IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Advances In Nanotechnology For Herbal Drug Delivery: A Comprehensive Review

Shashank R. Dudhe[1*], Dr. Gopal R. Sitaphale[2], Dr. Purushottam R. Laddha[3], Kishor B. Charhate[4], Dr. Prafulla R Tathe[5]

[1]M. Pharm Student, Department of Pharmacognosy, Samarth College of pharmacy, Deulgaon Raja, Buldhana
[2]Professor, Department of Pharmacognosy, Samarth College of pharmacy, Deulgaon Raja, Buldhana
[3]Professor, Department of Pharmaceutical Chemistry Samarth College of pharmacy, Deulgaon Raja, Buldhana
[4]Associate Professor, Department of Pharmaceutics, Samarth College of pharmacy, Deulgaon Raja, Buldhana
[5]Principal, Department of Pharmacology, Samarth College of pharmacy, Deulgaon Raja, Buldhana

Abstract:

Herbal medicines have been widely used around the world since ancient times. The advancement of phytochemical and phytopharmacological sciences has enabled elucidation of the composition and biological activities of several medicinal plant products. The effectiveness of many species of medicinal plants depends on the supply of active compounds. Most of the biologically active constituents of extracts, such as flavonoids, tannins, and terpenoids, are highly soluble in water but have low absorption because they are unable to cross the lipid membranes of the cells, have excessively high molecular size, or are poorly absorbed, resulting in loss of bioavailability and efficacy. Some extracts are not used clinically because of these obstacles. It has been widely proposed to combine herbal medicine with nanotechnology because nanostructured systems might be able to potentiate the action of plant extracts, reducing the required dose and side effects, and improving activity. Nanosystems can deliver the active constituent at a sufficient concentration during the entire treatment period, directing it to the desired site of action. Conventional treatments do not meet these requirements. The purpose of this study is to review nanotechnology-based drug delivery systems and herbal medicines. This study explores the synergistic potential of nanotechnology and herbal drugs in the field of disease therapy. By combining the targeted delivery capabilities of nanocarriers with the therapeutic properties of herbal compounds, this approach aims to enhance treatment efficacy while minimizing side effects. The investigation involves the development of novel nanocarrier systems for herbal drug encapsulation and delivery to target cells. The study further evaluates the bioavailability, cytotoxicity, and overall therapeutic impact of this integrated approach, offering promising insights into a potentially potent and more sustainable treatment strategy.

Keywords: Herbal medicines, phytopharmacology, bioavailability, nanotechnology, nanocarriers, herbal drug delivery, nanostructured systems, cytotoxicity.

I. INTRODUCTION

The WHO has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, and are still in use today. Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous systems of medicine. Traditional preparations comprise medicinal plants, minerals, and organic matter. Herbal drugs constitute only those traditional medicines that primarily use medicinal plant preparations for therapy. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman, and Syrian texts dates back to about 5000 years. The classical Indian texts include Rigveda, Atharvaveda, Charak Samhita, and Sushruta Samhita. The convergence of rich knowledge from different traditional systems of medicine can lead to new avenues in the herbal drug discovery process.

The combination of herbal medicine with nanotechnology has become a promising strategy for drug delivery. Using modern techniques, herbal drugs can provide novel molecular probes. It is now possible to explore the mechanisms of action of herbal drugs in terms of modern molecular pharmacology. Nanotechnology is defined as an applied science and technology that aims to develop devices and dosage forms in the range of 1 to 100 nm. The applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems have recently been referred to as nanomedicine. Nanosystems enable the active constituent to be delivered at a sufficient concentration throughout the entire treatment period, directing it to the desired site of action, a feature that conventional treatments fail to achieve.Most of the biologically active constituents of herbal extracts, such as flavonoids, tannins, and terpenoids, are highly water-soluble but exhibit low absorption because they are unable to cross lipid membranes, have high molecular sizes, and demonstrate poor absorption, resulting in loss of bioavailability and efficacy. Some studies have shown that while herbal medicines exhibit good activity in vitro, these effects are not always reproducible in vivo. Additionally, microspheres and liposomes have been widely explored for their drug delivery potential. Although most research has focused on microspheres, liposomes and gels have been limited to the delivery of macromolecules such as insulin and growth hormones.

Several nanotechnological strategies, such as polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursor systems for liquid crystals (PSLCs), liposomes, and microemulsions, have attempted to overcome these barriers. These systems allow substances with different properties to be incorporated into the same formulation and may even modify the properties and behavior of the active constituent in a biological environment. These technological advancements have revolutionized drug delivery. The new drug delivery systems not only increase the effectiveness of active components but also facilitate the reintroduction of additional components that aid in drug delivery, ultimately enhancing drug efficacy and therapeutic outcomes.

