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# ADVANCED DRUG DELIVERY SYSTEM FOR IMPROVING HERBAL COMPOUND BIOAVAILABILITY AND TARGET DELIVERY

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**1. ABSTRACT**
Nanotechnology has emerged as a highly progressive scientific approach in the 21st century. By exploring its association with biomedical sciences, particularly its influence on bioavailability, major developments and current limitations in this domain have been identified. The use of nanotechnology to investigate and enhance the bioavailability of herbal medicines is gaining significant attention. Present evidence shows that nanotechnology is among the fastest-growing and most promising high-tech fields globally, contributing remarkably to the advancement of biological medicine and herbal drug delivery. When herbal compounds are converted into nanosized formulations, their absorption and therapeutic effectiveness can be significantly improved. This has paved the way for the evolution of nano-herbal medicines with superior bioavailability, marking a new milestone in herbal drug innovation. Future breakthroughs are expected through the nano-formulation of key phytochemicals such as nanocurcumin, nanopiperine, nanoberberine, and others.

**KEYWORDS:** Nanotechnology; Bioavailability; Bioactivity; Herbal drugs.

## 2. INTRODUCTION

Herbal formulations continue to attract attention owing to the broad spectrum of biologically active phytochemicals they contain. However, their clinical utility is often curtailed by inherent challenges: many herbal actives suffer from poor aqueous solubility, limited intestinal absorption, rapid metabolism, and lack of targeted delivery, all of which contribute to low systemic bioavailability.[1,2]

In response to these limitations, the field of drug delivery has witnessed rapid innovation in advanced delivery platforms—such as nanoparticles, liposomes, nanoemulsions, and phospholipid-complex systems—that are designed to improve the solubility, protect against degradation, enhance permeability, and deliver the active compounds directly to target tissues.[3]

Integrating these advanced delivery technologies with herbal medicine bridges the gap between traditional phytopharmaceuticals and modern precision therapeutics. By embracing tailored delivery strategies, it becomes possible to unlock the full therapeutic potential of plant-derived compounds, improve their bioavailability, and achieve more effective and reliable treatment outcomes.[4,5] Herbal medicines are enjoying a resurgence in global healthcare, largely because they often offer broad therapeutic potential and tend to be perceived as more "natural" alternatives to synthetic drugs. These pharmacokinetic and biopharmaceutical limitations result in low systemic bioavailability, unpredictable therapeutic outcomes, and reduced patient compliance.[6]

For example, by incorporating a phytochemical into lipid-based vesicles or polymeric nanoparticles, one can improve its ability to cross lipid-rich biological membranes, avoid premature degradation, and release the active agent at the site of action.[8,9] Moreover, target delivery either passive (via enhanced permeability and retention in inflammatory or tumor tissue) or active (via ligand-modification of carriers) adds another layer of therapeutic precision.[10]

## 3. FACTORS AFFECTING BIOAVAILABILITY OF HERBAL COMPOUND

However, many herbal compounds exhibit low and inconsistent bioavailability due to several physiological, physicochemical, and formulation-related factors. The major factors influencing the bioavailability of herbal compounds are described below:[13]

- **Poor Aqueous Solubility**

A large proportion of phytochemicals are lipophilic in nature and have very low solubility in water. Due to insufficient dissolution in gastrointestinal fluids, these compounds are unable to reach the absorption membrane in adequate concentration, resulting in minimal systemic absorption.[14]

- **Limited Permeability Across Biological Membranes**

Even when solubilized, some herbal compounds show weak permeability through intestinal epithelial cells due to high molecular weight, structural complexity, or hydrophilic functional groups, which restrict transcellular and paracellular transport.[14]

- **Instability in Gastrointestinal Tract**

Phytochemicals may undergo chemical degradation because of variations in gastric pH, enzymatic hydrolysis, or interaction with food contents. This degradation reduces the amount of intact drug available for absorption.[15]

- **First-Pass Metabolism**

After absorption, many herbal constituents are rapidly metabolized in the liver and intestinal mucosa before entering systemic circulation. This extensive first-pass metabolism drastically decreases their active concentration in blood.[16]

- **Binding to Food Components**

Simultaneous intake of herbal products with certain foods may lead to complex formation with proteins, fibers, polyphenols, or minerals. These interactions can hinder dissolution and absorption of herbal actives.[19]

- **Variability in Herbal Extract Composition**

Unlike pure synthetic drugs, herbal extracts may vary in chemical composition depending on plant species, geographical location, harvesting season, and extraction method. Such variability results in inconsistent pharmacokinetic behavior, contributing to unpredictable bioavailability.[20]

- Need/Role of Advanced Drug Delivery Systems to Overcome Bioavailability Limitations of Herbal Compounds

Improving the bioavailability of herbal compounds has become a primary focus in modern phytopharmaceutical research because most plant-derived actives suffer from rapid metabolism, poor solubility, and limited intestinal absorption. Traditional dosage forms such as powders, decoctions, capsules, or tinctures are unable to address these challenges effectively.

