



## **From Phytochemicals to Smart Therapeutics: Recent Advances in Herbal Nanomedicine, Responsive Drug Delivery and Functional Pharmaceutical Excipients**

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### **ABSTRACT**

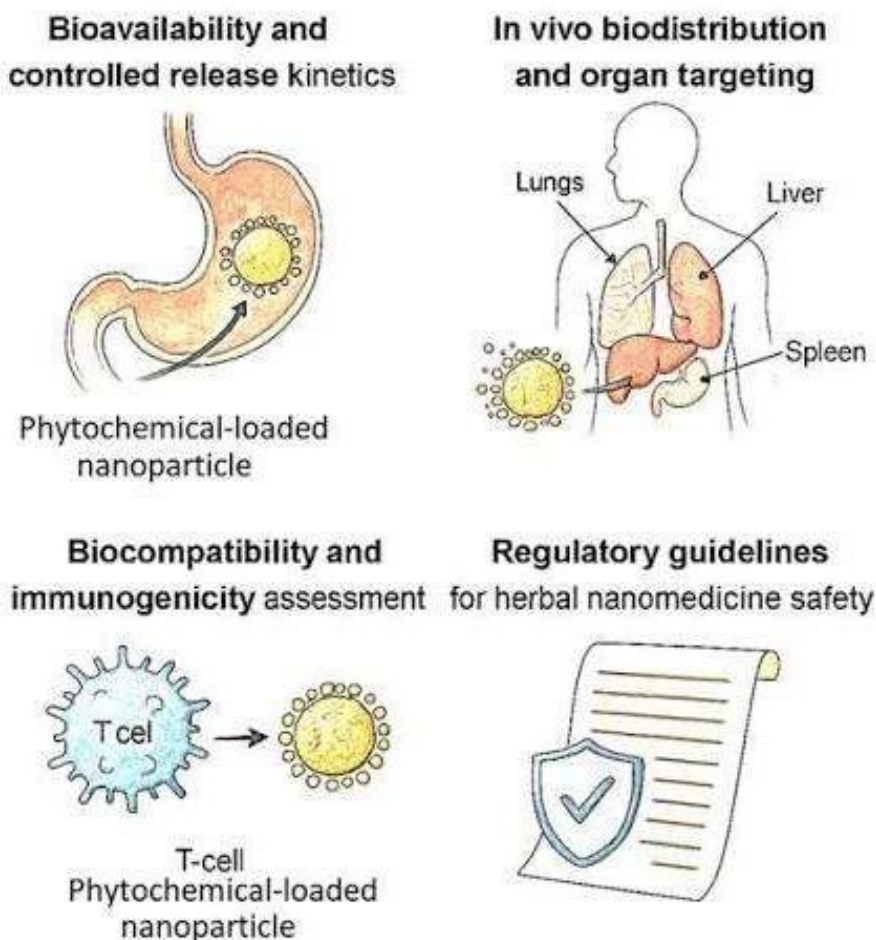
Phytochemicals represent a valuable source of biologically active compounds with considerable potential for the development of therapeutic agents. However, their pharmaceutical application is frequently restricted by poor aqueous solubility, chemical instability, limited bioavailability, rapid metabolism and inadequate site-specific delivery. Recent advances in nanotechnology have provided innovative approaches for overcoming these limitations through the development of herbal nanomedicine and phytochemical-loaded nanocarriers. This review examines recent developments in phytochemical delivery, focusing on nanocarriers, responsive drug-delivery systems and functional pharmaceutical excipients. Liposomes, phytosomes, lipid nanoparticles, polymeric nanoparticles and nanoemulsions are discussed in relation to their ability to enhance stability, solubility, absorption, controlled release and therapeutic performance. Particular attention is given to stimuli-responsive systems capable of responding to physiological or externally applied triggers, including pH, enzymes, redox conditions, temperature, light and magnetic stimuli. The emerging contribution of functional excipients, including natural polymers, lipids, cyclodextrins and biofunctional materials, is also considered. The review further examines therapeutic applications, formulation challenges, safety, standardisation, scalability and regulatory barriers. Overall, the convergence of phytochemistry, nanotechnology, responsive delivery and functional excipient engineering represents a promising pathway towards more precise, stable and effective herbal therapeutics.

**Keywords:** phytochemicals; herbal nanomedicine; nanocarriers; smart therapeutics; responsive drug delivery; stimuli-responsive systems; functional pharmaceutical excipients; phytosomes; controlled release; bioavailability

### **INTRODUCTION**

Medicinal plants have long represented an important reservoir of structurally diverse molecules with pharmacological potential. Contemporary natural-product research has demonstrated that plant-derived compounds can provide antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective and neuroprotective activities, thereby maintaining their relevance to modern pharmaceutical research. The renewed interest in natural products has been supported by advances in analytical chemistry, molecular biology, metabolomics

and drug-development technologies, which have improved the identification and characterisation of pharmacologically active constituents (Atanasov et al., 2021). Phytochemicals such as polyphenols, flavonoids, alkaloids, terpenoids, saponins and phenolic acids possess diverse molecular structures and biological activities, but their pharmaceutical translation is frequently restricted by physicochemical and pharmacokinetic limitations.



The therapeutic performance of a phytochemical depends not only on its intrinsic biological activity but also on its solubility, chemical stability, permeability, absorption, distribution, metabolism and elimination. Consequently, compounds demonstrating promising activity in experimental models may show limited efficacy when administered through conventional dosage forms. Recent research has therefore shifted from simply identifying bioactive plant constituents towards developing delivery systems capable of protecting, transporting and releasing these molecules in a controlled manner. Nanotechnology has become particularly important in this transition because nanoscale carriers can modify solubility, improve stability, facilitate cellular uptake and influence the biodistribution of encapsulated phytochemicals (Dewi et al., 2022).

Herbal nanomedicine extends this concept by incorporating whole herbal extracts, enriched fractions or selected phytoconstituents into nanoscale pharmaceutical systems. Such approaches include liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and polymeric micelles. The field



is now progressing further towards smart therapeutics, in which delivery systems are designed to respond to physiological or externally applied stimuli. Responsive systems can exploit pH, temperature, enzymes, redox conditions, light, magnetic fields or other biological signals to regulate drug release at specific sites (Fang et al., 2021). This transition from conventional delivery towards intelligent, stimulus-responsive and multifunctional systems provides a foundation for integrating phytochemicals with advanced pharmaceutical technologies.

### **PHYTOCHEMICALS AS THERAPEUTIC BIOACTIVE AGENTS**

Phytochemicals constitute a chemically heterogeneous group of secondary metabolites synthesised by plants for physiological, ecological and protective functions. Major groups include phenolic compounds, flavonoids, tannins, alkaloids, terpenoids, saponins, lignans and organosulphur compounds. Their structural diversity is associated with a broad spectrum of biological activities, including modulation of oxidative stress, inflammatory signalling, microbial growth, cellular proliferation and apoptosis. Altemimi et al. (2017) highlighted the extensive diversity of plant-derived phenolic compounds and their antioxidant, antimicrobial and anticancer potential, demonstrating the considerable pharmacological resource represented by botanical materials.

