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Review Article

Revolutionizing Chronic Disease Management: The Role of Herbal Nanomedicine

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ABSTRACT

Herbal nanomedicine represents a transformative approach to chronic disease management by merging the therapeutic benefits of natural bioactive compounds with nanotechnology. Chronic diseases such as diabetes, cardiovascular disorders, cancer, and neurodegenerative conditions often require long-term treatments, which are frequently limited by low bioavailability, poor targeting, and systemic side effects of conventional therapies. Incorporating herbal medicines into nanocarriers like nanoparticles, liposomes, and nanogels addresses these challenges by enhancing solubility, stability, and targeted drug delivery. This innovative strategy ensures controlled release and improved therapeutic efficacy, minimizing adverse effects while leveraging the inherent safety and efficacy of herbal compounds. Recent advancements have demonstrated promising outcomes in employing herbal nanomedicine to combat inflammation, oxidative stress, and metabolic dysregulation associated with chronic conditions. The integration of bioenhancers, such as quercetin, further amplifies the bioactivity of these formulations, paving the way for more effective and sustainable treatment options. This review explores the potential of herbal nanomedicine in addressing the complexities of chronic diseases, highlights the latest advancements in the field, and discusses the challenges and opportunities for clinical translation. Emphasizing its significant potential, herbal nanomedicine emerges as a future-ready solution for managing chronic diseases effectively and sustainably.

INTRODUCTION

Nanomedicine involves utilizing nano-sized tools for diagnosing, preventing, and treating diseases, as well as enhancing the understanding of the complex biological mechanisms that underlie diseases. Its ultimate objective is to enhance the quality of life. Broadly, the purpose of nanomedicine is to monitor, repair, and improve human biological systems at the molecular level

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through the use of engineered devices and nanostructures for medical benefits. Essentially, nanomedicine encompasses the processes of diagnosing, treating, preventing diseases and injuries, alleviating pain, and promoting human health by employing molecular tools and a deep understanding of the human body. This field presents the potential for innovative tools aimed at treating diseases and improving biological systems through molecular nanotechnology. (1)

Nanotechnology involves the design and production of materials at the atomic and molecular scale. Although it focuses on very small sizes, it generally applies to structures that can be as large as a few hundred nanometers. At this scale, atoms and molecules behave differently, leading to a range of unique and fascinating outcomes. (2)

History of Nanomedicine

Nanomedicine is a relatively new field, with its application in medicine, medical technology, and pharmacology only being explored since the 1990s. Nanotechnology itself has only been around for a few decades. It developed alongside advancements in biology, physics, and chemistry in the 20th century, after the invention of high-resolution microscopy. This technological breakthrough led to the emergence of new fields like microelectronics, biochemistry, and molecular biology. Nanomedicine and nanobiotechnology focus on studying the structure and function of cells, as well as the processes that occur within and between cells. These areas of research became possible in the early 20th century with the advent of advanced microscopes. Nanomedicine involves the monitoring, repairing, constructing, and controlling of human biological systems at the molecular level, using engineered nanodevices and nanostructures. (3)

Novel Drug Delivery System for Herbal Remedies

Before entering the bloodstream, many components of herbal drugs are broken down by the highly acidic environment of the stomach, while others may be metabolized by the liver. (4)If home-grown medications do not reach the bloodstream in adequate amounts, the drug may fail to reach the infected area at the "minimum effective level," meaning it will not produce the desired therapeutic effect .(5)

Nanoparticle Drug Delivery Systems (NDDS) are developed to address the limitations of traditional herbal medicine, offering broad benefits for human applications.

•Nanoparticles can be utilized to direct herbal medicines to specific organs, enhancing

•This improves selectivity, solubility, drug delivery, safety, and effectiveness, while also reducing the need for frequent dosing.

•Nanoparticle-sized drug delivery increases the total surface area of the drugs, allowing for faster dissolution in the bloodstream.

•Minimizing toxicity while preserving therapeutic benefits.

•Nanoparticles can penetrate the blood-brain barrier due to their enhanced permeability and retention.

