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A Comprehensive Review on Nano-Technology in Herbal Medicines

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Abstract- The utilization of nanotechnology in herbal medicine and drug delivery systems has been a topic of increasing interest. This comprehensive review explores the impact of nanotechnology on herbal medicines, covering targeted drug delivery, improved bioavailability, and increased efficacy. It also discusses the history and development of nanotechnology in herbal medicines, classification of nanoparticles, novel drug delivery systems for herbal remedies, formulation techniques, and recent developments in the field. The review emphasizes the potential of nanotechnology to revolutionize the field of herbal medicine and enhance the effectiveness and safety of herbal remedies. this review provides valuable insights into the use of advanced delivery systems to improve the efficacy of herbal medicines, offering a comprehensive overview of the applications, advancements, challenges, and regulatory aspects of nanotechnology in herbal medicine.

Keywords:- *Nanotechnology, Herbal Medicine, Drug Delivery Systems, Bioavailability, Nanoparticles, Targeted Drug Delivery, Nanobiomedicine, Nanosuspension Method, Cancer Immunotherapy, Herbal Drug Delivery, Derma Care, Macro Dosages Forms.*

I. INTRODUCTION

Nano-technology has emerged as a revolutionary approach in the field of herbal medicine, opening new avenues for enhanced therapeutic benefits. By manipulating particles at the nano-scale, scientists can unlock the full potential of herbal remedies. This breakthrough technology enables targeted drug delivery, improved bioavailability, and increased efficacy of herbal medicines. Nano-sized carriers can encapsulate active compounds, protecting them from degradation and ensuring controlled release within the body Nano-particles have shown promise in enhancing cellular uptake and crossing biological barriers for better absorption. The application of nano-technology in herbal medicine not only enhances the efficacy of traditional remedies but also offers opportunities to develop innovative formulations with precise dosage control [1,2].

Nano-technology has revolutionized the field of herbal medicine, offering numerous advantages that enhance the effectiveness and safety of these remedies. Firstly, nano-sized drug delivery systems enable targeted delivery to specific cells or tissues, ensuring optimal therapeutic outcomes with minimal side effects. This precise targeting reduces the required dosage and frequency of administration, enhancing patient compliance. Additionally, nanotechnology enhances the solubility and bioavailability of herbal compounds, increasing their absorption and utilization within the body [3,4].

Nano-encapsulation protects delicate herbal constituents from degradation during storage and transportation, prolonging their shelf life and maintaining their potency. Furthermore, nanoparticles can facilitate controlled release of herbal active ingredients over time, providing sustained therapeutic effects [5].

Nano-technology has revolutionized numerous industries, and now it is making its mark in the field of herbal medicines. This cutting-edge technology involves manipulating particles at the nanoscale, enabling scientists to enhance the therapeutic properties of herbal remedies. By reducing herbal extracts into nanoparticles, their bioavailability and absorption within the body are greatly increased. The smaller particle size allows for better solubility, improved stability, and targeted delivery to specific cells or tissues [6].

Nano-technology facilitates controlled release mechanisms that ensure a sustained and optimal dose of active compounds over time. Through this advanced approach, researchers aim to overcome limitations such as poor bioavailability and inconsistent efficacy often associated with traditional herbal medicines [7].

Nano-technology has revolutionized the field of herbal medicines, offering numerous applications that enhance their efficacy and safety. One key application lies in the targeted delivery of active herbal compounds to specific areas in the body. Nano-sized carriers allow for controlled release, ensuring optimal bioavailability and reducing side effects. Additionally, nano-formulations enable improved solubility of poorly soluble herbal extracts, enhancing their absorption and therapeutic potential [8].

Nano-particles can act as carriers for phytochemicals across biological barriers, such as the blood-brain barrier, enabling effective treatment of neurological disorders. Nano-engineering also facilitates the synthesis of hybrid materials by combining nanoparticles with herbal extracts or active compounds, leading to enhanced therapeutic properties [9].

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Nanoscale systems, with particle diameters of 0.1 µm or sub-micrometers, offer numerous benefits. These include improved administration routes and enhanced therapeutic effects, making nanotechnology a rapidly evolving and extensively researched field. Many researchers are merging herbal medicine with nanotechnology, as nano-sized systems can enhance activity, lower dosages, and reduce side effects [10].