Several phytochemicals have subsequently attracted substantial pharmaceutical interest because their molecular mechanisms can interact with multiple biological pathways. Curcumin, for example, has been investigated extensively for anti-inflammatory, antioxidant and anticancer effects, while quercetin, resveratrol, epigallocatechin gallate, silymarin and berberine have also demonstrated diverse pharmacological properties. Such compounds may act on multiple molecular targets rather than producing a single highly selective pharmacological effect, making them particularly relevant to complex disorders involving oxidative stress, inflammation and metabolic dysregulation. The modern drug-discovery perspective increasingly recognises natural products as sources of both therapeutic molecules and molecular templates for pharmaceutical development (Atanasov et al., 2021).

Despite this potential, the therapeutic value of a phytochemical cannot be assessed solely from its pharmacological activity. Molecular size, polarity, lipophilicity, ionisation behaviour and chemical stability strongly influence absorption and systemic exposure. Many phytochemicals exhibit low aqueous solubility, rapid degradation, extensive metabolism or poor membrane permeability. Consequently, an experimentally potent molecule may produce inadequate concentrations at its intended biological site following conventional administration. Barani et al. (2021) emphasised that poor bioavailability and selectivity represent important barriers to the clinical application of phytochemicals, particularly those with limited aqueous solubility.

The pharmaceutical development of phytochemicals therefore increasingly involves formulation strategies that preserve their biological integrity while improving their delivery characteristics. Rather than treating the phytochemical and its formulation as independent components, contemporary research considers the active compound, carrier system and biological environment as an integrated therapeutic platform.



## **LIMITATIONS OF CONVENTIONAL HERBAL AND PHYTOCHEMICAL DELIVERY**

Conventional herbal formulations, including powders, decoctions, tinctures, capsules and simple extracts, can provide a practical means of administering plant-derived therapeutics, but their pharmaceutical performance is often affected by considerable variability. Herbal extracts may contain numerous constituents with different physicochemical characteristics, and the concentration of individual bioactive compounds can vary according to plant species, geographical origin, cultivation conditions, harvesting period, extraction procedure and storage. Such variability creates difficulties in achieving reproducible composition and therapeutic performance. For pharmaceutical development, these factors necessitate systematic characterisation and standardisation of the botanical starting material and finished formulation.

A further limitation concerns the intrinsic physicochemical properties of many phytochemicals. Poor aqueous solubility can restrict dissolution in gastrointestinal fluids and subsequently limit absorption, whereas inadequate membrane permeability can restrict transport across biological barriers. Phytochemicals may also undergo oxidation, hydrolysis, photodegradation or enzymatic metabolism during formulation, storage and gastrointestinal transit. Ahmad et al. (2021) noted that gastrointestinal degradation and limited transport across biological barriers can substantially reduce the effective delivery of phytochemicals, thereby restricting their bioefficacy.

Conventional administration can also result in rapid metabolism and elimination. First-pass hepatic and intestinal metabolism may substantially reduce systemic exposure to orally administered phytochemicals. In addition, extensive protein binding, rapid clearance or transformation into metabolites with different biological properties can influence therapeutic outcomes. These pharmacokinetic limitations may require relatively high or repeated doses, which can reduce patient acceptability and potentially increase the likelihood of adverse effects.

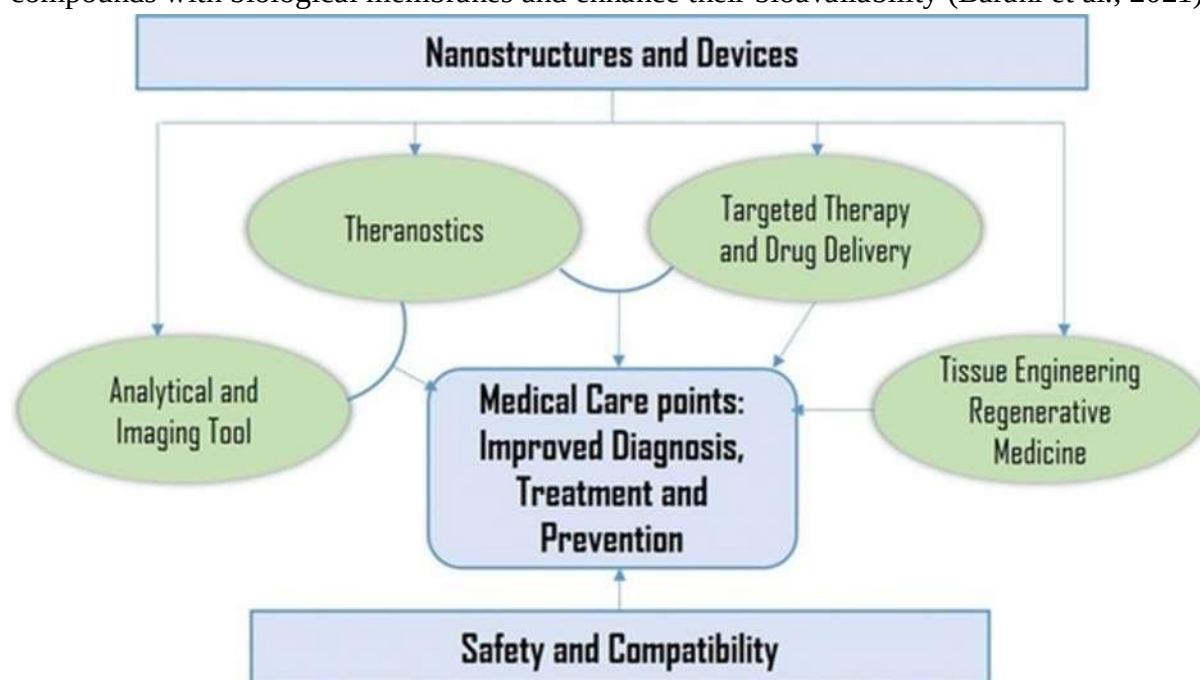
Another important challenge is the limited ability of conventional dosage forms to provide site-specific delivery. A phytochemical administered as a conventional tablet, capsule or extract generally undergoes distribution throughout the body rather than being selectively transported to the diseased tissue. Consequently, the concentration reaching the target site may be considerably lower than the administered dose. Conventional systems also provide limited control over the temporal pattern of drug release.