II. HISTORY AND DEVELOPMENT

Since ancient times, natural products, including plants, have been the basis of treatment for human diseases. The concept of modern medicine remains deeply rooted in traditional medicine and therapies. In different parts of the world, such as ancient China, Egypt, Africa, America, and India, plants were used for medicinal purposes long before recorded history. The earliest chemical analyses of medicinal plants became available in the early 19th century, leading to the extraction and modification of herbal ingredients. For a long time, herbal medicines were not considered for development into novel formulations due to a lack of scientific justification and processing challenges, including standardization, extraction, and identification of individual drug components in complex polyherbal systems. However, advancements in phytopharmaceutical research have addressed these challenges, enabling the scientific validation of herbal medicines and their integration into modern medicine. The development of novel formulations, such as nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, and SLNs, has significantly improved the efficacy and bioavailability of herbal drugs. Innovative nanotechnological approaches, including nanomicellar systems, nanotubes, and colloidal nanogels, have been developed to enhance the therapeutic effects of herbal compounds. For example, nanocarriers for curcumin have been designed for use alone or in combination with chemotherapeutic agents such as paclitaxel, improving drug delivery and efficacy.

These advancements have led to the exploration of nanotechnology-based delivery systems to overcome the limitations of conventional herbal formulations, opening new avenues for the development of effective and targeted therapies.

Need for Novel Drug Delivery Systems: Nanocarriers for Herbal Remedies

Herbal medicines contain bioactive compounds that offer therapeutic benefits. However, many of these compounds face challenges before reaching systemic circulation. They may degrade in the highly acidic environment of the stomach or undergo extensive metabolism in the liver, reducing their bioavailability. Consequently, an insufficient amount of the drug may reach the target site at the minimum effective concentration, leading to reduced or no therapeutic effect. Nanocarrier-based drug delivery systems can enhance the bioavailability of herbal drugs by protecting them from degradation, bypassing metabolic barriers, and ensuring sustained release. Due to their small size, nanocarriers facilitate prolonged circulation in the bloodstream, improving drug efficacy and reducing side effects.

Advantages of Herbal Nanoparticle Delivery Systems

- **Targeted Drug Delivery:** Nanocarriers enhance drug accumulation at disease sites due to their unique size and high loading capacities.
- **Enhanced Drug Absorption:** The small particle size increases the surface area of the drug, leading to faster dissolution and improved absorption.
- **Enhanced Permeation and Retention (EPR) Effect:** Nanoparticles exhibit enhanced permeation through biological barriers and increased retention at target sites due to poor lymphatic drainage, especially in tumors.
- **Passive Targeting:** These systems enable drug delivery to specific sites without requiring additional ligand modifications.
- **Reduced Side Effects:** Nanocarriers lower the incidence of adverse effects by improving drug selectivity and reducing off-target accumulation.
- **Lower Drug Dosage Requirement:** The improved bioavailability allows for reduced drug dosages while maintaining therapeutic efficacy.

III. NANOCARRIERS FOR HERBAL DRUG DELIVERY

Nanocarrier systems play a crucial role in enhancing the delivery of herbal bioactives by improving their solubility, bioavailability, and targeted delivery. These advanced drug delivery platforms protect herbal constituents from degradation, ensure controlled release, and enhance therapeutic efficacy. Below are some of the key nanocarriers utilized in herbal drug delivery:

Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers that encapsulate both hydrophilic and lipophilic herbal bioactives. They provide a protective barrier, preventing degradation caused by enzymes, pH changes, and environmental factors. The advantages of liposomal formulations include:

- Enhanced solubility of poorly water-soluble herbal extracts.
- Improved cellular uptake and bioavailability.
- Prolonged circulation time, leading to sustained drug release.

Recent studies have demonstrated the effectiveness of liposomal formulations in improving the therapeutic outcomes of herbal drugs, particularly in cancer therapy. For example, curcumin-loaded liposomes have shown increased anticancer activity due to enhanced cellular uptake and bioavailability.

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are solid, biodegradable nanocarriers composed of natural or synthetic polymers such as chitosan, polylactic-co-glycolic acid (PLGA), and alginate. They offer controlled and sustained release of herbal drugs, enhancing their therapeutic potential. The key benefits of polymeric nanoparticles include:

- Controlled drug release: Ensures prolonged therapeutic effects.
- Improved stability: Protects herbal bioactives from premature degradation.
- Targeted drug delivery: Functionalized PNPs can be modified for site-specific drug release.