Herbal medicines, when paired with nanotechnology-based delivery systems, exhibit immense potential and unique characteristics. They can transform less soluble, poorly absorbed, and unstable substances into potential drugs. Thus, nanotechnology-based delivery systems are a promising avenue for boosting the efficacy of herbal remedies and addressing the challenges associated with herbal medicine [11].

These nanotechnology-based delivery methods can mitigate these limitations, primarily by enhancing their bioavailability and absorption, thereby augmenting their activity [13].

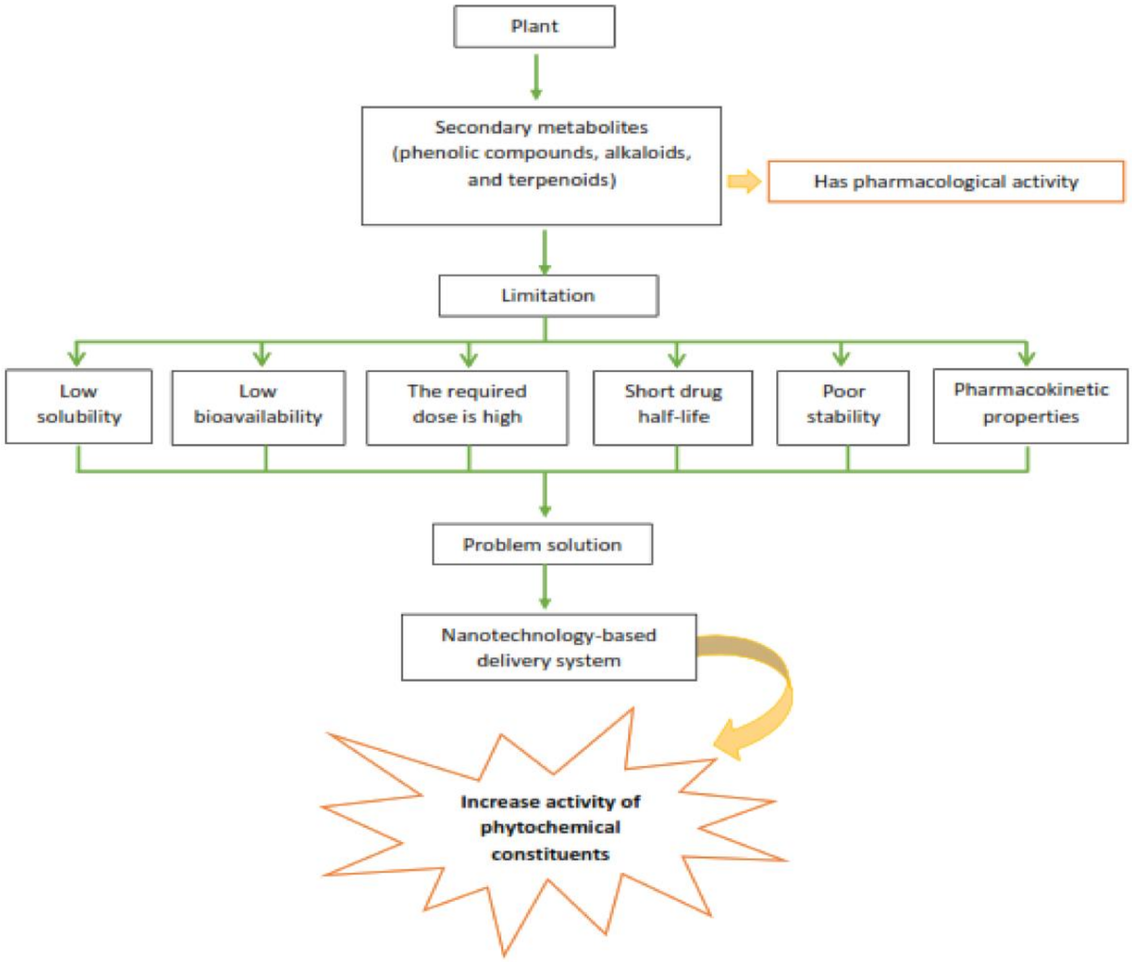

Fig 1. A diagram of phytochemicals that restrict their use in clinical practice [12].