Additionally, many systems provide controlled and sustained release, maintaining therapeutic drug levels in plasma over an extended period and minimizing dosing frequency. Some delivery platforms can also bypass first-pass metabolism and evade efflux pumps, reducing presystemic elimination. Recommend promising delivery platforms that could maximize efficacy, stability, and patient compliance.[11,22]

**Table 1: Factors Affecting Bioavailability of Herbal Compounds.**

| Sr. No. | Factor | Impact on Bioavailability | Underlying Reason |
|---|---|---|---|
| 1 | Poor aqueous solubility | Reduced dissolution and low absorption. | Most phytochemicals are lipophilic and do not dissolve well in water. |
| 2 | Low membrane permeability | Minimal uptake across intestinal epithelium. | High molecular weight or hydrophilic structure limits diffusion. |
| 3 | Instability in GI tract | Decreases intact drug available for absorption. | pH variations, enzymatic hydrolysis, and food interactions. |
| 4 | First-pass metabolism | Significant loss of active Compound before entering systemic circulation. | Rapid metabolism in liver and intestinal mucosa. |
| 5 | Interaction with gut microbiota | Alters pharmacological activity and exposure. | Microbial biotransformation produces metabolites of variable potency. |
| 6 | Efflux transporters | Pump actives back to intestinal lumen. | P-gp and other transporters expel absorbed molecules. |
| 7 | Food-herb interaction | Reduced availability of active phytochemicals. | Binding with dietary protein, fibers, minerals, or polyphenols. |
| 8 | Variability in extract composition | Inconsistent therapeutic effect. | Chemical profile depends on plant source, season, and extraction process. |

| | | | |
|---|---|---|---|
| 9 | Improper formulation properties | Poor dissolution and slow absorption. | Large particle size and absence of dispersibility in conventional forms. |

## 4. CONVENTIONAL TECHNIQUES FOR BIOAVAILABILITY ENHANCEMENT

Although these traditional approaches are relatively simple and cost-effective, their enhancement potential is often limited compared to modern nanocarrier systems. The major conventional techniques used to enhance herbal compound bioavailability are described below:

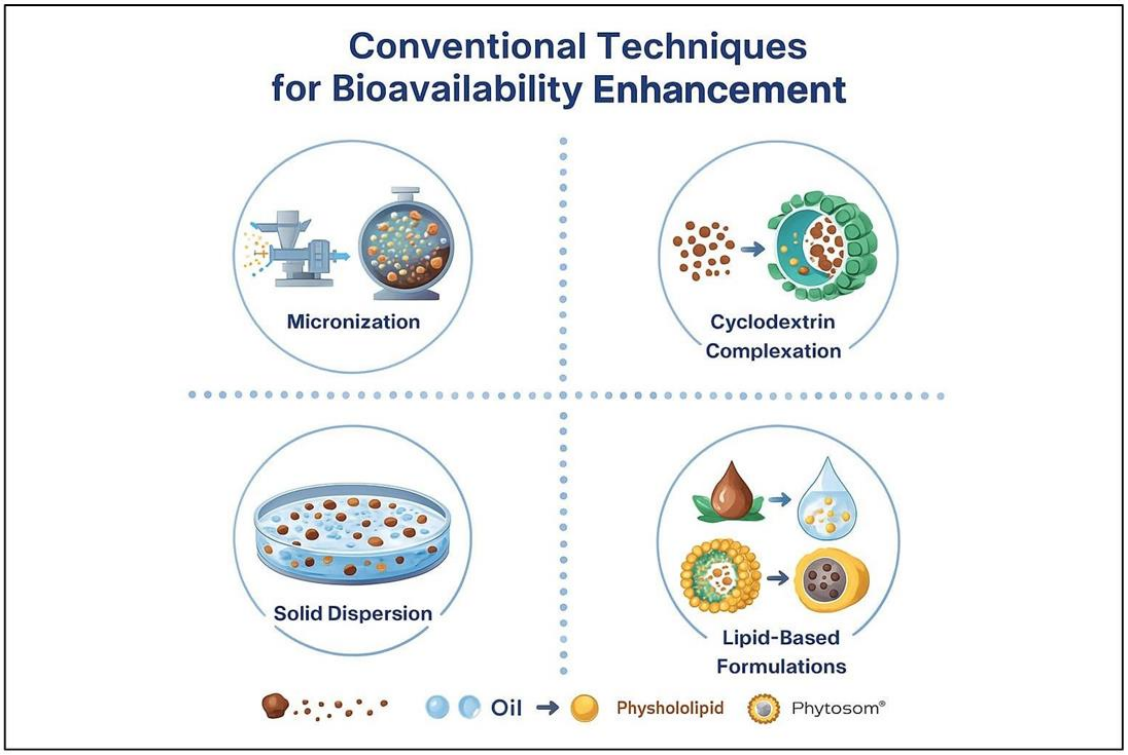


**Fig. 1: -Conventional Techniques for bioavailability enhancement.**

- **Particle Size Reduction (Micronization / Pulverization)**

Reducing the particle size of herbal powders increases the surface area exposed to gastrointestinal fluids. Greater surface area enhances the dissolution rate based on the Noyes–Whitney principle, which can improve absorption of poorly soluble phytochemicals. Techniques like milling, grinding, and air-jet micronization are commonly applied.

Advantages: -

- Increases surface area for faster dissolution.
- Improves dispersibility in gastrointestinal fluids.
- Does not require chemical modification of herbal Limitations: -
- Achieves solubility improvement but not permeability enhancement.
- Energy-intensive and costly equipment.
- Particle agglomeration may occur if not may occur stabilized properly.[23]

- **Use of Permeation Enhancers**

Certain excipients such as bile salts, surfactants, fatty acids, or terpenes can temporarily modify intestinal epithelial tight junctions, improving paracellular or transcellular transport. These permeation enhancers increase the permeability of compounds that otherwise have difficulty crossing biological membranes.[24]

- **Salt Formation**

Conversion of herbal actives into salt forms can increase solubility and dissolution rate. The salt form improves ionic interaction with gastrointestinal fluids, especially for compounds containing acidic or basic functional groups.[25]

- **Solid Dispersions**

In solid dispersions, the herbal compound is dispersed within a hydrophilic carrier matrix. This converts the phytochemical into an amorphous or molecularly dispersed state, leading to enhanced dissolution and absorption. Carriers like polyvinylpyrrolidone (PVP) and polyethylene glycols (PEGs) are commonly used.

Advantages: -

- Improves solubility of poorly water-soluble phytochemicals
- Enhances dissolution rate and absorption
- Can be prepared using low-cost carriers Limitation: -
- possible physical instability over time

- Risk of phase separation or crystallization during storage
- Scale-up difficulties at industrial level.[27]

- **Complexation (Cyclodextrin Complexes)**

Cyclodextrins form inclusion complexes with herbal actives, improving their water solubility and chemical stability. The hydrophobic cavity of cyclodextrins encapsulates the lipophilic part of the drug, while the hydrophilic outer surface ensures improved dispersion in aqueous environments.

Advantage: -

- Increases aqueous solubility and chemical stability of herbal actives.
- Masks unpleasant taste and odor.
- Enhances permeability across biological membranes Limitation: -
- Efficiency depends on suitability of host molecules for herbal phytochemicals.
- High cost of cyclodextrins or complexing agents.
- Limited loading capacity for certain compounds.[28]

- **Prodrug Approach**

In this approach, the herbal compound is chemically modified into a biologically inactive derivative that has better solubility, permeability, or stability. Once absorbed, the prodrug undergoes enzymatic conversion to release the active phytochemical in the body.[29]

- **Use of Bioenhancers**

Bioenhancers are natural substances that improve the absorption and efficacy of co-administered therapeutic molecules. Piperine, ginger extracts, quercetin, and glycyrrhizin are widely known bioenhancers that inhibit drug-metabolizing enzymes and efflux transporters.

Conventional bioavailability enhancement techniques—such as micronization, permeation enhancers, solid dispersions, cyclodextrin complexes, and lipid-based formulations—have significantly contributed to improving the absorption of herbal compounds. However, most of these approaches provide only partial and nonspecific enhancement. This limitation has accelerated the transition toward advanced drug delivery systems, which offer better control over solubility, permeability, stability, and targeted delivery.[31]

- **pH Modifiers**

Some herbal molecules are unstable or insoluble in certain pH ranges. pH modifiers maintain a favorable microenvironment to improve solubility and stability.

These limitations have driven interest toward advanced drug delivery systems, such as nanoparticles, liposomes, dendrimers, micelles, and nanoemulsions, which offer more efficient and precise enhancement of herbal bioavailability.