These limitations have encouraged the development of pharmaceutical carriers capable of protecting phytochemicals against degradation, increasing apparent solubility, improving absorption and controlling release. Such systems can additionally modify the interaction of phytochemicals with biological membranes and facilitate cellular uptake. The emergence of nanotechnology has therefore provided an important technological route for addressing several limitations simultaneously, although formulation complexity, scale-up, toxicity assessment and regulatory standardisation remain important considerations (Teja et al., 2022).

## **HERBAL NANOMEDICINE: CONCEPTS AND RECENT ADVANCES**

Herbal nanomedicine refers to the development of nanoscale pharmaceutical systems containing herbal extracts, enriched fractions, marker compounds or isolated phytochemicals. The fundamental objective is to modify the pharmaceutical and biopharmaceutical characteristics of plant-derived therapeutics without eliminating their biological activity. At the nanoscale, increased surface area, altered interfacial properties and controlled interactions with biological membranes can improve dissolution, dispersion, absorption and cellular uptake. Consequently, nanotechnology provides a bridge between traditional phytotherapy and contemporary drug-delivery science (Dewi et al., 2022).

The field encompasses a broad range of delivery platforms. Liposomes and phytosomes can improve the incorporation and transport of poorly water-soluble phytochemicals, whereas solid lipid nanoparticles and nanostructured lipid carriers provide lipid-based environments capable of enhancing protection and controlled release. Polymeric nanoparticles can provide sustained release and surface functionalisation, while nanoemulsions can improve the dispersion of lipophilic plant constituents. Phytosomes are particularly relevant because phospholipid–phytoconstituent complexes can improve the interaction of botanical compounds with biological membranes and enhance their bioavailability (Barani et al., 2021).



Recent advances have also moved beyond simple encapsulation. Herbal nanomedicines are increasingly designed according to the physicochemical characteristics of the active material, including molecular size, polarity, solubility and permeability. Teja et al. (2022) highlighted the importance of selecting appropriate nanocarriers and optimising parameters such as particle size, polydispersity, surface charge, encapsulation efficiency, drug loading and release characteristics. Such formulation-based optimisation is essential because different phytochemicals and herbal extracts require different carrier environments.

The development of herbal nanomedicine is also moving towards multifunctional systems capable of combining improved bioavailability with targeted delivery, sustained release and

protection from degradation. However, translating laboratory-scale nanoformulations into pharmaceutical products requires control of batch-to-batch consistency, manufacturing reproducibility, long-term stability, biocompatibility and regulatory quality. The complexity of botanical materials makes these requirements particularly important because variability in the chemical composition of extracts can influence nanoparticle characteristics and therapeutic performance.

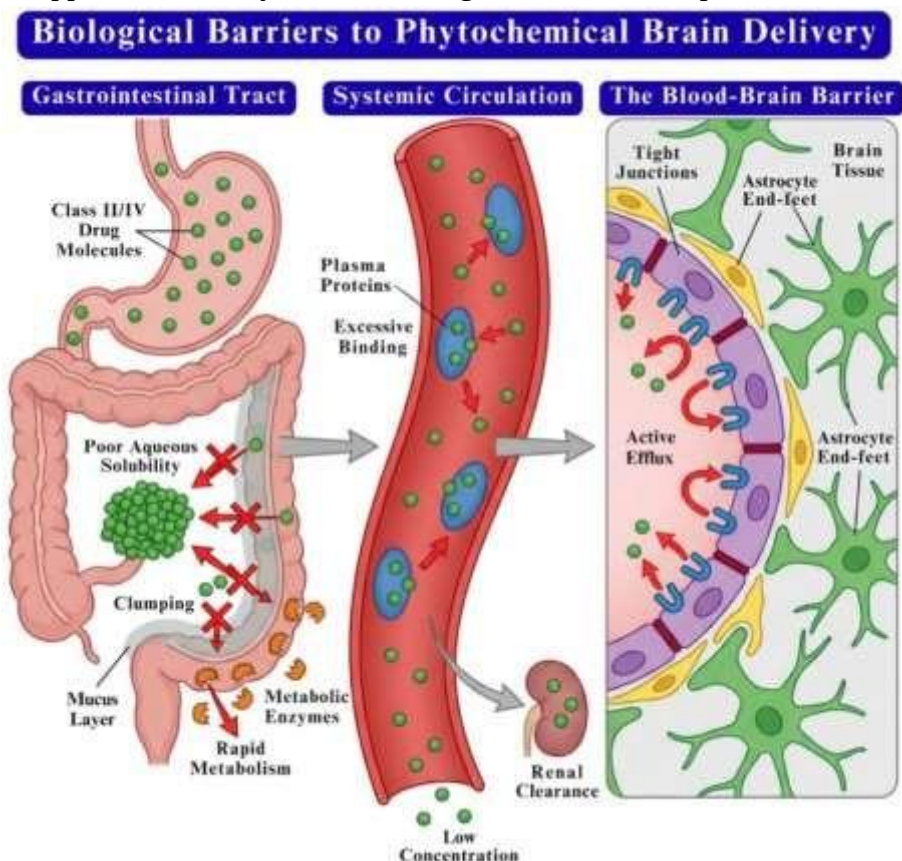
| <b>Nanomedicine platform</b>  | <b>Major formulation characteristic</b> | <b>Potential advantage for herbal bioactives</b>      |
|-------------------------------|-----------------------------------------|-------------------------------------------------------|
| Phytosomes                    | Phospholipid–phytoconstituent complex   | Improved membrane interaction and bioavailability     |
| Liposomes                     | Phospholipid bilayer vesicles           | Encapsulation of hydrophilic and lipophilic compounds |
| Solid lipid nanoparticles     | Solid lipid matrix                      | Protection and controlled release                     |
| Nanostructured lipid carriers | Mixture of solid and liquid lipids      | Improved loading and release characteristics          |
| Polymeric nanoparticles       | Biodegradable polymeric matrix          | Sustained and potentially targeted delivery           |
| Nanoemulsions                 | Nanoscale oil–water dispersion          | Improved dispersion of poorly water-soluble compounds |

## **NANOCARRIERS FOR PHYTOCHEMICAL DELIVERY**

Nanocarriers are central to the development of advanced phytochemical delivery systems because they can modify the physicochemical environment surrounding a bioactive molecule and consequently influence its absorption, distribution and release. Depending on the characteristics of the phytochemical, carriers may be constructed from lipids, phospholipids, biodegradable polymers, proteins, polysaccharides or combinations of organic and inorganic materials. Ahmad et al. (2021) described nanocarrier-based delivery as an approach capable of improving the stability, dispersion and bioavailability of phytochemicals while facilitating their delivery towards specific biological sites.

Lipid-based systems constitute one of the most extensively investigated categories. Liposomes provide an aqueous core surrounded by a phospholipid bilayer and can therefore accommodate compounds with different solubility characteristics. Phytosomes represent a related but distinct strategy in which phytoconstituents interact with phospholipids to form molecular complexes. Their ability to improve the interaction of phytochemicals with biological membranes has contributed to their development for compounds such as curcumin, silymarin, quercetin and resveratrol (Barani et al., 2021). Solid lipid nanoparticles and nanostructured lipid carriers provide alternative lipid matrices that can protect labile molecules and facilitate controlled release.