Nano-technology in herbal medicine presents both challenges and promising prospects. One significant challenge lies in the complexity of herbal medicines, which contain multiple active compounds that may interact differently when encapsulated at the nano-scale. Ensuring consistent and controlled release of these compounds poses a hurdle for researchers. Additionally, the potential toxicity associated with nanoparticles raises concerns regarding their safe use in herbal medicine formulations [14].

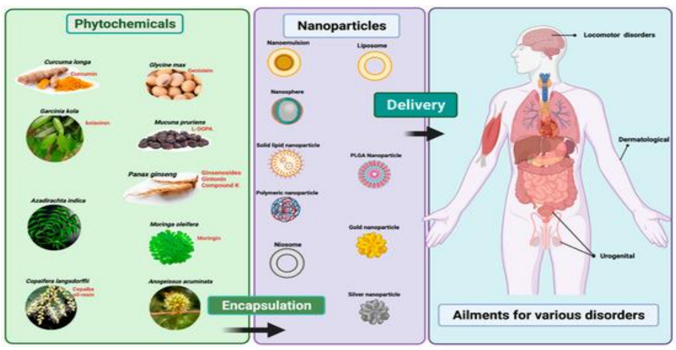

Fig 2. Representation of delivery of phytopharmaceutical using nanotechnology [15].

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II. HISTORY AND DEVELOPMENT

Nanotechnology has significantly impacted the field of herbal medicines. Here's a brief history and development of nanotechnology in herbal medicines:

A. Ancient Use of Herbal Medicines:

The age-old practice of utilizing plants, either directly or in extracted form, for medicinal purposes has been prevalent since antiquity. Particularly in India, Ayurveda stands as a testament to this, being one of the ancient medical sciences still in practice [16].

B. Challenges with Herbal Medicines:

Herbal medicines come with certain drawbacks, including low solubility, stability, and bioavailability. Some may experience physical and chemical degradation, leading to a reduction in their pharmacological effectiveness [17].

C. Introduction of Nanotechnology:

The creation of innovative drug delivery systems (NDDS) is crucial in addressing numerous challenges such as low bioavailability, stability in the body, water insolubility, absorption in the intestines, and non-specific action sites [18].

D. Nanotechnology-Based Herbal Drug Formulations:

Over the past few decades, herbal drug formulations utilizing nanotechnology have garnered interest due to their amplified effectiveness and potential to address issues inherent to herbal medicine. The use of nanotechnology-based delivery systems, which are biocompatible, biodegradable, and derived from lipids, polymers, or nano emulsions, can enhance solubility. This has led to a renewed focus on nanotechnology-based herbal drug formulations in recent years, as they offer enhanced activity and the potential to overcome the challenges associated with traditional herbal medicine.

➢ *Classification of Nanoparticles [20]:*

- Labile Nanoparticles: Liposomes, micelles, polymers, nano emulsions etc.
- Insoluble Nanoparticles: TiO2, SiO2, fullerens, quantum dots, carbon lattices, nanotubes etc.
- One dimensional Nanomaterial: Nanowire and nanotube.
- Two dimensional Nanomaterials: Self assembled monolayer film.

III. NOVEL DRUG DELIVERY SYSTEM FOR HERBAL REMEDIES

Traditional herbal remedies offer a wealth of potential health benefits, but they often face challenges in terms of effectiveness due to limitations in their delivery. Luckily, advancements in nanotechnology have opened doors to novel drug delivery systems (NDDS) that can significantly improve the efficacy and safety of these natural medicines [21].

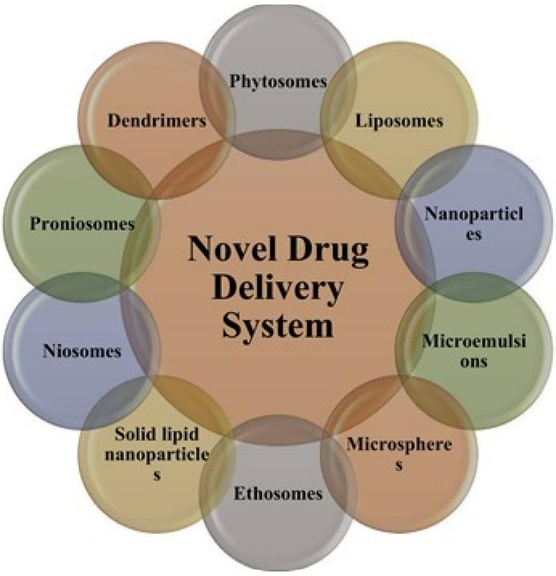

Fig 3. Recent advancement in herbal remedies delivery system [22]

Novel drug delivery systems (NDDS) have been developed to enhance the therapeutic benefits of herbal remedies.