Several preclinical and clinical studies have demonstrated the efficacy of polymeric nanoparticles in delivering herbal drugs for cancer treatment, neurological disorders, and inflammatory diseases. For instance, chitosan nanoparticles loaded with resveratrol have exhibited enhanced antioxidant and anticancer activity.

Dendrimers

Dendrimers are highly branched, nanoscale polymeric structures that enable efficient drug loading and targeted delivery of herbal bioactives. Their unique architecture provides:

- High drug encapsulation efficiency due to multiple functional groups.
- Enhanced pharmacokinetics by improving solubility and bioavailability.
- Reduced toxicity compared to conventional drug carriers.

Herbal bioactives incorporated into dendrimer-based systems have demonstrated improved therapeutic outcomes. For example, dendrimer-encapsulated quercetin has shown superior anti-inflammatory and anticancer effects compared to its free form.

Nanogels

Nanogels are cross-linked, three-dimensional hydrogel networks that possess high water content, making them ideal for the encapsulation and controlled release of herbal drugs. Their advantages include:

- Biocompatibility and biodegradability**,** reducing toxicity concerns.
- Stimuli-responsive behavior**,** allowing site-specific drug release based on pH, temperature, or enzyme activity.
- Effective transdermal and mucosal delivery**,** making them suitable for topical and oral applications.

Nanogels have been extensively studied for herbal drug delivery, particularly for wound healing, anti-inflammatory treatments, and cancer therapy. For example, curcumin-loaded nanogels have exhibited prolonged retention and enhanced wound healing properties.

IV. TYPES OF NANOPARTICLES IN HERBAL DRUG DELIVERY

Nanotechnology has revolutionized herbal drug delivery by enhancing the bioavailability, stability, and targeted release of phytoconstituents. Various types of nanoparticles are utilized for efficient drug delivery, each offering unique advantages. Below is a detailed description of different types of nanoparticles used in herbal drug delivery:

- Polymeric Nanoparticles
- Solid Lipid Nanoparticles
- Magnetic Nanoparticles
- Metal and Inorganic Nanoparticles
- Quantum Dots
- Polymeric Micelles
- Phospholipid Micelles
- Colloidal Nano-Liposomes
- Dendrimers
- Nanocrystals
- Nanospheres
- Nanocapsules

1. Polymeric Nanoparticles

Polymeric nanoparticles are biodegradable and biocompatible carriers made from natural or synthetic polymers such as chitosan, alginate, PLGA (poly(lactic-co-glycolic acid)), and gelatin. These nanoparticles can encapsulate herbal extracts and provide controlled and sustained drug release, improving therapeutic efficacy.

Advantages:

- Enhanced solubility of poorly water-soluble herbal compounds
- Controlled and targeted drug release
- Protection from enzymatic degradation

2. Solid Lipid Nanoparticles (SLNs)

SLNs are composed of solid lipids that remain in a solid state at room temperature. They serve as effective carriers for hydrophobic herbal compounds, enhancing their bioavailability and stability.

Advantages:

- Improved permeability and absorption
- Reduced toxicity and side effects
- Controlled drug release

3. Magnetic Nanoparticles

Magnetic nanoparticles are composed of iron oxide-based materials, which enable drug targeting using an external magnetic field. These are often used in cancer therapy and imaging.

Advantages:

- Site-specific drug delivery
- Non-invasive targeting through a magnetic field
- Enhanced accumulation at diseased sites

4. Metal and Inorganic Nanoparticles

These nanoparticles include gold, silver, silica, and zinc oxide nanoparticles. They have potent antimicrobial, antioxidant, and anticancer properties, making them useful for herbal drug delivery.

Advantages:

- High stability and surface functionalization
- Strong antimicrobial and anticancer activities
- Can be used for diagnostic and therapeutic purposes

5. Quantum Dots (QDs)

Quantum dots are semiconductor nanocrystals with unique optical properties. They are used in imaging and diagnostics, along with drug delivery applications.

Advantages:

- High fluorescence for bioimaging
- Enhanced stability and tracking of herbal drugs
- Potential for theranostic applications (therapy + diagnostics)

6. Polymeric Micelles

Polymeric micelles are amphiphilic block copolymers that self-assemble in aqueous solutions, forming a hydrophobic core and hydrophilic shell. They enhance the solubility of hydrophobic herbal drugs.

Advantages:

- Increased bioavailability of poorly soluble drugs
- Stability in biological fluids
- Controlled and prolonged drug release

7. Phospholipid Micelles

These micelles are composed of phospholipids, which improve the solubility and stability of herbal extracts. They are widely used for delivering lipophilic drugs.