Polymeric nanoparticles offer another important platform. Biodegradable polymers can encapsulate phytochemicals within a matrix from which release occurs through diffusion, swelling or polymer degradation. Surface modification can additionally influence biological interactions and may provide opportunities for targeted delivery. Nanoemulsions are particularly useful for hydrophobic phytochemicals because the dispersed oil phase can improve their apparent solubility and facilitate gastrointestinal dispersion.



The choice of nanocarrier must nevertheless be matched to the physicochemical properties of the phytochemical and the intended route of administration. Parameters such as particle size, surface charge, encapsulation efficiency, loading capacity, morphology, physical stability and release kinetics influence the performance of the final formulation. Dewi et al. (2022) reported that lipid-based systems, polymeric nanoparticles and nanoemulsions can improve the solubility, stability, bioavailability and pharmacological activity of herbal compounds. The increasing sophistication of these platforms is also creating opportunities to incorporate targeting ligands and stimulus-responsive components, thereby transforming conventional nanoencapsulation into more intelligent therapeutic delivery.

| Nanocarrier | Suitable phytochemical characteristics | Principal delivery function               | Representative phytochemicals |
|-------------|----------------------------------------|-------------------------------------------|-------------------------------|
| Liposomes   | Hydrophilic or amphiphilic compounds   | Protection and membrane-mediated delivery | Quercetin, catechins          |



|                               |                                                 |                                              |                                      |
|-------------------------------|-------------------------------------------------|----------------------------------------------|--------------------------------------|
| Phytosomes                    | Poorly bioavailable polar phytoconstituents     | Enhanced membrane interaction and absorption | Curcumin, silymarin                  |
| Solid lipid nanoparticles     | Lipophilic or poorly soluble compounds          | Protection and sustained release             | Curcumin, resveratrol                |
| Nanostructured lipid carriers | Lipophilic compounds requiring enhanced loading | Improved loading and controlled release      | Quercetin, curcumin                  |
| Polymeric nanoparticles       | Compounds requiring sustained delivery          | Controlled release and cellular uptake       | Curcumin, berberine                  |
| Nanoemulsions                 | Poorly water-soluble compounds                  | Improved dispersion and apparent solubility  | Curcumin, essential-oil constituents |

## PROBLEM STATEMENT

Despite the extensive pharmacological potential of phytochemicals, their translation into effective pharmaceutical therapeutics remains constrained by poor aqueous solubility, chemical instability, limited gastrointestinal absorption, low bioavailability, rapid metabolism and non-specific distribution. Conventional herbal formulations frequently provide inadequate control over the delivery, protection and release of bioactive constituents, while variations in botanical composition can further affect reproducibility and therapeutic consistency. Although nanotechnology has introduced promising strategies for improving the delivery of plant-derived compounds, substantial challenges remain regarding carrier selection, formulation stability, scalability, biocompatibility, reproducibility and regulatory acceptance. Moreover, emerging responsive drug-delivery systems capable of reacting to physiological or external stimuli have not yet been comprehensively integrated with herbal nanomedicine and functional pharmaceutical excipients. The fragmented nature of existing research makes it difficult to establish how these technologies collectively contribute to the transition from conventional phytochemical formulations towards smart therapeutic systems. Therefore, a systematic review of recent advances is required to examine the development of herbal nanomedicine, advanced nanocarriers, responsive delivery platforms and functional excipients, while identifying technological limitations, translational barriers and future research opportunities.

## SIGNIFICANCE OF THE STUDY

This review is significant because it examines the convergence of phytochemistry, nanotechnology and advanced pharmaceutical formulation within the emerging field of smart herbal therapeutics. By bringing together recent evidence on nanocarrier-based phytochemical delivery, responsive drug-release mechanisms and functional pharmaceutical excipients, the study provides an integrated understanding of how formulation science can



overcome important limitations associated with conventional herbal medicines. The review can help researchers identify promising carrier systems, formulation strategies and technological approaches for improving phytochemical stability, bioavailability, controlled release and therapeutic performance. It also highlights important gaps concerning safety, standardisation, scalability and regulatory translation, which are essential for progressing experimental formulations towards clinically relevant products. Furthermore, the study provides a conceptual foundation for future research involving stimulus-responsive and multifunctional herbal delivery platforms. By critically examining developments reported between 2015 and 2024, the review contributes to understanding the technological evolution of herbal nanomedicine and its potential role in developing more precise, efficient and patient-oriented pharmaceutical therapeutics.

### **LITERATURE REVIEW**

Atanasov et al. (2021) described medicinal plants and their constituents as an important reservoir of structurally diverse molecules with therapeutic potential across a broad range of pathological conditions. The renewed scientific interest in phytochemicals has been supported by advances in phytochemistry, metabolomics, molecular biology and pharmacological screening, enabling more detailed characterisation of plant-derived bioactive compounds. Polyphenols, flavonoids, alkaloids, terpenoids, saponins and phenolic acids have demonstrated antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective and neuroprotective properties. However, the therapeutic potential of a phytochemical is strongly influenced by its pharmaceutical and biopharmaceutical characteristics. Poor aqueous solubility, chemical instability, extensive metabolism, inadequate membrane permeability and rapid elimination can prevent biologically active concentrations from being achieved at the intended site of action. Consequently, contemporary phytopharmaceutical research has increasingly shifted from identifying bioactive compounds alone towards improving their delivery, stability and pharmacokinetic behaviour.

Ahmad et al. (2021) emphasised that many phytochemicals encounter substantial barriers during gastrointestinal digestion and systemic absorption. Their review demonstrated that nanocarrier-based delivery can address several of these limitations by protecting phytochemicals from enzymatic and environmental degradation and modifying their dispersion and absorption. Nanocarriers can encapsulate, adsorb or chemically associate with plant-derived compounds, thereby creating a protective microenvironment around the active constituent. This strategy is particularly relevant for poorly water-soluble phytochemicals because nanoscale systems can increase the effective surface area available for dissolution and improve dispersion in biological fluids. In addition, modification of particle size, surface characteristics and composition can influence cellular uptake and tissue distribution. These characteristics have encouraged investigation of liposomes, polymeric nanoparticles, lipid nanoparticles, nanoemulsions, micelles, dendrimers and hybrid systems for phytochemical delivery.

