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Review Paper

Herbal Bioactives and Nanotechnology: Enhancing Therapeutic Efficacy through Advanced Delivery Systems

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ABSTRACT

Herbal bioactives derived from medicinal plants have long been recognized for their diverse pharmacological activities, including antifungal, anti-inflammatory, antioxidant, and anticancer effects. However, their clinical application is often limited by poor aqueous solubility, low bioavailability, rapid metabolism, and instability under physiological conditions. In recent years, nanotechnology-based drug delivery systems have emerged as a promising strategy to overcome these limitations. The integration of herbal bioactives with nanocarriers such as liposomes, polymeric nanoparticles, nanoemulsions, and metallic nanoparticles has demonstrated significant improvements in therapeutic efficacy, targeted delivery, and controlled release profiles. This review highlights the classification and pharmacological potential of herbal bioactives, discusses the role of nanotechnology in enhancing their performance, and summarizes various nanoformulation approaches along with their mechanisms of action. Additionally, recent advancements, challenges, safety concerns, and future perspectives in the field of nano-herbal therapeutics are critically analyzed. The convergence of phytochemistry and nanotechnology holds immense potential for the development of safer, more effective, and targeted therapeutic systems

INTRODUCTION

Herbal medicine has served as a cornerstone of healthcare systems across the world for centuries, offering a rich repository of biologically active compounds derived from plants. These herbal bioactives, including alkaloids, flavonoids, terpenoids, and phenolic compounds, exhibit a wide spectrum of pharmacological activities. Despite their therapeutic promise, the clinical translation of many phytoconstituents remains

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limited due to inherent challenges such as poor solubility, low permeability, rapid degradation, and variable bioavailability [1].

Nanotechnology has revolutionized the field of drug delivery by enabling the design of nanoscale carriers that can encapsulate bioactive molecules and enhance their pharmacokinetic and pharmacodynamic profiles [2]. The application of nanotechnology in herbal medicine provides an innovative platform to improve the delivery efficiency, stability, and therapeutic outcomes of plant-derived compounds. This review aims to provide a comprehensive overview of herbal bioactives and their integration with nanotechnology-based delivery systems to enhance therapeutic efficacy [3].

Overview of Herbal Bioactives

Herbal bioactives, primarily secondary metabolites, are synthesized by plants as a defense mechanism and represent a cornerstone of traditional healthcare systems [3,4]. These compounds include diverse chemical classes such as alkaloids, flavonoids, tannins, and cardiac glycosides, which possess significant biological activities [5-8]. For instance, the latex of *Calotropis gigantea* is rich in proteolytic enzymes and secondary metabolites like calotropin, which have demonstrated potent inhibitory effects against various fungal pathogens, including *Aspergillus niger* and *Trichoderma viride* [6, 9, 10]. While Asian populations have utilized these extracts for centuries, their modern clinical application is often limited by physiological and chemical barriers [11, 12].

Challenges with Conventional Herbal Formulations

Despite their therapeutic potential, standard herbal formulations face significant pharmacological hurdles:

- **Low Solubility and Bioavailability:** Many phytochemicals, particularly flavonoids and terpenoids, exhibit poor aqueous solubility or are unable to pass through the lipid membranes of cells, resulting in suboptimal systemic absorption [8, 13, 14].

- **Instability:** Bioactive components are frequently prone to physical and chemical degradation, which reduces their pharmacological activity over time [8, 15].

- **Pharmacokinetic Drawbacks:** Crude extracts often suffer from limited absorption, rapid metabolism, and non-targeted delivery, necessitating higher dosages that can lead to undesirable toxic or mutagenic effects [14, 16].

- **Limited Penetration:** In conventional topical agents like standard soaps, large molecular sizes can impede the penetration of active constituents through biological barriers like the stratum corneum or the blood-brain barrier [13, 17].

Role of Nanotechnology in Herbal Drug Delivery

Nanotechnology has emerged as a transformative tool to overcome these limitations by encapsulating herbal ingredients within specialized nanocarriers [18]. By integrating phytomedicine with nanostructured systems, researchers can potentiate the action of plant extracts and ensure a sufficient concentration of active constituents at the preferred site of action [13]. Key delivery systems currently under investigation include:

- **Vesicular Carriers:** These include **liposomes** and **niosomes**, which can encapsulate both hydrophilic and lipophilic molecules, protecting them from degradation in physiological settings [19].

- **Lipid-based Systems: Nanoemulsions**, **solid lipid nanoparticles**, and **nanostructured lipid carriers** are utilized to enhance the solubility of hydrophobic extracts and improve their penetration through the reticuloendothelial system [19].
- **Polymeric Nanoparticles:** These systems provide a stable matrix for the controlled and sustained release of sensitive bioactives, extending their biological effect [15].

