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Translating Nanoparticle-Based Drug Delivery Systems for Natural Products into Clinical Practice: A Pharmacokinetic Perspective

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Abstract: Secondary metabolites derived from natural products, such as alkaloids, flavonoids, and polyphenols, have promising pharmacological activities, but their clinical use in humans is often restricted by poor solubility, limited gastrointestinal absorption, rapid metabolism, and low systemic bioavailability. Nanoparticle- and formulation-based delivery systems have been developed to address these pharmacokinetic limitations and improve the therapeutic feasibility of natural product-derived compounds. This literature review examines how nanoparticle- and formulation-based delivery systems improve the pharmacokinetic performance of selected natural product-derived secondary metabolites, with particular emphasis on their potential for clinical translation. The reviewed clinical and preclinical studies consistently demonstrated improvements in pharmacokinetic parameters, including AUC, Cmax, Tmax, half-life, bioavailability, systemic exposure, and tissue distribution, compared with conventional formulations. In addition to preclinical evidence, human pharmacokinetic studies on quercetin phytosome, berberine phytosome, and nano-sized curcumin formulation demonstrated improved systemic exposure in humans, further supporting the translational potential of these delivery systems. These findings support the potential role of nanoparticle- and formulation-based delivery systems as translational platforms for improving the clinical feasibility of natural product-derived secondary metabolites. However, improved pharmacokinetic performance alone does not guarantee clinical efficacy. Further studies in patient populations are required to establish long-term safety, optimal dosing strategies, and determine whether improved pharmacokinetic performance translates into clinically meaningful therapeutic outcomes.

Keywords: Clinical translation; natural product-derived compounds; nanoparticle delivery system; pharmacokinetics.

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Introduction

Natural products have long been recognized as an important source of bioactive compounds for disease prevention and therapy. Many plant-derived secondary metabolites, including alkaloids, flavonoids, polyphenols, terpenoids, and glycosides, exhibit broad pharmacological activities such as antioxidant, anti-inflammatory, anticancer, antimicrobial, antidiabetic, and neuroprotective effects. Their structural diversity and ability to modulate multiple biological targets make them attractive candidates for the development of therapeutic agents, particularly in complex diseases that involve more than one molecular pathway (Lv et al., 2024; Dewi et al., 2022). Previous literature in Lombok

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Medical Journal has also discussed the therapeutic potential of herbal-derived compounds, such as ginkgolide and bilobalide from *Ginkgo biloba*, reflecting continued interest in natural product-based therapies as complementary or alternative approaches in clinical medicine (Karima et al., 2023).

Despite their pharmacological potential, the clinical use of many natural product-derived compounds remains limited by unfavorable pharmacokinetic properties. Several compounds show poor aqueous solubility, limited gastrointestinal absorption, instability in physiological conditions, rapid metabolism, short systemic retention, and low oral bioavailability. These limitations can cause plasma concentrations to remain below therapeutic levels, making their biological effects inconsistent when translated from experimental models to human clinical use (Lv et al., 2024; Patel et al., 2024). For example, curcumin has been widely studied for its anti-inflammatory and antioxidant properties, but its clinical translation is hampered by poor water solubility, low gastrointestinal absorption, rapid metabolism, and systemic elimination (Arozal et al., 2021; Jabur et al., 2025). Similar limitations are also observed in berberine, quercetin, resveratrol, naringenin, and baicalin, which require formulation strategies to improve their systemic exposure and therapeutic feasibility.

Nanoparticle- and formulation-based delivery systems have been developed to overcome these pharmacokinetic barriers. These systems may improve drug performance by increasing solubility, enhancing stability, protecting compounds from degradation, improving intestinal absorption, prolonging circulation time, enabling controlled release, and modifying tissue distribution. Nanotechnology-based systems such as nanosuspensions, polymeric nanoparticles, lipid-polymer hybrid nanoparticles, micelles, nanosponges, phytosome-based systems, and nano-sized water-soluble formulations have been investigated for various natural product-derived compounds. According to Lv et al. (2024), nano-drug delivery systems may enhance the bioavailability, targeting ability, and controlled release of natural products, thereby improving shortcomings that limit their clinical application. Similarly, Dewi et al. (2022) emphasized that nanotechnology-based herbal formulations may improve solubility, stability, bioavailability, and pharmacological activity of phytochemicals.