Barani et al. (2021) reviewed the role of advanced delivery systems in improving the bioavailability of phytochemicals and highlighted the importance of matching carrier



characteristics with the physicochemical properties of the active compound. Lipid-based systems are particularly useful for hydrophobic phytochemicals, whereas polymeric systems can provide sustained release and opportunities for surface modification. Phytosomes have attracted particular attention because phospholipids can form complexes with phytoconstituents and improve their interaction with biological membranes. Such systems have been investigated for compounds including curcumin, silymarin, quercetin and other poorly bioavailable plant constituents. The delivery system can also influence the gastrointestinal fate of a phytochemical by modifying its exposure to digestive enzymes, pH variations and intestinal transport mechanisms. Thus, formulation design has become an essential component of phytochemical development rather than simply a method of converting an active compound into a conventional dosage form.

Rai et al. (2021) reported that herbal nanomedicines encompass a diverse range of platforms, including polymeric nanoparticles, solid lipid nanoparticles, phytosomes, nanoemulsions, nanomicelles, liposomes, dendrimers, nanofibres and nanosuspensions. Their review emphasised that the selection of an appropriate formulation should consider the solubility and permeability characteristics of the phytochemical or herbal extract. Important formulation attributes include particle size, polydispersity index, zeta potential, encapsulation efficiency, drug loading, morphology, stability and release behaviour. These parameters are particularly significant for herbal formulations because plant extracts contain multiple constituents with different physicochemical characteristics. Standardisation therefore represents a major requirement for reproducible herbal nanomedicine. In addition to improved bioavailability, nanoformulations may facilitate controlled release and potentially increase accumulation of bioactive compounds at selected biological sites, although the extent of targeting depends strongly on carrier composition and biological environment.

Chauhan et al. (2024) highlighted the continuing development of phytosome and other nanotechnology-based systems for enhancing the stability and therapeutic performance of phytochemicals. Phytosomes utilise phospholipids as functional components that can improve the solubilisation and membrane affinity of plant-derived compounds. Their development is particularly relevant to phytochemicals that possess adequate pharmacological activity but demonstrate poor absorption following conventional administration. Beyond phytosomes, current nanotechnology research encompasses lipid nanoparticles, polymeric nanoparticles, nanoemulsions, self-nanoemulsifying systems and hybrid nanostructures. These approaches can improve dissolution, protect labile constituents from degradation and alter pharmacokinetic characteristics. The increasing sophistication of these systems has also encouraged the incorporation of targeting ligands and stimuli-sensitive components, allowing researchers to progress from passive encapsulation towards controlled and potentially site-specific phytochemical delivery.

Kumar et al. (2022) discussed the broader development of herbal nanomedicines and identified formulation optimisation, physicochemical characterisation, reproducibility and regulatory considerations as major areas requiring attention. The development of a nanoformulation for a purified phytochemical is relatively straightforward compared with the



formulation of a complex herbal extract, in which multiple compounds may compete for incorporation into the carrier. The chemical composition of an extract can also vary according to botanical source, cultivation conditions, extraction procedure and storage. Such variability may influence particle formation, encapsulation efficiency, surface characteristics and release kinetics. Therefore, the application of nanotechnology to herbal medicines requires simultaneous attention to botanical standardisation and pharmaceutical quality control. The authors further highlighted the importance of evaluating parameters such as particle size, surface area, zeta potential, polydispersity, entrapment efficiency, drug loading and release behaviour to achieve consistent therapeutic performance.

Zandieh et al. (2023) extended the concept of phytochemical delivery towards stimuli-responsive nanoarchitectures, particularly in cancer therapy. Conventional nanocarriers may improve the systemic stability and bioavailability of phytochemicals, but uncontrolled release can still limit therapeutic precision. Stimuli-responsive systems are designed to alter their structure or release behaviour in response to specific endogenous or exogenous signals. Endogenous stimuli may include acidic pH, elevated reactive oxygen species, reducing environments and tumour-associated enzymes, whereas exogenous stimuli can include light, magnetic fields, ultrasound or temperature. In cancer-oriented systems, these characteristics can potentially facilitate preferential drug release within the tumour microenvironment. The incorporation of phytochemicals into such systems is particularly relevant because many natural compounds demonstrate promising anticancer mechanisms but suffer from poor bioavailability and inadequate accumulation at tumour sites.

Hamman et al. (2018) demonstrated that pharmaceutical excipients have evolved from being considered relatively inert formulation components to materials capable of directly influencing drug release, absorption and delivery. Plant-derived polymers, particularly polysaccharides, have received attention because of their availability, biodegradability, biocompatibility and capacity for physicochemical modification. Such materials can function as binders, matrix formers, viscosity enhancers, stabilisers, emulsifiers, gelling agents, bioadhesive materials and release modifiers. Their functional properties are particularly valuable in advanced herbal formulations because an excipient can simultaneously influence the stability of the active compound and the characteristics of the delivery system. Certain natural polymers can also exhibit pH-dependent or enzyme-mediated behaviour, making them relevant to site-specific and controlled-release formulations. This evolution supports the broader concept of functional pharmaceutical excipients in which formulation materials are deliberately selected according to their biological and delivery-related functions rather than simply their technological compatibility.

Tiwari et al. (2024) further reported growing interest in herbal excipients because of their potential biocompatibility, biodegradability and multifunctional behaviour. Natural gums, mucilages, starches, cellulose derivatives and other plant-derived materials can contribute to the physical stability and performance of pharmaceutical formulations. Their relevance to herbal nanomedicine is particularly significant because natural polymers can serve as matrices, stabilisers or release-controlling materials while maintaining compatibility with



plant-derived active constituents. Nevertheless, natural origin does not automatically guarantee safety or pharmaceutical consistency. Variations in botanical source, purification, molecular weight, chemical composition and microbial quality can influence excipient performance. Consequently, standardisation and appropriate quality-control procedures remain essential when plant-derived materials are incorporated into advanced pharmaceutical systems.

Mishra et al. (2024) highlighted the emergence of biofunctional excipients designed specifically to address inherent biopharmaceutical limitations such as poor solubility, inadequate permeability, low dissolution and inefficient targeting. Modern excipients increasingly include smart polymers, targeted polymers, bioadhesive polymers, lipids, amino acids, cyclodextrins and biosurfactants, many of which can modify the behaviour of the active pharmaceutical ingredient rather than merely provide physical support. Such excipients are particularly relevant to phytochemicals because poor solubility and limited permeability are among their most frequently reported pharmaceutical barriers. Functional excipients can therefore contribute to solubilisation, membrane permeation, mucoadhesion, controlled release and targeted transport. Their integration with nanocarriers provides an additional level of formulation control, potentially enabling the development of multifunctional systems in which the carrier and excipient collectively regulate the biological fate of the phytochemical. Dutta et al. (2024) reported that recent developments in nano-enabled herbal medicine increasingly focus on improving bioavailability, stability, controlled release and therapeutic precision. The current direction of the field therefore extends beyond simple nanoencapsulation towards multifunctional delivery platforms capable of integrating several mechanisms within one formulation. Lipid, polymeric and hybrid nanocarriers can provide protection and controlled release, while functional excipients can improve solubilisation, stability, mucoadhesion or permeability. Stimuli-responsive components can further regulate release according to the biological microenvironment. Such integration is particularly relevant for complex phytochemicals whose therapeutic potential is constrained by several simultaneous delivery barriers. However, the translation of these systems remains dependent on reproducible manufacturing, comprehensive toxicity evaluation, long-term stability, scalable production and appropriate regulatory characterisation.

