



Comparative Study of Conventional and Nanoformulated Herbal Medicines for Enhanced Therapeutic Efficacy

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ABSTRACT: Herbal medicines remain important components of healthcare worldwide; however, their therapeutic application is often constrained by poor aqueous solubility, limited membrane permeability, extensive first-pass metabolism, chemical instability, and variability in composition, resulting in low and inconsistent bioavailability. Nanotechnology-based delivery systems offer a promising approach to address these limitations by improving the physicochemical and biopharmaceutical properties of plant-derived bioactive compounds. This review critically evaluates recent advances in the nanoformulation of herbal medicines, covering liposomes, phytosomes, polymeric and protein-based nanoparticles, solid lipid nanoparticles, nanocrystals, nanoemulsions, and green-synthesized metallic nanoparticles. Particular emphasis is placed on four representative phytoconstituents, curcumin, quercetin, silymarin, and resveratrol, through comparison of their conventional and nanoformulated forms in terms of physicochemical properties, pharmacokinetic behavior, therapeutic performance, and safety. Evidence from the reviewed studies indicates that nanoformulation can substantially enhance solubility, stability, bioavailability, controlled delivery, and target-site accumulation of phytoconstituents, with corresponding improvements in antioxidant, hepatoprotective, anticancer, and antimicrobial activities, particularly in preclinical models. Nevertheless, clinical translation remains hindered by insufficient long-term nanotoxicological data, variability in formulation and characterization methods, limited clinical evidence, manufacturing challenges, and the absence of harmonized regulatory frameworks. Overall, nanotechnology provides a promising platform for improving the delivery and therapeutic performance of herbal medicines; however, successful translation into clinically applicable products will require standardized physicochemical characterization, rigorous safety and efficacy evaluation, scalable manufacturing approaches, and clearly defined regulatory pathways.

KEYWORDS: Herbal medicine; nanoformulation; bioavailability; phytoconstituents; therapeutic efficacy; nanotoxicology

1. Introduction

Plant-derived medicines have long formed an integral component of healthcare systems worldwide and continue to provide an important foundation for contemporary drug discovery and pharmacotherapy. Their therapeutic potential is largely associated with structurally and functionally diverse secondary metabolites, including polyphenols, flavonoids, alkaloids, terpenoids, glycosides, and related phytochemicals. These compounds exhibit a broad spectrum of biological activities, including antioxidant, anti-inflammatory, hepatoprotective, antimicrobial, cardioprotective, and anticancer effects [1–3]. Several phytoconstituents have consequently attracted considerable pharmaceutical interest as potential therapeutic agents or molecular scaffolds for drug development. Nevertheless, compelling biological activity demonstrated under experimental conditions does not necessarily translate into comparable *in vivo* or clinical efficacy because many phytoconstituents possess unfavorable physicochemical and biopharmaceutical properties.

Poor oral bioavailability represents one of the principal barriers to the therapeutic translation of herbal bioactives. Many phytoconstituents exhibit low aqueous solubility, limited dissolution, inadequate gastrointestinal permeability, chemical instability, or unfavorable lipophilicity, characteristics frequently associated with compounds in Biopharmaceutics Classification System (BCS) classes II and IV [2, 3]. These limitations can substantially reduce the fraction of an orally administered compound that reaches systemic circulation at therapeutically relevant concentrations. Moreover, the chemical complexity of herbal preparations may influence dissolution, absorption, metabolism, and interactions among individual constituents, further complicating prediction of their pharmacokinetic behavior.

The limitations extend beyond intrinsic solubility and permeability. Conventional herbal dosage forms, including crude powders, decoctions, tinctures, tablets, and capsules, may expose bioactive constituents to gastrointestinal degradation, extensive intestinal and hepatic metabolism, and rapid systemic elimination [1, 2]. At the formulation level, differences in plant genotype, geographical origin, cultivation and harvesting conditions, post-harvest processing, extraction procedures, and storage can also contribute to substantial variation in phytochemical composition. Such variability presents challenges for dose standardization, reproducibility, quality control, and ultimately therapeutic performance. Consequently, a major challenge in herbal drug development is not simply identifying pharmacologically active compounds, but designing delivery systems capable of maintaining their stability, improving systemic exposure, and delivering sufficient concentrations to the intended biological target.

