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# Revolutionising Herbal Medicine: Nanoparticle-Mediated Enhancement of Phytoconstituent Bioavailability and Therapeutic Efficacy

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**ABSTRACT**

The interest in herbal medicine has been revived in the world because of its therapeutic effects, safety record and its historic application in traditional healthcare systems. Nevertheless, phytoconstituents tend to be restricted to clinical use due to low bioavailability, solubility, fast metabolism, and unstable behaviour in physiological conditions. Nanotechnology has seen the light of day as a potential solution to these constraints by allowing the creation of enhanced drug delivery systems referred to as herbal nanoparticles. Such nano-engineered systems as phytosomes, liposomes, solid lipid nanoparticles, and polymeric nanoparticles improve the pharmacodynamics of the compounds of plant origin and their pharmacokinetics. Herbal nanoparticles can greatly increase the efficacy of the therapy, decrease systemic toxicity, and deliver the drug into a specific location by increasing solubility, preventing degradation, improving controlled release, and targeting localised delivery. This review presents an extensive discussion of phytoconstituent classification, problems related to bioavailability, and principles of designing nano-enabled delivery systems. It also brings out the processes through which nanoparticles enhance drug absorption and distribution, as well as the various clinical uses of nanoparticles in the treatment of cancer, diabetes, neurodegenerative and infectious diseases. Also, the major issues, including nanotoxicity, stability, mass production and regulatory issues, are addressed critically. The prospects are focusing on the importance of artificial intelligence, personalised phytotherapy, and the necessity of strong clinical validation and regulatory standards. In general, herbal nanomedicine is a paradigm shift that allows the reconciliation of traditional medicine with contemporary pharmaceutical innovation, which is less harmful, more effective, and specific therapy.

## Introduction: Bridging Traditional Wisdom with Modern Nanotechnology

The world renewal of herbal medicine indicates a trend toward the natural, holistic, and culturally-based healthcare systems. In both developing and developed countries, interest in plant-based therapeutics is renewed due to such factors as the increasing number of chronic conditions, the growing understanding of the negative consequences of synthetic drugs, and the traditional confidence in plant-based systems, such as Ayurveda, Traditional Chinese Medicine, and other folk therapies.(1). The World Health Organisation has also acknowledged the value of traditional medicine as a primary healthcare system that has encouraged new research and the introduction of herbal medications in contemporary therapeutic systems. This revival is not a revival of the past, but is getting more and more scientifically validated, through phytochemical research and pharmacological research that validates the medicinal potential of medicinal plants.(2).

The herbal medicine is based on phytoconstituents, which are biologically active compounds that are produced by plants. These consist of various classes of compounds like alkaloids, flavonoids, terpenoids, glycosides, polyphenols and saponins with a broad spectrum of pharmacological activity.(3). The compounds such as curcumin, quercetin, resveratrol and catechins have proven to be very effective in antioxidant, anti-inflammatory, anti-cancer, anti-diabetic and neuroprotective activities in preclinical and clinical research. They are multitargeted in their mechanisms of action, which is what makes them especially appealing in the treatment of complex and multi-factorial diseases, in which single-target drugs frequently fail.(4). Furthermore, phytoconstituents are considered to be safer with fewer side effects, which increases patient compliance and acceptance. In spite of such benefits, there is a paucity in the clinical translation of the most promising phytochemicals, mostly because of the inherent pharmacokinetic problems.(5).

This restriction leads to the so-called bioavailability paradox of herbal therapeutics. Although many phytoconstituents have high biological activity in vitro, their biological efficacy in vivo is often lost due to low bioavailability.(6). Low aqueous solubility, inadequate membrane permeability, instability in the gastrointestinal tract, high metabolism, and high first-pass hepatic clearance are all factors that can greatly decrease the systemic availability of such compounds.(7). An example is curcumin, which has an impressive therapeutic potential, but with very low oral bioavailability because of its quick metabolism and low absorption. Likewise, resveratrol and quercetin suffer in the area of high clearance and low stability. This gap between the pharmacological and clinical efficacies constitutes a significant obstacle in the design of pharmacokinetic herbal preparations and explains why new delivery methods should be developed.(8).

In this regard, nanotechnology has emerged as a radical solution that can overcome the bioavailability shortage of phytoconstituents. The solubility, stability and permeability of herbal compounds can be greatly improved by designing drug delivery systems at the nanoscale.(9). Nanoparticles like liposomes, phytosomes, solid lipid nanoparticles and polymeric nanoparticles allow effective encapsulation of phytoconstituents, and they protect them against degradation and allow them to be released in a controlled and targeted manner.(10). These systems have the potential to enhance intestinal absorption, circumvent first-pass metabolism, and targeted delivery to tissues, and thus maximise therapeutic effect with minimal adverse effects. Moreover, nanotechnology can be used to provide surface modification and functionalization, and thus active targeting to particular cells or tissues, which is especially useful in diseases like cancer and neurodegenerative diseases.(11).

The combination of nanotechnology and herbal medicine is a paradigm shift from traditional phytotherapy to modern herbal nanomedicine. The given practice not only revives the traditional remedies but also makes them consistent with the principles of modern pharmaceutical science, which provides an intermediate between traditional knowledge and modern innovation(12). With the current growth of research in this area, herbal nanoparticles will likely be critical in eliminating issues that have been encountered over time regarding the delivery of phytoconstituents. Therefore, the integration between the ancient knowledge and nanotechnological developments is incredibly promising in the future in relation to the creation of better, safer and more scientifically proven herbal therapeutics(13).