Naponelli et al. (2024) emphasised the increasingly sophisticated nature of nano-phytomedicine, in which plant-derived polyphenols, flavonoids and alkaloids are incorporated into liposomal, polymeric and hybrid nanocarriers to improve stability, pharmacokinetics, controlled release and tissue targeting. This development reflects a broader transition from traditional herbal medicine towards delivery-centred phytopharmaceutical development. The literature increasingly demonstrates that therapeutic activity alone is insufficient to establish pharmaceutical potential; the delivery system determines how effectively a phytochemical reaches and interacts with its biological target.

Chauhan et al. (2024) and Zandieh et al. (2023) collectively indicate that the next stage of herbal nanomedicine involves combining improved bioavailability with controlled and responsive delivery. Such systems can be designed to respond to pH, enzymes, redox



conditions, temperature or externally applied stimuli, creating opportunities for more precise temporal and spatial regulation of phytochemical release.

Ahmad et al. (2021) observed that important research gaps remain concerning the behaviour of nanocarriers during digestion, absorption and metabolism. Similar concerns apply to herbal nanomedicines, where in-vitro improvements in solubility or release do not necessarily translate into equivalent in-vivo therapeutic benefits. Differences between laboratory digestion models and physiological conditions, changes in nanocarrier structure after administration, interactions with biological proteins and possible alterations in phytochemical metabolism require systematic investigation.

Rai et al. (2021) also identified standardisation and regulatory assessment as important barriers to the wider pharmaceutical development of herbal nanomedicines. Complex botanical matrices, variable phytochemical composition and differences in manufacturing procedures can complicate the establishment of consistent quality attributes. For smart therapeutic systems, these challenges become more complex because researchers must characterise not only the active phytochemical but also nanocarrier architecture, surface properties, stimulus responsiveness, release kinetics and biological interactions.

Mishra et al. (2024) suggested that the development of biofunctional excipients represents an important direction for overcoming the biopharmaceutical limitations of difficult-to-deliver compounds. In the context of phytochemicals, this approach provides an opportunity to integrate excipient functionality with nanocarrier engineering rather than considering these components independently. Smart polymers, lipids, cyclodextrins and biosurfactants can potentially be incorporated into delivery platforms to influence solubility, permeability, targeting and release.

Dutta et al. (2024) indicated that the convergence of herbal medicines and nanotechnology is increasingly associated with targeted and controlled delivery, while safety assessment remains essential for determining translational feasibility. Naponelli et al. (2024) similarly demonstrated that current nano-phytomedicine research is progressing towards targeted and multifunctional systems incorporating diverse nanocarrier architectures. This body of literature provides the basis for examining herbal nanomedicine not merely as a strategy for improving phytochemical bioavailability, but as an emerging platform for developing responsive and functionally engineered therapeutics.

| Author(s) and Year     | Focus of Study                                                 | Major Findings                                                                                                                                                                        | Relevance to Present Review                                                                                       |
|------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Atanasov et al. (2021) | Therapeutic potential of medicinal plants and natural products | Highlighted the structural diversity and broad pharmacological activities of plant-derived compounds, while identifying challenges in translating natural products into therapeutics. | Establishes the therapeutic foundation for phytochemicals and supports the need for advanced delivery approaches. |



|                       |                                                            |                                                                                                                                                                |                                                                                           |
|-----------------------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Ahmad et al. (2021)   | Nanocarrier-based phytochemical delivery                   | Reported that nanocarriers can improve phytochemical solubility, stability, bioavailability and protection against degradation.                                | Provides evidence for using nanotechnology to overcome conventional delivery limitations. |
| Barani et al. (2021)  | Advanced delivery systems for phytochemicals               | Discussed phytosomes, lipid systems and other nanocarriers for improving absorption and bioavailability of poorly soluble phytochemicals.                      | Supports the development of carrier-based strategies for herbal bioactives.               |
| Rai et al. (2021)     | Herbal nanomedicine and nanoformulations                   | Reviewed liposomes, polymeric nanoparticles, lipid nanoparticles, nanoemulsions and other platforms, emphasising formulation optimisation and standardisation. | Provides a technological framework for comparing different herbal nanomedicine platforms. |
| Kumar et al. (2022)   | Development and characterisation of herbal nanomedicines   | Emphasised particle size, zeta potential, encapsulation efficiency, stability and reproducibility as critical formulation parameters.                          | Highlights important quality attributes for reliable herbal nanoformulations.             |
| Chauhan et al. (2024) | Phytosomes and nanotechnology-based phytochemical delivery | Demonstrated the potential of phytosomes and related nanotechnologies to improve stability, absorption and therapeutic performance.                            | Supports the role of phospholipid-based systems in smart phytochemical delivery.          |
| Zandieh et al. (2023) | Stimuli-responsive phytochemical nanocarriers              | Examined pH-, redox-, enzyme- and externally triggered systems for controlled phytochemical release, particularly in cancer applications.                      | Provides the basis for integrating responsive drug delivery with herbal nanomedicine.     |
| Hamman et al. (2018)  | Natural polymers as pharmaceutical excipients              | Demonstrated the functional roles of natural polymers in binding, stabilisation, controlled release, viscosity modification and bioadhesion.                   | Establishes the pharmaceutical importance of functional and plant-derived excipients.     |



|                         |                                                      |                                                                                                                                                       |                                                                                                        |
|-------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Tiwari et al. (2024)    | Herbal excipients in pharmaceutical formulations     | Discussed gums, mucilages, starches and other natural materials as multifunctional pharmaceutical excipients.                                         | Supports the integration of natural excipients with herbal delivery systems.                           |
| Mishra et al. (2024)    | Biofunctional and advanced pharmaceutical excipients | Highlighted smart polymers, lipids, cyclodextrins and biosurfactants for improving solubility, permeability, targeting and controlled delivery.       | Demonstrates the emerging role of functional excipients in next-generation phytochemical formulations. |
| Dutta et al. (2024)     | Nano-enabled herbal medicine                         | Reported advances in nanoformulations for improving bioavailability, stability, controlled release and therapeutic precision.                         | Supports the transition from conventional herbal formulations towards nano-enabled therapeutics.       |
| Naponelli et al. (2024) | Nano-phytomedicine and phytochemical delivery        | Discussed liposomal, polymeric and hybrid nanocarriers for improving pharmacokinetics, stability, controlled release and targeting of phytochemicals. | Reinforces the potential of multifunctional nanocarriers for smart herbal therapeutics.                |

## EVOLUTION OF HERBAL NANOMEDICINE AND IMPROVEMENT OF PHYTOCHEMICAL DELIVERY

The reviewed literature indicates that herbal nanomedicine has progressively evolved from a strategy primarily intended to improve the solubility of poorly water-soluble phytochemicals into a broader platform for regulating their stability, absorption, biodistribution and release. Conventional phytochemical formulations are frequently limited by low aqueous solubility, chemical instability, rapid metabolism and inadequate permeability, which can substantially reduce the concentration of active compounds reaching their biological targets. Nanotechnology addresses several of these limitations simultaneously by incorporating phytochemicals within or onto nanoscale carriers. Ahmad et al. (2021) reported that nanocarriers can protect phytochemicals from degradation and improve their dispersion, absorption and bioavailability, thereby increasing the possibility of translating experimentally promising compounds into more effective pharmaceutical formulations.