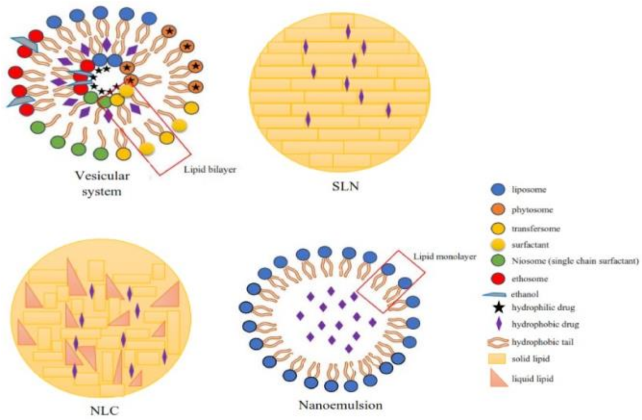

Fig 4. Classification of the lipid-based delivery system [23].

A. Phytosomes

Phytosomes and liposomes are complex compounds of phospholipids and phytoconstituents that boost the absorption and bioavailability of herbal drugs. These lipid-based delivery systems are formed by the reaction between phosphatidylcholine (or any hydrophilic polar head groups) and plant extracts in an aprotic solvent. The process of complexation between phospholipids and water-soluble active plant components in phytosomes involves the formation of chemical bonds, enhancing their stability [24].

A recent study examined the effects of high-dose silybin-phytosome on tissue and blood in prostate cancer patients. Patients were administered silybin-phytosome for a period ranging from 14 to 31 days (with an average of 20 days) before surgery. Silibinin blood levels, measured an hour after the first dose of silybin-phytosome, had an average value of 19.7 µM. One patient experienced a grade 4 post-operative thromboembolic event. Other observed side effects were mild, with four subjects experiencing diarrhea and one subject having transient asymptomatic grade 2 hyperbilirubinemia. The study concluded that high-dose oral silybin-phytosome results in transiently high blood concentrations, but silibinin levels in prostate tissue remain low.

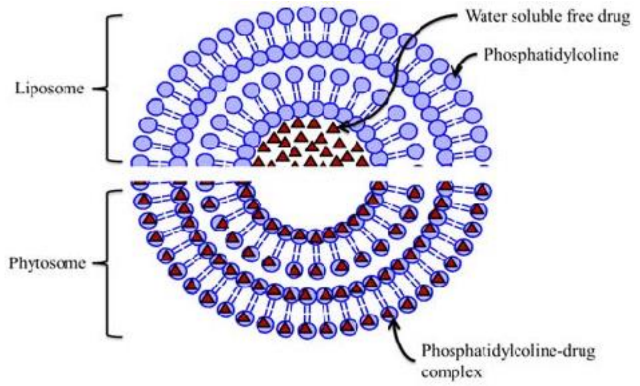

Fig 5. Difference-between-phytosome-and-liposomes [25].

B. Liposomes

These are spherical vesicles that can encapsulate herbal drugs, improving their stability and bioavailability.

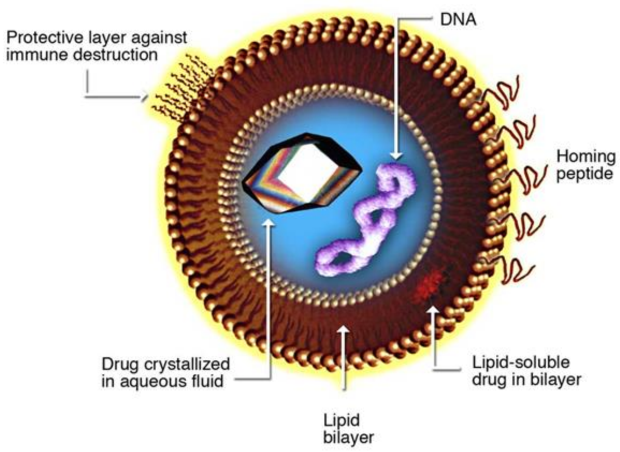

Fig 6. liposome [26].