**Phytoconstituents: Therapeutic Potential vs Bioavailability Barriers**

Phytoconstituents are the bioactive chemical compounds that confer therapeutic effectiveness of medicinal plants and constitute a wide array of structural classes, such as alkaloids, flavonoids, terpenoids, and polyphenols.(14). The nitrogen-containing alkaloids, which are characterised by their strong pharmacological properties (antimicrobial, analgesic, and antidiabetic actions), include berberine and morphine. Quercetin and catechins are flavonoids commonly known to have antioxidant, anti-inflammatory and cardioprotective properties.(15). The terpenoids, artemisinin and limonene, have strong anticancer, antimalarial and anti-inflammatory properties and polyphenols like resveratrol and curcumin have been extensively researched in regard to their use as chronic disease preventers, including cancer, diabetes and neurodegenerative disease.(16). Although they have an impressive therapeutic potential and are extensively used in both traditional and modern medicine, clinical translation of these phytoconstituents is severely curtailed by a number of biopharmaceutical issues that restrict their systemic availability and therapeutic effectiveness. Among the major challenges is low aqueous solubility, which affects a significant fraction of phytoconstituents, because they are hydrophobic and hence do not dissolve well in gastrointestinal fluids and, therefore, do not get absorbed(17). As an example, curcumin and resveratrol are highly insoluble in water, and this directly affects their bioavailability and restricts their use in clinical applications. The poor permeability across biological membranes also complicates their absorption, on top of solubility problems. The Biopharmaceutics Classification System (BCS) indicates that a large number of phytoconstituents belong to Class II or Class IV categories with low solubility and/or low permeability, leading to poor oral bioavailability. Moreover, the large amount of first-pass metabolism by the liver and intestinal mucosa prevents the concentration of active compounds in the systemic circulation to a considerable extent.(18). Quercetin, resveratrol and other compounds are rapidly broken down by metabolism to inactive or less active metabolites, which reduce their pharmacological activity. Chemical instability is also another important consideration because most phytoconstituents are very sensitive to environmental factors, including pH, light, oxygen, and enzyme degradation. To illustrate, catechins are likely to undergo oxidation, and curcumin cannot withstand alkalinity, which causes it to degrade very fast before it can take effect. All these barriers are interrelated, and together, they make up the so-called bioavailability gap in which strong in vitro performance fails to translate into good in vivo performance.(19).

**Table 1:** Key Phytoconstituents, Sources, and Bioavailability Constraints

| Phytoconstituent | Class | Natural Source | Therapeutic Activity | Bioavailability Constraints |
|---|---|---|---|---|
| Curcumin | Polyphenol | *Curcuma longa* (Turmeric) | Anti-inflammatory, anticancer, antioxidant | Poor solubility, rapid metabolism, and low absorption |
| Quercetin | Flavonoid | Onion, Apple, Tea | Antioxidant, anti-inflammatory, cardioprotective | Low permeability, extensive first-pass metabolism |
| Resveratrol | Polyphenol | Grapes, Red wine | Cardioprotective, anticancer, neuroprotective | Rapid metabolism, poor stability, low bioavailability |
| Berberine | Alkaloid | *Berberis* species | Antidiabetic, antimicrobial | Poor intestinal absorption, efflux by P-glycoprotein |
| Catechins | Flavonoid | Green tea (*Camellia sinensis*) | Antioxidant, anti-obesity | Chemical instability, poor bioavailability |
| Artemisinin | Terpenoid | *Artemisia annua* | Antimalarial, anticancer | Short half-life, poor |

| | | | | |
|---|---|---|---|---|
| | | | | solubility |
| Silymarin | Flavonoid | *Silybum marianum* (Milk thistle) | Hepatoprotective | Low water solubility, poor absorption |
| Luteolin | Flavonoid | Celery, Green pepper | Anti-inflammatory, anticancer | Poor solubility, rapid metabolism |
| Genistein | Isoflavone | Soybean | Anticancer, estrogenic activity | Low permeability, rapid metabolism |
| Piperine | Alkaloid | Black pepper (*Piper nigrum*) | Bioenhancer, anti-inflammatory | Poor solubility, limited bioavailability |

As highlighted in Table 1, important phytoconstituents of the different plant sources have severe limitations in terms of solubility, permeability, metabolic stability and chemical integrity, which ultimately limit their clinical performance. Thus, the effective application of phytoconstituents in the present-day therapy requires unprecedented approaches to address these inherent drawbacks, which has made the use of innovative drug delivery systems like nanotechnology-based preparations especially important.(20).

**Herbal Nanomedicine: Concepts and Design Principles**

Herbal nanomedicine is an emerging and cross-functional methodology that incorporates nanotechnology and traditional phytotherapy concepts in order to limit the intrinsic shortcomings of the plant-based bioactive compounds. The herbal nanoparticles may be broadly defined as nanoscale delivery systems, which are usually 1-1000 nm in diameter, aimed at encapsulating, protecting and delivering phytoconstituents in a controlled and targeted way(21). These nanocarriers can either be made of lipids, polymers or other biocompatible syntheses and are designed to increase the pharmacodynamics and pharmacokinetic properties of herbal medicines. Compared to traditional formulations, where phytoconstituents tend to be poorly soluble, degradable, and have low bioavailability, nanoparticle formulations have better dispersion, degradation protection and translocation across biological membranes(22). Key physicochemical properties are critical determinants of the design and performance of herbal nanoparticles, with particle size being central to performance. A smaller particle size increases surface area, which results in a high rate of dissolution and absorption in the gastroesophageal tract. In addition, the nanosized particles have the ability to promote cellular uptake through endocytosis and enhance tissue penetration, which enhances the effectiveness of therapy(23). Zeta potential is another crucial parameter that determines the surface charge of nanoparticles and determines their stability, aggregation behaviour, and interaction with biological membranes. The nanoparticles that have the best values of zeta potential are more colloidally stable and have a lower probability of aggregation, thus ensuring the delivery of the encapsulated phytoconstituents in a consistent manner(24). Surface modification is another design technique that allows the functionalization of nanoparticles with ligands, polymers, or targeting groups to allow site-specific delivery and increased circulation time. As an example, systemic stability can be improved, and immune recognition decreased by polyethene glycol (PEG) coating, and ligand conjugation can be used to target specific tissues or receptors. The reason why nano-enabled phytotherapy is relevant is due to its capacity to overcome the key obstacles in the clinical translation of herbal medicines, especially the challenge of low bioavailability and non-specific distribution(25). Through entrapment of phytoconstituents in nanocarriers, they can be protected against enzymatic degradation, and reduced premature metabolism, and sustained release or controlled release profiles can be attained. Also, nanoparticles have the potential to enhance tissue permeability to biological barriers, including intestinal epithelium and even the blood-brain barrier, to increase the therapeutic potential of herbal compounds to complex illnesses(26). This method can also be used to reduce the dose whilst preserving or increasing the therapeutic effects, which can reduce possible side effects and increase compliance with the patient. The herbal nanoparticles have a number of unique attributes over conventional dosage forms, including increased solubility of compounds that are insoluble in water, improved pharmacokinetic characteristics, targeting of delivery, and decreased variability in drug absorption. Also, nanoformulations allow the simultaneous delivery of several phytoconstituents, which can act in a synergistic manner and commonly occur in herbal treatment(27).