Nanotechnology-based drug delivery has emerged as a promising strategy for addressing several of these limitations. Reducing particle dimensions to the nanoscale or incorporating phytoconstituents within nanocarriers can modify dissolution behavior, surface area, stability, release kinetics, absorption, biodistribution, and cellular uptake. Depending on carrier composition and architecture, nanoformulation may increase apparent aqueous solubility, protect chemically labile phytoconstituents against gastrointestinal, enzymatic, and oxidative degradation, provide sustained or controlled release, and enhance accumulation at target tissues [3, 4]. These characteristics are particularly relevant for phytoconstituents with strong pharmacological activity but poor conventional pharmacokinetic profiles.

A diverse range of nanoplatforms has therefore been investigated for herbal drug delivery. Liposomes and phytosomes exploit lipid-based architectures to enhance incorporation and membrane interaction of phytoconstituents; solid lipid nanoparticles and nanostructured

lipid carriers combine lipid compatibility with controlled-release properties; polymeric and protein-based nanoparticles provide opportunities for encapsulation, surface modification, and targeted delivery; while nanocrystals increase dissolution primarily by reducing drug particle size and increasing surface area [5, 6]. Nanoemulsions have also gained attention for improving the dispersion and delivery of poorly water-soluble phytochemicals and essential oils. In parallel, plant-mediated synthesis of metallic nanoparticles has emerged as a distinct area in which phytochemicals can function as reducing and stabilizing agents while potentially contributing to the biological properties of the resulting nanomaterials. Collectively, these approaches demonstrate that nanoformulation is not a single delivery strategy but rather a spectrum of technologies whose suitability depends on the physicochemical properties of the phytoconstituent, therapeutic objective, administration route, and desired release profile.

Several extensively investigated phytoconstituents illustrate both the promise and challenges of this approach. Curcumin possesses well-established antioxidant, anti-inflammatory, and anticancer activities but is limited by extremely low aqueous solubility, rapid metabolism, and poor systemic exposure. Quercetin similarly demonstrates diverse pharmacological effects yet suffers from limited solubility and oral bioavailability. Silymarin, widely investigated for hepatoprotective applications, exhibits poor aqueous solubility and variable gastrointestinal absorption, whereas resveratrol undergoes extensive metabolism despite its broad biological activity. These compounds therefore provide useful models for evaluating whether nanoformulation can translate favorable *in vitro* pharmacology into improved pharmacokinetic and therapeutic performance. However, evidence of enhanced physicochemical properties or efficacy in experimental models alone is insufficient to establish clinical superiority [3–6].

Despite rapid advances in nanoformulated herbal medicines, substantial translational challenges remain. Differences in nanoparticle size distribution, surface charge, morphology, encapsulation efficiency, drug-loading capacity, release kinetics, and storage stability can influence biological performance and complicate comparisons across studies. Equally important are concerns regarding nanocarrier biodegradation, tissue accumulation, immunological responses, chronic toxicity, and potential interactions between the carrier and phytoconstituent. The diversity of herbal preparations adds another layer of complexity because regulatory assessment must simultaneously address botanical standardization and nanoscale formulation characteristics. The absence of universally harmonized characterization, safety-testing, manufacturing, and regulatory requirements therefore remains a major obstacle to reproducible development and clinical translation.

The fundamental distinction between conventional and nanoformulated herbal medicines is illustrated in Figure 1. Conventional formulations may retain major biopharmaceutical limitations, including poor solubility, restricted permeability, rapid metabolism, and variable systemic exposure. In contrast, incorporation of the same bioactive compounds into appropriately designed nanocarriers can improve solubilization, protect against degradation, modify release behavior, and enhance systemic retention. This conceptual framework provides the basis for evaluating whether such formulation-related improvements ultimately translate into superior therapeutic performance.