Conventional formulation approaches are widely used to improve the solubility, dissolution rate, stability, and intestinal absorption of poorly bioavailable herbal compounds. These techniques are well-established, cost-effective, and suitable for large-scale manufacturing.[32]

## 5. Novel Drug Delivery System for Herbal Compounds

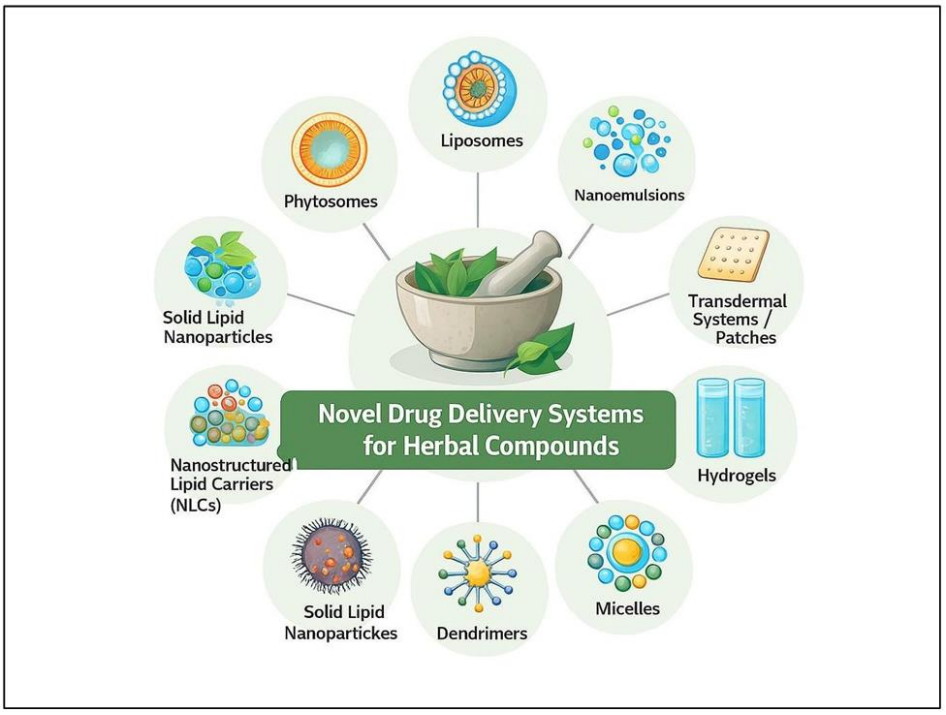


**Fig. 2: -Novel drug delivery system for herbal compound.**

 

Herbal medicine has been widely used for centuries due to its therapeutic benefits and reduced adverse effects. These barriers significantly reduce their systemic bioavailability and clinical efficacy.

To overcome these limitations, Novel Drug Delivery Systems (NDDS) have emerged as advanced platforms that improve the delivery, stability, and therapeutic performance of herbal molecules.[33]

- **Need for Novel Drug Delivery Systems in Herbal Therapy**

Traditional dosage forms such as powders, capsules, decoctions, and tablets often fail to deliver optimal therapeutic concentrations of herbal drugs. NDDS are designed to:
Increase solubility and permeability of poorly absorbed herbal compounds Protect bioactives from chemical and enzymatic degradation.

Provide sustained and controlled drug release Reduce dose frequency and toxicity
Enable targeted delivery to specific organs, tissues, or cells
Thus, NDDS enhance both pharmacokinetics and pharmacodynamics of plant-derived molecules.[34]

- **Types of Novel Drug Delivery Systems for Herbal Compounds**
- **Liposomes**

Liposomes are phospholipid-based vesicles capable of encapsulating hydrophilic and lipophilic herbal active compounds.
Advantages: Improved circulation time, enhanced skin penetration, reduced toxicity, and sustained release.[35]

- **Phytosomes**

Phytosomes are complexes of herbal extracts with phospholipids to enhance membrane permeability.
Advantages: Better intestinal absorption, improved bioavailability, and higher pharmacological activity than conventional extracts.[36]

- **Polymeric Nanoparticles**

Nanoparticles composed of natural or synthetic polymers encapsulate herbal molecules within a nanometric matrix.
Advantages: High drug entrapment efficiency, controlled release, enhanced stability, and potential for active targeting.[37]

- **Solid Lipid Nanoparticles (SLNs)**

SLNs contain herbal drugs dispersed in a solid lipid core stabilized by surfactants.
Advantages: Improved bioavailability, biocompatibility, controlled release, and protection of unstable compounds.[38]

- **Nanoemulsions**

Nanoemulsions are thermodynamically stable emulsions with droplet sizes below 200 nm.
Advantages: Increased solubilization of lipophilic herbal actives, rapid onset of action, and enhanced oral and topical absorption.[40]

- **Polymeric Micelles**

Micelles are self-assembling amphiphilic systems capable of solubilizing poorly water-soluble herbal compounds.
Advantages: Enhanced aqueous solubility, passive tumor targeting, and improved cellular uptake.[41]

- **Dendrimers**

Dendrimers are nanosized branched macromolecules that encapsulate or conjugate herbal molecules.
Advantages: High payload capacity, targeted delivery, and improved bioavailability.[42]

- **Transdermal Drug Delivery Systems**

Transdermal patches enable controlled release of herbal compounds through skin layers.
Advantages: Non-invasive administration, avoidance of first-pass metabolism, and prolonged plasma drug levels.[43]