Liposomes are complex structures composed of phospholipids and can include minor quantities of other molecules. While the size of liposomes can range from a few micrometers to tens of micrometers, unilamellar liposomes, as depicted here, are generally on the smaller end of the scale. They have various targeting ligands on their surface, which allows them to attach to surfaces and accumulate in disease areas for treatment purposes.

C. Microsphere:

These are small spherical particles, with diameters in the micrometer range, used for controlled release of drugs [27].

D. Nano capsules:

Nanocapsules are tiny, shell-like structures made from a harmless polymer. These vesicular systems consist of a polymeric membrane that envelops a nanoscale liquid core. This core is filled with an oil surfactant that is carefully chosen to interact with the encapsulated compound.

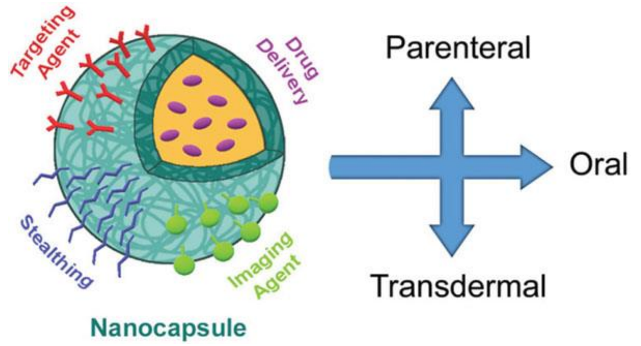

Fig 7. Nano capsules

Nanocapsules used in various fields typically measure between 10 and 1000 nm in size. The shell of a standard nanocapsule is formed by a polymeric membrane or coating. The core of the nanocapsule contains an oil surfactant, which is specifically chosen to interact with the drug enclosed within the polymeric membrane [28].

E. Ethosomes

Ethosomes are nanoscale vesicles made of phospholipids, designed for delivering molecules through the skin. They were first introduced by Touitou et al., in 1997, as innovative lipid carriers consisting of ethanol, phospholipids, and water. They have been found to enhance the delivery of various drugs to the skin.

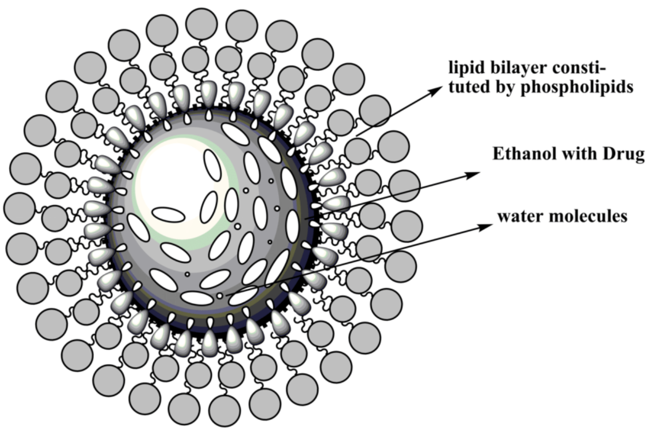

Fig 8. Structure of ethosomes

Primarily, ethosomes are made up of several flexible layers of phospholipid bilayers, with a relatively high concentration of ethanol (20-45%), glycols, and water. Their overall structure has been verified by 31 P-NMR, EM, and DSC. They are known for their high penetration through the stratum corneum of the skin, which improves the permeation of the drugs they encapsulate [29].

F. Transfersomes:

Transfersomes are a kind of vesicular system for drug delivery, designed to improve the penetration capabilities of drugs in a non-invasive way. They were first developed by Cevc et al. in the 1990s. The composition of transfersomes includes phospholipids and an edge activator (EA), a type of

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membrane-softening agent like Tween 80, Span 80, or sodium cholate, which gives transfersomes their ultra-deformable characteristic.