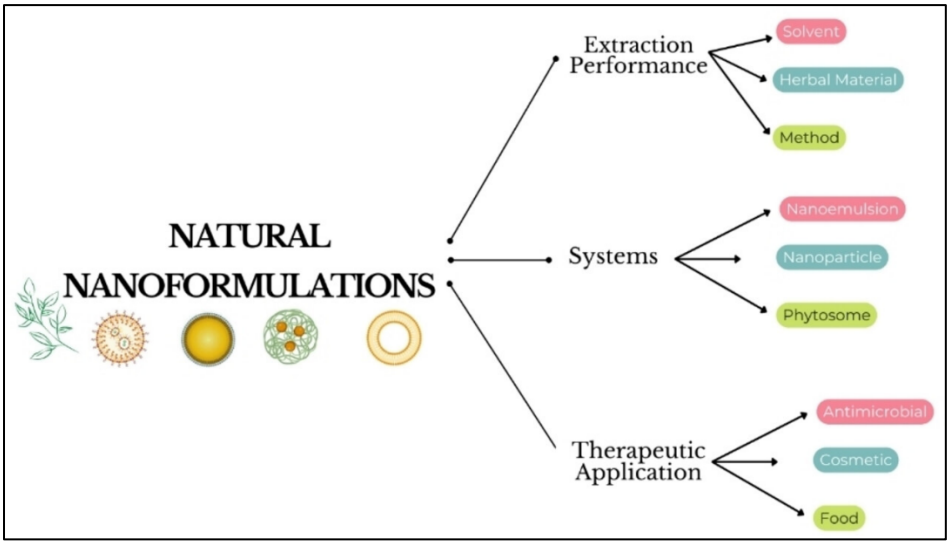

Figure 1. Natural Nanoformulations (https://onlinelibrary.wiley.com)

Advantages of Nano-enabled Delivery Systems

Nano-formulations provide several critical advantages over pure or conventionally formulated herbal drugs:

- **Improved Bioavailability:** Nanoencapsulation enhances the dissolution rate and absorption of poorly soluble phytochemicals, significantly increasing their bioavailability [20].
- **Site-Specific Targeting:** Nanocarriers can be tailored for precise distribution to specific tissues or cells, which is particularly beneficial for treating localized fungal infections or tumors while minimizing exposure to non-targeted areas [19].
- **Enhanced Antimicrobial Potency:** Research indicates that nanoparticles can exert greater inhibitory power against fungi at lower concentrations compared to conventional pure antibiotics or pure herbal extracts [21].
- **Reduced Toxicity:** By enabling lower therapeutic doses and providing a safer, more selective environment for the active substance, these systems reduce the risk of side effects and local skin irritation [20, 22]

2. Herbal Bioactives: Classification and Therapeutic Potential

Herbal bioactives encompass a diverse group of phytochemicals that contribute to the medicinal properties of plants. These compounds can be broadly classified into alkaloids, flavonoids, terpenoids, glycosides, tannins, and phenolic compounds. Each class exhibits distinct chemical characteristics and biological activities [23].

Flavonoids and phenolics are well-known for their antioxidant and anti-inflammatory properties, whereas alkaloids often exhibit potent antimicrobial and anticancer activities. Terpenoids contribute to antifungal and anti-inflammatory effects, while glycosides play a role in cardioprotective and antimicrobial functions. These phytoconstituents have been extensively studied for their therapeutic applications in

conditions such as fungal infections, cancer, cardiovascular diseases, and inflammatory disorders [24].

However, the therapeutic effectiveness of these bioactives is frequently compromised by poor water solubility, instability under physiological conditions, rapid first-pass metabolism, and inconsistent absorption. These limitations necessitate the development of advanced delivery systems to maximize their clinical potential [25].

3. Nanotechnology in Drug Delivery: An Overview

Nanotechnology involves the manipulation of materials at the nanoscale (1–100 nm) to create systems with unique physicochemical properties. In drug delivery, nanocarriers serve as vehicles that can encapsulate, protect, and transport bioactive compounds to targeted sites within the body [26].

The advantages of nanotechnology-based delivery systems include enhanced solubility, improved bioavailability, controlled and sustained drug release, and targeted delivery [27]. Additionally, the enhanced permeability and retention (EPR) effect allows nanoparticles to accumulate preferentially in diseased tissues, particularly in tumors and inflamed areas. These properties make nanotechnology an ideal approach for overcoming the limitations associated with conventional herbal formulations [2].

4. Types of Nanocarriers for Herbal Bioactives

A variety of nanocarriers have been developed to improve the delivery of herbal bioactives. Lipid-based systems such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are widely used due to their biocompatibility and ability to encapsulate both hydrophilic and lipophilic compounds [22].

Polymeric nanoparticles, prepared from natural polymers like chitosan or synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), offer controlled release and enhanced stability. Nanoemulsions and microemulsions are particularly effective in improving the solubility and dermal penetration of hydrophobic phytoconstituents [28].