To enhance patient compliance and reduce the need for frequent administration, phytotherapeutics should be delivered systematically over time. This can be achieved by developing nanodrug delivery systems (NDDSs) for the active components in herbs. NDDSs decrease the frequency of administration to address noncompliance while also enhancing therapeutic effectiveness by reducing toxicity and increasing bioavailability. (6) Herbal remedies were chosen as potential drug candidates for delivery via a nano delivery system due to their following characteristics:

1. Chloroform, petrol, acetone, and methanolic extracts are available, but they may not be

appropriate for direct delivery in their current forms.

2. These are the main drugs, so a reduction in dosage is planned.

3.The formulations currently available on the market lack target specificity for treating various chronic diseases.

4. Other side effects are linked to the formulations currently available on the market.

5. Patient non-compliance is caused by the high doses and reduced effectiveness of the existing formulations. (6)

Types of Nanoparticles

• Polymeric nanoparticles
•Solid lipid nanoparticles
• Magnetic nanoparticles
•Metal and inorganic nanoparticles
• Quantum dots
• Polymeric micelles
• Phospholipid micelles
• colloidal nano- liposomes
• Dendrimers (7)

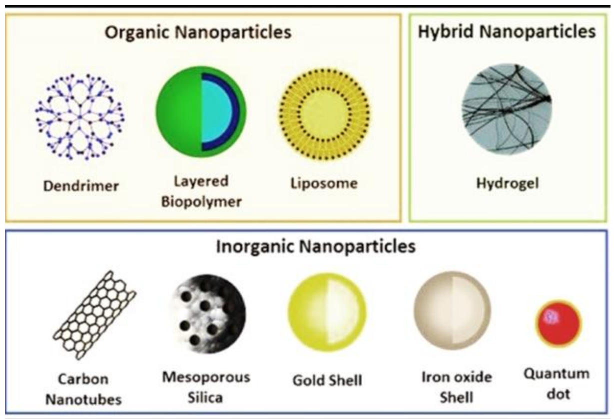

Figure. 1 Types of Nanoparticles

Figure 1 provides a schematic overview of various types of nanoparticles (NPs), categorized into organic, hybrid, and inorganic types. (8)

Nanomedicine in Respiratory Diseases

Respiratory diseases are becoming more prevalent in the aging population. Nanomedicine, which applies nanotechnology to medical challenges, introduces innovative approaches for diagnosis and treatment, encompassing three interconnected areas: molecular imaging, targeted drug delivery with controlled release, and regenerative medicine. Since nanocarrier systems can be easily administered through the airways, nanoparticles offer potential treatments for a range of respiratory conditions, including obstructive lung diseases, airway-related genetic disorders, and infectious diseases. (9)

1. **Nanospheres For Treatment of Allergic Asthma**

Asthma is a chronic condition marked by allergen-induced inflammation of the airways, leading to the infiltration of inflammatory cells like eosinophils and causing epithelial hyperplasia. This results in excessive mucus production and airway hyperresponsiveness (AHR) to various environmental triggers. The abnormal airflow in the airways can be improved, either partially or fully, through the use of bronchodilators and anti-inflammatory medications. Traditional treatments for asthma-related inflammation involve the use of non-steroidal anti-inflammatory drugs, while more advanced cases often require immunosuppressive agents such as methotrexate, cyclosporin, and azathioprine.

Nanotechnology for Treatment of Cystic Fibrosis

Cystic fibrosis is an inherited autosomal recessive disorder that primarily impacts the lungs, but also affects the digestive system, leading to progressive deterioration and early mortality. The production of thick mucus in the airways impairs muco-ciliary clearance, weakens the immune response, and triggers inflammation, which increases the risk of frequent lung infections like allergic bronchopulmonary aspergillosis and mycobacterium avium complex. The condition is caused by mutations in the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene. (10)

Nanomedicine in Neurodegenerative Diseases

The primary obstacle in treating neurodegenerative diseases is overcoming the protective barrier of the blood-brain barrier to deliver therapeutic agents to the brain.