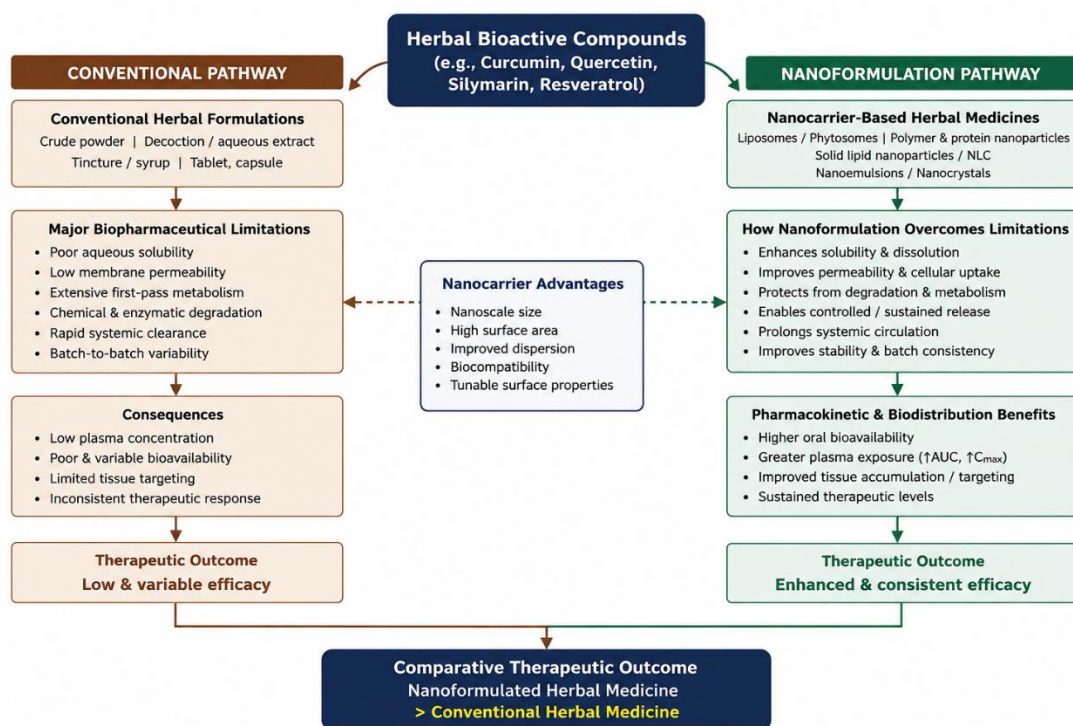


Figure 1. Comparative pathways and therapeutic outcomes of conventional and nanoformulated herbal medicines.

Against this background, this review aims to critically evaluate whether and how nanotechnology can overcome the physicochemical, pharmacokinetic, and therapeutic limitations of conventional herbal medicines. Curcumin, quercetin, silymarin, and resveratrol are used as principal representative phytoconstituents, complemented by plant-mediated metallic nanoparticles and essential-oil nanoemulsions as illustrative nanotechnology applications. Specifically, the review aims to: (i) examine the major physicochemical and pharmacokinetic barriers associated with conventional herbal formulations; (ii) critically compare the characteristics, advantages, and limitations of major nanocarrier platforms used for phytoconstituent delivery; (iii) evaluate evidence for improvements in bioavailability and therapeutic efficacy achieved through nanoformulation relative to conventional formulations; and (iv) assess nanotoxicological, manufacturing, standardization, and regulatory challenges affecting clinical translation. By integrating these dimensions, the review seeks to identify current evidence gaps and research priorities required to move nanoformulated herbal medicines from promising preclinical systems toward standardized, safe, and clinically relevant therapeutic products.

2. Limitations of Conventional Herbal Medicine Formulations

2.1. Physicochemical Limitations of Phytoconstituents.

Most pharmacologically active phytoconstituents possess physicochemical properties that are inherently unfavourable for oral or parenteral delivery. Curcumin, the principal curcuminoid of *Curcuma longa*, is virtually insoluble in water and undergoes rapid degradation under alkaline and physiological pH conditions, resulting in negligible unassisted oral bioavailability [5, 7]. Quercetin, a ubiquitous dietary flavonoid, exhibits aqueous solubility below 1 µg/mL

together with marked photochemical and thermal instability, which together restrict its dissolution and in vivo antioxidant performance [8, 9]. Silymarin, the flavanolignan complex obtained from *Silybum marianum*, is likewise practically insoluble in water, a property that directly limits hepatic drug concentrations achievable through oral administration despite its well-documented hepatoprotective pharmacology [10, 11]. These examples illustrate a broader pattern: because most bioactive phytoconstituents are polyphenolic or highly lipophilic, they frequently fail to satisfy the solubility and permeability criteria required for consistent gastrointestinal absorption.