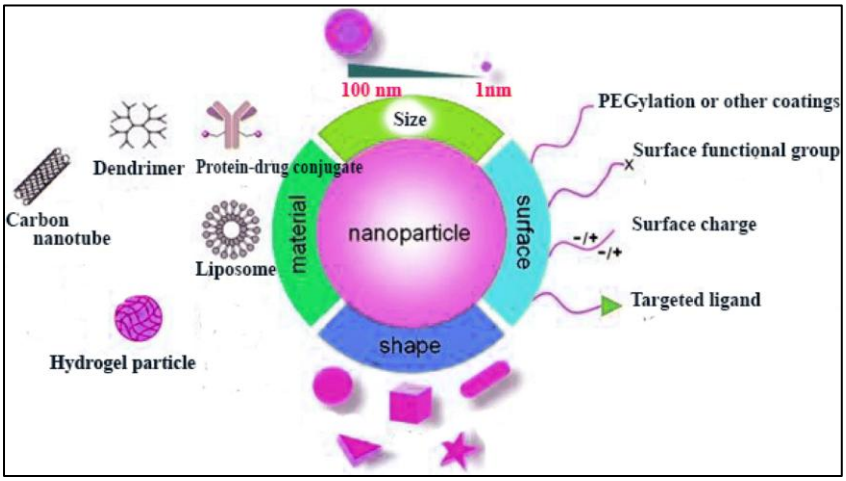

Figure 2. Types of Nanocarriers for Herbal Bioactives [https://link.springer.com/article/10.1186]

Metallic nanoparticles, including silver and gold nanoparticles, have gained attention due to their intrinsic antimicrobial properties and potential for green synthesis using plant extracts. Vesicular systems such as phytosomes, niosomes, and transferosomes further enhance the bioavailability and permeability of herbal compounds, particularly for topical and transdermal applications [29].

5. Preparation and Characterization of Nanoformulations

The preparation of nanoformulations involves various techniques such as solvent evaporation, nanoprecipitation, high-pressure homogenization, and ultrasonication. Green synthesis approaches utilizing plant extracts have also gained popularity due to their eco-friendly and cost-effective nature [30].

Characterization of nanoformulations is essential to ensure their quality, stability, and performance. Key parameters include particle size, zeta potential, morphology, drug entrapment efficiency, and in vitro release profile [31, 32]. Advanced analytical techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and dynamic light scattering (DLS) are commonly employed [31].

6. Mechanisms for Enhanced Therapeutic Efficacy

Nanocarriers enhance the therapeutic efficacy of herbal bioactives through multiple mechanisms. Encapsulation improves solubility and protects bioactives from degradation. The small size of nanoparticles facilitates better cellular uptake and penetration across biological barriers [33].

Targeted delivery systems can direct the bioactive compounds to specific tissues or cells, thereby reducing off-target effects and toxicity. Controlled and sustained release profiles maintain therapeutic drug concentrations over extended periods, improving treatment outcomes. Additionally, nanocarriers can enhance the interaction of bioactives with microbial cells, leading to improved antimicrobial and antifungal activity [34].

7. Applications of Herbal Nanocarriers

Herbal nanocarriers have demonstrated significant potential across various therapeutic areas. In antifungal therapy, nanoformulations of plant extracts have shown enhanced activity against pathogens such as *Candida*, *Aspergillus*, and dermatophytes, making them highly relevant for topical formulations like creams, gels, and soaps [35].

In oncology, nano-encapsulated phytoconstituents such as curcumin have exhibited improved tumor targeting and anticancer efficacy. Anti-inflammatory and antioxidant applications benefit from sustained release and improved bioavailability of herbal compounds [14]. In dermatology, nanoformulations are increasingly used for treating conditions such as acne, psoriasis, and wound healing.

8. Recent Advances in Nano-Herbal Therapeutics

Recent research has focused on the development of advanced nano-herbal systems with improved functionality. For instance, curcumin-loaded nanoparticles have demonstrated enhanced bioavailability and therapeutic efficacy in cancer and inflammatory diseases. Neem-based nanoformulations have shown potent antimicrobial and antifungal activity [36].

Emerging studies on plant-based nanoparticles synthesized using green methods highlight the potential of eco-friendly approaches. Additionally, nanoformulations incorporating medicinal plants such as *Calotropis gigantea* have shown promising antifungal and anti-inflammatory effects, indicating their potential for pharmaceutical applications [37].

CONCLUSION

The integration of herbal bioactives with nanotechnology-based delivery systems represents a promising strategy to overcome the limitations associated with conventional herbal formulations. Nano-herbal systems offer enhanced solubility, stability, bioavailability, and targeted delivery, leading to improved therapeutic efficacy. Despite

existing challenges, ongoing advancements in nanotechnology and pharmaceutical sciences are expected to drive the development of safe, effective, and clinically viable herbal nanomedicines.

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