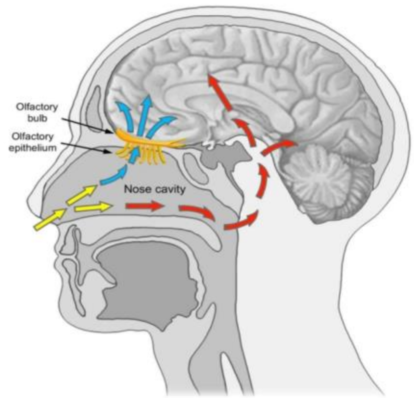

Figure. 2 Pathways for Intranasal Drug Delivery

Drugs administered intranasally quickly reach brain tissue through both the peripheral olfactory route (illustrated in blue) and the peripheral trigeminal route (illustrated in red). Various nanoparticle (NP) formulations have been studied for encapsulating proteins, notably liposomes, polymeric particles (PPs), and solid lipid nanoparticles (SLNs). Among these, liposomes are the most well-known and extensively researched systems for delivering proteins and small molecules. They have been widely utilized for the effective delivery of small molecule drugs, offering controlled release and targeted drug delivery.

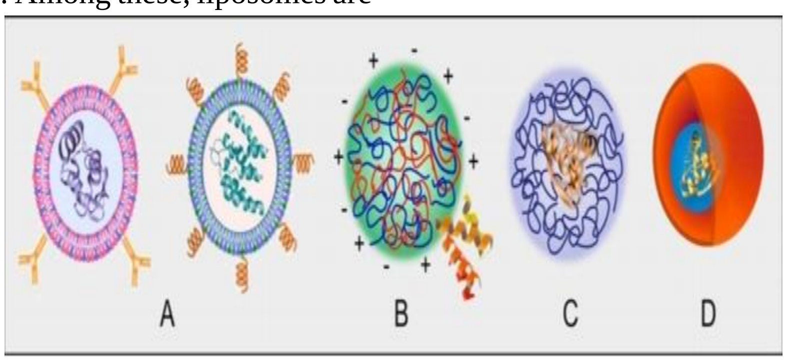

Figure. 3 use of nanoparticles for protein delivery.

Figure. 3 illustrates the use of nanoparticles for protein delivery. (A) Liposomes can be modified with antibodies for targeted delivery or with polymers to improve their ability to cross the blood-brain barrier. (B) Biodegradable polymer nanospheres are also shown. (C) Additionally, biodegradable polymer Nano capsules are included. (D) The figure features solid lipid particles as well. (11)

Nanomedicine in Inflammatory Diseases

Inflammation is a natural reaction that helps safeguard tissues against infection or injury. The typical process of acute inflammation consists of activating inflammatory mediators and drawing monocytes from the bloodstream to eliminate foreign pathogens at the site of inflammation. In contrast, chronic inflammation is characterized by the persistent activation of pro-inflammatory mediators and the ongoing infiltration of monocytes into the tissue, ultimately resulting in tissue damage. Factors such as genetics, environmental influences, and the adaptive immune response can contribute to the development of chronic inflammatory diseases. (12)