Advantages:

- Mimic biological membranes for better absorption
- Enhanced drug stability and bioavailability
- Suitable for oral and intravenous administration

8. Colloidal Nano-Liposomes

Nano-liposomes are spherical vesicles composed of lipid bilayers that encapsulate both hydrophilic and lipophilic drugs. They enhance the bioavailability and stability of herbal formulations.

Advantages:

- Efficient encapsulation of herbal bioactives
- Reduced degradation and enhanced absorption
- Targeted drug delivery to specific tissues

9. Dendrimers

Dendrimers are branched, tree-like macromolecules with a high degree of surface functionality, allowing multiple drug molecules to be attached. They offer precise drug delivery.

Advantages:

- High drug-loading capacity
- Controlled and targeted drug release
- Enhanced solubility and bioavailability

10. Nanocrystals

Nanocrystals are pure drug nanoparticles stabilized with surfactants or polymers. They improve the dissolution rate and bioavailability of poorly water-soluble herbal drugs.

Advantages:

- Enhanced drug solubility and bioavailability
- Rapid absorption and onset of action
- Suitable for oral, intravenous, and topical applications

11. Nanospheres

Nanospheres are solid, spherical particles in which the drug is uniformly dispersed. They provide controlled drug release and improve the stability of herbal bioactives.

Advantages:

- Sustained drug release
- Protection of herbal compounds from degradation
- Enhanced therapeutic efficacy

12. Nanocapsules

Nanocapsules are vesicular systems with a core-shell structure, where the herbal drug is confined in an oily or aqueous core surrounded by a polymeric shell.

Advantages:

- Targeted drug delivery
- Reduced toxicity and side effects
- Protection from enzymatic degradation

Nanocarrier-based drug delivery systems hold significant promise for improving the therapeutic potential of herbal medicines. By overcoming biological barriers, enhancing bioavailability, and ensuring targeted drug delivery, these systems can revolutionize the field of herbal therapeutics and personalized medicine.

Table 1: List of Some Herbal Drugs Used in Cancer Therapy

Sr. No	Common Name	Botanical Name	Active Constituents	Part Used	Family
1	Rauwolfia	Rauwolfia serpentina	Reserpine	Root	Apocynaceae
2	Picrorhiza	Picrorhiza kurroa	Picroside I, II, III	Rhizome, Root	Scrophulariaceae
3	Liquorice	Glycyrrhiza glabra	Glycyrrhizine	Rhizome, Root	Fabaceae
4	Meadow Saffron	Colchicum luteum	Colchicine	Corm	Liliaceae
5	Cinchona	Cinchona officinalis	Cinchonine	Bark	Rubiaceae
6	Pacific Yew	Taxus brevifolia	Paclitaxel	Bark, Leaves	Taxaceae
7	Indian Ipecac	Tylophora indica	Emetine, Cephaeline	Root, Leaf	Asclepiadaceae
8	Tobacco	Nicotiana tabacum	Nicotine	Plant leaves	Solanaceae
9	Mint	Mimosa pudica	Vitamin C	Whole plant	Mimosaceae
10	Lemon	Citrus medica	Citral, Limonene	Root	Rutaceae
11	Senna	Cassia senna	Sennoside A, Sennoside B	Leaves	Caesalpinaceae
12	Indian Aloe	Aloe barbadensis	Aloin, Barbaloin, Isobarbaloin	Leaves	Liliaceae
13	Amla	Emblica officinalis	Polyphenols, Flavones, Tannins	Fruit	Euphorbiaceae
14	Turmeric	Curcuma longa	Curcumin	Rhizome	Zingiberaceae

V. ADVANTAGES OF NANOTECHNOLOGY IN HERBAL MEDICINE

The integration of nanotechnology in herbal medicine has revolutionized drug delivery by addressing key challenges associated with conventional herbal formulations. Nanocarrier-based systems enhance the therapeutic efficacy of herbal drugs while minimizing limitations such as poor solubility, low bioavailability, and rapid degradation. Below are the major advantages of using nanotechnology in herbal medicine:

1. Enhanced Solubility and Bioavailability

Many herbal bioactives, such as flavonoids, tannins, and terpenoids, exhibit poor water solubility, which limits their absorption in the body. Nanotechnology-based drug delivery systems, such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles, enhance the solubility of these compounds, facilitating their absorption across biological membranes. This leads to improved systemic bioavailability and increased therapeutic efficacy.

