacterial diseases. In the meantime of 50s, academic publications on GA have remained released in systematic manner, with a noteworthy graded advancement in volume noted in the 21st era. In current years, research efforts focused on GA have seen a noticeable increase. Clinical studies report its use in treating a variety of conditions, including hepatitis, arthritis, diabetes, cancers, and skin related disorders. GA enhances the incorporation of fluorescein isothiocyanate-dextran as well as *S. enterica* in macrophages of chicken while inducing the face of inducible nitric oxide synthase (iNOS) & NADPH oxidase-1 (NOX-1), thereby stimulating nitric oxide as well as hydrogen peroxide formation in cells. For intracellular attacking pathogens nitric oxide is crucial in defending, by exhibiting strong bacteria killing ability in conjunction with reactive oxygen species. Additionally, GA exhibits a wide range of antibacterial activity by inhibiting bacterial growth through targeting enzymes of bacteria, disrupting cell membrane formation, and modifying permeability of cell membrane. [21, 22]

6. **Anti-Alzheimer's activity:** Dementia is a general term that refers to a range of progressive disorders affecting memory, thinking, and behavior, greatly impacting an ability of individual to perform normal household tasks. Alzheimer's disease (AD) is the utmost communal form of dementia, representing over 65% of all cases. Currently, Alzheimer's disease affects over five million people, and projections suggest that this number will exceed 13 million by 2050. The most prevalent form of dementia and a rapidly escalating global epidemic. Commonly known as senile dementia, it is the most widespread form of dementia and an age-related neurodegenerative disorder. With the global population aging, the number of people impacted by Alzheimer's disease is steadily increasing. An increasing body of research indicates that the overproduction of Reactive Oxygen Species is a significant factor in the development of this disease. It is marked by the build-up of beta-amyloid as well as tau proteins in the brain, disrupting normal cognitive processes. This is commonly manifested through memory problems, mood changes, impaired thinking, judgment difficulties, altered behaviour and emotions, and eventually a loss of corporeal regulator on the body. In neurological disorders, an imbalance between the production and clearance of Aβ leads to the formation of senile plaques. The previous studies reported that the GA significantly effective against generation of beta amyloid plaques as well as tau protein. GA also reduces neuroinflammation and level of reactive oxygen species in brain ultimately leads to possess anti-Alzheimer's activity. [23]

CONCLUSION:

Glycyrrhiza glabra, a plant belonging to the Glycyrrhiza genus within the Leguminosae family, is a well-known natural flora with a ironic past of medicinal usage that dates old times to ancient era. The utilization of licorice can be traced back to ancient civilizations, including the Greek as well as Roman empires. From the prehistoric times, glycyrrhizin, the primary active ingredient in GG, has been widely used as a therapeutic agent in clinical practice.[24] Glycyrrhizic acid (GA), a natural compound present in licorice, shows great medical potential and may aid in the treatment as well as prohibition of many ill conditions, counting infections of viral sources, inflammatory diseases, autoimmune disorders, metabolic disorders and in neurological diseases. Numerous reports have demonstrated significant enhancement of the solubility and influences the pharmacokinetic properties of molecular compounds by refining their cellular permeability, stability, and effectiveness by glycyrrhizin. GA's amphiphilic nature enables it to create water-soluble complexes with various hydrophobic drug compounds, significantly enhancing the solubility of these hydrophobic substances by several-fold. Studies have shown that the increased drug solubility achieved with GA is associated with a substantial reduction in the required therapeutic dose of the drug.[23] Previous researchers also reported the

multifaceted therapeutic action of glycyrrhizin in arthritis, cancer, diabetes, antibacterial, Alzheimer's as well as inflammatory diseases. The beneficial effect of GA as molecular level makes is a proper component for plant based therapeutic agent. Moreover the pharmacokinetic studies and clinical studies are further warranted to generate a prominent pharmaceutical agent of treating life threatening diseases.

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METALS IN THE ENVIRONMENT: CHEMICAL APPROACHES FOR REMOVAL AND REMEDIATION

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ABSTRACT:

Metal pollution in the environment poses significant risks to ecosystems and human health due to the persistence, toxicity, and bioaccumulate nature of metals. This research paper explores chemical approaches for the removal and remediation of metals from contaminated water, soil, and air. The study highlights the mechanisms, applications, and limitations of conventional chemical methods such as adsorption, precipitation, ion exchange, and electrochemical techniques. Additionally, emerging technologies, including nanotechnology, biotechnology, and advanced oxidation processes, are discussed for their potential to enhance remediation efficiency and sustainability. Integrated approaches that combine multiple remediation strategies are also examined, emphasizing their ability to address complex contamination scenarios and promote resource recovery. The paper underscores the importance of interdisciplinary and innovative solutions to mitigate metal pollution, protect ecosystems, and safeguard human health. By advancing chemical approaches and integrating emerging technologies, this research contributes to the development of sustainable and effective strategies for metal remediation in the environment.

Keywords: Metal Pollution, Chemical Remediation, Adsorption, Nanotechnology, Bioremediation, Integrated Approaches, Sustainability.

INTRODUCTION:

Background and Significance

Metals are naturally occurring elements essential to biological and industrial processes. However, their excessive presence in the environment, particularly heavy metals like lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As), has become a significant environmental concern. These metals are non-biodegradable and tend to accumulate in soil, water, and air, posing severe risks to ecosystems and human health.

Metals are released into the environment through both natural processes (e.g., volcanic eruptions, and rock weathering) and anthropogenic activities (e.g., mining, industrial discharges, agricultural runoff, and improper waste disposal). The persistence and toxicity of heavy metals necessitate effective strategies for their removal and remediation to mitigate their adverse effects.

Sources of Metal Pollution

Metal pollution in the environment is a significant global concern due to its persistence, toxicity, and potential to bioaccumulate in ecosystems. Metals can originate from both natural and anthropogenic sources, with human activities being the primary contributors to elevated metal concentrations in the environment. Below is an elaboration on the major sources of metal pollution, which can serve as a foundation for a research paper on "Metals in the Environment: Chemical Approaches for Removal and Remediation."

Natural Sources of Metal Pollution

Natural processes contribute to the presence of metals in the environment, though these are typically at background levels and rarely cause significant pollution.

- Geogenic Sources
- Biogenic Sources

Anthropogenic Sources of Metal Pollution

Human activities are the primary drivers of metal pollution, significantly increasing metal concentrations in the environment. These sources can be categorized into industrial, agricultural, domestic, and miscellaneous activities.

Pathways of Metal Pollution

Metals enter the environment through various pathways, including:

- Air: Atmospheric deposition of metal particulates and vapours.
- Water: Discharge of industrial effluents, agricultural runoff, and sewage.
- Soil: Contamination from waste disposal, mining, and agricultural practices.
- Biological Pathways: Bioaccumulation and biomagnification in food chains.

Implications of Metal Pollution

- Environmental Impact: Metals can disrupt ecosystems, reduce biodiversity, and contaminate water and soil resources.
- Human Health Risks: Exposure to toxic metals like lead, mercury, and cadmium can cause neurological, cardiovascular, and reproductive disorders.
- Economic Costs: Remediation of metal-contaminated sites is often expensive and time-consuming.

Environmental and Health Impacts of Metal Pollution

Metal pollution poses significant risks to both the environment and human health due to the persistence, toxicity, and bio accumulative nature of many metals. Understanding these impacts is critical for developing effective remediation strategies and mitigating the consequences of metal contamination. Below is an elaboration on the environmental and health impacts of metal pollution, which can serve as a foundation for a research paper on "Metals in the Environment: Chemical Approaches for Removal and Remediation."

Environmental Impacts of Metal Pollution

Metal contamination disrupts ecosystems, affects biodiversity, and degrades natural resources. The environmental impacts of metal pollution are multifaceted and can be observed in soil, water, and air.

Health Impacts of Metal Pollution

Exposure to toxic metals can have severe consequences for human health, affecting various organ systems and leading to chronic and acute health conditions. The health impacts of metal pollution depend on the type of metal, the route of exposure, and the duration and intensity of exposure.

a. Neurological Effects

b. Cardiovascular Effects

c. Renal and Hepatic Effects

d. Reproductive and Developmental Effects

e. Carcinogenic Effects

f. Immunological Effects

g. Respiratory Effects

Socioeconomic Impacts

- Healthcare Costs:
    - The treatment of metal-related health conditions places a significant burden on healthcare systems.
- Loss of Productivity:
    - Chronic health conditions caused by metal exposure can reduce workforce productivity and increase absenteeism.
- Environmental Remediation Costs:
    - Cleaning up metal-contaminated sites is expensive and resource-intensive.

Chemical Approaches for Metal Removal and Remediation

Metal pollution in the environment is a significant global challenge due to its persistence, toxicity, and potential to bioaccumulate in ecosystems. Address this issue, various chemical approaches have been developed for the removal and remediation of metals from contaminated water, soil, and air. These methods leverage chemical principles to immobilize, extract, or transform metals into less toxic or more manageable forms. Below is an elaboration on the chemical approaches for metal removal and remediation, which can serve as a foundation for a research paper on "Metals in the Environment: Chemical Approaches for Removal and Remediation."

Adsorption: Adsorption is one of the most widely used chemical methods for metal removal due to its simplicity, efficiency, and cost-effectiveness. It involves the attachment of metal ions onto the surface of an adsorbent material.

Ion Exchange: Ion exchange involves the replacement of metal ions in a solution with non-toxic ions attached to a solid resin or matrix.

a. Types of Ion Exchangers

- Synthetic Resins: Polystyrene-based resins with functional groups like sulfonic acid (-SO_3H) or quaternary ammonium (-NR_4^+).
- Natural Zeolites: Aluminosilicate minerals with high cation exchange capacities.

b. Mechanisms

- Cation Exchange: Replacement of toxic metal cations (e.g., Pb^{2+}, Cd^{2+}) with non-toxic cations (e.g., Na^+, H^+).
- Anion Exchange: Removal of metal anions (e.g., CrO_4^{2-}, AsO_4^{3-}) by exchanging them with non-toxic anions (e.g., Cl^-, OH^-).

c. Applications

- Water Softening: Removal of calcium and magnesium ions from hard water.
- Metal Recovery: Recovery of valuable metals like gold and silver from industrial effluents.

Emerging Technologies in Metal Remediation

As metal pollution continues to pose significant environmental and health risks, researchers and engineers are developing innovative technologies to enhance the efficiency, sustainability, and cost-effectiveness of metal remediation. These emerging technologies leverage advancements in nanotechnology, biotechnology, materials science, and electrochemistry to address the limitations of traditional remediation methods. Below is an elaboration on emerging technologies in metal remediation, which can serve as a foundation for a research paper on "Metals in the Environment: Chemical Approaches for Removal and Remediation."

Nanotechnology-Based Remediation

Nanotechnology has revolutionized metal remediation by offering highly efficient and targeted solutions for metal removal and recovery.

- Applications:
    - Treatment of chromium-contaminated groundwater.
    - Immobilization of lead and arsenic in contaminated soils.

Integrated Approaches for Metal Remediation

Metal pollution in the environment is a complex issue that often requires multifaceted solutions. Integrated approaches for metal remediation combine multiple techniques and strategies to enhance efficiency, address diverse contamination scenarios, and ensure long-term sustainability. These approaches leverage the strengths of chemical, biological, physical, and engineering methods to achieve comprehensive remediation. Below is an elaboration on

integrated approaches for metal remediation, which can serve as a foundation for a research paper on "Metals in the Environment: Chemical Approaches for Removal and Remediation."

Combining Chemical and Biological Methods

Integrating chemical and biological methods can enhance the efficiency and sustainability of metal remediation.

a. Chemically Enhanced Phytoremediation

- Mechanism:
    - Use of chemical agents (e.g., chelators, acids) to increase the bioavailability of metals in soil, enhancing their uptake by plants.
    - Example: Application of EDTA to solubilize lead, making it available for uptake by hyperaccumulator plants like *Brassica juncea*.
- Applications:
    - Remediation of metal-contaminated soils in agricultural and industrial sites.
    - Recovery of valuable metals (e.g., nickel, cobalt) from mining waste.

b. Bioaugmentation with Chemical Amendments

- Mechanism:
    - Introduction of metal-resistant microorganisms to contaminated sites, combined with chemical amendments (e.g., lime, phosphate) to immobilize metals.
    - Example: Use of sulphate-reducing bacteria (SRB) with calcium carbonate to precipitate metals as sulphides.
- Applications:
    - Treatment of acid mine drainage (AMD) containing high concentrations of metals like iron, copper, and zinc.
    - Stabilization of metals in contaminated sediments.

Coupling Physical and Chemical Methods

Combining physical and chemical methods can improve the removal and recovery of metals from contaminated environments.

a. Electrokinetic Remediation with Adsorption

- Mechanism:
    - Application of an electric field to mobilize metal ions in soil or water, followed by adsorption onto a permeable reactive barrier (PRB) containing adsorbents like activated carbon or biochar.
    - Example: Use of electro kinetics to move lead ions toward a PRB filled with zero-valent iron (ZVI) for immobilization.
- Applications:
    - Remediation of metal-contaminated soils and groundwater.
    - Treatment of industrial wastewater containing mixed metal contaminants.

b. Membrane Filtration with Chemical Precipitation

- Mechanism:
    - Use of membrane filtration (e.g., nanofiltration, reverse osmosis) to concentrate metal ions, followed by chemical precipitation to remove them.
    - Example: Combining reverse osmosis with lime addition to precipitate metals like cadmium and zinc.
- Applications:
    - Treatment of metal-laden industrial effluents.
    - Recovery of metals from electronic waste leachates.

Integrating Advanced Oxidation Processes (AOPs) with Adsorption

Combining AOPs with adsorption can enhance the degradation of metal-organic complexes and improve metal removal.

a. Photocatalysis with Adsorption

- Mechanism:
    - Use of photocatalysts (e.g., TiO_2) to degrade organic ligands binding metals, followed by adsorption onto nanomaterials or biochar.
    - Example: Degradation of EDTA-metal complexes using TiO_2 under UV light, followed by adsorption of free metal ions onto graphene oxide.
- Applications:
    - Treatment of wastewater containing metal-organic complexes.
    - Removal of persistent organic pollutants (POPs) associated with metals.

b. Electro-Fenton Process with Adsorption

- Mechanism:
    - Generation of hydroxyl radicals (•OH) to oxidize metal-organic complexes, followed by adsorption of released metal ions onto activated carbon or biochar.
    - Example: Treatment of chromium-organic complexes in tannery wastewater using the electro-Fenton process and activated carbon.
- Applications:
    - Remediation of industrial wastewater with mixed organic and metal contaminants.
    - Degradation of toxic metal complexes in groundwater.

Hybrid Nanotechnology and Bioremediation

Integrating nanotechnology with bioremediation can enhance the efficiency and selectivity of metal removal.

a. Nano bioremediation

- Mechanism:
    - Use of nanomaterials (e.g., nZVI, graphene oxide) in combination with microorganisms or plants for synergistic metal removal.