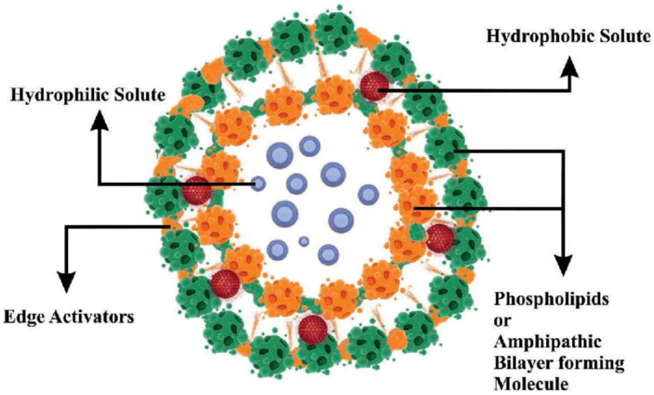

Fig 9. Structure of transfersomes.

The elasticity of transfersomes allows them to deform and pass through narrow pores that are much smaller than their own size, while maintaining their vesicle structure. This unique property helps them bypass the barrier function of the skin's outermost layer. Transfersomes have a bilayer structure that enables the encapsulation of lipophilic, hydrophilic, and amphiphilic drugs, offering higher permeation efficiencies compared to traditional liposomes [30].

G. Nano emulsions:

Nano emulsions are dispersions of two immiscible fluids, typically water-in-oil (w/o) or oil-in-water (o/w), that are kinetically stable and have droplet sizes around 100 nm. These droplets are kept stable by the addition of suitable amphiphilic emulsifiers.

These nanometric-sized emulsions are utilized in various fields including drug delivery, food, cosmetics, pharmaceuticals, and material synthesis. They also serve as model systems for studying nanoscale colloidal dispersions.

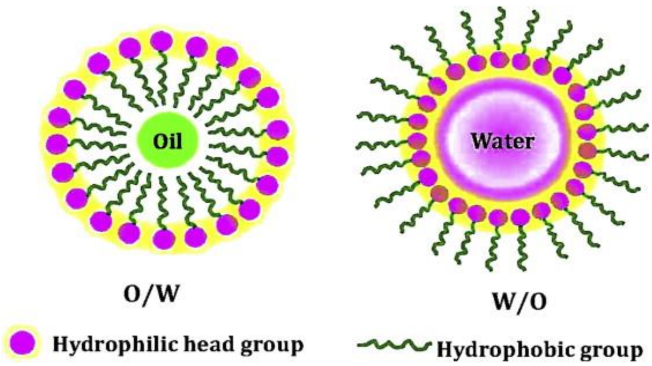

Fig 10. Nano emulsions

The small size of nano emulsions results in beneficial properties such as a large surface area per unit volume, strong stability, a clear appearance, and adjustable rheology. They are prepared using high and low energy methods, which include high pressure homogenization, ultrasonication, phase inversion temperature and emulsion inversion point methods, as well as newer techniques like the bubble bursting method [31].

H. Polymeric Nanoparticles [32-33]

These are nanoparticles made from polymers, used for controlled and targeted delivery of herbal drugs.

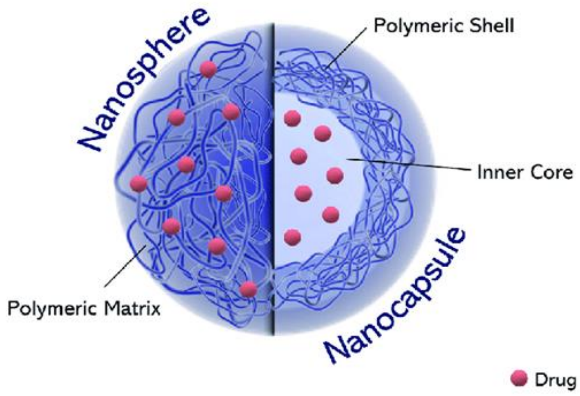

Fig 11. Schematic representation of polymeric nanoparticles as a function of their morphology.

Curcumin, a yellow polyphenol derived from the rhizomes of Curcuma longa, has shown strong antitumor effects in various studies involving human cancer cells and animal carcinogenesis models. This highly potent and non-toxic active ingredient, which is found in turmeric, is used as an alternative medicine for treating a range of disorders. its use in clinical applications is restricted due to its low solubility in water and poor bioavailability.

I. Solid lipid nanoparticles and nanostructured lipid carriers [34]

Solid Lipid Nanoparticles (SLNs), developed in the early 1990s, are a type of colloidal carrier system. They merge the benefits of other colloidal systems like emulsions, liposomes, and polymeric nanoparticles for drug delivery, while reducing or eliminating some of their disadvantages. SLNs are known for their superior physicochemical stability and their ability to protect labile drugs from degradation. Additionally, they can be produced on a large scale with relative ease.