- **Benefits of NDDS in Herbal Drug Delivery**
- Enhanced solubility and absorption
- Protection from gastric and enzymatic degradation
- Increased circulation half-life and sustained release
- Reduced dose frequency and improved patient compliance
- Targeted delivery with minimized systemic toxicity
- Potential to convert herbal compounds into clinically reliable formulations.[35]

- **Current Research and Future Prospects**

Recent studies highlight the application of nano-herbal formulations in cancer, diabetes, neurodegenerative and inflammatory disorders. The focus is shifting towards: Green synthesis of herbal nanoparticles, Combination therapy using phytochemicals and nanocarriers, Clinical translation and commercialization of nano-herbal products.

By ensuring enhanced bioavailability, stability, and targeted delivery, NDDS contribute to more predictable clinical outcomes and pave the way for integrating herbal medicine with modern pharmaceutical technology.[35,45]

## 6. TARGET DRUG DELIVERY APPROACHES

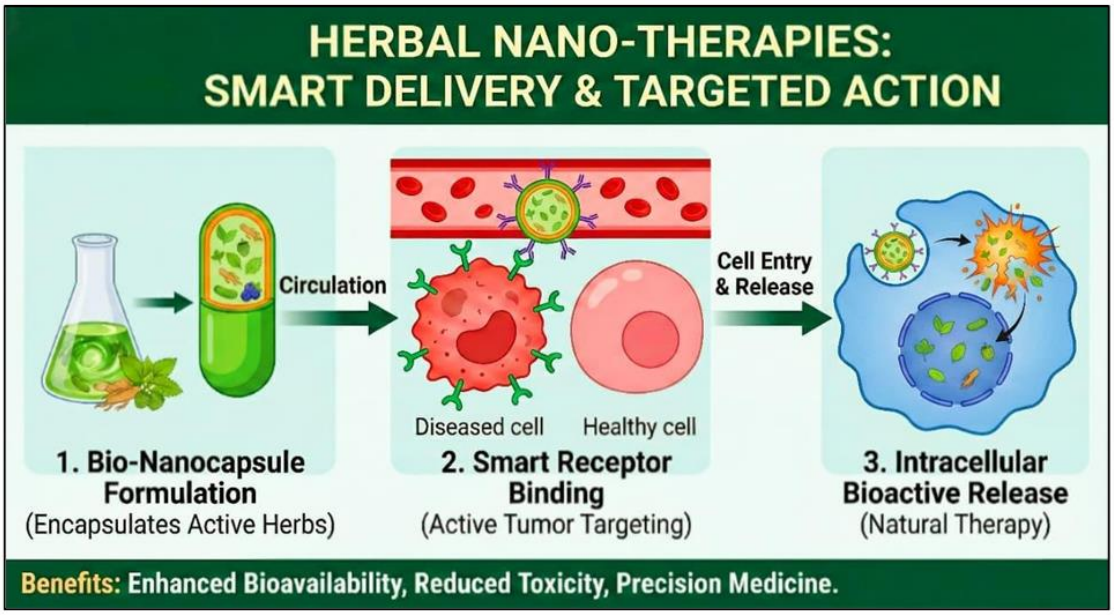


**Fig. 3: -Herbal Nano-Therapies: Smart Delivery and Target Action.**

Target drug delivery refers to specialized strategies that allow therapeutic agents to reach a specific site in the body while minimizing drug exposure to healthy tissues. These systems improve efficacy, safety, bioavailability, and patient compliance, especially for drugs that have poor solubility, rapid metabolism, or high toxicity.[46]
Main Approaches to Target Drug Delivery

- **Passive Targeting**

Utilizes natural physiological mechanisms such as Enhanced Permeability and Retention (EPR) effect, particularly in tumors and inflamed tissues. Nanocarriers accumulate at target sites due to leaky vasculature and poor lymphatic drainage.
Examples: liposomes, polymeric nanoparticles, micelles.

Advantages: Non-invasive approach, automatically guided by physiology, Useful for treating solid tumors and inflammatory diseases.
Limitations: Less effective in tissues without EPR effect, Variability among patients.[47]

- **Active Targeting**

Involves the attachment of specific ligands on drug carriers to recognize receptors or antigens overexpressed at target tissue. Ligands used: antibodies, peptides, folic acid, aptamers, sugars.[48]
Advantages: High precision and binding affinity., Suitable for cancer, autoimmune disorders, and targeted gene delivery.
Limitations; Complex preparation and high cost., Potential immunogenicity of ligands.[47]

- **Stimuli-Responsive Targeting (Smart Delivery)**

Drug release is triggered by external or internal stimuli.
Internal stimuli: pH, enzymes, temperature, redox gradient.
External stimuli: Ultrasound, magnetic field, light, electrical signal.[49]
Advantages: Controlled drug release only at target site, Minimizes systemic toxicity. Limitations: Stimulus control can be technically challenging.[50]