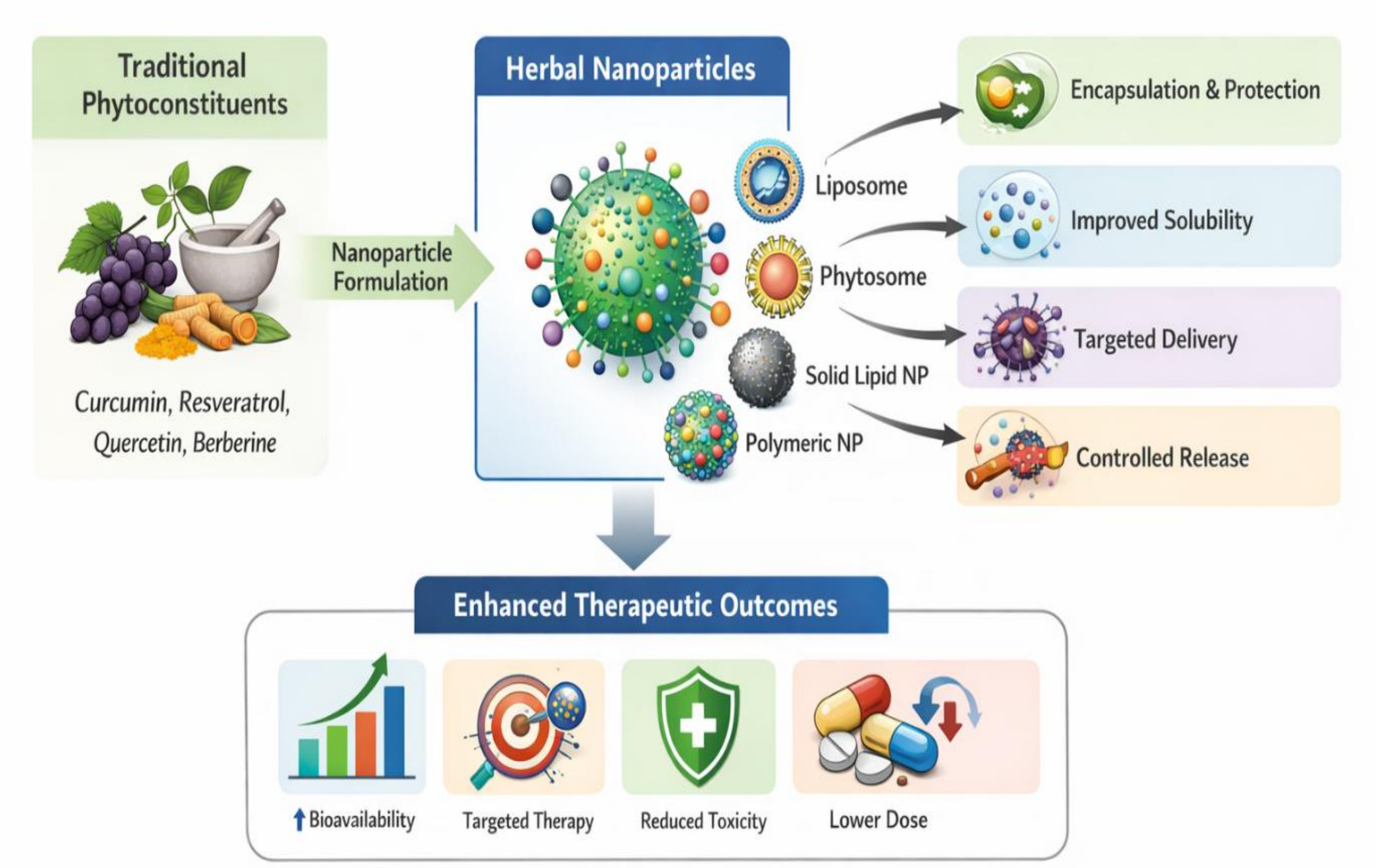


**Figure 1:** Conceptual Framework of Nano-Enabled Herbal Drug Delivery

As demonstrated in Figure 1, the theoretical framework of nano-enabled herbal drug delivery underlines the change of traditional phytoconstituents into nanoparticle-based systems with improved ability of encapsulation, protection, targeted transportation, and controlled release, which results in improved therapeutic responses and clinical outcomes. This is the incorporation of nanotechnology into herbal medicine, and it marks a paradigm shift to more specific, more efficient, and more scientifically proven phytotherapeutic interventions.(12).

**Nano-Engineered Delivery Systems for Phytoconstituents**

Nano-engineered delivery systems have become a platform in the development of the therapeutic potential of phytoconstituents to overcome the key constraints of solubility, stability and bioavailability. The phytosomes are one of such systems whereby the phytoconstituents are chemically conjugated to the phospholipids, which are usually phosphatidylcholine, making them more lipid soluble and improving their absorption across biological membranes(28). This type of structural integration enables phytosomes to resemble components of cell membranes, and in doing so enables effective transport and enhanced systemic availability of other compounds that are poorly absorbed, like flavonoids and polyphenols. Liposomes, on the other hand, are flexible vesicular carriers that are composed of a phospholipid bilayer or a series of phospholipid bilayers, which surround aqueous cores, allowing the simultaneous incorporation of hydrophilic and lipophilic phytoconstituents(29). Their biocompatibility, toxicity reduction capability and possible surface modification also make them very useful in targeted and controlled drug delivery applications. The use of liposomes in the delivery of compounds such as curcumin and quercetin has been widely studied, and it has shown better pharmacokinetic and pharmacodynamic results. Another promising method is solid lipid nanoparticles (SLNs), which use a solid lipid matrix to entrap phytoconstituents, thus providing improved stability, resistance to degradation, and controlled release of the drug(30). Their solid-state nature at room and body temperature provides SLNs with opportunities to avoid the premature release of active substances and secure the long-term release, which is especially useful in the management of chronic diseases. Moreover, SLNs are highly tolerant and scalable, which makes them interesting to use in industries. Conversely, polymeric nanoparticles are produced by the biodegradable polymers, including polylactic acid (PLA) or poly (lactic-co-glycolic acid) (PLGA), and are intended to deliver specific control over the drug release kinetics and targeting properties(31). These systems may be designed to obtain site-specific delivery by means of surface functionalization with ligands or antibodies, to increase the therapeutic effect and reduce systemic side effects. Polymeric nanoparticles are particularly beneficial in the delivery of sensitive phytoconstituents, which need protection against unfavourable physiological conditions, and the attainment of sustained and controlled release profiles(32). The performance of these nano-engineered systems is determined by a number of critical factors, such as the physicochemical behaviour of the phytoconstituent, the release profile of the desired properties, target location, and the method of administration. As an example, phytosomes are especially convenient to enhance the oral bioavailability of lipophilic compounds, but liposomes are better when it is necessary to encapsulate a large variety of compounds and deliver them directly to the target. SLNs have been shown to be beneficial in improving stability and long release, whereas polymeric nanoparticles are more versatile in customisation and precision targeting(24). All the nanocarrier systems have unique merits and demerits as summarised in Table 2, and their choice should be determined depending on the therapeutic needs and properties of the phytoconstituent.