2.2. Pharmacokinetic and Bioavailability Challenges.

Even when a phytoconstituent is adequately absorbed, systemic bioavailability is further eroded by extensive presystemic metabolism. Curcumin undergoes rapid glucuronidation and sulfation in the intestinal epithelium and liver, while efflux transporters such as P-glycoprotein actively extrude absorbed drug back into the intestinal lumen, together limiting oral bioavailability to a small fraction of the administered dose [7, 12]. Resveratrol is similarly subject to rapid hepatic and intestinal metabolism, together with dose-limiting toxicity at pharmacologically relevant concentrations, which constrains its translation from promising in vitro anticancer activity to reproducible in vivo efficacy [13]. These pharmacokinetic constraints mean that the therapeutic potential demonstrated for isolated phytoconstituents under controlled in vitro conditions is frequently not realised when the same compounds are administered in conventional dosage forms.

2.3. Standardization, Quality Control, and Stability Issues.

Conventional herbal formulations are additionally constrained by variability in raw material composition, extraction efficiency, and finished-product stability. Because phytoconstituent content in plant material varies with species, geographic origin, harvesting season, and post-harvest processing, conventional extracts and decoctions frequently show substantial batch-to-batch variation in active-compound concentration, complicating dose standardization and reproducible clinical evaluation [1, 2]. Conventional formulations are further prone to physical and chemical instability during storage, including oxidative degradation, photolysis, and precipitation of poorly soluble actives, which can reduce potency over shelf life and complicate regulatory quality assurance [4]. Taken together, poor aqueous solubility, chemical instability, extensive presystemic metabolism, and variability in absorption represent recurring barriers to the effective delivery of major phytoconstituents. These limitations are particularly evident for curcumin, quercetin, silymarin, and resveratrol. As summarized in Table 1, nanoformulation approaches have been developed to address these compound-specific limitations through improved stability, sustained delivery, enhanced absorption, and greater systemic or tissue exposure [7–13].

Table 1. Physicochemical/pharmacokinetic comparison of conventional vs. nanoformulated herbal actives.

Herbal Active	Conventional-Form Limitation	Nanoformulation Type	Reported Improvement (vs. Conventional)	Ref.
Curcumin	Very poor aqueous solubility; extensive first-pass glucuronidation limiting unassisted oral bioavailability	Pickering-emulsion-stabilised nanocrystals	Markedly enhanced oral bioavailability and prolonged plasma exposure relative to crude curcumin	[7]
Quercetin	Aqueous solubility below 1 µg/mL; photochemical and thermal instability	PLGA polymeric nanoparticles	Particle-size-dependent increase in antioxidant activity with preserved hemocompatibility	[8]
Quercetin	Poor dissolution and environmental stability	Zein/carboxymethyl-chitosan nanoparticles	Encapsulation efficiency > 90%; improved stability and antioxidant retention	[9]
Silymarin	Practically insoluble in water; oral bioavailability below 50%	Chitosan nanoparticles	Enhanced, sustained hepatoprotective activity in CCl ₄ -induced hepatotoxicity model	[10]
Silymarin	Poor water solubility restricting hepatic absorption	Emulsion solvent-evaporation nanoparticles	Higher antioxidant activity and greater hepatic absorption after oral delivery	[11]
Resveratrol	Rapid hepatic metabolism; dose-limiting toxicity; low systemic bioavailability	Polymeric, lipid, and metallic nanocarriers	Improved solubility, tumour accumulation, and anticancer potency vs. free resveratrol	[13]

3. Nanotechnology-Based Approaches for Herbal Medicine Delivery

3.1. Lipid-Based Nanocarriers.

Lipid-based nanocarriers, including liposomes, phytosomes, solid lipid nanoparticles, and nanostructured lipid carriers, are among the most extensively applied platforms for herbal drug delivery. Phytosome technology, in which a standardized phytoconstituent is complexed with phosphatidylcholine to form a lipid-compatible molecular complex, has been used to enhance the oral and topical bioavailability of numerous polyphenol-rich extracts, including milk thistle, ginkgo, and green tea, by improving membrane permeability relative to the unbound phytoconstituent [6]. Chitosan-based and emulsion-derived lipid nanoparticles have similarly been applied to silymarin, achieving passive hepatic targeting and sustained release that enhance hepatoprotective activity in carbon-tetrachloride-induced hepatotoxicity models relative to free silymarin suspensions [10, 11].