- **Prodrug-Based Targeting**

Parent drug is chemically modified into an inactive form (prodrug). It becomes active only after enzymatic or chemical conversion at target tissue.[51]

Advantages: Enhances solubility, absorption, and tissue specificity, Reduces adverse effects. Limitations: Requires detailed knowledge of metabolic pathways.[52]

- **Receptor-Mediated Endocytosis**

Drug carriers are engineered to bind receptors on cell membranes. The cell internalizes the drug via endocytosis.
Examples: transferrin-mediated targeting to brain[53], folate-receptor targeting in cancer cells.[54]

- **Physical Targeting**

Uses external physical forces to accumulate drugs at the target site.[55] Types

- Magnetic targeting: Magnetic nanoparticles guided by external magnetic field.[56]
- Ultrasound-mediated delivery: Focused ultrasound enhances drug penetration.[57]
- Thermal targeting: Heat triggers drug release from thermosensitive materials.[58]

- **Common Carriers Used in Target Delivery**
- Liposomes
- Polymeric nanoparticles
- Dendrimers

- Solid lipid nanoparticles
- Nanogels
- Micelles
- Exosomes
- Carbon nanotubes

- **Benefits of Target Drug Delivery**
- Higher therapeutic index
- Reduced dosing frequency
- Minimized toxicity and side effects
- Enhanced pharmacokinetics and bioavailability
- Site-specific controlled drug release.[60]

- **Challenges and Future Perspectives**

While target drug delivery offers promising results, challenges include high cost, scale-up issues, immune reactions, and variability among patients.[61] Future development aims at:
Personalized nanomedicine.[61], Hybrid multifunctional drug carriers.[62], Artificial intelligence-guided design of delivery systems.[63]

## 7. HERBAL COMPOUND COMMONLY IMPROVED USING ADVANCED DELIVERY

Herbal Compounds Commonly Improved Using Advanced Delivery Systems.

Herbal compounds have been used for centuries due to their therapeutic potential, but many face challenges such as low solubility, poor stability, rapid metabolism, and limited bioavailability. To overcome these limitations, advanced drug delivery systems (ADDS) have been developed, enabling targeted delivery, controlled release, and enhanced therapeutic efficacy.[64] Some of the most commonly improved herbal compounds include:

- **Curcumin**

Source: Turmeric (Curcuma longa).
Challenges: Poor water solubility, low oral bioavailability, rapid metabolism.
Advanced Delivery Approaches: Liposomes, nanoparticles, solid lipid nanoparticles (SLNs), nanoemulsions, and polymeric micelles.
Benefits: Improved solubility, increased absorption, sustained release, and enhanced anti-inflammatory and anticancer effects.[65]

- **Quercetin**

Source: Fruits, vegetables, and herbs like onions, apples, and Ginkgo biloba. Challenges: Low stability and poor aqueous solubility.
Advanced Delivery Approaches: Nanocapsules, nanocrystals, and cyclodextrin inclusion complexes.
Benefits: Enhanced bioavailability, improved antioxidant activity, and targeted delivery to inflamed tissues.[66]

- **Resveratrol**

Source: Grapes, berries, peanuts, and Polygonum cuspidatum. Challenges: Rapid metabolism and low systemic bioavailability.
Advanced Delivery Approaches: Liposomes, polymeric nanoparticles, solid lipid nanoparticles, and micellar systems.
Benefits: Sustained release, protection from degradation, and improved cardiovascular and anticancer activity.[67]

- **Epigallocatechin-3-gallate (EGCG)**

Source: Green tea (Camellia sinensis).
Challenges: Poor stability, low absorption, and rapid degradation in the gastrointestinal tract.
Advanced Delivery Approaches: Nanoemulsions, chitosan nanoparticles, and polymeric carriers.
Benefits: Enhanced stability, improved bioavailability, and potentiated anticancer and anti-obesity effects.[68]

- **Berberine**

Source: Berberi's species, goldenseal, and barberry.
Challenges: Poor solubility, limited intestinal absorption, and extensive first-pass metabolism.
Advanced Delivery Approaches: Lipid-based nanoparticles, self-emulsifying drug delivery systems (SEDDS), and solid lipid nanoparticles.
Benefits: Improved absorption, sustained therapeutic levels, and enhanced antidiabetic and antimicrobial activities.[69]

- **Ginsenosides**

Source: Panax ginseng.
Challenges: Poor oral bioavailability and extensive metabolism.
Advanced Delivery Approaches: Nanoparticles, liposomes, and phospholipid complexes. Benefits: Enhanced neuroprotective, anti-inflammatory, and immunomodulatory activities.[70]