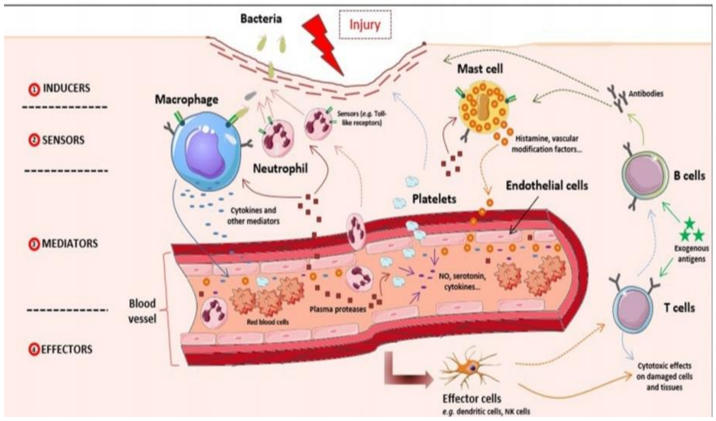

Figure. 4 Inflammatory response

Figure 4. illustrates the inflammatory response. Initially, inducer signals (1), such as wounds or pathogens, activate sensors (2) on inflammatory cells located in the affected area. This activation prompts the production and release of various mediators (3), including plasma proteases, chemokines, cytokines, and factors that modify blood vessels. These mediators lead to changes in blood vessels, the recruitment of platelets, and the influx of other inflammatory cells, such as phagocytic leukocytes (e.g., neutrophils), which then act on effector cells (4) and tissues to help resolve inflammation. The adaptive immune system also plays a role in the inflammatory response, with B and T lymphocytes recognizing and responding to antigens presented by antigen-presenting cells like dendritic cells. Adaptive mechanisms can operate through direct cytotoxic actions or by secreting antibodies that interact with elements of the innate inflammatory response. (13)

Nanomedicine in Cancer Therapy

Nanomedicine is a groundbreaking area with significant promise for enhancing cancer treatment, leading to the development of various established drug delivery systems. Clinical applications frequently utilize nanoconstructs like liposomes, while polymer micelles are currently in advanced clinical trials across multiple countries. At present, the nanomedicine field is witnessing a surge in innovative nanoscale drug delivery strategies, focusing on functionalizing these constructs with specific moieties to improve targeted delivery. Liposomes are nanoscale constructs, typically around 100 nm in diameter, characterized by a bilayer membrane made of phospholipids. These lipids feature hydrophilic heads and hydrophobic tails, which can be either anionic or cationic. The aqueous core of liposomes enables the encapsulation of various hydrophilic substances, such as drugs and siRNA, while the hydrophobic membrane can trap hydrophobic drug molecules, preventing the escape of hydrophilic agents from the core. In 1995, the FDA approved a PEGylated liposomal formulation of doxorubicin, known as Doxil, for treating Kaposi's sarcoma.

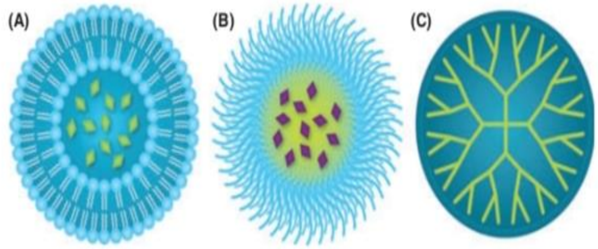

Figure. 4 nanoparticle platforms for delivering anticancer drugs

Figure 5. Established nanoparticle platforms for delivering anticancer drugs. (A) Liposomes feature a hydrophobic membrane surrounding an aqueous core that can hold hydrophilic drugs. (B) Polymer micelles are made up of a hydrophilic outer layer and a hydrophobic core designed to encapsulate lipophilic drugs. (C) Dendrimers consist of multiple branches extending from a central core. (14)

Nanomedicine in Diabetes System

Diabetes is a significant health issue in the 21st century, ranked as the sixth leading cause of death, with projections suggesting that over 642 million people will be affected by 2040. There are three main types of diabetes, each with different causes: Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), and Gestational Diabetes Mellitus (GDM). Although treatments such as insulin and oral antidiabetic medications are available, all types of diabetes are linked to both acute and chronic complications, as well as adverse effects from drug therapies. T1DM occurs when the β cells in the pancreatic islets are destroyed by an autoimmune disorder, leading to a lack of insulin production. In contrast, T2DM arises from the body's inadequate response to insulin, resulting in insulin resistance. GDM, the third type, poses risks such as fetal death, preeclampsia, and eclampsia. (15)

For more than 50 years, Type 2 Diabetes Mellitus (T2DM) has been managed with synthetic oral antihyperglycemic medications. These include sulfonylureas, such as chlorpropamide, tolbutamide, and glimepiride, as well as biguanides like metformin, which is regarded as the first-line treatment. As illustrated in the figure, various other therapeutic agents have also been employed, each differing in their mechanisms of action at the target organ. (16)