The analysis of the literature demonstrates that lipid-based systems, polymeric nanoparticles, nanoemulsions and phospholipid-based systems remain among the most extensively investigated platforms. Liposomes can accommodate both hydrophilic and lipophilic compounds, while solid lipid nanoparticles and nanostructured lipid carriers provide a lipid matrix capable of protecting labile phytochemicals. Phytosomes are particularly relevant to



herbal medicine because the formation of phospholipid–phytoconstituent complexes can improve membrane affinity and absorption. Barani et al. (2021) identified phytosomes as an important strategy for improving the bioavailability of compounds that demonstrate significant pharmacological activity but inadequate absorption following conventional administration.

The reviewed evidence also indicates that nanocarrier selection cannot be standardised for all phytochemicals. Differences in molecular polarity, molecular weight, lipophilicity, chemical stability and intended administration route influence the most appropriate carrier. For example, hydrophobic phytochemicals may benefit from lipid-based carriers or nanoemulsions, whereas polymeric nanoparticles may be more appropriate when sustained release or surface modification is required. Rai et al. (2021) emphasised that particle size, polydispersity, zeta potential, encapsulation efficiency and release characteristics are important quality attributes for evaluating herbal nanomedicines.

| <b>Nanocarrier</b>            | <b>Primary formulation role</b>        | <b>Major benefit</b>                                       | <b>Main consideration</b>       |
|-------------------------------|----------------------------------------|------------------------------------------------------------|---------------------------------|
| Phytosomes                    | Phospholipid complexation              | Improved membrane interaction and bioavailability          | Complex formation and stability |
| Liposomes                     | Vesicular encapsulation                | Protection and improved delivery of diverse phytochemicals | Physical stability and leakage  |
| Solid lipid nanoparticles     | Lipid matrix encapsulation             | Protection and controlled release                          | Drug loading limitations        |
| Nanostructured lipid carriers | Mixed lipid matrix                     | Improved loading and release characteristics               | Lipid composition optimisation  |
| Polymeric nanoparticles       | Matrix or reservoir delivery           | Sustained release and surface functionalisation            | Polymer safety and scale-up     |
| Nanoemulsions                 | Dispersion of poorly soluble compounds | Improved solubilisation and dispersion                     | Physical stability              |

The overall results therefore demonstrate that nanotechnology can substantially modify the delivery behaviour of phytochemicals. However, improved physicochemical characteristics do not automatically establish improved clinical efficacy. The biological performance of a nanomedicine depends on the stability of the carrier under physiological conditions, interaction with proteins and biological membranes, gastrointestinal behaviour where applicable, cellular uptake and eventual clearance. Consequently, future development requires a shift from formulation-centred optimisation towards integrated evaluation of formulation characteristics and pharmacological outcomes.

## **RESPONSIVE DRUG DELIVERY AND FUNCTIONAL PHARMACEUTICAL EXCIPIENTS**



The second major finding from the literature is the movement towards responsive drug-delivery systems capable of controlling phytochemical release according to specific physiological or externally applied stimuli. Conventional sustained-release systems generally depend on predetermined diffusion or degradation mechanisms, whereas responsive systems are designed to alter their physicochemical behaviour when exposed to particular environmental signals. Zandieh et al. (2023) demonstrated the relevance of stimuli-responsive nanostructures for phytochemical delivery, particularly in cancer therapy, where differences in pH, enzyme activity and redox conditions between diseased and normal tissues can potentially be exploited for selective drug release.

Endogenous stimuli such as acidic pH, elevated reactive oxygen species, glutathione concentration and disease-associated enzymes can provide molecular triggers for drug release. Exogenous stimuli, including light, magnetic fields, ultrasound and temperature, offer additional opportunities for spatial and temporal control. Such approaches are particularly attractive for phytochemicals because they can address two major limitations simultaneously: poor bioavailability and inadequate localisation. A phytochemical can theoretically remain protected during circulation and undergo enhanced release when the carrier encounters a particular biological microenvironment.

| <b>Responsive mechanism</b> | <b>Trigger</b>                         | <b>Potential application</b>            | <b>Principal advantage</b>    |
|-----------------------------|----------------------------------------|-----------------------------------------|-------------------------------|
| pH-responsive               | Acidic or alkaline environment         | Gastrointestinal and tumour delivery    | Site-dependent release        |
| Redox-responsive            | Reactive oxygen species or glutathione | Cancer and inflammatory conditions      | Environment-sensitive release |
| Enzyme-responsive           | Disease-associated enzymes             | Targeted therapeutic delivery           | Biological specificity        |
| Thermo-responsive           | Temperature variation                  | Local or externally controlled delivery | Temporal release control      |
| Light-responsive            | Specific wavelength of light           | Localised treatment                     | External control              |
| Magnetic-responsive         | Applied magnetic field                 | Targeted localisation and release       | Remote stimulation            |

The literature further indicates that responsive systems are closely connected with advances in functional pharmaceutical excipients. Hamman et al. (2018) demonstrated that natural polymers can provide functions extending beyond conventional formulation support, including controlled release, viscosity modification, stabilisation, bioadhesion and matrix formation. Plant-derived gums, mucilages, starches, cellulose derivatives and other biopolymers are consequently being investigated as functional materials for pharmaceutical delivery. Their biodegradability and structural versatility make them attractive for developing formulations containing natural bioactive compounds.



Mishra et al. (2024) described the emerging role of biofunctional excipients capable of influencing solubility, permeability, targeting and drug release. This represents an important conceptual change because excipients are increasingly being selected according to their functional contribution to therapeutic performance rather than solely their ability to facilitate manufacturing. Cyclodextrins, smart polymers, lipids, biosurfactants and mucoadhesive materials can be incorporated into advanced formulations to improve the delivery environment surrounding a phytochemical.