2. Protection from Enzymatic Degradation

Herbal compounds often undergo rapid enzymatic degradation in the gastrointestinal tract or liver, leading to reduced bioactivity. Nanocarriers provide a protective shield around the bioactive molecules, preventing premature degradation by enzymes and enhancing the stability of the active ingredients. This ensures that the drug reaches the target site in its active form, maintaining its potency over an extended period.

3. Targeted and Controlled Drug Release

Nanotechnology allows for the development of targeted drug delivery systems, ensuring that the active herbal constituents reach specific diseased tissues or cells with high precision. Functionalized nanoparticles, such as ligand-conjugated nanocarriers, enable site-specific delivery, reducing off-target effects. Additionally, controlled-release mechanisms in nanosystems provide a sustained release of bioactives over time, maintaining optimal therapeutic levels in the body.

4. Reduced Toxicity and Side Effects

Traditional herbal formulations may cause toxicity due to high doses or non-specific distribution within the body. Nanotechnology enables precise drug delivery at the desired site of action, reducing systemic toxicity. By optimizing drug concentration at the target site while minimizing exposure to healthy tissues, nanocarriers help mitigate adverse effects, making herbal therapies safer for long-term use.

5. Improved Patient Compliance

Nanotechnology-based formulations offer enhanced therapeutic benefits while minimizing dosing frequency. The sustained and controlled release of herbal drugs reduces the need for frequent administration, improving patient adherence to treatment regimens. Additionally, the non-invasive nature of some nano-formulations, such as microneedles and transdermal patches, enhances patient comfort and acceptance.

VI. CHALLENGES AND FUTURE PROSPECTS

Despite the numerous advantages of integrating nanotechnology with herbal medicine, several challenges must be addressed to ensure its successful clinical application. Key challenges include:

- Large-Scale Production: The synthesis of herbal nanoparticles at an industrial scale remains a significant hurdle due to complex fabrication techniques, high production costs, and the need for reproducibility.
- Regulatory Approval: Stringent regulatory requirements for nanomedicine demand extensive safety, efficacy, and stability assessments, making the approval process time-consuming and resource-intensive.
- Potential Toxicity**:** While nanocarriers enhance drug delivery, their long-term toxicity, biocompatibility, and impact on human health require further investigation through rigorous preclinical and clinical studies.
- Standardization and Stability: Variability in herbal extracts and their nanoformulations can affect consistency, requiring standardization of extraction, formulation, and storage conditions.

Future Prospects

To overcome these challenges, future research should focus on:

- Developing Cost-Effective and Scalable Production Methods: Advancements in green nanotechnology and sustainable manufacturing approaches can help reduce costs and improve large-scale synthesis.
- Ensuring Biocompatibility and Safety: The design of nanocarriers using biodegradable and non-toxic materials will enhance their safety profile while minimizing adverse effects.
- Clinical Evaluations and Regulatory Compliance: Extensive clinical trials and regulatory harmonization will be essential for validating the efficacy and safety of herbal nanomedicines before market approval.
- Personalized and Targeted Therapies: Innovations in nanomedicine, such as stimuli-responsive and targeted drug delivery systems, can further improve treatment outcomes in cancer and other diseases.

VII. CONCLUSION

The integration of nanotechnology with herbal medicine offers a promising solution to overcome the challenges associated with the bioavailability and therapeutic efficacy of medicinal plant products. This study highlights the potential of nanosystems in delivering active herbal constituents at targeted concentrations throughout the treatment period, particularly in cancer therapy. By developing advanced nanocarrier systems, this approach aims to enhance treatment efficacy while minimizing side effects, contributing to a more sustainable and potent cancer treatment strategy.

The historical foundation of herbal medicine, combined with cutting-edge advancements in nanotechnology, showcases the transformation of traditional remedies into scientifically validated formulations. This evolution not only addresses issues like poor bioavailability and inconsistent efficacy of herbal extracts but also enables precise drug delivery using nanocarrier systems. This review underscores the historical significance of herbal medicine while emphasizing recent breakthroughs in nanotechnology, highlighting the synergy between the two in modern drug delivery systems. The advantages of herbal nanoparticle-based drug delivery, such as enhanced drug concentration at disease sites, improved stability, and reduced toxicity, make them a compelling alternative for improving therapeutic outcomes. A comprehensive analysis of various nanocarrier types and an extensive compilation of herbal drugs used in cancer therapy contribute to a deeper understanding of this innovative approach. Overall, this study provides valuable insights into the potential of combining nanotechnology with herbal medicine, paving the way for more effective, targeted, and sustainable treatment strategies in the future.

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