**Table 2:** Comparative Analysis of Herbal Nanocarrier Systems

| Nanocarrier System | Composition | Key Features | Advantages | Limitations |
|---|---|---|---|---|
| **Phytosomes** | Phospholipid complexes (e.g., phosphatidylcholine) | Chemical bonding of phytoconstituent with phospholipids | Improved lipid solubility, enhanced absorption, better bioavailability | Limited drug loading capacity, relatively expensive |
| **Liposomes** | Phospholipid bilayer vesicles | Encapsulation of hydrophilic & lipophilic compounds | Biocompatible, reduced toxicity, targeted delivery possible | Stability issues, leakage, and high production cost |
| **Solid Lipid Nanoparticles (SLNs)** | Solid lipid core stabilised by surfactants | Solid matrix structure for drug entrapment | Controlled release, high stability, protection from degradation | Limited drug loading, risk of drug expulsion during storage |
| **Polymeric Nanoparticles** | Biodegradable polymers (PLA, PLGA, chitosan) | Matrix or reservoir systems | Sustained release, precise targeting, high stability | Possible polymer toxicity, complex preparation methods |
| **Nanoemulsions** *(optional addition for strength)* | Oil-in-water or water-in-oil emulsions | Nanosized droplets for improved dispersion | Enhanced solubility, rapid absorption | Physical instability, surfactant-related toxicity |

Moreover, Figure 2 shows how herbal nanocarriers are categorised and structurally differentiated to emphasise the differences in architecture, composition, and functional properties, which make them perform differently. This heterogeneity highlights the need to rationalise design and the need to select suitable nanocarrier systems to enhance the delivery and efficacy of herbal therapeutics. Together, these nano-engineered delivery systems can be seen as a breakthrough in the field of phytotherapy, allowing the conversion of conventional herbal products into very effective and clinically feasible therapeutic products(33).

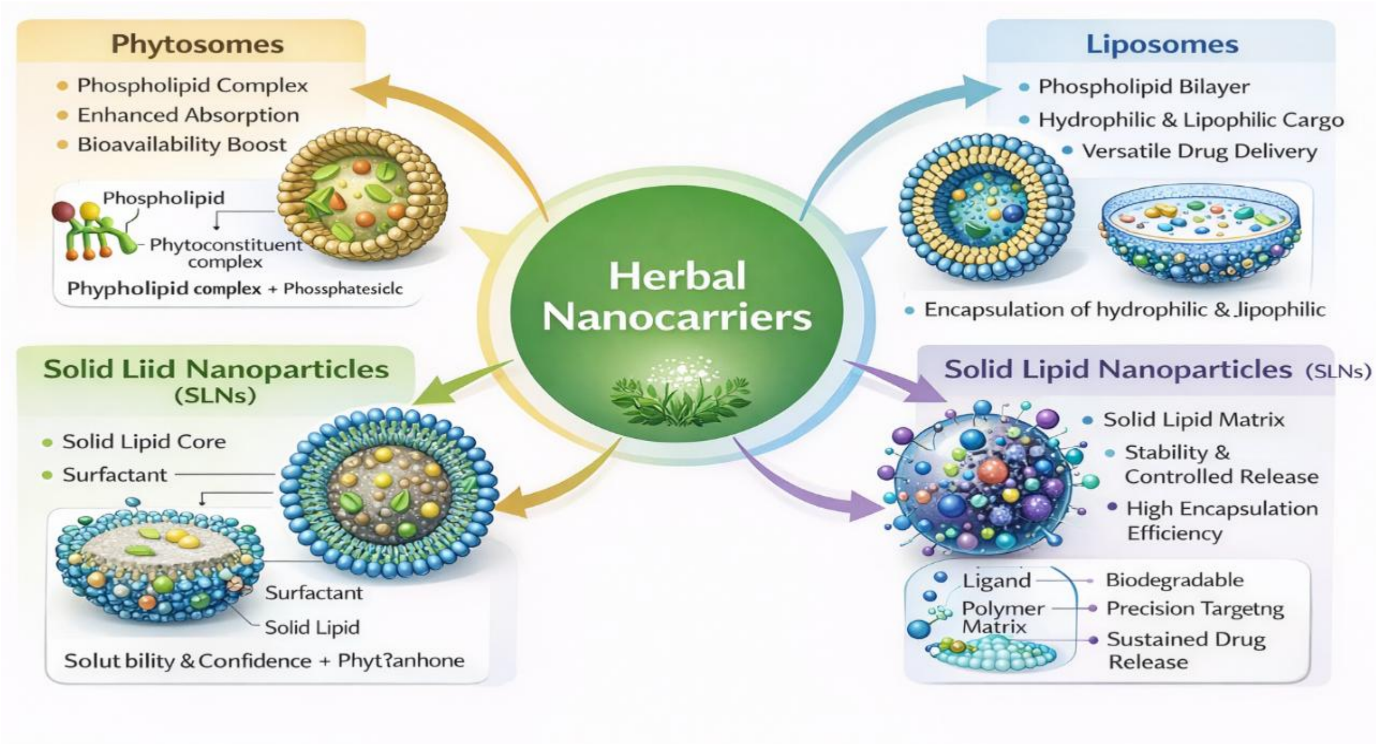


**Figure 2:** Classification and Structural Diversity of Herbal Nanocarriers

**Mechanistic Insights: How Nanoparticles Enhance Bioavailability**

Nanoparticle-based delivery systems enhance the bioavailability of phytoconstituents through a combination of interrelated physicochemical and biological mechanisms that collectively overcome the inherent limitations of conventional herbal formulations. One of the most fundamental factors is the nanoscale size of these carriers, which typically ranges from 1 to 1000 nm. Reduction of particle size dramatically increases the surface area-to-volume ratio, leading to enhanced dissolution rates according to the principles of surface-driven solubility(9). This is particularly important for poorly water-soluble phytoconstituents such as curcumin and resveratrol, whose limited dissolution in gastrointestinal fluids restricts their absorption. By converting these compounds into nanosized systems, their apparent solubility is significantly improved, thereby facilitating faster and more efficient drug release(34). In addition to size reduction, nanoparticles enhance dissolution and solubilization through the use of surfactants, lipids, or polymeric matrices that maintain the drug in a solubilised or amorphous state, preventing precipitation and ensuring sustained availability in the absorption window. Another critical mechanism involves enhanced intestinal permeability and uptake pathways(35). Nanoparticles can interact with the intestinal epithelium and be absorbed via multiple routes, including transcellular transport, paracellular diffusion, and endocytosis-mediated uptake. Specialised pathways such as Peyer’s patches and M-cells in the intestinal lymphatic system further facilitate nanoparticle absorption, allowing them to bypass traditional absorption barriers and, in some cases, avoid first-pass hepatic metabolism. This contributes to a significant increase in systemic bioavailability(36). Moreover, nanoparticle encapsulation provides a protective barrier around phytoconstituents, shielding them from harsh physiological conditions such as acidic pH in the stomach, enzymatic degradation in the gastrointestinal tract, and oxidative or hydrolytic breakdown. This protection preserves the structural integrity and pharmacological activity of sensitive compounds until they reach their target site. Another key advantage of nanoparticle systems is their ability to enable targeted delivery and controlled release kinetics(37).