  - Example: Application of nZVI to reduce Cr(VI) to Cr(III), followed by microbial immobilization of Cr(III) as chromium hydroxide.
- Applications:
  - Treatment of chromium-contaminated groundwater and soils.
  - Remediation of sites with mixed metal contaminants.

b. Biochar-Nanomaterial Composites

- Mechanism:
  - Combination of biochar with nanomaterials (e.g., Fe_3O_4, TiO_2) to create hybrid adsorbents with enhanced metal-binding capacity.
  - Example: Use of biochar-Fe_3O_4 composites for the removal of arsenic and lead from contaminated water.
- Applications:
  - Water treatment in rural and urban areas.
  - Soil amendment for immobilizing metals in agricultural fields.

Multi-Barrier Remediation Systems

Multi-barrier systems sequentially combine several remediation techniques to address complex contamination scenarios.

a. Permeable Reactive Barriers (PRBs) with Phytoremediation

- Mechanism:
  - Installation of PRBs containing reactive materials (e.g., ZVI, activated carbon) to intercept and immobilize metals in groundwater, combined with phytoremediation to treat residual contamination.
  - Example: Use of ZVI-PRBs to treat uranium-contaminated groundwater, followed by planting of sunflowers for phytoremediation.
- Applications:
  - Remediation of metal-contaminated aquifers.
  - Treatment of mining-impacted sites.

b. Sequential Electrokinetic and Phytoremediation

- Mechanism:
  - Application of electro kinetics to mobilize metals in soil, followed by phytoremediation to uptake and accumulate the mobilized metals.
  - Example: Electrokinetic treatment of lead-contaminated soil, followed by planting of *Brassica juncea* for lead uptake.
- Applications:
  - Remediation of heavy metal-contaminated soils.
  - Treatment of industrial brownfield sites.

Sustainable and Circular Economy Approaches

Integrated approaches can also focus on resource recovery and sustainability, aligning with circular economy principles.

a. Metal Recovery and Recycling

- Mechanism:
    - Use of integrated chemical and biological methods to recover valuable metals (e.g., copper, gold, rare earth elements) from waste streams.
    - Example: Bioleaching of electronic waste using acidophilic bacteria, followed by electrochemical recovery of metals.
- Applications:
    - Recycling of metals from electronic waste and industrial sludge.
    - Recovery of metals from mining and metallurgical waste.

b. Green Remediation

- Mechanism:
    - Use of environmentally friendly materials (e.g., biochar, biodegradable chelators) and energy-efficient technologies (e.g., solar-powered electro kinetics) for metal remediation.
    - Example: Solar-powered electrokinetic remediation of arsenic-contaminated soils combined with biochar amendment.
- Applications:
    - Sustainable remediation of contaminated sites in developing countries.
    - Low-carbon footprint solutions for metal pollution.

CONCLUSION:

Metal pollution in the environment remains a significant global challenge, with far-reaching implications for ecosystems, human health, and socio-economic development. The persistence, toxicity, and bioaccumulate nature of metals necessitate the development and implementation of effective remediation strategies. This research paper has explored various chemical approaches for the removal and remediation of metals, highlighting their mechanisms, applications, and limitations. Additionally, emerging technologies and integrated approaches have been discussed, highlighting the potential for innovative and sustainable solutions to address metal contamination.

Chemical methods such as adsorption, precipitation, ion exchange, and electrochemical techniques have proven effective in removing metals from contaminated water, soil, and air. These methods leverage the principles of chemistry to immobilize, extract, or transform metals into less toxic or more manageable forms. However, the efficiency of these techniques often depends on factors such as pH, temperature, and the presence of competing ions, necessitating careful optimization and customization for specific contamination scenarios.

Emerging technologies, including nanotechnology, biotechnology, and advanced oxidation processes, offer promising avenues for enhancing the efficiency and sustainability of metal remediation. Nanomaterials, such as graphene oxide and zero-valent iron nanoparticles, provide high surface areas and reactivity for metal adsorption and reduction. Biotechnological approaches, such as microbial remediation and phytoremediation, harness the natural capabilities of microorganisms and plants to absorb, accumulate, and stabilize metals. These technologies not only improve remediation outcomes but also align with the principles of green chemistry and environmental sustainability.

Integrated approaches, which combine multiple remediation techniques, offer a holistic solution to the complex problem of metal pollution. By leveraging the strengths of chemical, biological, physical, and engineering methods, integrated approaches enhance the efficiency, selectivity, and long-term effectiveness of remediation efforts. Examples include the combination of electrokinetic remediation with adsorption, chemically enhanced phytoremediation, and multi-barrier systems. These integrated strategies not only address diverse contamination scenarios but also promote resource recovery and circular economy principles.

In conclusion, the remediation of metal pollution requires a multifaceted and interdisciplinary approach. Chemical methods, emerging technologies, and integrated strategies each play a crucial role in addressing the challenges posed by metal contamination. Future research should focus on optimizing these techniques, exploring novel materials and processes, and developing sustainable and cost-effective solutions. By advancing our understanding and application of chemical approaches for metal removal and remediation, we can protect ecosystems, safeguard human health, and promote environmental sustainability for future generations.

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AN EXAMINATION OF VALIDATION FOR PHARMACEUTICAL CLEANING

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ABSTRACT:

Establishing the importance of cleaning validation in the pharmaceutical sector is the aim of this review. Active pharmaceutical ingredients (APIs) and pharmaceutical products can get contaminated by other APIs or pharmaceutical products, cleaning agents, pathogens, or other elements such as dust, lubricants, airborne particles, raw materials, intermediates, etc. The process of ensuring that potentially hazardous materials are successfully removed from equipment is known as cleaning procedures. Proper cleaning of the processing space, equipment, and apparatus helps reduce this. In order to guarantee the safety, effectiveness, and quality of the ensuing medicinal product batches as well as to comply with regulatory standards in the manufacturing of pharmaceutical products, it is required to validate the cleaning techniques. An outline of the sampling procedures, cleaning methods, cleaning chemicals, and contamination processes is given in brief.

INTRODUCTION:

The term "validation" was initially used in the United States in 1978.Over time, the idea of validation has broadened to include everything from computerised systems for clinical trials, labelling, or process control to analytical techniques used for the quality control of medicinal ingredients and drug products. Validation is best understood as a crucial and essential component of cGMP, while it is not required by regulatory regulations. One documented proof that a system or piece of equipment can be regularly cleaned to specified and accepted limits is known as cleaning validation.[1-2]

One of the goals of good manufacturing procedures (GMP) is to minimise potential contamination and cross-contamination of pharmaceutical products and starting materials. Two It is imperative that cleaning validation in manufacturing processes be planned and executed to minimise cross-contamination. Since the majority of equipment is used to produce various goods, cleaning methods must be able to eliminate residues from equipment to a level that is acceptable.[3]

Cleaning of processing areas and equipment is crucial in the pharmaceutical sector. Analytical analysis of a cleaning process is aided by cleaning validation. The main goal of

maintaining a high standard of cleanliness is to prevent contaminated products from being manufactured using the same machinery. The goal is to give our patients top-notch pharmaceutical items.[4]

Examine the equipment design, especially in big systems that could use fully automatic or semi-automated clean-in-place (CIP) systems, since these systems are a major source of risk. For instance, sanitary pipes without ball valves ought to be utilised. Cleaning becomes more challenging when such unhygienic ball valves are utilised, as is typical in the bulk medicine market.[5-6]

Operators carrying out cleaning procedures should be aware of issues and possess specialised training in cleaning these systems and valves once such systems have been discovered. Assess the degree of training and experience the cleaning operators have in cleaning these systems, as well as their familiarity with them. To find out if these systems have been correctly recognised and validated, you should also review the documented and verified cleaning procedure.

Look for valve identification and documented cleaning processes in flow charts and piping diagrams for bigger systems, such as those that use long transfer lines or piping. The operator carrying out the cleaning task should be able to quickly identify and tag the piping and valves. Inadequate identification of valves, both physically and on printouts, has occasionally resulted in improper cleaning procedures.[7-9]

Always make sure that the documentation of the cleaning procedures includes an often crucial component: determining and managing the amount of time that passes between the conclusion of processing and each cleaning stage. This is particularly crucial for bulk drug operations, topicals, and suspensions. The effectiveness of a cleaning procedure in such activities will be directly impacted by the drying of residues.

Microbiological features of equipment cleaning should be taken into account whether or not CIP systems are employed for cleaning processing equipment. Instead than cleaning up contamination after it has already happened, this mostly consists on preventative efforts. There should be proof that regular equipment cleaning and storage prevents the growth of microorganisms.[10]

Validation Types: [11]

There are four main categories of pharmaceutical validation.

1. Procedure verification
2. Validation of equipment
3. Validation of analytical methods
4. Validation of cleaning

1. Procedure verification

Process validation is the process of gathering and proving empirical evidence from the design phase all the way through to production completion. As "Establishing documented evidence which provides the high degree of evidence that a specific process will consistently produce a product, meeting its predetermined specifications and quality characteristics," the USFDA overstated the importance of process validation. The gathering and assessment of data, which is done from the process design stage all the way through production, is another way to describe process validation. It provides scientific proof that a process can reliably produce items of a standard calibre.[12]

2. Validation of equipment [13]

Equipment validation is referred to as qualifying. The three categories of equipment validation are Performance Qualification (PQ), Operational Qualification (OQ), and Installation Qualification (IQ). An IQ records particular static characteristics of a facility or item to demonstrate that the unit was installed correctly and that the manufacturer's installation requirements were fulfilled. Following installation, the equipment's ability to deliver the operating ranges listed in the purchase order must be confirmed. We call this OQ.

3. Validation of analytical methods [14]

Analytical validation is the process of confirming that the chosen analytical technique will produce accurate findings suitable for the intended use. Validation of analytical methods involves many factors. They are as follows:

- Repeatability
- Specification
- Linearity
- Precision
- Quantitation limit
- Accuracy
- Reproducibility
- Detection limit

4. Validation of cleaning [15-16]

Evidence that one can reliably clean a system or piece of equipment to specified and acceptable limits has been established with a high degree of surety. The pharmaceutical business is the one that uses cleaning validation the most, especially when it comes to cleaning process production equipment. The cleaned surfaces that might potentially contaminate the product that is later made in that same equipment if they are not cleaned thoroughly are the subject of cleaning validation. This mostly covers the equipment's product-contact surfaces after cleaning. Validation of cleaning is not done only to appease regulatory bodies. For every pharmaceutical

producer or contract organisation, product contamination poses significant liability concerns, and patient safety is the first priority.

OBJECTIVES:

The cleaning validation's goal is to confirm that the cleaning process is efficient in eliminating product residues, degradation products, preservatives, excipients, or cleaning agents, as well as controlling any possible microbiological contamination.

The following justifies the need to confirm the cleaning process:

- It guarantees the product's safety and purity and is a customer demand.
- In products containing active pharmaceutical ingredients (APIs), it is a regulatory necessity.
- Additionally, it guarantees process quality from the perspective of internal control and compliance.[17-18]

Regulatory Conditions for Validation of Cleaning:

Regulations and rules pertaining to pharmaceutical-grade items that are commercially distributed in the United States are established by the Food and Drug Administration, or FDA. These rules, which fall under Title 21, part 211 of the Code of Federal Regulation (CFR), are known as current good manufacturing practices (cGMP). According to 21 CFR 211.67. These regulations are currently applicable, but they are broad and a little ambiguous. In order to prevent contamination, cross-contamination, and malfunctioning of the final product, this regulation requires that the food and pharmaceutical industries adhere to the cleaning validation program.[19-22]

What is the purpose of cleaning validation?

Cleaning practices must be verified to guarantee that there are no dangers related to active component or detergent/sanitizer cross-contamination.

Effective cleaning is essential to GMP patient safety and quality assurance. A product that has been contaminated by the prior product, cleaning chemicals, or other foreign elements created throughout the process might result from inefficient cleaning.[22]

Contamination mechanism: cross-contamination with the active component:

One of the real risks of cross-contamination of active chemicals is that the result is a product with numerous active compounds rather than one active ingredient. The contaminant may have completely different health and medical consequences, or it may augment or nullify the activity, depending on the medicine.[23]

Microbiological contamination:

This type of contamination is especially dishonest as it might appear at any time, even after cleansing. Equipment storage that is moist or wet is a major contributing factor. Bacteria are able to flourish in this natural setting.[24]

Contamination from several additional substances:

A variety of less common substances can potentially contaminate goods, regardless of the typical or expected list of possible contaminants in a pharmaceutical operation. Filling equipment, brush bristles for packaging, excipients, paper filters, micron filters, glove fibres and rubber particles, cleaning supplies like cloth and cotton fibres from rags and wiping materials, lubricants, etc. are all included in a partial list.[25]

Contamination from sanitising or cleaning products:[26-28]

In certain pharmaceutical processes, removing obstinate residues may require the use of fairly harsh and dangerous compounds. When it comes to the production of active pharmaceutical ingredients (APIs), this is particularly true. These substances pose a risk to the product by contaminating it. It should go without saying that using cleaning products with the lowest toxicity that are nonetheless effective at getting rid of residue in the particular cleaning scenario is the best and most efficient method to handle this probable issue. The same considerations hold true for sanitising compounds that are used to clean equipment.

Mechanisms for Cleaning:

Cleaning is the process of clearing a production surface of contaminants or undesired materials. Various techniques are used to eliminate or help remove impurities from the surfaces of equipment.[29]

Among the several cleaning methods are:

Spreading:

Wetting, desegregation, and the creation of a solid particle suspension in water are all steps in the dispersion process. This process is similar to emulsification, with the exception that dispersion is employed to remove solid residues.

Solubilization:

In essence, solubilisation and solubility are the same thing; the only distinction is that solubilisation entails adding a material to a pure solvent to make the residue soluble. For example, adding a pH modifier or surfactant to purified water will make the residue ionised or unionised and therefore soluble.

Solubility:

Here, solubility refers to the contaminant's ability to dissolve in a liquid or solvent. For example, salt may dissolve in water but other components may dissolve in hexane. However, solubility takes into account the rate of solubility, the amount of insoluble form that remains, and the cleaning solvent.

Emulsification:

The main idea behind this technique is to break up an insoluble liquid residue into small droplets, which are subsequently suspended in water or another particular solvent.

Hydrolysis:

This entails the breaking of several bonds inside an organic molecule. Because it breaks down large water-insoluble molecules into smaller, water-soluble ones—the latter being slightly more polar—hydrolysis is a very effective cleaning method. The residues that are left over after hydrolysis may be water soluble or solubilise depending on the pH of the cleaning solution. Therefore, water or any other solvent with a certain pH can be used for cleaning following hydrolysis.

Oxidation:

Strong oxidising agents, such sodium hypochlorite, cleave a variety of organic bonds during oxidation. The oxidants break down organic molecules at different points in the larger molecule, producing smaller, more polar molecules that make the broken-down components more soluble in water. Although the phenomenon of oxidation is more widespread (and less particular) than hydrolysis, the result is comparable.[30]

Choosing a Cleaning Agent:[30]

Water:

The all-purpose solvent is this one. Use water alone if it will clean the product efficiently and eliminate residues without requiring excessive time or physical effort. However, many people find that using water alone takes an unacceptably longer amount of time to complete the cleaning. It is imperative that one of the alternative strategies be followed for these individuals.