Quercetin, a natural flavonoid, shows increased effectiveness when integrated into lipid carriers. A study by Li et al demonstrated this by incorporating Quercetin, which has low solubility in water, into SLNs (referred to as QU-SLN) using a low-temperature emulsification-solidification method. The process involved mixing QU, glyceryl monostearate, and soy lecithin with a solvent (a 1:1 v/v ratio of chloroform and acetone). The resulting SLNs were spherical and had an average size of 155.3±22.1 nm, which is within the nanoscale range (20–500 nm). In vitro tests showed that QU-SLN had a controlled release. In vivo experiments revealed that the bioavailability of QU-SLN was over five times higher than that of free QU, and it showed improved absorption in the intestine compared to the stomach.

These innovative drug delivery systems have been utilized to address various challenges associated with herbal medicines, such as poor bioavailability, instability in vivo, aqueous insolubility, intestinal absorption, and unspecific site of action. For more comprehensive information, you might want to consult additional resources

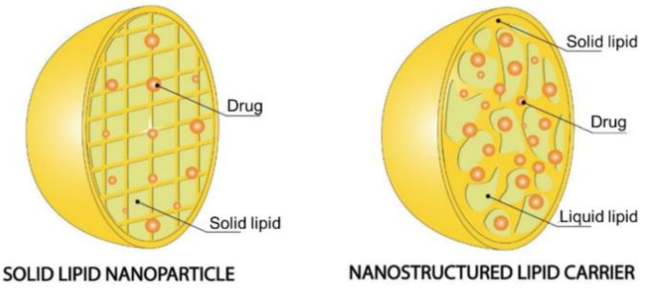

Fig 12. Structural matrix of SLN and NLC. Adapted with permission from

Phytochemical compounds are substances produced by plants, also known as secondary metabolites, that play an important role in traditional medicine. They exhibit variousbiological activities and can be used to treat a range of conditions, from bacterial and fungal infections to chronic.

Table 1. Some Herbal Drug Nanoparticles [35]

Formulation	Active Ingredients	Biological Activity	Method of Preparation
Curcuminoids Solid-Lipid Nananoparticles	Curcuminoids	Anticancer And Antioxidant	Micro-Emulsion Technique
Glycyrrhizin Acid Loaded Nanoparticles	Glycyrrhizin Acid	Anti-Inflammatory Antihypertensive	Rotary-Evaporated Film Ultra Sonication Method
Nanoparticles Of CuscutaChinensis	Flavnoids And Lignans	Heptoprotective And Antioxidant Effect	Nanosuspension Method
Taxel- Loaded Nanoparticles	Taxel	Anticancer	Emulsion Solvent Evaporation Method
ArtemisininNanocapsules	Artemisinin	Anticancer	Self-Assembly Procedure
CPT Encapsulated Nanoparticles	Camptothecin	Anticancer	Dialysis Method
Berberine Loaded Nanoparticles	Berberin	Anticancer	Ionic Gelation Method

These nanotechnology-based drug delivery systems have the potential to significantly enhance the therapeutic efficacy of phytochemical compounds and reduce their side effects. There are still challenges to be addressed, such as the need for more research on the safety and efficacy of these systems, and the need for standardized methods for their production and characterization.

Nanotechnology-based drug delivery systems have been developed to overcome these limitations. These systems function as drug carriers that can increase the bioavailability and bioactivity of phytochemicals.

IV. TECHNIQUES [36-38]

The techniques usually applied for the formulation are:

A. High-Pressure Homogenization Method

In this method, the lipid is subjected to high pressure (ranging from 100 to 2000 bar) and exposed to extreme shear stress. This results in the breakdown of particles to the submicrometer or nanometer scale. The high-pressure homogenization technique is a highly reliable and potent process for large-scale applications.

B. Complex Coacervation Method

Complex coacervation method a spontaneous phase partition practice of two liquid phases in colloidal systems, which outcome by the interference of two oppositely emotional polyelectrolytes upon blending in an aqueous solution.

C. Co-precipitation method

This process is an alteration of the complex coacervation method for the formulation of nanoscale core-shell particles. This technique has been proved to afford good dispersion stability to inadequately water-soluble drugs.