Through surface modification and functionalization, nanoparticles can be engineered to recognise specific receptors or tissues, ensuring that the encapsulated phytoconstituents are delivered preferentially to the desired site of action. This not only enhances therapeutic efficacy but also minimises off-target effects and systemic toxicity. Controlled release mechanisms further allow for sustained drug release over an extended period, maintaining therapeutic concentrations and reducing the frequency of dosing(25). Additionally, certain nanocarriers can respond to environmental triggers such as pH, temperature, or enzymatic activity, enabling site-specific release in pathological conditions. The integration of these mechanisms results in a synergistic improvement in the pharmacokinetic profile of phytoconstituents, transforming them from poorly bioavailable compounds into highly efficient therapeutic agents(38).

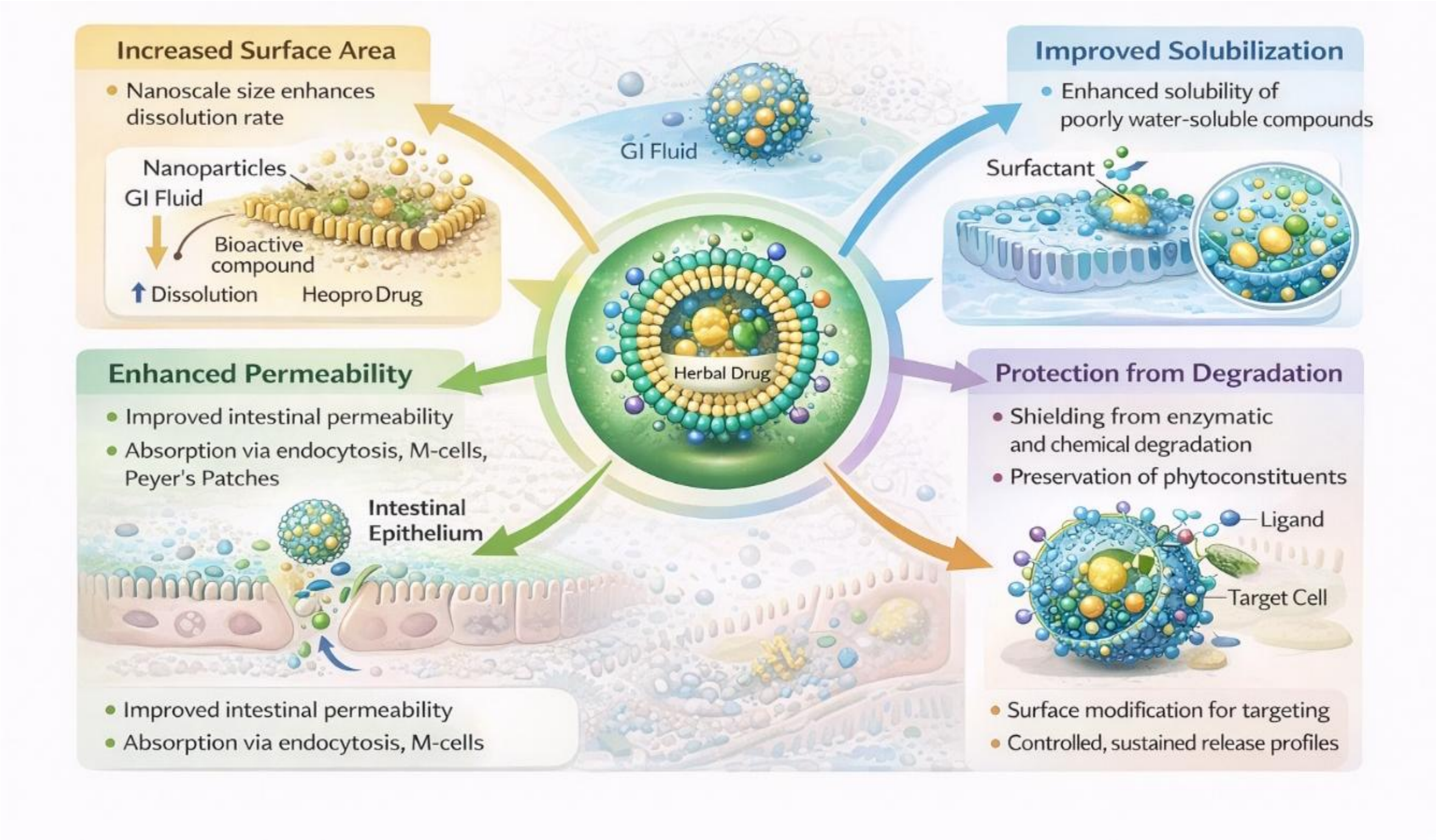


**Figure 3:** Multifactorial Mechanisms of Bioavailability Enhancement

As illustrated in Figure 3, the multifactorial mechanisms of bioavailability enhancement by nanoparticles encompass increased surface area, improved solubilization, enhanced permeability, protection from degradation, and targeted controlled delivery, all of which contribute to maximising the therapeutic potential of herbal drugs. Collectively, these mechanistic insights highlight the critical role of nanotechnology in overcoming traditional barriers in phytotherapy and advancing the clinical applicability of herbal medicines.(9).