Solvent:

These are usually used in procedures when the manufacturing process already requires the use of solvents. Mother liquors, for instance, are frequently employed as the solvents for API cleaning. There is less danger when using mother liquors for cleaning because they are already recognised to dissolve the principal residue.

Commodity chemicals:

Chemicals like NaOH might also be utilised for cleaning in this situation. These materials may have the same hazards and effluent problems as their solvent cousins. However, they are frequently useful in inactivation procedures because to their generally high alkalinity or low acidity. These compounds, however, don't have the same deterrent power as designed cleaning agents, and they could be more difficult to rinse off of systems, requiring more water to do so.

Formulated cleaning agent:

The largest type of cleansers is the manufactured cleaning agent. Aqueous and solvent-based formulations fall within this group. One or more alkalinity or acidity sources, surfactant builders, sequestrants, chelants, and either water or a solvent are common ingredients in cleaning solutions. These materials are designed to be low foaming for industrial applications, making

them more easily rinsed and suitable for high impingement or high turbulence cleaning, in contrast to consumer-use solutions.

Cleaning Procedure:

In order to completely remove the potential of any irregularities throughout the cleaning process, cleaning protocols should be adequately thorough. When choosing the best cleaning method for the equipment, it is critical to thoroughly assess the equipment design in combination with the product residues to be eliminated, the cleaning solutions that are available, and the cleaning processes.

Equipment parameters to be evaluated:

- Identification of the equipment to be cleaned
- Difficult to clean areas
- Property of materials
- Ease of disassembly
- Fixed or not

Residues to be cleaned:

- Cleaning limits
- Solubilities of the residues
- Length of campaign

Cleaning agent parameters to be evaluated:

- Preferably materials that are normally used in the process
- Detergents available (as a general guide, minimize use of detergents unless absolutely required)
- Solubility properties
- Environmental considerations.
- Health and safety considerations

Cleaning techniques to be evaluated:

- Manual cleaning
- CIP (Clean-in place)
- COP (clean-out-of-place)
- Semi-automatic
- Automatic
- Time considerations
- Number of cleanings cycles

SAMPLING TECHNIQUES:[31]

Either of these methods must be used in accordance with good scientific judgement and in support of the study's goal, which is to show that the equipment's residual material content has been brought down to levels that are acceptable.

There are three known sampling methods

- Direct surface sampling
- Swab sampling
- Rinse sampling

Direct Surface Sampling:[31]

In order to verify if the sample material interferes with the test, it entails identifying the kind of sampling technique that is employed and how it affects the test results. As a result, it is essential to confirm early in the validation procedure that the solvent and sample medium are suitable and ready for usage. Direct sampling has the benefit of allowing for the evaluation of regions that are most difficult to clean and that are reasonable and acceptable. This makes it possible to determine the amount of contamination or residue per unit of surface area. Since the sample material may interfere with the test, find out what kind of material was used and how it affected the test results. For instance, it has been discovered that the swab adhesive obstructs sample analysis. Therefore, it is crucial to ensure that the solvent (used for extraction from the medium) and sample media are suitable and easily used early in the validation procedure.

Swab Sampling:

Sites must be carefully selected because the swabbing (or direct surface sample) approach does not cover the complete equipment surface area. The swab sites should, at the very least, reflect the worst-case positions on the apparatus, and the outcome should be extrapolated to take into consideration the whole product contact surface area. The swabbing solvent ought to give the substance high solubility and not promote deterioration.

Rinse Sampling:

One widely used technique to assess cleanliness is the sampling and testing of rinse samples for the remaining active component. In many situations, this is a pretty convenient procedure that necessitates control over the washing solvent, contact duration, and mixing. Based on the active ingredient's solubility, the solvent should be chosen to either replicate a later batch of product or at the very least offer sufficient solubility.

REVALIDATION:

To guarantee that any modification that might affect the cleaning procedure is evaluated and recorded, a change control system is in place. After the documented change request has been satisfactorily reviewed and approved through the change control method, significant modifications should be made. The documentation system should be used for minor adjustments or modifications that don't directly affect the quality of the final or in-process product.

At certain intervals, the cleaning procedure should be reviewed and revalidated as needed. Clean-in-place (CIP) technologies should be evaluated more frequently than manual approaches.

Benefits of Validation Cleaning:

- Lower utility costs, Market recall is prevented, Equipment maintenance is made easier, and capital expenses are avoided. A decrease in reworks and rejections. Minimise accidents and increase safety.

Cleaning Validation Drawbacks:

- This takes a lot of time.
- The manufacturing process is frequently expensive and intricate.

CONCLUSIONS:

This article offers a summary of cleaning validation in the pharmaceutical industry. A clean environment and clean procedures are the foundation of pharmacological activity. Cleaning validation is an essential component of GMP. A cleaning process and the proper validation can satisfy the four basic GMP requirements of safety, identification, strength, and purity. and this page primarily covers all aspects of cleaning validation, such as sample protocols, cleaning methods, contamination mechanisms, cleaning agent selection, and regulatory requirements for cleaning validation.

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A REVIEW ON DIABETES MELLITUS: SYMPTOMS, DIAGNOSIS, TREATMENT, AND THEIR HERBAL REMEDIES

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ABSTRACT:

Diabetes Mellitus (DM) is a metabolic issue portrayed by the nearness of interminable hyperglycemia either safe interceded (Type 1 diabetes), insulin obstruction (Type 2), gestational or others (condition, hereditary deformities, diseases, and certain medications). The overall predominance of diabetes has kept on expanding drastically. Comprehensively, starting in 2011, an expected 366 million individuals had DM, with type 2 creation up about 90% of the cases. There is an immediate connection among hyperglycemia and physiological and conduct reactions. At whatever point there is hyperglycemia, the mind remembers it and communicates something specific through nerve-driving forces to the pancreas and different organs to diminish its impact. The 1997 American Diabetes Association (ADA) proposals for the determination of DM centre around Fasting Plasma Glucose (FPG), while WHO centres around the Oral Glucose Tolerance Test (OGTT). As of now accessible pharmacotherapy for the treatment of diabetes mellitus incorporates insulin and oral hypoglycemic specialists. Such medications act by either expanding the discharge of insulin from the pancreas or diminishing plasma glucose fixations by expanding glucose take-up and diminishing gluconeogenesis. This is significant for the standard line up of diabetic patients with the social insurance supplier is of incredible criticalness in turning away any drawn-out inconveniences. Different homegrown medications have been likewise demonstrated viable because of their valuable substance in the treatment of diabetes. The current survey in this manner is an endeavour to concentrate on the physiological parts of diabetes, its complexities, the objectives of the executives, and engineered and natural treatment of diabetes.

Keywords: Diabetes mellitus; Epidemiology; Diagnosis; Glycemic Treatment.

INTRODUCTION:

Diabetes is a mind boggling, interminable disease requiring nonstop clinical consideration with multifactorial hazard decrease systems outside glycemic ability to control. It is an endocrine issue described by the nearness of incessant hyperglycemia joined by more noteworthy or lesser hindrance in the digestion of sugars, lipids and proteins.[1]It is start to harm a considerable lot of body frameworks especially veins, eyes, kidney, heart and nerves. Diabetes mellitus has been characterized into two kinds for example insulin subordinate diabetes mellitus (IDDM, Type I) and non-insulin subordinate diabetes mellitus (NIDDM, Type II). Type I

diabetes is an immune system illness portrayed by a neighborhood incendiary response in and around islets that is trailed by particular demolition of insulin emitting cells while Type II diabetes is described by fringe insulin obstruction and debilitated insulin secretion.[2] Chronic hyperglycemia in cooperative energy with the other metabolic abnormalities in patients with diabetes mellitus can make harm different organ frameworks, prompting the advancement of impairing and dangerous wellbeing complexities, generally conspicuous of which are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular intricacies prompting a 2-crease to a 4-overlay expanded danger of cardiovascular diseases.3 Drugs are utilized for the most part to spare life and lighten side effects. Optional points are to forestall long haul diabetic intricacies and, by taking out different hazard factors, to upgrade delayed presence. Insulin trade treatment is the support for patients with type 1 DM while diet and way of life adjustments are very much idea out the reason for the treatment and the board of type 2 DM.[4] Various kinds of hypoglycemic specialists, for example, biguanides and sulfonylureas are likewise accessible for treatment of diabetes. Anyway, none of these meds is perfect because of their harmful symptoms and reduction of reactions is watched rarely in their far reaching utilize 5. The primary insufficiency of as of now open medications is that they must be given for the duration of the life and produce side effects[6]. Therapeutic plants and their bioactive constituents can be utilized for therapeutics of DM all through the world especially in nations where access to the regular enemy of DM operators is lacking. an assortment of test models are likewise accessible to screen antidiabetic action of plant[7]. The current survey thus is a test to know more specifically about diabetes mellitus, its epidemiological information, pathogenesis, finding, clinical introduction, and standards of the board of diabetes.

EPIDEMIOLOGY:

The malady trouble identified with diabetes is high and ascending in each nation, fuelled by the worldwide ascent in the event of heftiness and unfortunate lifestyles.[8] As of 2015, >415 million grown-ups have diabetes mellitus, and this number is unsurprising to increment to 642 million by 2040. More than 95% of all grown-ups with diabetes mellitus have type 2 diabetes mellitus (T2DM). India is one of the epi-focuses of the worldwide diabetes mellitus scourge and has the second most elevated number of individuals with the malady on the planet (~69 million people as of 2015[9]. The most recent assessments show a worldwide commonness of 382 million individuals with diabetes in 2013, expected to ascend to 592 million by 2035. The etiological arrangement of diabetes has now been generally acknowledged. Type 1 and type 2 diabetes are the two primary sorts, with type 2 diabetes representing the greater part (>85%) of complete diabetes predominance. The two types of diabetes can prompt multisystem complexities of microvascular endpoints, including retinopathy, nephropathy and neuropathy, and macrovascular endpoints including ischaemic coronary illness, stroke and fringe vascular malady. The untimely dismalness, mortality, decreased future and monetary and different

expenses of diabetes make it a significant general wellbeing condition.8 The first multicentre concentrate on diabetes mellitus in Quite a while was started by the Indian Council of Medical Research (ICMR) in 1971[10]. the World Health Assembly received an extensive worldwide checking structure in 2013, included nine intentional worldwide focuses to reach by 2025. This was joined by the WHO Global activity plan for the anticipation and control of NCDs 2013–2020 (WHO NCD Global Action Plan), embraced by the 66th World Health Assembly.[11]

CLASSIFICATION OF DIABETES MELLITUS:

Type 1 diabetes: (recently known as insulin-reliant, adolescent or adolescence beginning diabetes) is described by insufficient insulin creation in the body. Individuals with type 1 diabetes require day by day organization of insulin to control the measure of glucose in their blood. On the off chance that they don't approach insulin, they can't endure. The reason for type 1 diabetes isn't known and it is at present not preventable. Manifestations incorporate unreasonable pee and thirst, consistent yearning, weight reduction, vision changes and weariness.

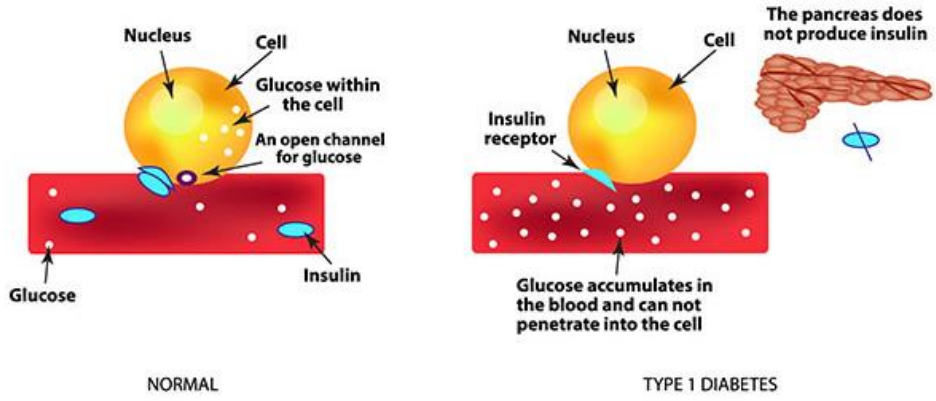

Figure 1: Type 1 Diabetes

(Adapted from https://www.intolife.in/about-diabetes/types-of-diabetes/type-1-diabetes/)

Type 2 diabetes: (once in the past called non-insulin-needy or grown-up beginning diabetes) Results from the body's incapable utilization of insulin.

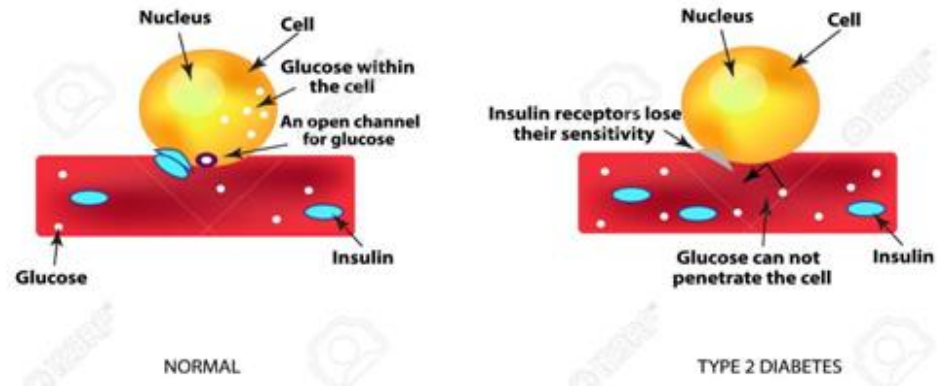

Figure:2 Type 2 Diabetes

(Adapted from https://www.intolife.in/about-diabetes/types-of-diabetes/type-1-diabetes/)

Type 2 diabetes represents by far most of individuals with diabetes around the globe [1] Manifestations might be like those of type 1 diabetes, yet are frequently less stamped or missing. Subsequently, the infection may go undiscovered for quite a while, until confusions have just emerged. For a long time type 2 diabetes was seen uniquely in grown-ups yet it has started to happen in children.[12]

Impaired glucose tolerance (IGT) and **impaired fasting glycaemia (IFG):** are middle of the road conditions in the change between ordinary blood glucose levels and diabetes (particularly type 2), however the progress isn't unavoidable. Individuals with IGT or IFG are at expanded danger of cardiovascular failures and strokes

Gestational diabetes (GDM): is a transitory condition that happens in pregnancy and conveys long haul danger of type 2 diabetes.[13]. The condition is available when blood glucose esteems are better than average yet at the same time beneath those analytic of diabetes. Women with gestational diabetes are at expanded danger of certain complexities during pregnancy and conveyance, just like their babies. Gestational diabetes is analyzed through pre-birth screening, as opposed to announced symptoms.[14]

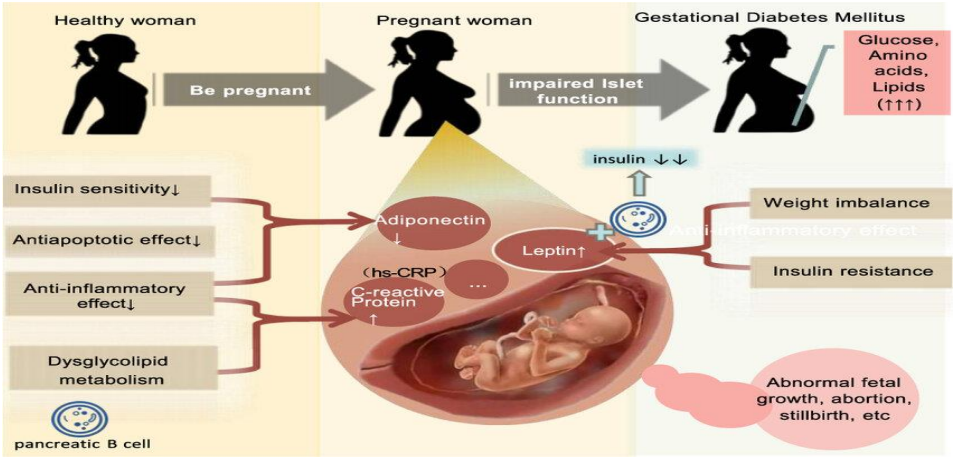

Figure 3: Gestational diabetes (Refer from Liu Y, Li DY, Bolatai A *et al.*, 2023)

Hazard Factors for Diabetes:

Type 1. The specific reasons for type 1 diabetes are obscure. It is commonly concurred that type 1 diabetes is the consequence of an unpredictable cooperation among qualities and natural elements, however no particular ecological hazard factors have been appeared to cause a critical number of cases. Most of type 1 diabetes happens in kids and young people.

