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A REVIEW ON NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR HERBAL MEDICINES: RECENT ADVANCES, CHALLENGES, AND FUTURE PERSPECTIVES

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ABSTRACT

Because of their many pharmacological actions and good safety profiles, herbal medicines have been an essential part of healthcare systems all over the world for centuries. Polyphenols, flavonoids, alkaloids, terpenoids, and glycosides are among the many phytoconstituents that have substantial therapeutic promise against metabolic syndromes, cancer, inflammatory illnesses, cardiovascular diseases, neurological conditions, and microbial infections. However, because to their poor aqueous solubility, low gastrointestinal absorption, quick metabolism, instability under physiological conditions, extensive first-pass metabolism, and lack of target selectivity, many herbal bioactive substances still have limited clinical translation. These restrictions often lead to variable therapeutic results and decreased bioavailability. Drug delivery technologies based on nanotechnology have shown promise as ways to get over these obstacles. Phytochemicals' physicochemical stability is increased by nano-sized carriers, which also improve permeability and solubility, extend systemic circulation, enable regulated and site-specific drug release, and reduce systemic toxicity. The therapeutic efficacy of herbal medicines has been shown to be significantly enhanced by a

variety of nanocarriers, including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, phytosomes, nanoemulsions, dendrimers, polymeric micelles, and metallic nanoparticles.

Recent advances in nanomedicine have made it possible to create multifunctional delivery systems that can be used for theranostic applications, combination therapy, stimuli-responsive release, and targeted drug delivery. Furthermore, a number of issues pertaining to environmental sustainability and nanotoxicity have been resolved by developments in green synthesis methods and biodegradable nanomaterials. Regulatory obstacles, manufacturing scalability, quality control, and long-term safety evaluation are still crucial factors to take into account prior to widespread clinical deployment, notwithstanding notable advancements.

The limitations of traditional herbal drug delivery, different nanotechnology-based delivery platforms, mechanisms of enhanced drug delivery, characterization methods, therapeutic applications, toxicological considerations, regulatory viewpoints, and recent developments in nano-herbal formulations are all thoroughly covered in this review. Future research avenues that focus on translargetable nanomedicine, AI-assisted formulation development, and customized medicine are also highlighted.

KEYWORDS: Herbal medicines, Nanotechnology, Nanoparticles, Phytochemicals, Drug delivery systems, Nanoformulations, Liposomes, Phytosomes, Solid lipid nanoparticles, Targeted drug delivery.

1. INTRODUCTION

For thousands of years, herbal remedies have been an essential part of both traditional and contemporary healthcare systems. For primary healthcare, almost 80% of the world's population depends in part on medicinal plants, especially in underdeveloped nations where traditional medicine is still very important. Because of their wide range of pharmacological actions, comparatively low frequency of side effects, and growing acceptability as complementary or alternative treatments, plant-derived therapies are gaining popularity.

Many physiologically active phytochemicals, such as flavonoids, alkaloids, phenolic acids, tannins, terpenoids, lignans, saponins, glycosides, and polysaccharides, are found in medicinal plants. Antioxidant, anti-inflammatory, antibacterial, antiviral, hepatoprotective, neuroprotective, cardioprotective, antidiabetic, and anticancer activities are all demonstrated

by these naturally occurring substances. Curcumin from Curcuma longa, berberine from Berberis vulgaris, resveratrol from grapes, quercetin from apples and onions, green tea's epigallocatechin gallate (EGCG), thymoquinone from Nigella sativa, and silymarin from Silybum marianum are notable examples. Numerous preclinical studies have validated these phytoconstituents' therapeutic potential against a variety of chronic illnesses.

Unfavorable physicochemical and biological characteristics sometimes undermine the clinical efficacy of herbal medications, despite their promising pharmacological actions. The majority of phytochemicals have a short biological half-life, high first-pass metabolism, quick elimination, chemical instability, limited membrane permeability, poor water solubility, and sensitivity to enzyme degradation. As a result, treatment efficacy is limited and repeated or higher dosing is required because only a tiny portion of the delivered dose reaches the target area. Inconsistent clinical results are further exacerbated by variations in phytochemical composition brought forth by geographic origin, growth circumstances, harvesting methods, and extraction procedures.