D. Nanoprecipitation method or solvent displacement method

This method operates on the principle of interfacial deposition of a polymer. This occurs after the displacement of a semi-polar solvent, which is miscible with water, from a lipophilic solution. This displacement results in a decrease in the interfacial tension between the two phases, leading to an increase in the surface area. This process subsequently forms small droplets of the organic solvent, even in the absence of mechanical stirring.

E. Solvent emulsification–diffusion method

The method involves creating an oil-in-water (o/w) emulsion. This is done by combining an oil phase, which contains a polymer and oil in an organic solvent, with an aqueous phase that contains a stabilizer. This mixture is then emulsified using a high-shear mixer. Following this, water is added to trigger the transfer of the organic solvent, resulting in the formation of nanoparticles.

F. Supercritical fluid methods

This technique involves the use of a supercritical fluid (SCFs), which can exist as either a liquid or a gas, when used above its critical temperature and pressure points. This method is employed to create formulations of submicrometer and nanometer sizes. Typically, carbon dioxide and water are used as the supercritical fluids in this process.

G. Self-assembly methods

Self-assembly is the physical method in which pre-existing disarranged constituents, atoms, or particles establish themselves into synchronized nanoscale configurations by physical or chemical reactions deprived of the help from any external source.

V. RECENT DEVELOPMENTS [39-41]

Recent developments in nanotechnology have had a significant impact on the field of herbal drugs, particularly in the development of herbal nanomedicine (HNM) delivery systems. These advancements have led to precise drug delivery, reduced toxicity, enhanced activity, and the potential to overcome herb-related problems.

One of the key developments is the use of colloidal nanoparticles (NPs) in the fabrication of herbal nanocarriers. Nanoparticles prepared through herbal extracts, also known as green technology, have shown promising results in terms of biocompatibility and enhanced bioactivities compared to traditional grinding techniques.

Metal nanoparticles, such as silver (Ag) and gold (Au) NPs, have been synthesized using plant extracts as reducing and stabilizing agents. These nanoparticles have demonstrated unique inherent activities, with silver nanoparticles showing germicidal properties against various microbes.

Furthermore, the development of polymeric nanofibers blended with herbal extracts, such as neem (Azadirachta indica), has shown potential for biomedical applications, indicating the versatility of nanotechnology in incorporating herbal components into various delivery systems.

The green synthesis of tellurium nanoparticles (TeNPs) using herbal extracts has also been explored, demonstrating no significant cytotoxic effects towards human dermal fibroblasts at certain concentrations.

Overall, the recent development of nanotechnology in herbal drugs has paved the way for the development of various delivery systems, including polymer nanoparticles, hydrogels, micelles, nanotubes, dendrimers, liposomes, and nanofibers, all of which aim to improve bioavailability, reduce toxicity, and enhance the effectiveness of herbal medicines.

These advancements in nanotechnology have opened up new possibilities for the utilization of herbal components in drug delivery, wound healing, tissue regeneration, and other biomedical applications, marking a significant milestone in the field of herbal medicine.

In conclusion, the recent developments in nanotechnology have provided innovative tools for the release of natural extracts with antimicrobial properties, identified new pathways and targets for wound healing and therapeutics from natural sources, and enabled the development of polydopamine-doped supramolecular chiral hydrogels for tumor recurrence inhibition and enhanced wound repair.

These developments have the potential to revolutionize the field of herbal medicine, offering new opportunities for the utilization of herbal components in advanced drug delivery systems and biomedical applications.

VI. CONCLUSION

The integration of nanotechnology into herbal medicine has shown significant promise in enhancing drug delivery systems, improving bioavailability, and increasing the efficacy of herbal remedies. Using various nanoparticles and formulation techniques, such as polymeric nanoparticles and lipid carriers, targeted and controlled delivery of herbal drugs has become a reality. These advancements not only reduce toxicity but also open up new avenues for utilizing herbal components in diverse biomedical applications beyond traditional medicine. The potential of nanotechnology to revolutionize the field of herbal medicine is evident, offering a comprehensive approach to improving the safety and effectiveness of herbal remedies. As research in this area continues to evolve, the future holds great promise for the development of advanced delivery systems that can further enhance the therapeutic benefits of herbal medicines.

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