## Therapeutic Landscape of Herbal Nanoparticles

In recent years, herbal nanoparticles have greatly expanded their therapeutic portfolio and provide novel solutions to the treatment of difficult and chronic illnesses due to their improved delivery and activity of phytoconstituents. Nanoparticle-based herbal formulations are very promising in the targeted anticancer approach in oncology by enhancing the concentration of drugs at the tumour site and reducing the systemic toxicity(39). The nanocarriers like liposomes, polymeric nanoparticles and solid lipid nanoparticles allow passive targeting through the enhanced permeability and retention (EPR) effect, and active targeting through ligand functionalization, making them useful in selectively delivering phytoconstituents, including curcumin, resveratrol and quercetin to cancer cells. Such systems exhibit increased apoptosis, anti-tumour growth, and minimise destruction of normal tissues, which makes them potential complements or substitutes to standard chemotherapy(40). Nano-enabled phytotherapy has been a promising field in the context of diabetes management regarding the enhancement of glycemic control and insulin sensitivity. When prepared using nanoparticles, phytoconstituents like berberine and curcumin are better absorbed and have a longer shelf life, which results in improved control of glucose metabolism and the insulin-resistant state(41). Sustained release profiles are also facilitated by these nanoformulations and are useful in ensuring sustained therapeutic concentration, and the frequency of doses is reduced, thus enhancing compliance among patients. Another important field, which has witnessed the strong benefits of herbal nanoparticles, is the area of neuroprotective applications, especially in circumventing the inhibitory property of the blood-brain barrier (BBB). Nanocarriers have the potential of enhancing the therapeutic effectiveness of neuroactive phytoconstituents like resveratrol and curcumin in neurodegenerative diseases like Alzheimer's and Parkinson's disease by transporting them to the central nervous system(42). These systems are linked to reduced oxidative stress, neuroinflammation prevention, and improved cognitive performance through improving brain bioavailability. Moreover, the antimicrobial and anti-inflammatory properties of herbal nanoparticles have become more and more popular, especially in light of the growth of antimicrobial resistance. Nanoformulations of plant derivatives have better penetration into microbial cells, biofilm disruption, as well as pharmacokinetics, and have a higher level of efficacy when used against resistant pathogens. The anti-inflammatory effects of phytoconstituents, as well, are enhanced by the use of nanoparticle delivery, which allows for controlling the inflammatory pathways and mitigating chronic inflammation(43).

**Table 3:** Disease-Specific Applications of Herbal Nanoparticles with Mechanistic and Therapeutic Insights

| Disease Domain | Phytoconstituent (Source) | Nanocarrier Platform | Molecular/Cellular Mechanism | Pharmacokinetic Advantage | Therapeutic Outcome |
|---|---|---|---|---|---|
| **Cancer (Oncology)** | Curcumin (*Curcuma longa*) | Liposomes / Polymeric Nanoparticles | Induction of apoptosis (↑ caspase activity), inhibition of NF-κB signalling, and anti-angiogenesis | Enhanced tumour accumulation (EPR effect), improved stability | Targeted tumour suppression with reduced systemic toxicity |
| | Resveratrol (Grapes) | SLNs / Polymeric Nanoparticles | Cell cycle arrest (G1/S phase), ROS modulation, anti-proliferative activity | Sustained release, protection from rapid metabolism | Improved anticancer efficacy and bioavailability |
| | Quercetin (Fruits, Tea) | Liposomes | Inhibition of the PI3K/Akt pathway, anti-inflammatory action | Increased cellular uptake and permeability | Enhanced tumour targeting and therapeutic response |
| **Diabetes Mellitus** | Berberine (*Berberis spp.*) | Polymeric Nanoparticles / SLNs | Activation of the AMPK pathway, modulation of glucose metabolism enzymes | Improved oral absorption, reduced first-pass metabolism | Superior glycemic control and insulin sensitisation |
| | Curcumin (*Curcuma longa*) | Nanoemulsion / Liposomes | Anti-inflammatory (↓ TNF-α, IL-6), antioxidant (↓ oxidative stress) | Enhanced solubility and systemic availability | Improved glucose homeostasis and metabolic |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | regulation |
| **Neurodegenerative Disorders** | Resveratrol (Grapes) | Polymeric Nanoparticles | Anti-amyloid aggregation, neuroprotection, mitochondrial stabilisation | Enhanced BBB penetration and brain targeting | Improved cognitive function and neuroprotection |
| | Curcumin (*Curcuma longa*) | SLNs / Liposomes | Inhibition of neuroinflammation, reduction of oxidative stress | Increased brain bioavailability and retention | Enhanced neuronal protection and therapeutic efficacy |
| **Antimicrobial Therapy** | Berberine (*Berberis spp.*) | Liposomes | Disruption of bacterial membrane integrity, inhibition of efflux pumps | Improved intracellular delivery and retention | Enhanced activity against resistant microbial strains |
| | Eugenol (Clove oil) | Nanoemulsion | Membrane destabilisation, antifungal and antibacterial effects | Increased dispersion and penetration | Broad-spectrum antimicrobial efficacy |
| **Anti-inflammatory Disorders** | Quercetin (Vegetables, Fruits) | Polymeric Nanoparticles | Downregulation of pro-inflammatory cytokines (IL-1β, TNF-α) | Sustained release and targeted delivery | Reduced inflammation and tissue damage |
| | Catechins (Green tea) | SLNs | Free radical scavenging, inhibition of inflammatory pathways | Enhanced stability against oxidation | Improved therapeutic response and bioavailability |

As summarised in Table 3, a range of herbal nanoparticles have been effectively used in a wide array of disease states, and the individual phytoconstituents have shown improved therapeutic response to be achieved using nano-engineered delivery systems.