Nanotechnology has become a revolutionary solution to these problems. Although many pharmacological nanocarriers are typically between 10 and 200 nm in size, nanotechnology involves the design, production, and application of materials with dimensions ranging from around 1 to 1000 nm. Nanocarriers have special physicochemical qualities that allow for effective encapsulation, protection, and targeted distribution of bioactive substances because of their small particle size, large surface-area-to-volume ratio, and adjustable surface characteristics.

Nano-based delivery systems offer several benefits over conventional dosage forms. Nanoparticle-encapsulated phytochemicals are protected from chemical and enzymatic degradation during storage and after administration. Particle size reduction improves oral bioavailability by significantly increasing the rate of gastrointestinal absorption and dissolution. Surface modification using polymers, ligands, antibodies, peptides, or polysaccharides allows for active targeting to diseased tissues while lowering off-target toxicity. Controlled and extended pharmaceutical release reduces dose frequency and increases patient compliance. Furthermore, some nanocarriers can pass through biological barriers like the blood-brain barrier, which makes it feasible to treat neurological disorders that would otherwise be difficult to treat.

Many nanocarrier platforms for the delivery of herbal drugs have been created throughout the last 20 years. Excellent stability and controlled release properties are offered by polymeric nanoparticles. Both hydrophilic and lipophilic phytochemicals are effectively encapsulated by liposomes, which have a high biocompatibility. The benefits of lipid compatibility are combined with enhanced drug loading capacity and long-term stability in solid lipid nanoparticles and nanostructured lipid carriers. Through phospholipid complexation, phytosomes greatly increase the membrane permeability of polyphenolic substances. Dendrimers and polymeric micelles provide targeted administration and combination therapy, whereas nanoemulsions enhance the oral absorption of lipophilic phytoconstituents. Due to their inherent antibacterial and anticancer properties, metallic nanoparticles made from plant extracts have also garnered a lot of interest.

Recent developments in technology, such as stimuli-responsive nanocarriers, intelligent drug delivery systems, multifunctional nanoparticles, and theranostic platforms that may diagnose and treat patients simultaneously, have further broadened the application of nano-herbal medicine. In order to speed up optimization and lower development costs, nanoformulation design is increasingly incorporating artificial intelligence, machine learning, and computational modeling. While reducing the toxicity of nanoparticles, green nanotechnology that uses biodegradable polymers and plant-mediated synthesis has also enhanced environmental sustainability.

Clinical translation is nevertheless hampered by a number of issues despite these impressive developments. Reproducibility, long-term stability, quality control, pharmacovigilance, regulatory harmonization, large-scale production, and thorough toxicological evaluation continue to be important issues. For nano-herbal compositions to be successfully commercialized, standardized procedures for characterization, efficacy assessment, and safety evaluation are crucial.

With a focus on recent scientific advancements, formulation strategies, characterization techniques, therapeutic applications, regulatory considerations, and future research directions, this review attempts to give a thorough overview of nanotechnology-based drug delivery systems for herbal medicines. This study emphasizes the revolutionary significance of nanomedicine in enhancing the clinical efficacy, safety, and worldwide acceptance of herbal therapies by fusing the therapeutic potential of medicinal plants with the latest developments in nanotechnology.

2. Challenges Associated with Conventional Herbal Drug Delivery

Because of their wide range of pharmacological activity and generally good safety profile, herbal medicines have garnered a lot of scientific and commercial attention. Poor pharmacological and pharmacokinetic properties seriously impede the successful clinical application of many plant-derived bioactive substances, notwithstanding their medicinal potential. The target site frequently does not receive adequate concentrations of active phytochemicals from conventional dose forms as powders, capsules, tablets, decoctions, tinctures, and extracts. Higher dosages or longer treatment times may be necessary as a result of variable therapeutic results.