Type 2. The danger of type 2 diabetes is controlled by an exchange of hereditary and metabolic elements. Ethnicity, family ancestry of diabetes, and past gestational diabetes join with more established age, overweight and corpulence, undesirable eating regimen, physical dormancy and smoking to build hazard. A few dietary practices are connected to unfortunate body weight as well as type 2 diabetes hazard, including high admission of soaked unsaturated fats, high all out fat admission and lacking utilization of dietary fibre [15,16,17]. High admission of sugar-

improved drinks, which contain extensive measures of free sugars, 1 improves the probability of being overweight or stout, especially among children. [18,19]. Recent proof further recommends a relationship between high utilization of sugar-improved refreshments and expanded danger of type 2 diabetes

Gestational Diabetes: Hazard factors and hazard markers for GDM incorporate age (the more established a lady of conceptive age is, the higher her danger of GDM); overweight or corpulence; unreasonable weight gain during pregnancy; a family ancestry of diabetes; GDM during a past pregnancy; a background marked by stillbirth or bringing forth a newborn child with inborn irregularity; and abundance glucose in pee during pregnancy .Diabetes in pregnancy and GDM increment the danger of future stoutness and type 2 diabetes in offspring.[20]

Entanglements of Diabetes: When diabetes isn't very much overseen, difficulties build up that undermine wellbeing and jeopardize life. Intense entanglements are a critical supporter of mortality, expenses and low quality of life. Strangely high blood glucose can have a perilous effect in the event that it triggers conditions, for example, diabetic ketoacidosis (DKA) in types 1 and 2, and hyperosmolar trance state in type 2. Anomalous low blood glucose can happen in a wide range of diabetes and may bring about seizures or loss of awareness. It might occur subsequent to avoiding a dinner or practicing more than expected, or if the measurement of hostile to diabetic medicine is excessively high. After some time diabetes can harm the heart, veins, eyes, kidneys and nerves, and increment the danger of coronary illness and stroke. Such harm can bring about diminished blood stream, which – joined with nerve harm. (neuropathy) in the feet – expands the opportunity of foot ulcers, disease and the possible requirement for appendage removal. Diabetic retinopathy is a significant reason for visual deficiency and happens because of long haul aggregated harm to the little veins in the retina. Diabetes is among the main sources of kidney failure.[21]

PATHOPHYSIOLOGY:

Starting revelations: Initial disclosures Initial revelations in the pathophysiology of diabetes mellitus are characteristically connected to polyuria, verifiably viewed as its fundamental (and symptomatic) trademark. The term 'diabetes' is gotten from the antiquated Greek word 'diabainen', signifying 'experience', to show the extreme going of pee through the kidney. It was not until the 1600s, notwithstanding, that Willis included the term 'mellitus' ('sweet') to recognize this condition from an over the top creation of non-sweet pee (diabetes 'insipidus'). Almost 200 years after the fact (1776), Dobson showed that the sweet taste of pee was because of an overabundance of sugar in the pee and blood. An additional 100 years were important to explain the pathogenesis of diabetes mellitus. In 1889, Minkowski and von Mering found that pancreatectomized hounds created side effects of diabetes, in this way connecting diabetes just because to a particular organ. In 1910, Sharpey-Schafer proposed that individuals with diabetes were lacking in a substance created in the pancreatic islets (found in 1869 by Langerhans) and

called it 'insulin'; hence, a connection between the pancreas, insulin and diabetes was beginning to develop and frame the premise of the cutting-edge comprehension of the infection. It was uniquely in 1921, nonetheless, that a progressively exact picture developed: Banting, Best and Macleod indicated that diabetes in pancreatectomised pooches could be switched after the intravenous organization of the 'islet' extraction from typical canine pancreata. In this way, Banting, Best and Collip refined this substance from ox-like pancreata, and the primary patient was effectively treated in 1922, bringing about a decrease in blood glucose and glycosuria.[22]

In type 1 diabetes, the liver can fabricate glucose, however there are just restricted stores of glycogen. At the point when insulin is missing, gluconeogenesis is uncontrolled, and blood glucose levels become raised. Simultaneously, fat and muscle cells can't take up accessible blood glucose by means of glucose transporter 4 (GLUT4). The body can't expel the raised blood glucose. While glucose is extremely high in the blood, the fringe muscle and fat tissues are famished for glucose. Glucagon discharge is "uncoupled" from blood glucose levels. Insulin is significant in the guideline of glucagon discharge. Subsequently, unopposed glucagon, with counter-administrative hormones, for example, catecholamines, cortisol, and development hormone, restrains the blend of glycogen.

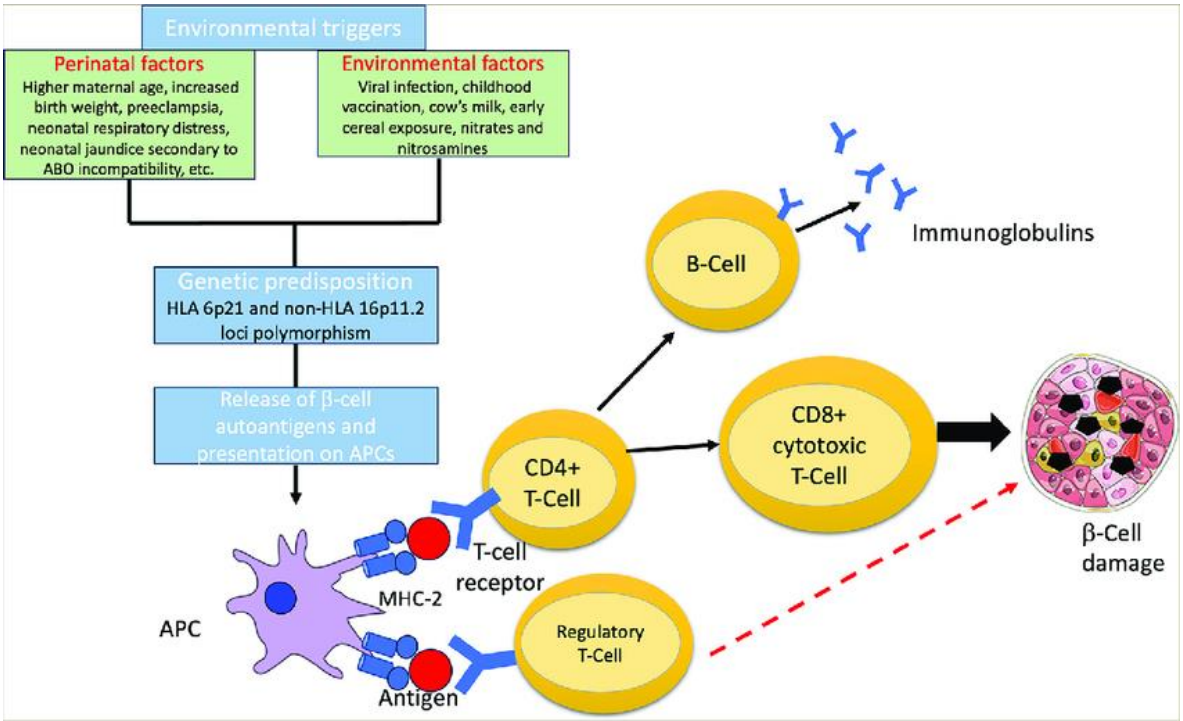

Figure 4: Pathophysiology of type 1 diabetes

(Adapted form Simran Thakka *et al* touch Reviews in Endocrinology.2023;19(2))

In type 2 diabetes, insulin opposition makes the body respond as though the body needs insulin, despite the fact that it is available at elevated levels. Like sort 1 diabetes from various perspectives, this structure contrasts in that the liver is as yet ready to make glycogen, and lipolysis is controlled because of insulin being available. Plasma lipoproteins are typically raised,

regularly on account of poor nourishment and weight. Ketoacidosis isn't typically identified with type 2 diabetes, however it might happen in view of other metabolic stressors, and if pancreatic disappointment happens, it prompts diminished insulin creation and discharge. More established sort 2 diabetics may build up a genuine condition called hyperosmolar hyperglycemic nonketotic disorder. The body endeavors to evacuate overabundance sugar by passing it into the pee. This condition is generally brought about by a disease, contamination, or in view of different components.

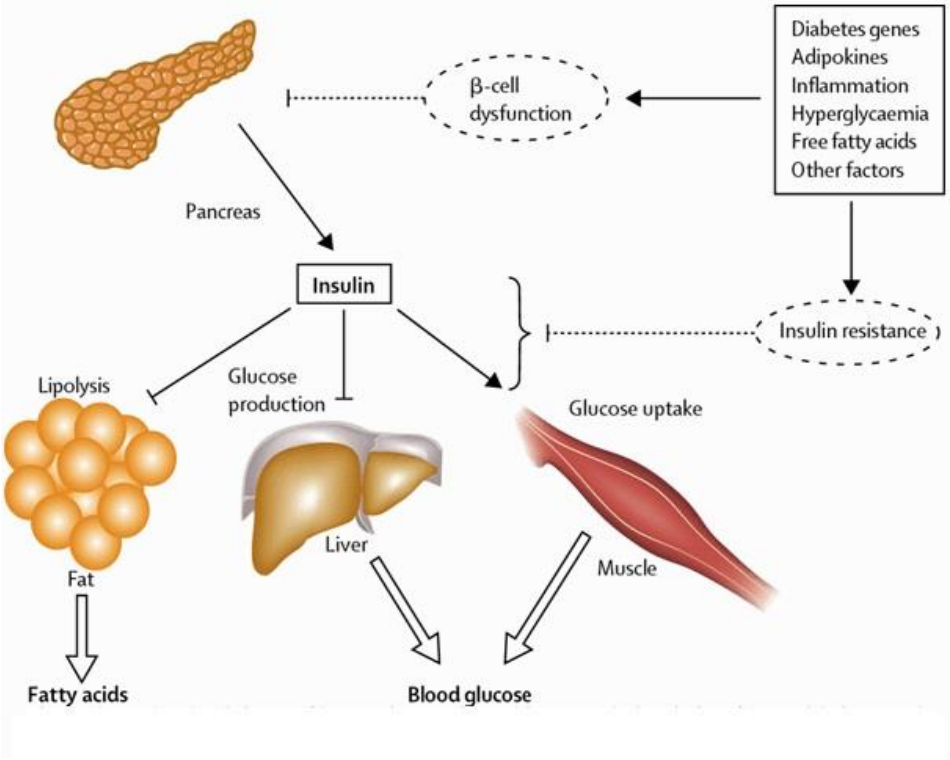

Figure 5: Pathophysiology of type 2 diabetes
(Source: Michael Stumvoll *et al.*, Lancet, April 9 2005; 365: 1333-46)

Role of Insulin in Metabolism: Insulin is an anabolic hormone that is regularly present in people with solid eating regimens. It is a significant flagging variable that invigorates capacity of abundance supplements as glycogen and triglycerides, as fat tissue fat. Insulin principally focuses on the liver, fat tissue, and striated muscles. Insulin union and discharge is animated by glucose, yet potentiated by the amino acids. Inside the liver, insulin invigorates glycogenesis, union of unsaturated fats, glycolysis, and the pentose phosphate pathway. In fat tissue, insulin invigorates take-up of glucose and unsaturated fats, just as triglyceride blend, otherwise called vitality stockpiling. In the skeletal muscles, insulin invigorates glucose take-up, glycogenesis, and the union of proteins. It ought to be comprehended that insulin doesn't impact digestion of glucose in the cerebrum, or in the red platelets. The pancreatic beta cells discharge insulin because of expanded blood glucose focuses. Glucose enters these cells by means of GLUT2

through aloof vehicle. This glucose transporter has powerless fondness glucose. It just favors glucose in the wake of eating a supper, when blood glucose levels are high, and not when fasting. After glucose is oxidated, expanded grouping of adenosine triphosphate (ATP) animates potassium channels, depolarizing cell layers. This opens the voltage-gated ionized calcium (Ca2+) channels. Signs identified with creation of the subsequent ambassador called inositol trisphosphate animate ionized calcium discharge from the endoplasmic reticulum. This outcomes in high intercellular Ca2 1 focuses, activating insulin discharge. Insulin influences digestion of cells with insulin receptors. These incorporate the hepatocytes, adipocytes, and muscle cells. The impacts of insulin on digestion are summed up in. Insulin utilizes a tyrosine kinase receptor that phosphorylates target proteins, prompting numerous metabolic impacts. The fast translocation of the GLUT4 glucose transporter from vesicles to cell surfaces of skeletal and heart muscle cells, just as fat cells, expands glucose transport into these cells. Moreover, insulin controls metabolic proteins, including glycogen synthase and phosphorylase, by means of enactment of type I phosphatase and dephosphorylation.[23]

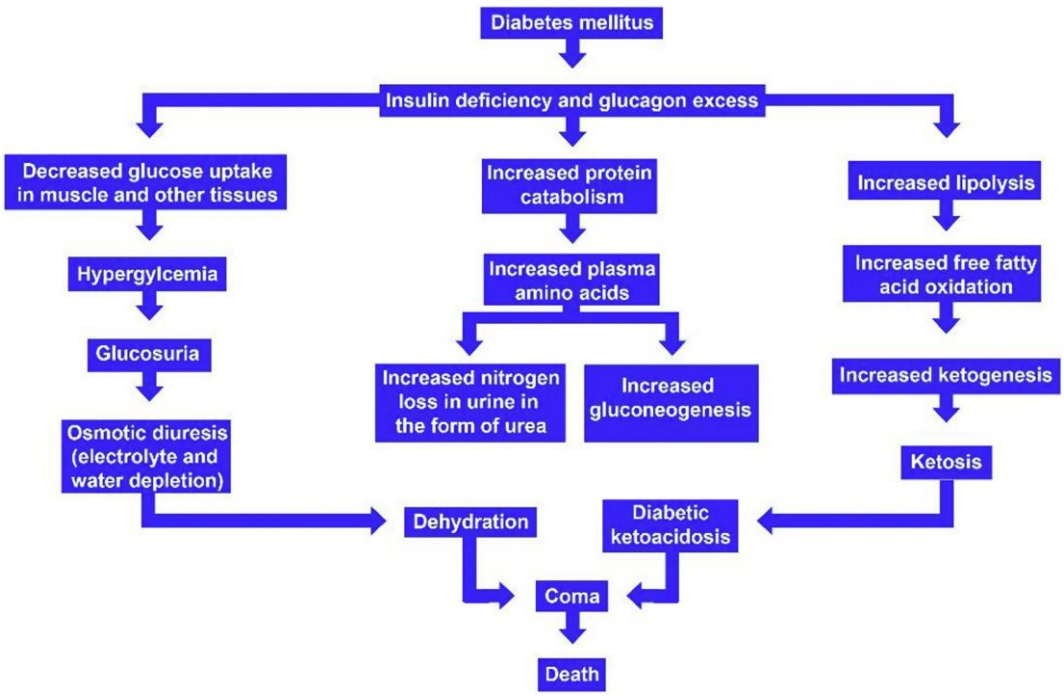

Figure 6: Overview of insulin deficiency and excess glucagon

Diagnosis of Diabetes: The accompanying tests are utilized for the determination of diabetes: A fasting plasma glucose test quantifies your blood glucose after you have gone in any event 8 hours without eating. This test is utilized to identify diabetes or prediabetes.