- **Silymarin (from Silybum marianum)**

Source: Obtain from seed/fruit of Silybum marianum (Milk thistle)
Challenges: Poor water solubility., Low oral bioavailability., Extensive first-pass metabolism., Limited intestinal permeability, Short biological half-life.
Advanced Delivery Used: Phytosomes, liposomes, nanosuspensions.
Benefits: Significantly enhanced hepatoprotective activity and improved bioavailability.[71]

- **Piperine (from Black Pepper)**

Source: It is primarily obtained from black pepper (Piper nigrum) and long pepper (Piper longum).
Challenges: Poor water solubility, Low oral bioavailability, Rapid metabolism and elimination, Chemical instability, Dose variability.
Advanced Delivery Used: Nanocrystals, solid dispersions, nanoemulsions. Benefits: Better solubility and enhanced bioenhancer activity.[72]
Advanced drug delivery systems significantly improve the therapeutic performance of herbal compounds. By

enhancing solubility, stability, and bioavailability, these systems not only optimize efficacy but also reduce dosage requirements and minimize side effects. Continuous research is needed to develop more efficient and safe delivery platforms tailored to specific herbal compounds.[73]

## 8. CHARACTERIZATION TECHNIQUES

Characterization techniques play a crucial role in the development and evaluation of advanced drug delivery systems, as they ensure the formulation is safe, stable, and therapeutically effective. These techniques help determine the physical, chemical, thermal, and biological properties of the formulation, allowing researchers to understand how the delivery system behaves both in vitro and in vivo.[74]

- **Particle Size and Size Distribution**

Particle size is a key factor influencing dissolution rate, cellular uptake, biodistribution, and drug-release behavior.
Common Techniques: Dynamic Light Scattering (DLS), Laser Diffraction Analysis, Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM).
Importance: Uniform and nanoscale particles generally enhance solubility, permeability, and therapeutic efficiency.[75]

- **Zeta Potential**

Zeta potential describes the surface charge of particles and estimates the colloidal stability of the formulation.
Common Technique: Electrophoretic Light Scattering.
Importance: High magnitude of zeta potential—positive or negative—helps prevent particle aggregation and improves storage stability.[77]

- **Encapsulation Efficiency and Drug Loading**

These parameters determine the quantity of active compound entrapped within the delivery system relative to the total amount used.
Common Techniques: HPLC, UV-Visible Spectroscopy, Centrifugation/Ultrafiltration.
Relevance: High encapsulation efficiency reduces dose frequency and enhances sustained therapeutic action.[78]

- **In-Vitro Drug Release Studies**

Drug-release profiling helps predict the in-vivo performance of the delivery system.
Common Techniques: Dialysis membrane method, USP dissolution apparatus, Franz diffusion cell.
Relevance: Enables evaluation of immediate, controlled, or sustained-release patterns and kinetic modeling.[79]

- **Spectroscopic Characterization**

Spectroscopic techniques identify chemical structure, purity, and possible interactions between drug molecules and excipients.
Common Techniques: Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR), Ultraviolet–Visible (UV–Vis) Spectroscopy, Raman Spectroscopy.
Use: Confirms chemical compatibility and detects structural modifications during formulation.[80]

Characterization techniques collectively provide a comprehensive assessment of advanced drug delivery systems. By integrating physicochemical, structural, and biological evaluations, researchers can predict formulation performance, ensure reproducibility, and support regulatory approval. Thorough characterization is therefore indispensable for the successful translation of innovative delivery systems into clinical application.[84]

## 9. CHALLENGES AND LIMITATIONS OF ADVANCED DRUG DELIVERY SYSTEMS

Although advanced drug delivery systems (ADDS) have significantly improved the therapeutic performance of conventional and herbal compounds, their development and translation into clinical use still face multiple challenges and limitations. These obstacles arise from formulation complexity, scale-up issues, regulatory concerns, and cost factors, which collectively restrict their widespread application.[61]

- **Formulation Complexity**

Most ADDS require sophisticated preparation methods involving nanotechnology, polymer chemistry, or lipid engineering.
Minor changes in material grade, processing temperature, pH, or mixing rate can drastically alter the physicochemical properties of the final formulation.
Reproducibility across multiple batches remains a persistent challenge, especially in nano-based carriers.[61]

- **Limited Stability**

Many nanoformulations are prone to aggregation, drug leakage, hydrolysis, or oxidation during storage.
Instability of labile bioactives (e.g., polyphenols and flavonoids) further complicates formulation development.
Maintaining stability under varying environmental conditions (temperature, humidity, and light) is difficult.[85]

- **Low Drug Loading and Burst Release**

Some delivery systems, particularly nanoparticles and polymeric micelles, may offer limited drug-loading capacity.
This leads to higher carrier consumption, increased excipient load, and elevated formulation cost. Sudden burst release in initial stages can lead to toxicity and suboptimal therapeutic concentration.[86]

- **Regulatory and Safety Concerns**

ADDS involve novel materials such as synthetic polymers, surfactants, and nanocarriers, which raise regulatory challenges.