2.1 Poor Aqueous Solubility

Many therapeutically active phytochemicals are poorly soluble in water or hydrophobic. Extremely low aqueous solubility limits the dispersion of compounds like curcumin, resveratrol, quercetin, boswellic acid, and thymoquinone in gastrointestinal fluids after oral ingestion. Low solubility immediately leads to low bioavailability because dissolution is the initial stage of medication absorption. Many herbal components fall into Class II or Class IV of the Biopharmaceutics Classification System (BCS), where permeability and dissolution become rate-limiting variables for absorption. As a result, only little of the given dosage enters the bloodstream.

2.2 Low Oral Bioavailability

Poor oral bioavailability remains one of the greatest obstacles in phytopharmaceutical development. Several factors contribute to reduced absorption

- Poor dissolution in gastrointestinal fluids
- Limited membrane permeability
- Rapid intestinal metabolism
- Active efflux by transport proteins such as P-glycoprotein
- Enzymatic degradation within the gastrointestinal tract
- Extensive hepatic first-pass metabolism

For example, curcumin demonstrates oral bioavailability of less than 1% because of rapid metabolism and poor absorption, despite exhibiting remarkable pharmacological activities in vitro.

2.3 Chemical and Physical Instability

Many phytoconstituents are chemically unstable and undergo degradation during manufacturing, storage, or after administration.

Factors responsible include:

- Oxidation
- Hydrolysis
- Photodegradation
- Thermal degradation
- Moisture sensitivity
- pH-dependent degradation

Polyphenols and flavonoids are particularly susceptible to oxidation, resulting in reduced potency and shorter shelf life.

2.4 Rapid Metabolism and Elimination

Hepatic enzymes, especially cytochrome P450 isoenzymes and conjugation routes involving glucuronidation and sulfation, quickly biotransform many herbal substances after absorption.

Before sufficient therapeutic concentrations are reached, rapid metabolism generates inactive metabolites that are removed by bile or urine.

Examples include:

- Curcumin
- Resveratrol
- EGCG
- Quercetin.

2.5 Poor Permeability Across Biological Membranes

Numerous phytochemicals possess high molecular weight or unfavorable lipophilicity, limiting passive diffusion across biological membranes.

Biological barriers include:

- Intestinal epithelium
- Blood-brain barrier
- Tumor microenvironment
- Skin barrier
- Ocular tissues

Poor permeability significantly reduces drug accumulation at target tissues.

2.6 Lack of Target Specificity

Conventional herbal preparations distribute systemically following administration without preferential localization to diseased tissues.

This non-specific distribution results in:

- Reduced therapeutic efficacy
- Increased dosing frequency
- Greater systemic exposure
- Potential adverse effects
- Drug wastage

Targeted delivery remains particularly important for cancer, neurological disorders, inflammatory diseases, and chronic infections.

2.7 Variable Composition of Herbal Extracts

Unlike synthetic drugs, herbal medicines contain complex mixtures of hundreds of phytochemicals.

The concentration of active constituents depends upon:

- Geographic location
- Climate
- Soil composition
- Harvest season
- Plant age
- Extraction method
- Storage conditions

This variability affects reproducibility, therapeutic consistency, and regulatory acceptance.

2.8 Poor Patient Compliance

Repeated administration caused by low bioavailability and short biological half-life often decreases patient adherence.

Additional concerns include:

- Large dosage volumes
- Unpleasant taste
- Poor stability
- Multiple daily dosing

- Gastrointestinal irritation

2.9 Limited Ability to Cross Physiological Barriers

Certain diseases require drug delivery across highly selective biological barriers.

Examples include:

- Blood-brain barrier
- Blood-retinal barrier
- Pulmonary mucus
- Tumor extracellular matrix

Conventional herbal formulations are generally incapable of efficiently crossing these barriers.

2.10 Regulatory and Standardization Challenges

Herbal medicines often suffer from inadequate standardization because:

- Active markers vary
- Manufacturing processes differ
- Quality specifications are inconsistent
- Bioavailability studies are limited

These issues complicate regulatory approval and commercialization.

3. Fundamentals of Nanotechnology in Drug Delivery

The engineering and use of materials with dimensions usually between 1 and 1000 nanometers is referred to as nanotechnology. Materials have special physicochemical properties at the nanoscale, such as increased surface area, changed optical properties, improved biological interactions, and higher reactivity. Nanotechnology in pharmaceutical sciences makes it possible to create nanosized carriers that can encapsulate therapeutic chemicals and more precisely transport them to target tissues.