An oral glucose resilience test quantifies your glucose after you have gone at any rate eight hours without eating and two hours after you drink a glucose-containing refreshment. This test can be utilized to analyze diabetes or prediabetes.

In random plasma glucose test, your primary care physician checks your glucose regardless of when you ate your last dinner. This test, alongside an appraisal of manifestations, is utilized to analyze diabetes, however not prediabetes.

Positive test outcomes ought to be affirmed by rehashing the fasting plasma glucose test or the oral glucose resilience test on an alternate day. At the point when previously determined to have diabetes, your primary care physician may propose a zinc transporter 8 autoantibody (ZnT8Ab) test. This blood test - alongside other data and test outcomes - can help decide whether an individual has type 1 diabetes and not another sort. The objective of having the ZnT8Ab test is a brief and exact finding and that can prompt opportune treatment.

Fasting Plasma Glucose (FPG) Test

The FPG is most solid when done in the first part of the day. Results and their significance are appeared in table 1. In the event that your fasting glucose level is 100 to 125 mg/dL, you have a type of prediabetes called debilitated fasting glucose (IFG), implying that you are bound to create type 2 diabetes however don't have it yet. A degree of 126 mg/dL or above, affirmed by rehashing the test on one more day, implies that you have diabetes.

Table 1: Fasting Plasma Glucose Test

Plasma Glucose Result (mg/dL)	**Diagnosis**
99 and below	Normal
100 to 125	Prediabetes (impaired fasting glucose)
126 and above	Diabetes*

*Confirmed by repeating the test on a different day

Oral Glucose Tolerance Test (OGTT): The OGTT is more touchy than the FPG test for diagnosing prediabetes, yet it is less helpful to manage. The OGTT expects you to quick for in any event eight hours before the test. Your plasma glucose is estimated preceding and two hours after you drink a fluid containing 75 grams of glucose broke up in water. Results and what they mean are appeared in table 2. On the off chance that your glucose level is somewhere in the range of 140 and 199 mg/dL 2 hours in the wake of drinking the fluid, you have a type of prediabetes called impeded glucose resilience or IGT, implying that you are bound to create type 2 diabetes yet don't have it yet. A two-hour glucose level of 200 mg/dL or above, affirmed by rehashing the test on one more day, implies that you have diabetes.

Table 2: Oral Glucose Tolerance Test

2-Hour Plasma Glucose Result (mg/dL)	**Diagnosis**
139 and below	Normal
140 to 199	Prediabetes (impaired glucose tolerance)
200 and above	Diabetes*

*Confirmed by repeating the test on a different day.

Gestational diabetes: is likewise analyzed dependent on plasma glucose esteems estimated during the OGTT. Glucose levels are checked multiple times during the test. On the off chance that your glucose levels are better than average in any event twice during the test, you have gestational diabetes. Table 3 shows the better than average outcomes for the OGTT for gestational diabetes.

Table 3: Gestational Diabetes: Above-Normal Results for the Oral Glucose Tolerance Test

When	Plasma Glucose Result (mg/dL)
Fasting	95 or higher
At 1 hour	180 or higher
At 2 hours	155 or higher
At 3 hours	140 or higher

Note: Some laboratories use other numbers for this test.

For additional information about the diagnosis and treatment of gestational diabetes,

Random Plasma Glucose Test

An Random blood glucose level of 200 mg/dL or increasingly, in addition to nearness of the accompanying side effects, can imply that you have diabetes:

- Increased pee
- Increased thirst
- Unexplained weight reduction

Different side effects incorporate weakness, obscured vision, expanded yearning, and injuries that don't recuperate. Your primary care physician will check your blood glucose level on one more day utilizing the FPG or the OGTT to affirm the finding of diabetes. Newer rules use hemoglobin A1c as a screening apparatus for prediabetes or diabetes (the test is regularly used to quantify blood glucose control in diabetes patients more than a while). A HbA1c of 5.7% to 6.4% is predictable with prediabetes and marks when it tends to be turned around by way of life changes. A HbA1c of 6.5% or higher is predictable with diabetes [24]

The executives of Diabetes: 19th years on, the administration of type 1 and type 2 diabetes centers around improve glycemic control by methods for way of life modification and pharmacological treatment with the point of diminishing danger and movement of microvascular and full scale vascular entanglements. Diabetes care is conveyed comprehensively by a multidis-ciplinary group (MDT) in essential and optional consideration with the accentuation on individual glycaemic focuses as indicated by quiet conditions, for example, hypoglycaemia hazard, weight and comorbidities. Patients are effectively urged to self-deal with their condition and take part in the dynamic procedure with the help of this group. The utilization of innovation has changed the observing and conveyance of treatment in diabetes and communication with medicinal services experts while new glucose-bringing treatments are utilized down to target key pathophysiological absconds in the advancement of diabetes.[25]

Way of life alteration, organized training and self administration

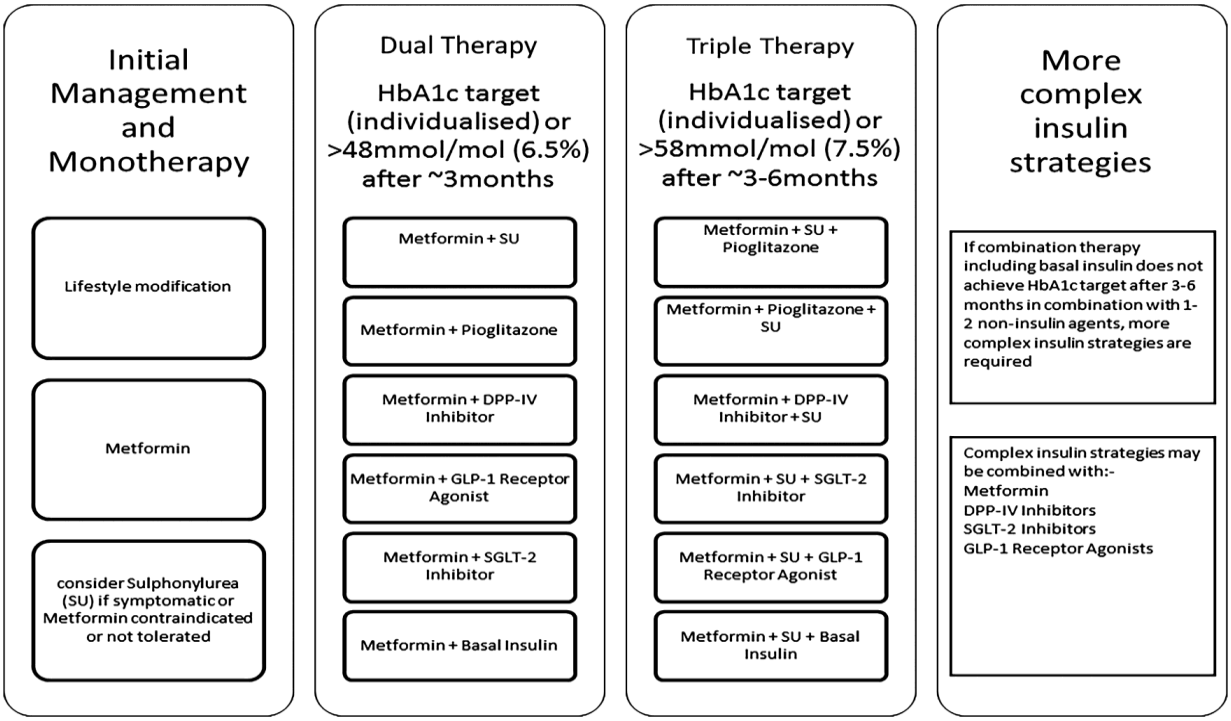

Figure 7: Antihyperglycaemic treatment of type 2 diabetes (based on the National Institute for Health and Care Excellence and the American Diabetes Association/European Association for the Study of Diabetes recommendation. DPP-IV, dipeptidyl-peptidase IV; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.

In 1926, Prof MacLean expressed that "there are just two strategies by which we can would like to do any great to the diabetic patient: - (a) by the utilization of suit-capable eating regimen, and (b) by giving insulin. The presentation of insulin following its disclosure by Banting and Best in 1922 proclaimed another period of diabetes the executives, which was not, at this point dependent on seriously starch confined diets.6 While this despite everything remains the case for the administration of type 1 diabetes today, low calorie consumes less calories are being utilized to oversee type 2 diabetes and have even been appeared to turn around the condition.[7] Bariatric medical procedure, for example, Roux-en-Y gastric detour or sleeve gastrectomy can likewise prompt improved glycemic control through significant weight loss.26Thirty years after the revelation of insulin, oral treatments, for example, sulfonylureas (SU)27 and biguanides[28] opened up for the treatment of type 2 diabetes. Just about a century later, oral treatments are additionally being considered for type 1 diabetes as sodium-glucose cotransporter-2 (SGLT-2) inhibitors [29] and dipeptidyl-peptidase IV (DPP-IV) inhibitors. Organized instruction programs are viewed as fundamental to improve persistent inspiration, self-administration abilities and strengthening. The educating of starch tallying principles and insulin the executive's abilities in the Dose Adjustment for Normal Eating project to patients with type 1 diabetes has been appeared to improve personal satisfaction and glycaemia control and is likewise cost-effective.[30]

Herbal treatment of Diabetes: Traditional Medicines got from restorative plants are utilized by about 60% of the total populace. This audit centers around Indian Herbal medications and plants utilized in the treatment of diabetes, particularly in India. Diabetes is a significant human disease harrowing numerous from different backgrounds in various nations. In India it is ending up being a significant medical issue, particularly in the urban regions. Despite the fact that there are different ways to deal with decrease the evil impacts of diabetes and its auxiliary inconveniences, natural definitions are favored because of lesser reactions and minimal effort. A rundown of restorative plants with demonstrated antidiabetic and related useful impacts and of home-grown medications utilized in treatment of diabetes is gathered. These incorporate, Allium sativum, Eugenia jambolana, Momordica charantia Ocimum sanctum, Phyllanthus amarus, Pterocarpus marsupium, Tinospora cordifolia, Trigonella foenum graecum and Withania somnifera. One of the etiologic variables ensnared in the improvement of diabetes and its complexities is the harm incited by free radicals and subsequently an antidiabetic compound with cancer prevention agent properties would be progressively helpful. Therapeutic plants are being gazed upward by and by for the treatment of diabetes. Numerous regular medications have been gotten from prototypic atoms in therapeutic plants. Metformin represents an effective oral glucose-bringing down operator. Its advancement depended on the utilization of Galega officinalis to treat diabetes. Galega officinalis is rich in guanidine, the hypoglycemic part. Since guanidine is unreasonably poisonous for clinical use, the alkyl biguanides synthalin An and synthalin B were presented as oral enemy of diabetic operators in Europe during the 1920s however were suspended after insulin turned out to be all the more broadly accessible. In any case, involvement in guanidine and biguanides incited the advancement of metformin. Until this point, more than 400 conventional plant medications for diabetes have been accounted for, albeit just few these have gotten logical and clinical assessment to evaluate their viability. The hypoglycemic impact of some home-grown concentrates has been affirmed in human and creature models of type 2 diabetes. The World Health Organization Expert Committee on diabetes has suggested that customary restorative herbs be further investigated.[31]

CONCLUSION:

As the pervasiveness and quantities of individuals with diabetes keep on rising – an aftereffect of changes in the manner individuals eat, move and live, and a maturing worldwide populace – the effectively enormous wellbeing and financial effects of diabetes will develop. These effects can be diminished through compelling activities. With adequate deep-rooted administration and customary development, individuals with a wide range of diabetes can live more and more advantageous lives. The event of type 2 diabetes can be decreased through populace based and singular anticipation gauges that target key hazard factors. Handling diabetes is vital to the accomplishment of the general reaction to NCDs. In many nations, duties made through the Sustainable Development Goals – to decrease untimely NCD mortality by a third by

2030, and to accomplish all inclusive wellbeing inclusion – will require concentrated consideration on diabetes avoidance and the board. As of late, it has additionally been accounted for that around 30% of diabetic patients utilize some type of correlative and elective medication. Complementary and elective prescriptions are the utilization of restorative plants and other dietary enhancements, which are utilized as options in contrast to standard Western clinical treatment. Different restorative plants have been investigated for the recuperating and control of diabetes. Home grown treatment for diabetes has been followed everywhere throughout the World effectively. Herbs are utilized to oversee Type 1 and Type II diabetes and their confusions. For this, treatments created along the standards of western medication (allopathic) are regularly restricted in adequacy, convey the danger of antagonistic impacts, and are frequently excessively expensive, particularly for the creating scene. The previously mentioned plants have been considered for their conceivable hypoglycemic activities and the scientists have completed some primer examinations. Home grown prescription of diabetes is far superior to allopathic.

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METHODS FOR EXTRACTING BIOACTIVE COMPOUNDS FROM PLANT SOURCES: A REVIEW

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ABSTRACT:

Medicinal plants, whether in the form of pure compounds or standardized extracts, offer endless possibilities for discovering new drug candidates due to their exceptional chemical diversity. As the demand for diverse chemical compounds in drug screening programs continues to rise, there has been a growing global attention in discovering natural products, especially those originated from edible plants, for therapeutic purposes. Medicinal botanicals and herbal formulations contain an extensive variety of bioactive components. The application of these compounds across various industries, including pharmaceuticals, food, and chemicals, highlights the importance of developing optimal and standardized extraction methods to efficiently obtain these active ingredients from plant sources. In addition to conventional techniques, several new extraction methods have been established; however, none of the approach has been universally recognized as the reference for extracting bioactive substances from plants. The effectiveness of both traditional and modern extraction methodologies largely hinges on key input parameters, the composition of the plant matrix, the chemical properties of bioactive components, and scientific proficiency. This review focuses on exploring various extraction methodologies, together with their fundamental mechanisms, for isolating bioactive components from medicinal herbs.