Long-term toxicity and biodegradability data are often insufficient.
Lack of harmonized global regulatory guidelines delays product approval.[87]

- **High Cost of Production**

Advanced formulations require high-purity excipients, costly analytical characterization, and specialized storage conditions.
Economic feasibility becomes difficult for drugs used in chronic diseases or low-income clinical settings.[88]

- **Patient and Market Acceptance**

Despite improved efficacy, patient acceptance may be limited due to high price, unfamiliar administration route, or concerns regarding nanoparticle safety.
Health professionals may hesitate to adopt products with insufficient long-term clinical evidence.[90]

## 10. Future Prospects

Advanced drug delivery systems (ADDS) have shown remarkable potential in overcoming the intrinsic limitations of herbal compounds such as low solubility, poor permeability, rapid metabolism, and non-specific distribution. With continuous advancements in material science, nanotechnology, and biomedical engineering, the future of herbal medicine is expected to shift from conventional crude extracts to scientifically optimized delivery platforms that offer improved therapeutic outcomes and precision targeting.[92]

- **Personalized and Precision Herbal Medicine**

Future delivery systems will aim to tailor therapeutic interventions based on individual genetics, disease phenotype, and metabolic profile.
Integration of pharmacogenomics and nanotechnology can optimize drug concentration and responsiveness in different patient groups.
Personalized dosing models may reduce toxicity and enhance clinical effectiveness.[61]

- **Smart and Stimuli-Responsive Carriers**

Next-generation carriers are expected to respond to internal or external stimuli such as pH, temperature, enzymes, redox conditions, magnetic fields, or ultrasound.
These systems can release herbal actives at the diseased site only, reducing systemic exposure.
Responsive delivery is highly promising for cancer, inflammation, and neurological disorders.[93]

- **Targeted Delivery via Ligand and Receptor Engineering**

Future formulations will incorporate ligands such as folic acid, transferrin, peptides, antibodies, or aptamers to selectively target receptors that are overexpressed on diseased cells.
This strategy minimizes off-target toxicity and significantly enhances intracellular uptake of herbal actives.[94]

- **Hybrid and Multifunctional Nanocarriers**

Emerging research focuses on combining the advantages of multiple carrier types—such as liposomes with polymeric nanoparticles or inorganic nanomaterials with lipid cores.
Hybrid systems can ensure high drug loading, controlled release, imaging capability, and synergistic therapy in a single platform.[95]

- **Biodegradable and Natural Delivery Materials**

Future work will prioritize biodegradable, biocompatible, and plant-derived polymers to improve safety and reduce regulatory barriers.
Examples include chitosan, alginate, cellulose, lignin, and zein.
Environment-friendly materials will support sustainable development of herbal therapeutics.[96]

- **Artificial Intelligence and Digital Formulation Techniques**

AI-assisted prediction tools will help optimize formulation components, processing conditions, and stability models.
Machine learning will accelerate development cycles and reduce formulation cost. In-silico modeling will enhance in-vivo predictability before clinical trials.[61]

## 11. CONCLUSION

Herbal compounds possess immense therapeutic potential, but their clinical translation has been constrained by intrinsic limitations such as low solubility, poor permeability, rapid metabolism, and lack of target specificity. Advanced drug delivery systems (ADDS) offer a scientific solution to these challenges by improving pharmacokinetic and pharmacodynamic performance through enhanced absorption, protection from degradation, controlled release, and site-specific targeting. Nanocarriers, lipid-based systems, polymeric platforms, micelles, nanoemulsions, phytosomes, and ligand-modified formulations have emerged as effective strategies that significantly elevate biological availability and therapeutic efficiency of herbal actives. Despite the remarkable progress, certain barriers—including formulation complexity, scale-up difficulties, regulatory uncertainty, biological variability, and high manufacturing cost—still hinder the widespread commercialization of ADDS-based herbal products. Continued innovation in biodegradable materials, stimuli-responsive carriers, molecular targeting, hybrid nanosystems, and personalized medicine will be essential for realizing full clinical impact. Moreover, harmonized global regulatory frameworks and long-term safety evaluation will play a crucial role in promoting acceptance among healthcare systems and the pharmaceutical industry. Overall, the integration of herbal medicine with advanced drug delivery technology demonstrates a transformative approach that bridges traditional therapeutic knowledge with modern scientific advancements. With sustained research, interdisciplinary collaboration, and industry adoption, ADDS is expected

to redefine the future of herbal therapeutics by enabling safer, more effective, and patient-centric treatment outcomes.

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