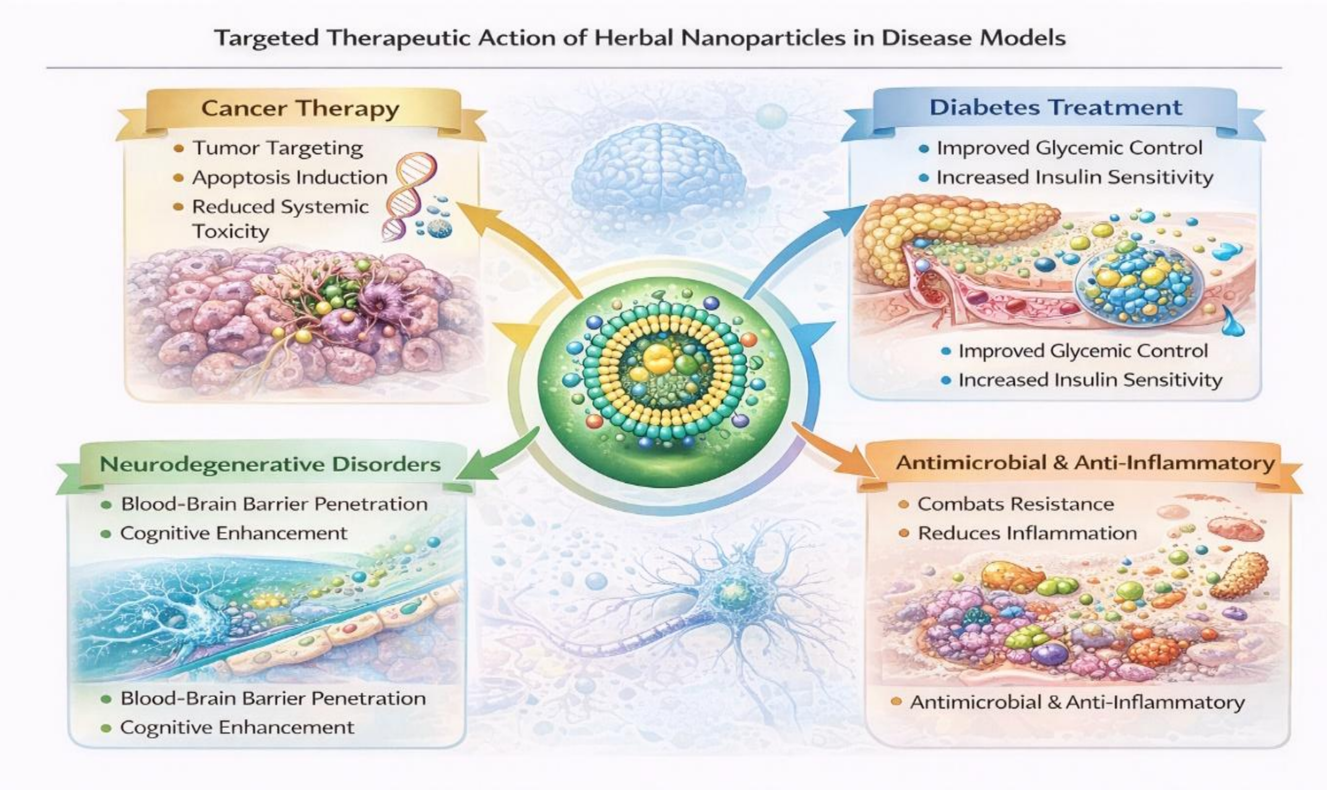


**Figure 4:** Targeted Therapeutic Action of Herbal Nanoparticles in Disease Models

Additionally, Figure 4 represents the therapeutic action targeted by the herbal nanoparticle in various disease models, and it shows that nanoparticles can deliver the therapeutic agent to a specific site, with controlled release, and enhanced pharmacological effects. All these developments highlight the revolutionary nature of herbal nanomedicine in the medical field as it seeks to fill the divide between the ancient practice of using plants as medicine and the state-of-the-art drug delivery methods, and provide patients with a safer, more effective, and convenient way to treat their ailments.(44).

## Clinical and Pharmacological Advantages

Drug delivery systems based on herbal nanoparticles have profound clinical and pharmacological benefits, which make them an exceptional innovative method in contemporary therapeutics, especially in improving the efficacy of phytoconstituents, which are characterised by low solubility, instability, and high metabolic rates(45). Among the most significant advantages, there is an increase in bioavailability and therapeutic index by a significant factor because nanoscale carriers have a greater surface area, better dissolution, and increased absorption across biological membranes, leading to an increase in systemic availability and more predictable and steady drug concentrations at the target site(12). This enhanced delivery guarantees a larger proportion of the dose used is pharmacologically active, therefore maximising therapeutic effect and minimising variability in response. Nanoparticle encapsulation also helps to protect phytoconstituents against enzyme degradation and unfavourable physiological environments, extending their circulation time and drug delivery(46). A second significant benefit is that it is possible to reduce dose and minimize drug adverse effects; targeted delivery enables lower doses to be used to achieve the desired therapeutic effect and reduce systemic exposure and off-target interactions; this is especially particularly useful in diseases like cancer, where nanoparticle-mediated delivery can concentrate on tumor tissue and avoid normal cells and thus improves safety profiles(47). Moreover, patient compliance to herbal nanoparticles is greatly enhanced by the capacity to attain controlled and long-term drug delivery, thereby decreasing the number of doses and keeping therapeutic concentrations constant over a long duration of time, which is of particular importance in chronic disease management, such as diabetes and neurodegenerative conditions(48). Better adherence to treatment regimens is also associated with a lower rate of side effects. Furthermore, nanoparticle systems have the benefit of adjusting to various routes of administration, including, but not limited to, oral, topical, and parenteral delivery, and enhance further convenience and acceptability. Notably, the possibility of site-specific targeting is one of the largest improvements in herbal therapeutics, because nanoparticles can be surface-modified with ligands or antibodies to prevent selective binding to certain cells or tissues, which will provide precise drug delivery and increased therapeutic effects(49). Further enhancement of targeting specificity and effectiveness occurs through stimulus-sensitive nanoparticles that can release their cargo in response to environmental factors, e.g. pH or temperature. All these benefits prove the idea that herbal nanoparticles not only address the shortcomings of traditional herbal preparations but also conform to the ideals of contemporary precision medicine, providing safer, more effective, and patient-centred treatment methods(50).

## Challenges and Translational Barriers

Although herbal nanoparticles hold promise as a therapeutic agent, numerous challenges and translational issues limit their effective clinical application and large-scale commercialisation, and consideration of these challenges and appropriate measures should be undertaken. Among the key issues, one can distinguish nanotoxicity and safety assessment, because due to the specific physicochemical characteristics of nanoparticles, including small size, high surface area, and surface reactivity, they can engage in unexpected biological interactions, including cytotoxicity, immunogenicity, and organ accumulation(29). In spite of the fact that most nanocarriers are fabricated with biocompatible and biodegradable materials, extensive in vitro and in vivo toxicity analyses are necessary to determine the long-term safety, pharmacokinetics, and biodistribution of nanocarriers. The other huge constraint is the stability and storage aspect, whereby in most cases, nanoparticles tend to be affected by aggregation, sedimentation or even chemical degradation with time, and thus affecting their effectiveness and reproducibility.(28). Nanoparticle stability can be affected by temperature, pH, light exposure and formulation composition; thus, it is important to establish optimal storage conditions and stabilising agents to preserve the integrity of the product during its shelf life of the product. Along with these difficulties, the scale-up and manufacturing complications are another significant barrier to commercial viability when it comes to the scale-up of laboratory-scale formulations into commercial products.(51). Reproducibility of nanoparticle fabrication, regulation of the dispersion of the size of particles, encapsulation and consistency across batches are challenging to sustain in large-scale fabrication. In addition, the high price of the sophisticated equipment, raw materials, and quality control procedures may equally constrain industrial feasibility. The solution to these concerns is to establish standardised, cost-effective and scalable manufacturing methods that deliver uniform quality of products without negatively affecting therapeutic performance.(52). The regulatory and quality control issues are also critical towards the delay in clinical translation of herbal nanomedicines. Presently, there is no clearly defined and internationally agreed regulatory policy specifically designed to be applied to nanoparticle-based herbal preparations because they lie at the border between pharmaceuticals, nanotechnology and traditional medicine. The regulatory ambiguity does not make the approval process easier because manufacturers have to satisfy high standards regarding safety, efficacy, characterisation, and quality assurance. Moreover, the standardisation and quality control are further complicated by the variability of the herbal raw materials because of differences in the source of plants, cultivation conditions, and methods used to extract them.(53).