Keywords: Bio Active Compounds, Herbal Preparations, Extraction Methodologies

INTRODUCTION:

The analysis of bioactive components in plant constituents, both qualitatively and quantitatively, largely depends on selecting an appropriate extraction method [1,2]. As the initial step in medicinal plant research, extraction plays a vital role in determining the final results and outcomes. It is often referred to as a "sample preparation technique." However, this crucial stage is frequently overlooked and carried out by untrained personnel, despite the fact that sample preparation accounts for nearly two-thirds of an analytical chemist's efforts [3]. Research by Majors (1999) revealed that most researchers recognize the significance of sample preparation in analytical studies [4]. Although modern chromatographic and spectrometric techniques have improved the accessibility of bioactive compound analysis, success still depends on the selected

extraction methods, operational parameters, and the unique properties of the plant materials [5]. Key factors influencing the extraction process include the plant matrix properties, solvent type, temperature, pressure, and duration [6]. Over the past decade, a deeper understanding of the dynamic chemical nature of diverse bioactive molecules has been a driving force behind progress in bioactive compound analysis [7].

With substantial technological and technical progress, industries like pharmaceuticals, food additives, and natural pesticides have increasingly focused on bioactive molecules obtained from natural sources [8]. Typically, bioactive compounds coexist with other plant constituents and can be identified and categorised from different plant portions, including leaves, stems, flowers, and fruits.

EXTRACTION OF BIOACTIVE COMPOUNDS

Considering the immense variety of bioactive compounds and the numerous plant species available, establishing a standardized and integrated approach is essential for identifying compounds with potential health benefits. Farnsworth et al. proposed a structured approach to medicinal plant research, beginning with the compilation of commonly used plant names and culminating in industrial application [9].

The successful isolation, identification, and classification of bioactive components can only be achieved after applying an appropriate extraction procedure. Various extraction procedures should be employed under different conditions to assess extraction selectivity from diverse natural sources. While some methods have remained largely unchanged for centuries, they continue to be effective in extracting bioactive components. All these techniques aim to achieve common goals: (a) isolating specific bioactive compounds from complex plant matrices, (b) enhancing the selectivity of analytical methods, (c) increasing bioassay sensitivity by concentrating target compounds, (d) converting bioactive compounds into a more detectable and separable form, and (e) developing a reliable and reproducible method that remains consistent despite variations in the sample matrix [10].

CONVENTIONAL EXTRACTION TECHNIQUES

Various classical extraction techniques can be used to extract bioactive compounds from plant materials. These methods primarily rely on the solvent's extraction capability, along with the application of heat and/or agitation. The commonly used classical techniques for obtaining bioactive compounds from plants include: (1) Soxhlet extraction, (2) Maceration, and (3) Hydrodistillation.

The Soxhlet extractor was foremost introduced by German chemist Franz Ritter Von Soxhlet in 1879. Originally constructed for lipid extraction, its application has since expanded beyond this purpose. Soxhlet extraction is widely utilized for obtaining important bioactive components from several natural resources and serves as a reference model for evaluating new

extraction techniques. Typically, a slight quantity of dried sample is positioned in a thimble during the process. The thimble is then positioned inside a distillation flask containing the selected solvent. When the solution reaches the overflow level, it is siphoned from the thimble holder and redirected to the distillation flask. This movement transfers the extracted solutes into the main liquid, where they stay while the solvent recirculates through the plant material. The cycle repeats continuously until the extraction is fully completed.

Maceration has long been utilized in the homemade tonics preparation and has become a widely adopted, cost-effective method for extracting essential oils and bioactive components. In small-scale extraction, maceration typically involves numerous steps. First, plant constituents are ground into small particles to upsurge surface area and enhance solvent interaction. Next, the process involves adding an appropriate solvent, known as menstruum, into a sealed container for extraction. Afterward, the liquid is separated, and the solid deposit, known as marc, is pressed to extract as much of the retained solution as possible. The strained and pressed liquids are then combined and filtered to eliminate impurities. Periodic shaking during maceration enhances the extraction procedure in both ways: (a) by promoting diffusion and (b) by removing the concentrated solution from the sample surface, allowing fresh solvent to reach the menstruum and improve extraction yield.

Hydrodistillation is a conventional method for extracting essential oils and bioactive compounds from plants without relying on organic solvents. It can also be performed prior to drying plant materials. This process is categorized into three main types: water distillation, water-steam distillation, and steam distillation [11]. The process starts by placing the plant materials in a still compartment, then adding an adequate amount of water and heating it to a boil. Alternatively, steam can be directly injected into the plant sample. Hot water and steam play a crucial role in releasing bioactive compounds from plant tissues. In hydrodistillation, indirect water cooling condenses the vapor mixture of water and oil [12]. The condensed liquid then moves from the condenser to a separator, where the oil and bioactive compounds naturally separate from the water. This process operates through three main physicochemical mechanisms: hydrodiffusion, hydrolysis, and heat-induced decomposition. However, elevated extraction temperatures can lead to the loss of certain volatile components, making this method less ideal for extracting thermolabile compounds.

NON-CONVENTIONAL EXTRACTION TECHNIQUES

Conventional extraction methods face several challenges, including lengthy extraction periods, the requirement for costly and high-purity solvents, excessive solvent evaporation, low extraction selectivity, and the thermal degradation of heat-sensitive compounds [13]. To overcome these drawbacks, advanced techniques known as non-conventional extraction methods have been introduced. Some of the most effective approaches include ultrasound-assisted

extraction, enzyme-assisted extraction, microwave-assisted extraction, pulsed electric field-assisted extraction, supercritical fluid extraction, and pressurized liquid extraction.

ULTRASOUND-ASSISTED EXTRACTION (UAE)

UAE utilizes cavitation and intense shear forces generated by ultrasound waves, typically ranging from 20 kHz to 100 MHz, to enhance extraction efficiency and reduce processing time. During sonication, microbubbles rapidly form, oscillate, and eventually collapse with significant force when acoustic pressure reaches a high level. This collapse occurs near the solid surface, creating high-speed micro-jets of liquid that impact the surface, facilitating the extraction process. When these jets interact with shock waves, they can fracture solid surfaces. This phenomenon operates through two distinct mechanisms. The first involves the intense pressure and temperature generated within the bubbles during adiabatic compression, leading to molecular bond cleavage and radical formation. The second mechanism is driven by micro-discharges caused by strong electrical fields [14-17].

The benefits of ultrasound-assisted extraction (UAE) include reduced extraction time, lower energy consumption, and decreased solvent usage. Additionally, ultrasound energy enhances mixing efficiency, accelerates energy transfer, minimizes thermal gradients, lowers extraction temperatures, enables selective extraction, reduces equipment size, improves process control responsiveness, allows for rapid start-up, increases production efficiency, and eradicates unnecessary processing steps [18].

UAE is recognized as an efficient technique for extracting bioactive compounds from herbal plants. Rostagno et al. demonstrated its effectiveness in extracting four isoflavone derivatives—daidzin, genistin, glycitin, and malonyl genistin—from soybeans using a mix-stirring approach with different extraction times and solvents [19]. Furthermore, ionic liquid-based UAE has proven highly effective in extracting three alkaloids—vindoline, catharanthine, and vinblastine—from Catharanthus roseus [20]. UAE was successfully utilized to extract anthocyanins and phenolic compounds from grape peel, with optimization based on solvent type, extraction temperature, and duration [21]. Likewise, an ionic liquid-based UAE technique was employed to extract phenolcarboxylic acids, carnosic acid, and rosmarinic acid from Rosmarinus officinalis, demonstrating greater efficiency and reduced extraction times compared to traditional methods [22].

Ultrasound-assisted extraction (UAE) combined with deep eutectic solvents (DES) is regarded as an eco-friendly alternative to traditional extraction methods. This combination offers advantages from both techniques, including reduced extraction time and lower solvent usage compared to orthodox solvent extraction [23]. Sukor et al. presented an enhanced DES-facilitated ultrasound extraction method for obtaining tannic acids from onion peels, demonstrating that DES yielded advanced tannic acid extraction efficiency than methanol (MeOH) [24]. The tannic

acid concentration was optimized by setting the DES ratio to 1:1, the solid-to-solvent ratio to 1:10, and the duty cycle to 10%. Aslan Türker and Doğan [25] utilized a choline chloride-based mixture with five different components. In the middle of the tested DESs, choline chloride–based DES prepared with citric acid obtained the best solvent. This finding demonstrated that ultrasound could be used as a substituent energy source. Using DESs would also improve the flavonoid yield and maintain the color of the black carrot extract.

PULSE ELECTRIC FIELD EXTRACTION

The pulsed electric field (PEF) methodology, or PEF pre-treatment, is recognized for enhancing pressing, drying, extraction time, and diffusion processes without requiring high temperatures [26]. As an emerging non-thermal and eco-friendly technique, PEF is used to isolate phytochemical components from various plant parts, including leaves, roots, and fruits. The process works by disrupting cell membrane structures to facilitate extraction. When an electric potential is applied across a living cell membrane, molecules are separated based on their charge because of dipole nature of membrane components. Once the transmembrane potential surpasses 1V, repulsion occurs, leading to a significant increase in membrane permeability.

The efficiency of pulsed electric field (PEF) treatment on bioactive compounds depends on factors such as field strength, specific energy input, pulse number, treatment temperature, and plant material characteristics [27]. Moderate electric field treatment (500–1000 V/cm for 10^{-4} to 10^{-2} seconds) has been found to disrupt plant cell membranes through localized heating, resulting in enzyme and microorganism inactivation. This process helps protect heat-sensitive compounds from degradation. In industrial applications, batch PEF extraction of polyphenols from grape peels is typically carried out at 50–60°C for 20 hours [28-31]. Corrales et al. [32] explored the extraction of anthocyanins (ANCs) from grape by-products using different isolation techniques. Their study revealed that pulsed electric field (PEF) treatment significantly enhanced the extraction of ANC monoglucosides compared to acylated glucosides. PEF is especially advantageous when applied before the maceration stage in winemaking, as it helps shorten extraction time. Moreover, increasing the electric field strength from 5 to 10 kV/cm resulted in a substantial rise in total ANC content and overall polyphenol yield after maceration [33-35].

MICROWAVE-ASSISTED EXTRACTION

Compared to conventional solid–liquid extraction, microwave-assisted extraction (MAE) provides higher recovery efficiency and improved product quality at a reduced cost. MAE employs microwave energy to stimulate molecular movement and rotation in liquids with a permanent dipole, resulting in rapid heating of both the solvent and sample. This method enhances extraction efficiency, reduces processing time, decreases solvent consumption, and enables a high level of automation. During microwave heating, the elevated temperature lowers the extract's viscosity, enhancing the solubility of compounds such as tannins. Additionally,

microwave radiation alters the microstructure of plant cells, lowering mass transfer resistance and facilitating the diffusion of bioactive compounds from the raw material. Recently, MAE has been employed to extract compounds from various plant sources, comprising purple sweet potato, red cabbage, blackberry, cranberry, and sour cherry. However, the use of MAE and UAE requires careful regulation, as these techniques may lead to the degradation of flavonoids and tannins due to extreme heat and intense vibrations, respectively [36,37].

PRESSURIZED LIQUID EXTRACTION (PLE)

In 1996, Richter et al. first described PLE. This method is now known by several names; pressurized fluid extraction (PFE), accelerated fluid extraction (ASE), enhanced solvent extraction (ESE), and high pressure solvent extraction (HSPE) [38]. PLE involves applying high pressure to keep solvents in a liquid state beyond their normal boiling point, which enhances the extraction process. The advancement of automation techniques has significantly contributed to the development of PLE, reducing both extraction time and solvent consumption. Due to the combined effect of high pressure and temperature, PLE requires only minimal amounts of solvents while enabling faster extraction. Higher temperatures improve analyte solubility by increasing solubility and mass transfer rates, while also lowering solvent viscosity and surface tension, ultimately boosting overall extraction efficiency [39].

PLE has been effectively employed to extract bioactive compounds from various plant materials. Under optimized conditions, isoflavones were successfully extracted from freeze-dried soybeans without degradation using PLE [40]. Shen and Shao compared accelerated solvent extraction (ASE) with Soxhlet extraction and ultrasound-assisted extraction for isolating terpenoids and sterols from tobacco [41]. Considering factors such as yield, reproducibility, extraction time, and solvent consumption, PLE is recognized as a promising alternative to conventional methods due to its faster processing and lower solvent requirements. Flavonoids extracted from spinach using PLE with a 70:30 ethanol-water mixture at 50–150°C demonstrated higher effectiveness compared to extraction with water alone at 50–130°C. Luthria (2008) demonstrated that factors such as temperature, pressure, particle size, flush volume, static time, and solid-to-solvent ratio significantly affect the extraction of phenolic compounds from parsley (Petroselinum crispum) flakes using PLE [42]. Additionally, PLE was optimized for extracting lycorine and galanthamine (Amaryllidaceae alkaloids) from Narcissus jonquilla, proving to be more effective than hot-solvent extraction, microwave-assisted extraction (MAE), and ultrasound-assisted extraction (UAE) [43]. Furthermore, individual phenolic compounds—including gallocatechin (GCT), catechin, epicatechin gallate, caffeic acid, chlorogenic acid, and myricetin—along with total phenolic content, were successfully extracted from various parts of Anatolian propolis using PLE under optimal conditions (40°C, 1500 psi, 15 minutes).

SUPERCRITICAL FLUID EXTRACTION (SFE)

Since its introduction, supercritical fluid extraction (SFE) has attracted considerable scientific attention and has been effectively utilized in environmental research, pharmaceuticals, the polymer industry, and food analysis [44]. This technique has been widely adopted across various industries, particularly in the production of decaffeinated coffee [45]. SFE, conducted at temperatures between 313 and 343 K and pressures ranging from 14 to 24 MPa, has been used to extract purine alkaloids such as caffeine, theobromine, and theophylline from Ilex paraguariensis (herbal mate tea). Supercritical CO_2 modified with 15 wt.% ethanol yielded higher extraction efficiencies of naringin, a flavonoid, from Citrus paradisi compared to pure supercritical CO_2 at 9.5 MPa and 58.6°C [46]. SFE was also employed to extract polyphenols and procyanidins from grape seeds, using methanol as a modifier. Methanol-modified CO_2 (40%) enabled the extraction of over 79% of catechin and epicatechin from grape seeds [47]. Verma et al. (2008) optimized SFE conditions for extracting indole alkaloids from Catharanthus roseus leaves, achieving the highest catharanthine recovery at 25 MPa and 80°C with 6.6% methanol as a modifier over a 40-minute extraction period [48].