3.2. Polymeric, Protein-Based, and Nanocrystal Systems.

Polymeric and protein-based nanoparticles offer tunable encapsulation efficiency, controlled release kinetics, and surface modifiability for targeted delivery. Quercetin has been successfully encapsulated within poly(lactic-co-glycolic acid) (PLGA) nanoparticles, yielding particle-size-dependent improvements in antioxidant activity while maintaining favourable hemocompatibility [8], and within zein/carboxymethyl-chitosan nanoparticles, achieving encapsulation efficiencies exceeding 90% together with improved stability against environmental degradation [9]. Nanocrystal engineering, in which the pure phytoconstituent is reduced to nanoscale particles without a carrier matrix, has also been applied to herbal actives to increase specific surface area and dissolution rate; Pickering-emulsion-stabilised curcumin nanocrystals, for example, have demonstrated markedly enhanced oral bioavailability compared with unmodified curcumin [5, 7].

3.3. Metallic/Inorganic Nanoparticles and Nanoemulsion-Based Systems.

Beyond organic nanocarriers, metallic nanoparticles and nanoemulsion-based systems have expanded the range of nanotechnology approaches available for improving herbal therapeutics. Green synthesis of metallic nanoparticles using plant extracts as reducing and capping agents offers an environmentally favorable approach that minimizes the use of potentially hazardous chemical reagents while exploiting phytochemicals during nanoparticle formation. Plant-mediated silver nanoparticles, commonly ranging from 10–100 nm, have demonstrated broad-spectrum antibacterial activity that may exceed that of the corresponding plant extract, potentially through enhanced microbial membrane interactions, oxidative stress generation, and sustained release of silver ions [14]. Nanoemulsions provide a complementary strategy for volatile and highly lipophilic herbal constituents, particularly essential oils. Their nanoscale droplets increase interfacial surface area, improve aqueous dispersibility and physical stability, and facilitate interactions between encapsulated phytochemicals and microbial membranes. Consequently, essential-oil nanoemulsions can exhibit enhanced antimicrobial performance compared with free oils while reducing volatility and undesirable organoleptic characteristics, supporting their potential application in pharmaceutical and food-delivery systems [15]. Collectively, these delivery systems demonstrate that no single nanocarrier is universally optimal for herbal medicines. Carrier selection should instead consider the physicochemical properties of the phytoconstituent, intended route of administration, therapeutic target, required release profile, and safety characteristics. Table 2 compares the principal nanocarrier platforms discussed above, including their representative compositions, typical particle-size ranges, and major applications in herbal drug delivery [5–15].

Table 2. Nanocarrier systems used for herbal drug delivery.

Nanocarrier Type	Representative Composition	Typical Particle Size	Principal Application in Herbal Delivery	Ref.
Liposomes / phytosomes	Phosphatidylcholine bilayer vesicles complexed with phytoconstituents	100–400 nm	Bioavailability enhancement of milk thistle, ginkgo, and green tea extracts	[6]
Polymeric / protein nanoparticles	PLGA, zein, chitosan, carboxymethyl-chitosan matrices	50–300 nm	Encapsulation and controlled release of flavonoids (e.g., quercetin)	[8, 9]
Solid lipid / emulsion-based nanoparticles	Solid lipid matrix or emulsified lipid-solvent systems	100–300 nm	Hepatic-targeted delivery of silymarin and related hepatoprotective actives	[10, 11]
Nanocrystals / Pickering nanoemulsions	Pure phytoconstituent nanocrystals stabilised by particle emulsifiers	150–500 nm	Solubility and oral bioavailability enhancement of poorly soluble actives	[5, 7]
Green-synthesised metallic nanoparticles	Plant-extract-reduced silver/gold nanoparticles	10–100 nm	Antimicrobial and catalytic applications of phytochemical-capped nanoparticles	[14]
Nanoemulsions (essential-oil based)	Oil-in-water nanoscale dispersion stabilised by surfactants	< 200 nm	Antimicrobial delivery of volatile essential oils in food/pharmaceutical matrices	[15]