The combination of functional excipients with nanocarriers may therefore produce multifunctional systems in which each component performs a specific role. For example, a lipid or polymeric carrier may provide protection, a functional excipient may enhance solubility or permeability, and a responsive component may regulate release. Such integration has considerable potential for transforming conventional nanoencapsulation into smart therapeutic systems. Nevertheless, increasing formulation complexity also introduces challenges relating to manufacturing reproducibility, excipient compatibility, physicochemical stability and regulatory characterisation.

#### **THERAPEUTIC POTENTIAL, TRANSLATIONAL CHALLENGES AND FUTURE DEVELOPMENT**

The results of the reviewed literature indicate that smart herbal delivery systems have potential applications across several therapeutic areas, including cancer, inflammation, metabolic disorders, cardiovascular diseases, neurological disorders and infectious diseases. The principal advantage is not necessarily the discovery of new phytochemicals, but the possibility of improving the pharmaceutical performance of compounds whose therapeutic development has previously been restricted by delivery barriers. Dutta et al. (2024) reported that nano-enabled herbal medicines are increasingly being investigated for enhanced bioavailability, stability, controlled release and therapeutic precision.

In oncology, responsive nanocarriers are particularly promising because the tumour microenvironment can provide distinctive physicochemical signals. Phytochemicals with anticancer activity can be incorporated into nano systems designed to respond to acidic pH, redox conditions or enzymes. Such approaches may reduce premature release and increase the availability of the active compound within the target microenvironment. In inflammatory disorders, nanocarriers may similarly facilitate controlled exposure of anti-inflammatory phytochemicals, potentially reducing the requirement for repeated administration. In metabolic and cardiovascular applications, improved oral bioavailability of poorly soluble compounds could enhance systemic exposure while reducing formulation-related limitations.

| <b>Therapeutic area</b> | <b>Relevant phytochemical examples</b> | <b>Delivery objective</b>        | <b>Potential benefit</b>                      |
|-------------------------|----------------------------------------|----------------------------------|-----------------------------------------------|
| Cancer                  | Curcumin, quercetin, resveratrol       | Targeted and responsive delivery | Improved localisation and controlled exposure |
| Inflammatory            | Curcumin, resveratrol,                 | Sustained delivery               | Prolonged                                     |



| disorders                | flavonoids                                |                                       | pharmacological activity                 |
|--------------------------|-------------------------------------------|---------------------------------------|------------------------------------------|
| Cardiovascular disorders | Quercetin, resveratrol, polyphenols       | Improved bioavailability              | Enhanced systemic exposure               |
| Metabolic disorders      | Berberine, curcumin, polyphenols          | Improved absorption and stability     | Greater therapeutic availability         |
| Neurological disorders   | Curcumin, resveratrol, flavonoids         | Enhanced biological barrier transport | Potential improvement in tissue delivery |
| Infectious diseases      | Plant phenolics, alkaloids and terpenoids | Controlled antimicrobial delivery     | Improved stability and local exposure    |

Despite these opportunities, the analysis reveals a substantial gap between experimental development and pharmaceutical translation. Naponelli et al. (2024) demonstrated the increasing sophistication of nano-phytomedicine, but the majority of reported systems remain at preclinical or formulation-development stages. Evidence of improved particle characteristics, dissolution or cellular uptake does not necessarily establish therapeutic superiority in humans. Differences in experimental models, doses, administration routes, carrier compositions and phytochemical standardisation also make direct comparison between studies difficult.

Another important issue is the complex nature of herbal materials. A purified phytochemical can be chemically characterised with considerable precision, whereas a botanical extract may contain dozens or hundreds of compounds. Variations in extraction methods, geographical origin, harvesting conditions and processing can consequently influence both biological activity and nanocarrier performance. Rai et al. (2021) identified standardisation and quality control as important considerations for the development of herbal nanomedicines. Establishing consistent marker compounds, chemical fingerprints and critical quality attributes will therefore be essential for reproducible manufacturing.

Safety represents another major translational consideration. Although nanocarriers may improve therapeutic delivery, nanoscale materials can demonstrate biological behaviours that differ from their bulk counterparts. Particle size, surface charge, composition, degradation products and accumulation within tissues may influence toxicity and pharmacokinetics. Functional excipients must similarly undergo appropriate safety evaluation, even when derived from natural sources. The assumption that “natural” materials are automatically safe is scientifically inappropriate, particularly when materials are chemically modified or incorporated into nanoscale systems.

Scale-up and regulatory requirements also represent significant barriers. Laboratory formulations may rely on specialised preparation methods that are difficult to reproduce consistently at industrial scale. Changes in mixing conditions, temperature, solvent removal, homogenisation or polymer characteristics can influence particle size and drug loading. Responsive systems introduce additional critical quality attributes because the sensitivity and



reproducibility of the triggering mechanism must be demonstrated. Therefore, future research should increasingly employ quality-by-design principles, systematic optimisation and robust analytical characterisation.

Overall, the evidence demonstrates a clear transition from conventional phytochemical formulations towards integrated smart therapeutic platforms. The combination of nanocarriers, responsive mechanisms and functional pharmaceutical excipients offer a rational strategy for addressing multiple delivery barriers simultaneously. However, successful translation will depend on reproducibility, long-term safety, scalable manufacturing, standardised botanical materials, clinically meaningful pharmacokinetic studies and well-designed clinical trials. The future of herbal nanomedicine is consequently likely to depend not simply on developing increasingly sophisticated nanosystems, but on establishing scientifically reproducible and clinically translatable platforms capable of converting the pharmacological potential of phytochemicals into reliable therapeutic outcomes.

## **CONCLUSION**

Herbal nanomedicine is emerging as an important bridge between the pharmacological potential of phytochemicals and the requirements of modern pharmaceutical therapeutics. The reviewed evidence demonstrates that nanocarriers can address major limitations of conventional phytochemical delivery, including poor solubility, instability, low bioavailability, rapid metabolism and uncontrolled distribution. Phytosomes, liposomes, lipid nanoparticles, polymeric nanoparticles and nanoemulsions have demonstrated considerable potential for improving the stability, absorption and controlled release of herbal bioactives. The incorporation of stimuli-responsive mechanisms further provides opportunities for more precise temporal and spatial regulation of phytochemical release. Functional pharmaceutical excipients, particularly natural polymers, lipids, cyclodextrins and biofunctional materials, can complement these systems by improving solubility, permeability, stability and formulation performance. Nevertheless, challenges concerning botanical standardisation, nanocarrier safety, reproducibility, scale-up, regulatory requirements and clinical validation remain significant. Future research should therefore focus on integrating nanotechnology, responsive delivery and functional excipient design through systematic formulation development and clinically relevant evaluation. Such convergence could facilitate the transition of promising phytochemicals from experimental candidates into safer, more effective and precisely controlled smart herbal therapeutics.

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