CONCLUSION:

The increasing demand for extracting bioactive compounds from plants drives the ongoing search for more efficient extraction methods. Advancements in chromatography and growing ecological awareness are key aspects contributing to the development of many unorthodox extraction techniques. Though, a thorough knowledge of each non-conventional method is essential, as they operate based on different mechanisms, and extraction efficiency varies depending on the process. Additionally, the integration and refinement of hybrid techniques should be explored, considering the properties of plant materials and the specific compounds being targeted. There is still a lack of sufficient experimental data for some existing extraction methods. Additionally, the selection of appropriate standard techniques plays a crucial role in accurately measuring extraction efficiency. Meanwhile, the increasing economic significance of bioactive compounds and bioactive-rich products may stimulate the advancement of more refined and sophisticated extraction technologies in the future.

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THE ROLE OF NANOTECHNOLOGY IN THE MEDICAL FIELD AND FUTURE SCOPE

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ABSTRACT:

Nanotechnology is the field that concentrates on the examination of minuscule structures within the size range of 0.1 to 100 nm. It encompasses various subjects, such as many medical sub-specialties including cardiovascular disease, eye disease, hormonal disorders, tumors, immunology, molecular biology, biophysics, and biological engineering. Nanotechnology is extensively utilized in the field of nanomedicine within the medical profession. Specific nanoparticles have potential applications in tissue engineering, medicines, targeted drugs, biomedical implants, novel diagnostic instruments, imaging, and methods. In modern times, nanotechnology enables the safer delivery of highly toxic treatments, like cancer chemotherapy drugs. This chapter discusses the potential applications of nanotechnology in the field of medicine. Furthermore, there is an ongoing discourse on the benefits and drawbacks associated with employing nanomedicines to convey pharmaceuticals from both artificial and organic origins to medical environments.

Keywords: Nano Technology, Application, Future Prospects, Nano Medicines

INTRODUCTION:

Throughout ancient history, humans have utilized natural plant-based substances as remedies for a diverse array of ailments. Modern drugs are mostly derived from plants, drawing upon traditional practices and historical knowledge. Approximately 25% of the primary pharmaceutical compounds and their derivatives now available on the market are sourced from natural resources [1, 2]. The process of discovering new drugs begins by identifying natural compounds that possess a wide range of chemical structures. There is a recent trend in the creation of drugs based on natural products, where there is a focus on creating lead compounds that can be easily synthesized and have similar chemical properties to their natural counterparts [3]. Nanotechnology has proven to be effective in connecting the fields of biology and physics by utilizing their nanostructures and nanophases in various scientific disciplines [4]. Specifically, the use of nanomedicine or nano-based systems for drug delivery, which are of great significance for these particles, showcase this capability [5,6]. Nanomaterials can be defined as materials with dimensions that fall within the range of 1 to 100 nm. The materials mentioned have a significant

influence on the limits of nanomedicine, namely in the areas of biological sensors, microfluidics, delivery of drugs, and microarray biology studies [7-9]. Nanomedicines are produced by employing nanotechnology to manipulate medicinal compounds at the microscopic level. Nanoparticles have significantly advanced the field of bio-medicine, encompassing tissue engineering, drug transport, nano-biotechnology, and biosensors [10]. Nanoparticles are often minuscule nanospheres due to their composition of materials designed at the molecular or atomic level [11]. Consequently, smaller materials exhibit enhanced mobility inside the human body compared to bigger ones. Nanoparticles exhibit distinct biological, chemical, mechanical, electrical work, magnetic, and structural properties. In recent years, the utilization of nanoparticles as carriers to package or attach therapeutic drugs and transport them more accurately to target tissues with a controlled release has gained more recognition, leading to the rising appreciation of nanomedicines [12]. Nanomedicine is a burgeoning field that involves the use of information and techniques derived from nanoscience to medical biology, to prevent and treat illnesses.

NANO-PHARMACEUTICAL SYSTEMS:

A. Polymeric nanoparticles: Having a size range of 10 to 1000 nm, they provide complete drug protection. Additionally, they are biodegradable and bio-compatible. Polymeric nanoparticles are used as drug carriers, allowing for controlled and progressive drug delivery [13, 14].

B. Dendrimers: Made of less than 10 nm in size, dendrimers are produced by precisely controlled polymerization. These polymeric structures have a high branching ratio and are mono-dispersed. Dendrimers can be used to target and deliver drugs to the liver and macrophages under control [15–17].

C. Metallic nanoparticles: Colloids less than 100 nm in size composed of gold and silver are known as metallic nanoparticles. Because of their small size, they have more surface area, which also boosts their stability and bioavailability—ideal characteristics for a drug. These are used in drug and gene delivery, heat ablation, radiotherapy augmentation, and sensitive diagnostic testing [18–22].

THE NECESSITY OF NANOTECHNOLOGY IN THE MEDICAL FIELD:

The domains of nanotechnology & nano-drug discovery possess immense breadth and multiplicity. The medication has reached a new level due to significant breakthroughs in nanomedicine, which have crucial implications for healthcare. It is vital to research the vast potential of nanoparticles in the medical field. Research on the best methods and strategies is ongoing in the medical sector. Examples of these include kidney disease, gene therapies for heart disease, and cancer therapy. Significant progress has been made in conventional therapy, and positive results have been achieved in both nanotechnology and nanoparticle quality.20–21 In

gene therapy, nanoparticle-based medications have also been employed. A large body of research focused on the usage of viral vectors, which were believed to be drug-delivery vehicles[23–25].

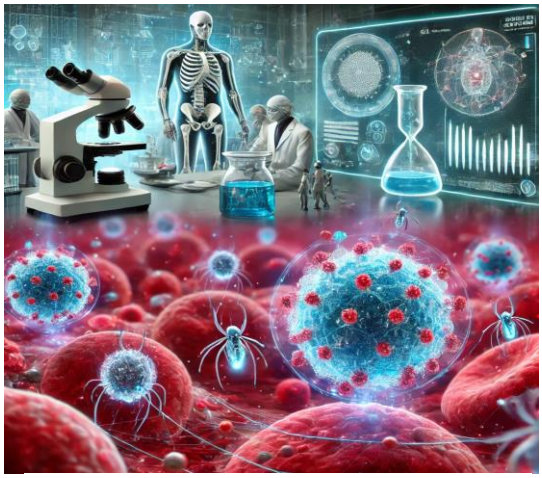

Fig 1: Nanotechnology in the Medical field

ASSOCIATED CHARACTERISTICS AND FEATURES OF NANOTECHNOLOGY IN THE MEDICAL DOMAIN:

Many traditional features and components are associated with the medical field of nanotechnology, including healing wounds, treating bacteria, preventing damage to healthy cells, and creating diagnostic tools for nanomedicine. With the use of nanovesicles, nanoparticles, carbon nanotubes, and other materials, the applications of nanotechnology-based principles in medicine—where accuracy and intelligence are critical at the bigger site—have become even more profitable and effective[26, 27]. Nanotechnologies have equal use in the fields of preventative and reactive medicine. The ability of wearable monitors to provide data to hospital systems may simplify the treatment of elderly patients, who often require care in remote areas. Similarly, it is possible to control the tumour cells that are in circulation by employing nanomaterials, which are long believed to be the precursors of malignancies that spread to other parts of the body. The technical sector uses individual atoms and molecules; in particular, nanoscience holds potential ramifications for science, engineering, and technology. It may have a noticeable impact on the synthesis, characterization, use, and application of specific atoms and molecules. The fields of medicine, energy, food production, basic chemicals, cosmetics, farming, machinery, biotechnology, and textiles have all seen significant changes[28–30].

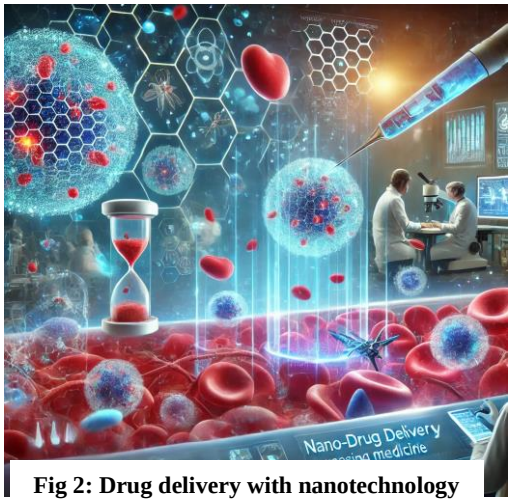

Fig 2: Drug delivery with nanotechnology

DRUG DELIVERY WITH NANOTECHNOLOGY:

Recent years have seen breakthroughs in the area of delivery systems, with the goal of transferring therapeutic agents, or active compounds obtained from nature, to their designated location for the management of various ailments [31, 32]. Even though there have been a lot of successful drug delivery systems utilized recently, to correctly carry pharmaceuticals to their intended places, some problems still need to be fixed and novel methods need to be developed. In order to create more advanced medication delivery systems, the investigation is now being conducted on nano-based systems for drug delivery.

POTENTIAL UTILISATIONS OF NANOTECHNOLOGY IN THE FUTURE:

Nanomedicine will undoubtedly play a crucial role in the future of personalized medicine, including several aspects such as monitoring and prognosis. Nanoscale materials form the basis for more accurate sensors and biomarkers, enabling the precise and simultaneous detection of a wider range of diseases in their early stages. Nanomedicine enables very accurate disease mapping with enhanced targeting and chemical sensitivity. Nanomedicine can be employed with more efficacy to specifically target cells and minimize harm to healthy cells after a medical condition has been identified and diagnosed. Several goods, including the previously mentioned doxorubicin nano-encapsulated product, are now being utilized. The challenges of the future mostly revolve around harnessing the diagnostic and therapeutic capabilities of metallic nanoparticles, as well as optimizing the load and release of medicinal substances.

NANOMATERIALS APPLICATIONS IN THE FIELD OF MEDICINE:

The ultimate goal of nanomedicine research is to characterize the measurable molecular-scale components referred to as nanomachinery. Accurate regulation and manipulation of intracellular nanomachinery can enhance our understanding of the functioning of living cells and facilitate the development of novel methods for the early identification and treatment of different diseases [33]. The integration of molecules and nanotechnology provides a versatile platform for creating novel nanoprobes that can greatly enhance the precision, accuracy, and signaling characteristics of several biomarkers in human diseases [34]. Nanoparticle probes enhance signal sensitivity, spatial accuracy, and the ability to convey knowledge regarding biological processes at both the molecular and cellular levels. Magnetic nanoparticles can serve as effective MRI contrast enhancement probes. These nanoparticles, which possess magnetic characteristics, can serve as a core base for incorporating additional functional substances like fluorescent tags, radionuclides, and biomolecules. This makes them suitable for applications involving multimodal imaging, transfer of genes, and cell trafficking. The localization of target cells may be achieved by the use of a magnetic resonance imaging (MRI) technique that employs hybrid magnetic nanoparticles and viral probes. This method allows for the monitoring of fluorescent green protein expression and delivery of genes [35]. Theranostics refers to the simultaneous monitoring of the distribution of a substance in the body and its therapeutic effects. This is made feasible by using nanoparticles that might potentially carry both a contrast agent and a drug. The nanofiber-based scaffolds are available in different distributions of pore sizes, levels of porosity, and ratios of surface area to volume. In the future, the optimization of an electrically spun nanofibrous scaffold for tissue engineering purposes can be achieved due to the diverse array of variables that promote cell adhesion, growth, and proliferation [36].

CONCLUSION:

Nanotechnology is leading the way in revolutionizing healthcare by focusing on proactive population health management. Nanotechnology reduces the likelihood of negative consequences, enhances the effectiveness of medical treatment, and addresses the challenge of targeted medicine administration. This technology can be employed for the diagnosis and treatment of cancer through the utilization of gene therapy. Nanomedicine represents the most promising use of nanorobotics. It is utilised in several industries, such as vaccine research, medicine delivery, wearable technology, diagnosing and imaging devices, and antimicrobial items. Pharmaceutical nanotechnology provides novel opportunities for study and enhanced prospects in several areas of diagnosis and therapy.

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ULTRASOUND-MEDIATED DRUG DELIVERY ACROSS THE BLOOD-BRAIN BARRIER

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ABSTRACT:

The blood-brain barrier (BBB) is a highly selective physiological barrier that poses a significant challenge in delivering therapeutic agents to the central nervous system (CNS). Traditional drug delivery methods often fail to achieve sufficient drug penetration into the brain, limiting treatment efficacy for neurological disorders such as brain tumors, Alzheimer's disease, and Parkinson's disease. Ultrasound-mediated drug delivery has emerged as a promising non-invasive strategy to transiently and reversibly disrupt the BBB, facilitating targeted drug transport into the brain. This chapter explores the principles and mechanisms of ultrasound interaction with biological tissues, focusing on the role of microbubbles in enhancing BBB permeability. Various ultrasound-based techniques, including focused ultrasound (FUS) and low-intensity pulsed ultrasound (LIPU), are discussed in the context of their applications in treating brain tumors, neurodegenerative disorders, and other CNS diseases. Additionally, safety considerations, optimization parameters, and recent preclinical and clinical advancements are highlighted. The chapter concludes with future directions, emphasizing the integration of ultrasound technologies with nanomedicine and gene therapy for precision-targeted CNS drug delivery.

Keywords: Blood-brain barrier (BBB), Ultrasound-Mediated Drug Delivery, Focused Ultrasound (FUS). Microbubbles in Drug Delivery, Neurodegenerative Disease Treatment, Sonoporation, Targeted Brain Drug Delivery, Non-Invasive CNS Therapy

1. INTRODUCTION:

The blood-brain barrier (BBB) plays a crucial role in maintaining central nervous system (CNS) homeostasis by tightly regulating the exchange of molecules between the bloodstream and the brain parenchyma. While this selective permeability is essential for protecting the brain from toxins and pathogens, it also presents a significant challenge in the delivery of therapeutic agents for neurological disorders. The impermeability of the BBB limits the effectiveness of conventional pharmacological interventions, necessitating the development of novel strategies to facilitate drug transport into the CNS. In this context, ultrasound-mediated drug delivery has emerged as a promising non-invasive technique to transiently disrupt the BBB and enhance the penetration of therapeutic agents. This chapter explores the principles, mechanisms, and

techniques underlying ultrasound-mediated BBB opening and its potential applications in the treatment of neurological diseases.

1.1 Overview of the Blood-Brain Barrier (BBB)

The BBB is a highly specialized and selective interface formed by brain microvascular endothelial cells, pericytes, and astrocytic end-feet. The endothelial cells are interconnected by tight junction proteins, including occludins, claudins, and zonula occludens, which create a paracellular barrier that restricts the passive diffusion of most molecules. Unlike peripheral capillaries, brain capillaries lack fenestrations, further limiting the movement of substances into the brain interstitium. The presence of efflux transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), further impedes the entry of many therapeutic compounds by actively transporting them back into the bloodstream.(1)

In addition to its structural components, the BBB exhibits a dynamic regulatory role in response to physiological and pathological stimuli. Astrocytes and pericytes contribute to the maintenance of BBB integrity and modulate its permeability under various conditions. While this barrier serves as a protective mechanism against neurotoxic agents, it also significantly limits the delivery of pharmacological agents intended for the treatment of brain tumors, neurodegenerative diseases, and other CNS disorders.