4. Comparative Therapeutic Efficacy of Conventional versus Nanoformulated Herbal Medicines

The therapeutic value of nanoformulation should ultimately be assessed not only by improvements in particle size, solubility, or encapsulation efficiency, but also by whether these physicochemical modifications translate into meaningful biological advantages over

conventional formulations. Across the available studies, nanoformulated phytoconstituents generally demonstrate enhanced therapeutic performance through a combination of improved aqueous dispersion, protection against degradation, prolonged release, increased cellular uptake, and altered tissue distribution. However, the magnitude of improvement varies according to the phytoconstituent, carrier composition, particle characteristics, administration route, and experimental model. Therefore, direct comparisons between nanoformulated and conventional preparations are particularly important for determining whether the additional complexity of nanoscale delivery provides a meaningful pharmacological benefit.

4.1. Antioxidant and Anticancer Efficacy.

Nanoformulation has demonstrated considerable potential for improving the antioxidant and anticancer activities of poorly soluble phytoconstituents. Quercetin represents a relevant example because its strong antioxidant properties are accompanied by limited aqueous solubility and consequently restricted bioavailability. Quercetin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles exhibited antioxidant activity that varied according to particle size and exceeded that of free quercetin at equivalent nominal concentrations [8]. This enhancement may be associated with improved dispersion of quercetin in aqueous environments, protection of the encapsulated compound against premature degradation, and sustained release, thereby maintaining biologically available concentrations for longer periods. These findings demonstrate that nanoparticle characteristics themselves can influence the biological performance of encapsulated phytochemicals and should therefore be considered when comparing formulations.

A similar advantage has been observed for resveratrol, whose therapeutic application is limited by poor aqueous solubility, rapid metabolism, and low systemic bioavailability. Nanoparticle-based resveratrol delivery using polymeric, lipid-based, and metallic nanocarriers has been associated with greater tumor accumulation, enhanced cellular internalization, increased induction of apoptosis, and stronger inhibition of tumor-cell proliferation compared with free resveratrol [13]. Nanocarriers may protect resveratrol from rapid metabolic transformation while increasing its effective concentration within tumor tissues. Depending on their physicochemical properties and surface functionality, these systems may additionally promote passive or ligand-mediated tumor targeting. Nevertheless, much of the reported evidence remains preclinical, and improved cytotoxicity or tumor suppression should not automatically be interpreted as clinical superiority without corresponding pharmacokinetic, toxicity, and human efficacy data.

4.2. Hepatoprotective and Metabolic Efficacy.

Silymarin provides a particularly informative model for evaluating the therapeutic advantages of nanoformulation because its established hepatoprotective activity is constrained by poor water solubility and limited gastrointestinal absorption. In carbon tetrachloride-induced hepatotoxicity models, silymarin-loaded chitosan nanoparticles produced greater hepatoprotective effects than equivalent doses of free silymarin [10]. The improved response has been associated with sustained drug release and enhanced hepatic exposure, potentially increasing the duration and concentration of active constituents available at the site of liver injury. Such delivery characteristics are particularly relevant for hepatoprotective compounds,

for which maintaining sufficient hepatic concentrations may be necessary to counteract oxidative stress, inflammation, and cellular injury.

Comparable improvements have been reported for silymarin nanoparticles prepared using emulsion-solvent evaporation, which demonstrated greater antioxidant activity and enhanced hepatic absorption following oral administration compared with unformulated silymarin [11]. Importantly, the benefits of nanoformulation are not restricted to chemically induced hepatotoxicity. In a murine model of *Schistosoma mansoni*-associated hepatic injury, silybin nanoparticles improved biochemical and pathological indicators of liver damage relative to conventional silybin/silymarin treatment [12]. Collectively, these findings suggest that nanoformulation may enhance hepatoprotection through improved absorption, sustained exposure, and favorable biodistribution. However, comparisons among studies remain complicated by differences in nanoparticle composition, administered dose, treatment duration, animal model, and measured endpoints. Standardized comparative studies are therefore required before definitive conclusions regarding therapeutic superiority can be established.