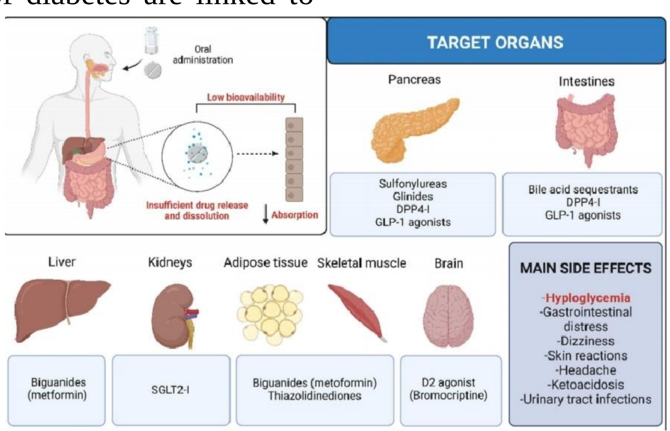

Figure. 6 Effects of oral administration of traditional diabetes medications

Figure 6 illustrates the effects of oral administration of traditional diabetes medications, highlighting the absorption barriers, the targeted organs affected by these drugs, and the primary side effects associated with their use.

Advantages of Herbal Nanomedicine

1. The World Health Organization (WHO) defines herbal medicines as plant-based substances that occur naturally and undergo little to no industrial processing, traditionally utilized for treating illnesses in specific local or regional healing practices. (17)

2.Nanotechnology is viewed positively in medicine because it can contribute to the creation of new medications. These medications can help patients recover more quickly and with fewer side effects compared to conventional treatments.

3. The development of nanotechnology in medicine is currently focused on areas such as tissue and bone repair, immunology, and treatments for diseases like cancer, insulin-related conditions, and other life-threatening disorders.

4.This method produces more efficient electricity, power generation, and energy storage products within smaller and more effective systems.

Disadvantages of Nanomedicine

1. The progress of nanotechnology could lead to a decline in the value of oil and gemstones due to the potential for developing more affordable alternative energy sources that do not rely on the combustion of fossil fuels.

2.Nanotechnology has become extremely expensive, and its production can be quite costly as well. Additionally, manufacturing nanotechnology-based products is difficult, which contributes to their higher prices. (18)

3.Currently, researchers and the US Food and Drug Administration (FDA) are working to establish guidelines for evaluating the safety profiles and immunogenicity of nanotherapeutics.

4. A high level of free radicals can harm DNA, proteins, lipids, and other biological elements.

5. The toxic effects of nanoparticles may result from oxidative stress induced by the generation of free radicals. (19)

6. The application of nanoparticles in medicine is still an emerging area, and understanding their long-term toxicity is limited. Research indicates that certain nanoparticles can build up in the body and lead to harm in organs and tissues.

7. The creation and manufacturing of nanoparticles can be costly, potentially restricting their accessibility and affordability. (20

Application-

1. Therapeutic Application

   Nanotechnology can lead to innovative drug formulations that have fewer side effects and enhanced methods for drug delivery.

1. Drug delivery

• Nanoparticles used as therapeutics can be directed to specific sites, including areas that are difficult for standard drugs to access

•Nanodrugs can be engineered to activate only in the presence of certain molecules or in response to external triggers like infrared heat. This approach also minimizes harmful side effects from powerful drugs by lowering the required dosage for treatment.

•By enclosing drugs in nanoscale materials like organic dendrimers, hollow polymer capsules, and nanoshells, drug release can now be controlled with much greater precision than previously possible.

2. Nanotechnology in dental care

•Nanotechnology will play a significant role in the future of dentistry, with the use of nanomaterials, biotechnology, and nanorobotics contributing to improved oral health through advancements in nanodentistry.

3. Biopharmaceuticals

• Nanobiotechnology has the potential to create treatments for diseases that traditional pharmaceuticals are unable to address.

• The pharmaceutical industry typically concentrates on creating medications aimed at a known set of around 500 identified disease targets. (21)

• Nanomaterials are being explored as potential tools for creating diagnostic biosensors and delivering drugs or genes due to their unique physicochemical and biological characteristics.