1.2 Challenges in Brain Drug Delivery

One of the primary challenges in brain drug delivery is the inability of most therapeutic molecules to cross the BBB due to their physicochemical properties. Hydrophilic drugs and large macromolecules, such as monoclonal antibodies and nucleic acids, are particularly restricted from passive diffusion into the brain parenchyma. Even small lipophilic drugs that can diffuse across endothelial membranes are often subject to rapid efflux via active transport mechanisms, reducing their therapeutic efficacy.(2)

Another major challenge is the limited effectiveness of systemic drug administration in achieving therapeutic concentrations within the CNS. High systemic doses are often required to compensate for poor BBB penetration, leading to off-target effects and potential toxicity in peripheral tissues. Moreover, certain neurological diseases, such as Alzheimer's disease and glioblastoma, are characterized by altered BBB integrity, further complicating drug delivery strategies. These challenges necessitate the exploration of alternative approaches, such as ultrasound-mediated drug delivery, to transiently modulate BBB permeability and facilitate targeted drug transport into the brain.

1.3 Need for Novel Drug Delivery Strategies

Given the limitations of conventional drug delivery methods, innovative strategies are required to overcome the restrictive nature of the BBB while maintaining its protective function. Several approaches have been investigated, including receptor-mediated transcytosis, nanoparticle-based drug carriers, and chemical modifications to enhance drug permeability.

However, these strategies often face challenges related to specificity, efficiency, and clinical translation.

Ultrasound-mediated BBB opening has emerged as a promising technique due to its ability to transiently and reversibly increase BBB permeability in a spatially controlled manner. This non-invasive approach utilizes focused ultrasound (FUS) in conjunction with intravenously administered microbubbles to induce localized BBB disruption, thereby facilitating the transport of therapeutic agents into the brain. Compared to other invasive methods, ultrasound-mediated drug delivery offers the advantage of precise targeting with minimal systemic toxicity, making it a highly attractive strategy for the treatment of CNS disorders.(3)

2. PRINCIPLES OF ULTRASOUND-MEDIATED DRUG DELIVERY

Ultrasound technology exploits acoustic waves to interact with biological tissues, enabling controlled modulation of the BBB. The fundamental mechanisms underlying ultrasound-mediated drug delivery involve both mechanical and thermal effects, with mechanical forces playing a predominant role in BBB disruption. The use of microbubbles further enhances the efficiency of ultrasound-induced permeability modulation, allowing for precise and localized drug delivery.

2.1 Mechanisms of Ultrasound Interaction with Biological Tissues

Ultrasound waves propagate through biological tissues by inducing mechanical pressure oscillations, which can result in cavitation, acoustic streaming, and radiation forces. The interaction of ultrasound with tissues can be classified into thermal and mechanical effects. Thermal effects occur when prolonged ultrasound exposure leads to tissue heating, which can induce protein denaturation and coagulative necrosis. While high-intensity focused ultrasound (HIFU) exploits thermal effects for ablative therapies, the use of lower intensities minimizes tissue damage in drug delivery applications.(4)

Mechanical effects, particularly cavitation, play a crucial role in ultrasound-mediated BBB opening. Cavitation refers to the formation, oscillation, and collapse of microbubbles in response to ultrasound pressure waves. Stable cavitation involves sustained microbubble oscillation, generating shear stress that transiently disrupts the tight junctions of the BBB. In contrast, inertial cavitation leads to the violent collapse of microbubbles, producing high-energy shock waves that can cause endothelial cell damage. By carefully controlling ultrasound parameters, stable cavitation can be harnessed to achieve controlled and reversible BBB disruption for drug delivery.(5)

2.2 Role of Microbubbles in BBB Disruption

Microbubbles serve as ultrasound contrast agents and play a critical role in enhancing the efficiency of ultrasound-mediated BBB opening. Composed of gas cores encapsulated within lipid, protein, or polymer shells, microbubbles undergo volumetric oscillations in response to ultrasound, amplifying cavitation effects. The expansion and contraction of microbubbles within

brain capillaries generate mechanical forces that transiently increase endothelial permeability, facilitating the transport of drugs across the BBB.(6)

The use of targeted microbubbles, functionalized with ligands or drug payloads, offers additional advantages by enabling site-specific drug delivery. Upon ultrasound activation, these microbubbles can release encapsulated therapeutic agents directly at the BBB, enhancing drug bioavailability while minimizing systemic exposure. Optimizing microbubble properties, such as size, composition, and concentration, is crucial for achieving effective and safe BBB modulation.(7)

2.3 Factors Influencing Ultrasound-Induced Permeability

Several factors influence the extent and duration of ultrasound-induced BBB opening. Ultrasound parameters, including frequency, intensity, and pulse duration, play a significant role in determining the efficiency and safety of BBB disruption. Lower ultrasound frequencies (0.2–1 MHz) are typically more effective in inducing cavitation, while pulsed ultrasound reduces the risk of thermal damage. The concentration and size distribution of microbubbles also impact cavitation dynamics, with smaller microbubbles exhibiting enhanced stability and controlled oscillation.

The physicochemical properties of the delivered drug influence its transport across the disrupted BBB. Small, lipophilic molecules generally exhibit higher permeability, while hydrophilic and macromolecular therapeutics may require additional targeting strategies. Additionally, factors such as cerebral blood flow, vascular integrity, and disease pathology can affect the efficacy of ultrasound-mediated drug delivery. Optimizing these parameters is essential for achieving safe and effective BBB modulation in clinical applications.(8)

3. ULTRASOUND TECHNIQUES FOR BBB OPENING

Several ultrasound-based approaches have been developed to achieve controlled and transient BBB opening. These include focused ultrasound (FUS), low-intensity pulsed ultrasound (LIPU), and sonoporation, each of which offers distinct advantages and applications in CNS drug delivery.

3.1 Focused Ultrasound (FUS)

Focused ultrasound (FUS) is a non-invasive technique that uses an external transducer to generate ultrasound waves that converge at a specific target within the brain. When combined with microbubble administration, FUS induces localized and transient BBB opening, allowing for precise drug delivery. The ability to control the focal region with high spatial accuracy makes FUS particularly suitable for treating focal CNS pathologies, such as brain tumors and neurodegenerative diseases.(9)

3.2 Low-Intensity Pulsed Ultrasound (LIPU)

Low-intensity pulsed ultrasound (LIPU) employs intermittent ultrasound pulses at lower energy levels to minimize thermal effects while maintaining effective BBB modulation. This

approach is particularly advantageous for repeated drug administration in chronic neurological conditions, reducing the risk of tissue damage.(10)

3.3 Sonoporation and Its Implications

Sonoporation involves the formation of transient pores in endothelial cell membranes through ultrasound-induced cavitation, facilitating the transport of large molecules such as antibodies and nucleic acids. This technique has potential applications in gene therapy and targeted drug delivery.(11)

4. APPLICATIONS IN NEUROLOGICAL DISORDERS

The use of ultrasound-mediated drug delivery across the blood-brain barrier (BBB) has opened new avenues for the treatment of various neurological disorders. This technique enables the localized and controlled delivery of therapeutic agents to the brain, overcoming the inherent limitations imposed by the BBB. Several preclinical and clinical studies have demonstrated the efficacy of focused ultrasound (FUS) in facilitating the transport of small molecules, biologics, and gene therapy vectors for the treatment of brain tumors, neurodegenerative diseases, and cerebrovascular disorders. The ability to transiently and reversibly disrupt the BBB without causing permanent damage makes ultrasound-based drug delivery an attractive strategy for addressing the unmet medical needs of CNS diseases.

4.1 Drug Delivery for Brain Tumors

Brain tumors, particularly glioblastoma multiforme (GBM), pose a significant therapeutic challenge due to their highly invasive nature and poor response to conventional treatments. The BBB restricts the penetration of most chemotherapeutic agents, necessitating the development of alternative drug delivery strategies. Ultrasound-mediated BBB opening has been extensively investigated as a method to enhance the delivery of chemotherapy drugs, such as temozolomide, doxorubicin, and paclitaxel, to brain tumor tissues. Preclinical studies have demonstrated that FUS in combination with microbubbles significantly increases drug accumulation within glioma regions, leading to improved therapeutic outcomes.(12)

Clinical trials have also provided promising results, with ultrasound-mediated BBB opening demonstrating safety and feasibility in patients with recurrent glioblastoma. This approach allows for repeated drug administration at the tumor site while minimizing systemic toxicity. Additionally, ultrasound technology can be integrated with real-time imaging techniques, such as magnetic resonance imaging (MRI), to monitor BBB permeability and optimize drug delivery. The combination of ultrasound-mediated drug delivery with targeted nanoparticles and immunotherapy holds great potential for advancing glioblastoma treatment.

4.2 Treatment of Neurodegenerative Diseases

Neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease, are characterized by progressive neuronal loss and the accumulation of pathological protein aggregates. The BBB presents a major hurdle in the effective delivery of

disease-modifying therapies, such as monoclonal antibodies, neurotrophic factors, and gene-editing tools. Ultrasound-mediated BBB opening has emerged as a promising technique to enhance the transport of therapeutic agents into the CNS and facilitate the clearance of toxic protein aggregates.(13)

In Alzheimer's disease, preclinical studies have demonstrated that FUS-mediated BBB opening promotes the clearance of amyloid-beta plaques by enhancing microglial phagocytosis and cerebrospinal fluid (CSF) drainage. This effect occurs even in the absence of exogenous drug administration, suggesting that ultrasound may have an intrinsic neuroprotective role. Additionally, the delivery of monoclonal antibodies, such as aducanumab and bapineuzumab, has been significantly improved through ultrasound-assisted BBB disruption, leading to increased target engagement and reduced amyloid burden.

For Parkinson's disease, ultrasound-mediated drug delivery has been explored for the targeted administration of neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF), to restore dopaminergic neuron function. Similarly, gene therapy approaches, including CRISPR-Cas9 and RNA interference (RNAi)-based strategies, can benefit from ultrasound-enhanced BBB permeability, facilitating the precise modulation of disease-associated genes. These findings highlight the potential of ultrasound-mediated drug delivery in addressing the complex pathophysiology of neurodegenerative disorders.(14)

4.3 Applications in Stroke and Neuroinflammation

Stroke is a leading cause of disability and mortality worldwide, often resulting in irreversible neuronal damage due to ischemia and inflammation. The BBB plays a dual role in stroke pathophysiology, initially protecting the brain from systemic insults but later becoming dysfunctional, contributing to secondary injury. Ultrasound-mediated drug delivery has been investigated as a strategy to enhance the transport of neuroprotective agents, thrombolytics, and anti-inflammatory drugs to ischemic brain regions.

Preclinical studies have shown that FUS can improve the delivery of tissue plasminogen activator (tPA) for thrombolysis in acute ischemic stroke, reducing clot burden and improving cerebral perfusion. Additionally, ultrasound-assisted delivery of anti-inflammatory agents, such as corticosteroids and monoclonal antibodies targeting pro-inflammatory cytokines, has been explored for mitigating secondary neuroinflammation. The potential of ultrasound-mediated gene therapy to enhance neuronal recovery following stroke is also under investigation, offering a novel approach to promote post-stroke neuroregeneration.

5. SAFETY AND EFFICACY CONSIDERATIONS

The clinical translation of ultrasound-mediated drug delivery requires careful evaluation of its safety and efficacy to ensure its viability as a therapeutic strategy for neurological disorders. While preclinical and early-phase clinical studies have demonstrated the feasibility of this approach, several factors must be optimized to achieve a favorable risk-benefit profile. Key

considerations include the potential for tissue damage, the reversibility of BBB opening, and the long-term effects of repeated ultrasound exposure.

One of the primary safety concerns associated with ultrasound-mediated BBB opening is the risk of vascular injury due to excessive cavitation. While stable cavitation facilitates controlled BBB disruption, inertial cavitation can lead to endothelial cell damage, hemorrhage, and inflammation. The optimization of ultrasound parameters, including frequency, pressure amplitude, and pulse duration, is essential to minimize these risks. Real-time imaging guidance, such as MRI or ultrasound-based monitoring, can further enhance safety by allowing precise control over cavitation dynamics.(15)

The reversibility of BBB opening is another critical factor in ensuring the safety of ultrasound-mediated drug delivery. Studies have shown that the BBB typically restores its integrity within hours to days following ultrasound exposure, reducing the risk of prolonged barrier dysfunction and increased susceptibility to infections or toxic insults. However, repeated BBB modulation over extended treatment durations requires further investigation to determine its cumulative effects on brain homeostasis.(16)

Efficacy considerations include the ability of ultrasound-mediated drug delivery to achieve therapeutic concentrations of drugs in target brain regions while minimizing off-target effects. The pharmacokinetics of drug transport across the ultrasound-disrupted BBB must be carefully characterized to optimize dosing regimens and enhance treatment efficacy. Furthermore, individual variability in BBB properties and disease pathology may influence treatment outcomes, necessitating personalized approaches to ultrasound-mediated therapy.

FUTURE PERSPECTIVES AND CHALLENGES:

Despite the promising potential of ultrasound-mediated drug delivery, several challenges must be addressed to facilitate its widespread clinical adoption. One of the key areas of research involves the refinement of ultrasound technology to improve targeting accuracy and minimize adverse effects. Advances in transducer design, real-time monitoring techniques, and automated feedback control systems can enhance the precision and reproducibility of BBB opening.

Another important aspect is the integration of ultrasound with nanotechnology-based drug delivery systems. The development of smart drug carriers, such as liposomes, polymeric nanoparticles, and exosomes, can improve drug stability, prolong circulation time, and enable controlled release at the target site. Functionalized microbubbles and ultrasound-responsive nanoparticles offer additional opportunities for enhancing the specificity and efficiency of drug delivery.(17)

Regulatory and clinical translation challenges must also be addressed to establish ultrasound-mediated drug delivery as a standard therapeutic modality. Large-scale clinical trials are needed to validate its safety and efficacy across different neurological disorders and patient populations. Standardization of treatment protocols, including ultrasound parameters, drug

formulations, and monitoring strategies, will be essential for regulatory approval and clinical implementation.

Moreover, ethical considerations surrounding BBB disruption and potential unintended effects must be carefully evaluated. Long-term studies assessing the impact of repeated ultrasound exposure on cognitive function, neuroinflammation, and BBB integrity will provide crucial insights into the safety of this approach. Collaborative efforts among researchers, clinicians, and regulatory agencies will be instrumental in overcoming these challenges and advancing the field of ultrasound-mediated drug delivery.

CONCLUSION:

Ultrasound-mediated drug delivery presents a transformative approach to overcoming the challenges of transporting therapeutic agents across the blood-brain barrier. By leveraging focused ultrasound and microbubble-assisted cavitation, this technique enables precise, non-invasive, and transient BBB disruption, enhancing drug bioavailability for treating neurological disorders. Preclinical and clinical studies have demonstrated its potential in managing brain tumors, neurodegenerative diseases, and stroke. While safety, efficacy, and regulatory hurdles remain, advancements in nanotechnology and gene therapy integration promise to refine this strategy. Continued research and clinical validation will be essential to fully harness the potential of ultrasound-mediated drug delivery in neurology.

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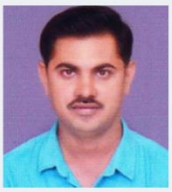

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