**Table 4:** Challenges, Regulatory Concerns, and Emerging Solutions in Herbal Nanomedicine

| Challenge Category | Key Issues | Regulatory Concerns | Impact on Development | Emerging Solutions/Strategies |
|---|---|---|---|---|
| **Nanotoxicity & Safety Evaluation** | Cytotoxicity, immunogenicity, organ accumulation, and long-term | Lack of standardised toxicity assessment | Delays in clinical approval, safety concerns | Advanced in vitro/in vivo models, nanotoxicology studies, use of |

| | | | | |
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| | toxicity | protocols for nanomaterials | | biocompatible materials |
| **Stability & Storage Limitations** | Aggregation, sedimentation, chemical degradation, and poor shelf-life | Requirements for stability data under ICH guidelines | Reduced efficacy, variability in product quality | Lyophilisation, use of stabilisers, optimised storage conditions |
| **Scale-up & Manufacturing Complexities** | Reproducibility issues, batch-to-batch variability, and high production cost | GMP compliance challenges, lack of standardised manufacturing processes | Difficulty in commercialisation and industrial translation | Scalable fabrication techniques, process optimisation, and cost-effective methods |
| **Regulatory Framework Gaps** | Lack of clear guidelines for herbal nanomedicine classification | Ambiguity between herbal, pharmaceutical, and nanotech regulations | Delayed approvals, inconsistent evaluation criteria | Development of harmonised global guidelines, regulatory standardisation |
| **Quality Control of Herbal Raw Materials** | Variability in phytoconstituent content due to source, climate, and extraction methods | Requirement for strict standardisation and authentication | Inconsistent therapeutic outcomes | Use of chromatographic techniques, fingerprinting, and standardisation protocols |
| **Characterization Challenges** | Difficulty in measuring size, zeta potential, and drug loading accurately | Requirement for validated analytical methods | Poor reproducibility and lack of comparability | Advanced analytical tools (DLS, TEM, SEM), standardised characterisation methods |
| **Clinical Translation Barriers** | Limited clinical trials, lack of human data | Strict clinical validation requirements | Slow transition from lab to clinic | Increased clinical studies, interdisciplinary collaboration |
| **Intellectual Property (IP) Issues** | Difficulty in patenting natural product-based nanoformulations | Complex patent regulations for herbal products | Reduced commercial incentives | Innovative formulation strategies, stronger IP frameworks |

To develop consistent therapeutic effects, it is important to ensure consistency in the content of phytoconstituents and nanoparticle development. These obstacles include safety issues, stability in formulation, scalability in production, and regulatory obstacles, in addition to new strategies to address these obstacles, including improved characterisation methods, green synthesis methods, and regulatory harmonisation, as listed in Table 4. Together, these translational challenges would be essential in unlocking the full potential of herbal nanomedicine and enabling it to enter mainstream clinical practice(54).

**Future Perspectives: Towards Precision Herbal Nanomedicine**

The future of herbal nanomedicine is more inclined towards a precision-based approach, which incorporates modern technologies with traditional therapeutic knowledge in the development of more effective and individual treatment outcomes. One of the main sources of this change is the use of artificial intelligence (AI) in the design of formulations, whereby computational models and machine learning algorithms can be used to analyse multifaceted relationships between phytoconstituents, nanocarrier traits, and biological processes to optimise drug delivery with additional precision and effectiveness.(55). This not only increases the speed of the development process but also increases predictability in terms of bioavailability, stability, and therapeutic performance. In conjunction with this, individualised phytotherapy is becoming an interesting approach, whereby the formulations of herbs in the form of nanoparticles are customised to suit unique patient factors like genetic profile, disease status, and metabolic variability, hence maximising efficacy with minimal adverse effects. The combination of herbal nanomedicine with contemporary pharmacology makes it even more clinically relevant in that it can be used to combine phytoconstituents with standard drugs, better targeting, and be integrated into evidence-based clinical regimens.(44). This kind of integration helps reduce the traditional-modernity rift between conventional and modern pharmaceutical science, and thus, herbal therapies are more acceptable in mainstream healthcare systems. Nevertheless, scientific validation of these innovations by properly designed preclinical and clinical trials is a solid background for successful translation into clinical practice.(56). Even now, the absence of large human trials is an important drawback, as it is evident that high-quality clinical testing is much-needed to determine safety, efficacy, and standardisation of dosage. Secondly, it is imperative to create transparent and cohesive regulatory systems that can be used to guarantee quality control, standardisation, and international acceptance of formulations based on herbal nanoparticles.(57). The regulatory bodies should respond to the specific issues arising with the integration of herbal medicine and nanotechnology by setting up certain guidelines on characterisation, safety evaluation and approval procedures. Taken together, these developments suggest that precision herbal nanomedicine can transform the approaches to treatments by integrating innovation, personalisation, and rigor and eventually lead to more efficient and patient-centred treatment solutions(58).

**Conclusion: The Future of Herbal Therapeutics in the Nano Era**

The unification of nanotechnology and herbal medicine is a milestone shift in the history of modern medicine, with a bright future of breaking the traditional constraints that have been facing the conventional use of phytotherapy. Herbal nanoparticles have shown great potential in improving the bioavailability, stability, and targeted delivery of phytoconstituents and opening up their complete therapeutic promise in a broad array of diseases. Nano-enabled systems can overcome the important pharmacokinetic and pharmacodynamic obstacles to clinical translation of herbal medicines by enhancing solubility, preventing degradation of bioactive compounds, and providing control and local (site) delivery of the active compounds. Moreover, the combination of the innovative nanocarrier platforms with the conventional plant-based molecules will be suitable in the context of the increased need for safer, more effective, and more patient-focused treatment options. Safety, scalability, standardization, and regulatory approval issues, despite these improvements, should be addressed in a systematic manner to enable more widespread clinical adoption. Further studies, interdisciplinary efforts and solid clinical validation will be required to determine the effectiveness and safety of these novel formulations. In the future, the future of herbal therapeutics under the nano era is in precision medicine solutions under this method; personalised, targeted, and scientifically validated herbal nanomedicines can be designed to address individual patient needs. Finally, herbal nanomedicine has tremendous potential to fill the gap between traditional and modern pharmaceutical science to create a new era of effective and sustainable therapeutic solutions.

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