Nano-drug delivery systems generally consist of

- Active phytoconstituent
- Carrier material
- Surface modifier
- Stabilizer
- Targeting ligand (optional)

The small particle size enhances cellular uptake through endocytosis while protecting encapsulated drugs from degradation.

4. Advantages of Nanotechnology-Based Herbal Drug Delivery

Nanotechnology addresses nearly all limitations associated with conventional herbal formulations.

4.1 Improved Solubility

Reduction of particle size dramatically increases surface area according to the Noyes–Whitney equation.

Consequently,

- dissolution rate increases
- saturation solubility improves
- gastrointestinal absorption becomes more efficient

4.2 Enhanced Bioavailability

Nanocarriers improve absorption through multiple mechanisms

- Increased residence time
- Improved membrane penetration
- Protection from enzymatic degradation
- Lymphatic transport
- Reduced first-pass metabolism

Several studies have demonstrated 5- to 50-fold increases in bioavailability for nanoformulated phytochemicals.

4.3 Protection Against Degradation

Nanocarriers shield sensitive phytochemicals from

- light
- oxygen
- moisture
- enzymes
- acidic gastric environment

This significantly prolongs shelf life and therapeutic activity.

4.4 Controlled Drug Release

Nanoformulations can provide

- sustained release
- controlled release
- pulsatile release
- stimuli-responsive release

Controlled release maintains therapeutic plasma concentrations while minimizing peak-trough fluctuations.

4.5 Targeted Drug Delivery

Surface functionalization enables nanoparticles to selectively accumulate in diseased tissues through.

Passive targeting

Based upon

- Enhanced Permeability and Retention (EPR) effect
- Tumor angiogenesis
- Leaky vasculature

Active targeting

Using ligands such as

- antibodies
- folic acid
- peptides
- aptamers
- transferrin

4.6 Reduced Toxicity

Because nanocarriers selectively deliver drugs to diseased tissues, they reduce

- systemic exposure
- adverse effects
- dose requirements

  This is especially valuable for anticancer phytochemicals.

4.7 Improved Pharmacokinetics

Nanocarriers improve

- half-life
- circulation time
- tissue distribution
- cellular uptake
- therapeutic index

4.8 Combination Therapy

Multiple phytochemicals can be encapsulated within a single nanoparticle.

Examples include

- Curcumin + Piperine
- Curcumin + Doxorubicin
- Resveratrol + Quercetin

Combination therapy often produces synergistic therapeutic effects.

4.9 Personalized Medicine

Recent advances permit formulation of nanoparticles according to

- disease biomarkers
- genetic profile
- receptor expression
- disease severity

Personalized nano-herbal therapy represents an emerging field.

5. Comparison Between Conventional and Nanotechnology-Based Herbal Drug Delivery

Parameter	Conventional Herbal Formulations	Nano-Herbal Drug Delivery Systems
Particle size	Micrometer scale	10–500 nm
Solubility	Poor	Significantly enhanced
Bioavailability	Low	High
Stability	Limited	Excellent
Drug protection	Minimal	High
Target specificity	Poor	Excellent
Drug release	Immediate	Controlled/Sustained
First-pass metabolism	Extensive	Reduced
Dose required	High	Lower
Toxicity	Higher systemic exposure	Reduced systemic toxicity
Patient compliance	Moderate	Improved
Therapeutic efficacy	Variable	Enhanced

6. CONCLUSION

The inherent physicochemical and pharmacokinetic limitations of conventional herbal medicines significantly restrict their therapeutic performance despite the remarkable biological activities of many phytochemicals. Nanotechnology-based drug delivery systems provide innovative solutions by enhancing solubility, stability, bioavailability, targeted delivery, and controlled release while minimizing systemic toxicity. These advantages have positioned nanomedicine as one of the most promising approaches for improving the clinical efficacy of herbal therapeutics. Continued research into advanced nanocarriers, scalable manufacturing processes, and regulatory standardization is expected to accelerate the translation of nano-herbal formulations from laboratory research to clinical practice.

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