4.3. Antimicrobial and Anti-inflammatory Efficacy.

Nanotechnology also provides several mechanisms through which the antimicrobial performance of plant-derived materials can be enhanced. Green-synthesized metallic nanoparticles are particularly distinctive because phytochemicals can participate in nanoparticle synthesis as reducing and stabilizing agents while the resulting metallic nanostructure contributes additional antimicrobial activity. Plant-mediated silver nanoparticles have demonstrated substantial antibacterial effects against both Gram-positive and Gram-negative microorganisms, often exceeding the activity observed for the corresponding plant extracts [14]. Their enhanced performance may result from the combined effects of nanoscale interactions with bacterial surfaces, disruption of membrane integrity, generation of oxidative stress, interference with intracellular biomolecules, and release of biologically active silver ions. Thus, the observed antimicrobial effect cannot necessarily be attributed exclusively to the original phytochemicals, but rather to interactions between the plant-derived capping constituents and the metallic nanoparticle system.

Nanoemulsion-based delivery provides a different mechanism for enhancing the antimicrobial activity of volatile and lipophilic herbal constituents. Essential oils commonly exhibit antimicrobial activity but are limited by poor water miscibility, volatility, chemical instability, and difficulty in achieving homogeneous dispersion in biological, pharmaceutical, or food matrices. Incorporation into oil-in-water nanoemulsions increases interfacial surface area and improves contact between active constituents and microbial membranes, while potentially reducing volatility and enabling more controlled release. Consequently, essential-oil nanoemulsions have demonstrated stronger antibacterial performance than corresponding free oils against several pathogenic and foodborne microorganisms [15].

Although anti-inflammatory effects are frequently reported for nanoformulated phytoconstituents, direct head-to-head evidence demonstrating superiority over conventional preparations should be interpreted carefully. Improvements may arise from enhanced cellular uptake and sustained exposure rather than changes in the intrinsic pharmacological activity of the phytoconstituent itself. Future comparative studies should therefore incorporate equivalent-dose controls, standardized inflammatory biomarkers, pharmacokinetic measurements, and

appropriate carrier-only controls to distinguish formulation effects from the inherent biological activity of the active compound.

Overall, the comparative evidence indicates that nanoformulation can improve therapeutic performance across several biological applications, although the magnitude of improvement varies substantially with the active compound, nanocarrier, dose, and experimental model. As summarized in Table 3, the reported advantages include enhanced antioxidant activity of quercetin, improved hepatoprotection by silymarin and silybin, greater anticancer activity of resveratrol, and stronger antimicrobial effects of essential-oil nanoemulsions and plant-mediated silver nanoparticles [8,10,12–15]. Importantly, most of these comparisons remain based on *in vitro* or animal models; therefore, therapeutic superiority in humans has yet to be established conclusively.

Table 3. Comparative efficacy outcomes: conventional vs. nanoformulated herbal medicines.

Disease / Biological Model	Conventional Herbal Treatment Outcome	Nanoformulated Treatment Outcome	Ref.
Oxidative stress (in vitro antioxidant assay)	Moderate, concentration-limited radical-scavenging activity of free quercetin	Significantly enhanced, size-dependent antioxidant activity of quercetin-PLGA nanoparticles	[8]
CCl ₄ -induced hepatotoxicity (murine model)	Partial hepatoprotection with free silymarin suspension	Superior, sustained-release hepatoprotection with silymarin-chitosan nanoparticles	[10]
Schistosoma mansoni-induced liver damage (murine model)	Limited hepatoprotection with conventional silybin/silymarin	Improved control of hepatic injury markers with silybin nanoparticles	[12]
Tumour / cancer cell models (various)	Limited anticancer potency of free resveratrol due to poor bioavailability	Enhanced apoptosis, tumour accumulation, and anticancer potency with resveratrol nanocarriers	[13]
Foodborne / pathogenic bacterial models	Reduced antibacterial efficacy of free essential oils due to poor aqueous dispersion	Significantly improved antibacterial activity of essential-oil nanoemulsions	[15]
Antibacterial susceptibility (Gram +/- panels)	Weak or negligible intrinsic antimicrobial activity of plant extract alone	Broad-spectrum antibacterial activity of phytochemical-capped silver nanoparticles	[14]

5. Safety, Regulatory Landscape, and Future Perspectives

5.1. Nanotoxicology and Biocompatibility Considerations.

The same physicochemical properties that confer therapeutic advantages on nanoformulated herbal medicines – small size, high surface-area-to-volume ratio, and enhanced cellular uptake – also underlie potential nanotoxicological concerns. Mechanistic studies indicate that nanoparticles can induce oxidative stress, disrupt cellular membranes, dysregulate autophagy, and trigger inflammatory signalling through direct interaction with cellular and subcellular structures, with the magnitude of these effects influenced by nanoparticle composition, size, surface charge, and dose [16]. Because herbal nanoformulations often combine a bioactive phytoconstituent with an additional carrier material (lipid, polymer, or metal), comprehensive safety evaluation must consider the toxicological profile of the carrier as well as the encapsulated active, together with the potential for organ-specific nanoparticle accumulation following repeated administration [16].