• The interactions between nanomaterials and biomolecules or cells can be significantly influenced by various factors such as their shape, size, chemical composition, surface structure, surface charge, degree of agglomeration, aggregation, and solubility. (22)

4. Diagnostic Application

• Nanoscale particles (NPs) can provide valuable insights throughout the clinical process. While improved imaging for gross anatomical and cellular data is essential, the accurate detection of disease-related agents is equally important. NPs have been integrated into various new assays to enhance diagnostics, supporting sensitive and specific disease detection.

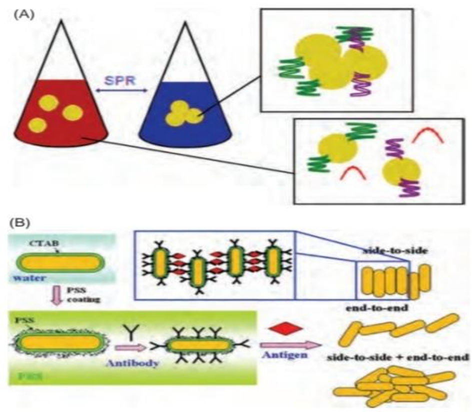

Figure 7. (A) Nanoparticle-based diagnostic assays

This example demonstrates an assay used to detect endonuclease activity. In the general scenario, gold nanoparticles (GNPs) aggregate, causing a color change in the solution from red to blue due to surface plasmon resonance (SPR) effects. In inset A, complementary oligonucleotides (green and purple) induce particle aggregation. In inset B, the presence of an endonuclease (red) prevents aggregation, maintaining the red color of the solution. (B) Depicts a schematic of gold nanorod bioconjugation and the detection of g-IgG through particle aggregation (23).

Microfluidization

The development of nanodelivery systems based on plant bioactive compounds using microfluidization is a new approach aimed at improving the stability and bioavailability of the incorporated plant compounds.

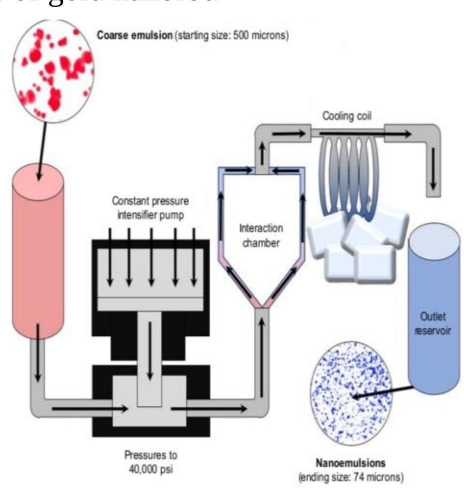

Figure 8. Microfluidization process used in the development of nanodelivery systems.

• Plant bioactive compounds are essential in preventing and treating a range of chronic diseases such as cancer, type 2 diabetes, hypertension, obesity, and neurological disorders.

• In general, plant bioactive compounds are typically taken orally as extracts or nutraceuticals, offering health benefits by preventing or reducing the onset of diseases through mechanisms such as anticancer, anti-inflammatory, antidiabetic, anti-obesity, and antioxidant effects. (24)

Work Done On Different Formulation

Sr. No	Formulation	Pharmacological activity	Reference
1.	Topical declofenac cream	Osteoarthritis	25
2.	Nanosuspension coriandrum sativum	Antioxidant	26
3.	Poly (lactic -co - glycolic acid) Nanoparticles	Alzheimer's and Parkinson disease	27
4.	Nanopaste of Aloe vera	Osteoporosis	28
5.	Luteolin loaded pegylated bilosomes	Breast cancer	29
6.	Nanogel	CNS disorders	30
7.	Polysaccharides Nanoparticles	Diabetes mellitus	31.
8.	Hisperidin and citrus food	Anti-inflammatory, Antimicrobial	32
9.	Cycodextrin Nanoparticles	Hypertension	33.
10.	Berberine loaded Nanoparticles	Antidiabetic	34

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