5.2. Regulatory Challenges and Standardization Needs.

Regulatory frameworks for nanomedicines generally, and nanoformulated herbal medicines specifically, have not kept pace with the rapid expansion of the underlying science. Existing pharmaceutical and herbal-product regulations were largely developed for conventional dosage forms and do not adequately address nanoscale-specific properties such as particle size distribution, surface functionalization, and batch-to-batch consistency of encapsulation efficiency, resulting in inconsistent evaluation criteria across regulatory jurisdictions [16]. This regulatory gap is compounded, for herbal nanoformulations, by the pre-existing standardization challenges associated with plant-derived raw materials described in Section 2.3, such that both the phytoconstituent content and the nanocarrier characteristics require harmonized quality control before consistent regulatory evaluation becomes feasible [1,4]. These considerations demonstrate that successful clinical translation requires simultaneous control of biological safety, nanoparticle biodistribution, botanical composition, formulation reproducibility, and manufacturing quality. The principal nanotoxicological and regulatory concerns, together with commonly applied assessment approaches, are summarized in Table 4. Particular attention should be directed toward cellular toxicity, long-term organ accumulation, batch-to-batch consistency, and the development of harmonized regulatory criteria [1,4,16].

Table 4. Nanotoxicity and regulatory considerations for nanoformulated herbal medicines.

Aspect	Key Safety / Regulatory Concern	Common Assessment Approach	Ref.
Cellular / molecular toxicity	Oxidative stress, membrane disruption, and inflammatory responses induced by nanoparticle physicochemical properties	In vitro cytotoxicity assays and molecular toxicity screening	[16]
Biodistribution and accumulation	Organ-specific nanoparticle accumulation and unpredictable long-term biological interactions	In vivo biodistribution and histopathological evaluation	[16]
Manufacturing standardization	Batch-to-batch variability in particle size, encapsulation efficiency, and phytoconstituent content	Standardized physicochemical characterization (size, zeta potential, entrapment efficiency)	[1,4]
Regulatory framework	Absence of harmonized, nanoparticle-specific regulatory guidelines for herbal nanomedicines	Comparative regulatory gap analysis across national/regional authorities	[16]

5.3. Clinical Translation, Conclusion, and Future Directions.

The evidence reviewed here indicates that nanoformulation offers a mechanistically justified and empirically supported strategy for enhancing the therapeutic efficacy of herbal medicines. Across curcumin, quercetin, silymarin, and resveratrol, as well as plant-mediated metallic nanoparticles and essential-oil nanoemulsions, nanoscale reformulation consistently improved solubility, stability, and bioavailability relative to conventional forms, translating into superior antioxidant, hepatoprotective, anticancer, and antimicrobial outcomes in preclinical models [5-15]. Nonetheless, clinical translation remains constrained by incomplete nanotoxicological characterization, the absence of harmonized regulatory pathways specific to nanoherbal products, and persistent manufacturing scale-up challenges [16]. Future research should prioritise standardized physicochemical characterization protocols, long-term in vivo safety and biodistribution studies, and well-designed randomized clinical trials directly comparing nanoformulated and conventional herbal medicines, so that the substantial preclinical efficacy advantages documented in this review can be translated into reproducible clinical benefit.

Author Contributions

Both authors contributed equally to the conceptualization, literature review, writing, and revision of this manuscript. A.R. led the analysis of physicochemical and pharmacokinetic evidence and drafted the introduction and Sections 1–2; M.I.H. led the analysis of comparative efficacy and safety/regulatory evidence and drafted Sections 3–4. Both authors jointly designed the tables and figure, and both authors read, critically revised, and approved the final manuscript.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review.

Data Availability Statement

No new experimental data were generated or analysed in this review..

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