However, improvement in pharmacokinetic parameters does not automatically indicate clinical efficacy in humans. Many studies remain preclinical, and available human pharmacokinetic studies are still limited to selected formulations and healthy volunteers. Therefore, it is important to interpret nanoparticle-based pharmacokinetic enhancement not only as a pharmaceutical achievement, but also as a translational step toward clinical application. This literature review aims to discuss the pharmacokinetic enhancement of natural product-derived secondary metabolites using nanoparticle- and formulation-based delivery systems and to evaluate their potential relevance for human clinical translation.

Materials and Methods

This study was conducted as a narrative literature review to discuss the potential clinical relevance of nanoparticle- and formulation-based delivery systems for natural product-derived secondary metabolites. The review emphasized pharmacokinetic outcomes as a basis for understanding how improved bioavailability, systemic exposure, and tissue distribution may support future clinical use in humans.

Literature was searched through PubMed, ScienceDirect, Springer, MDPI, and other relevant databases using keywords such as "natural product pharmacokinetics," "secondary metabolites bioavailability," "nanoparticle drug delivery natural products," "phytosome pharmacokinetics," "human pharmacokinetic study," and "clinical translation." Articles published within the last 10 years were considered for inclusion. The literature search was performed using English-language keywords, while eligible articles published in either English or Indonesian were included in this review. Reference lists of relevant articles were also manually screened to identify additional eligible studies.

Studies were selected according to the following predefined inclusion and exclusion criteria. Inclusion criteria included: (1) original research articles published in English or Indonesian within the last 10 years; (2) studies investigating natural product-derived compounds formulated using nanoparticle or formulation based drug delivery systems; (3) studies reporting pharmacokinetic outcomes such as AUC, Cmax, Tmax, half-life, clearance, bioavailability, systemic exposure, or tissue distribution; and (4) clinical or relevant preclinical studies evaluating the pharmacokinetic performance of these formulations. Exclusion criteria included: (1) review articles, conference abstracts, editorials, and opinion papers; (2) duplicate publications; (3) studies without relevant pharmacokinetic evaluation; and (4) studies unrelated to nanoparticle- or formulation-based delivery systems for natural product-derived compounds.

Both clinical and relevant preclinical studies were included. Human pharmacokinetic studies were considered particularly valuable for evaluating clinical translation, whereas preclinical studies were included to provide mechanistic evidence regarding formulation performance and pharmacokinetic enhancement. A total

of 35 records were identified, and 30 records remained after duplicate removal. After title and abstract screening, 12 records were excluded due to irrelevance to natural products, nanoparticle- or formulation-based systems, or pharmacokinetic outcomes. Of these, 18 full-text articles were considered potentially eligible because they provided sufficient information regarding nanoparticle formulation characteristics, pharmacokinetic evaluation, and potential relevance to clinical translation. Four articles were subsequently excluded because they lacked pharmacokinetic data, used unclear formulation systems, or had limited relevance to the objectives of this review. Finally, 14 articles were included in the qualitative synthesis, with 10 key pharmacokinetic studies summarized in **Table 2**. The screening process is summarized in **Figure 1.** Data extracted from each eligible study included the author and publication year, natural product derived compound, formulation or nanoparticle type, study model (clinical or preclinical), pharmacokinetic parameters (e.g., AUC, Cmax, Tmax, half-life, clearance, bioavailability, systemic exposure, and tissue distribution), and the principal findings related to pharmacokinetic enhancement and clinical translation.

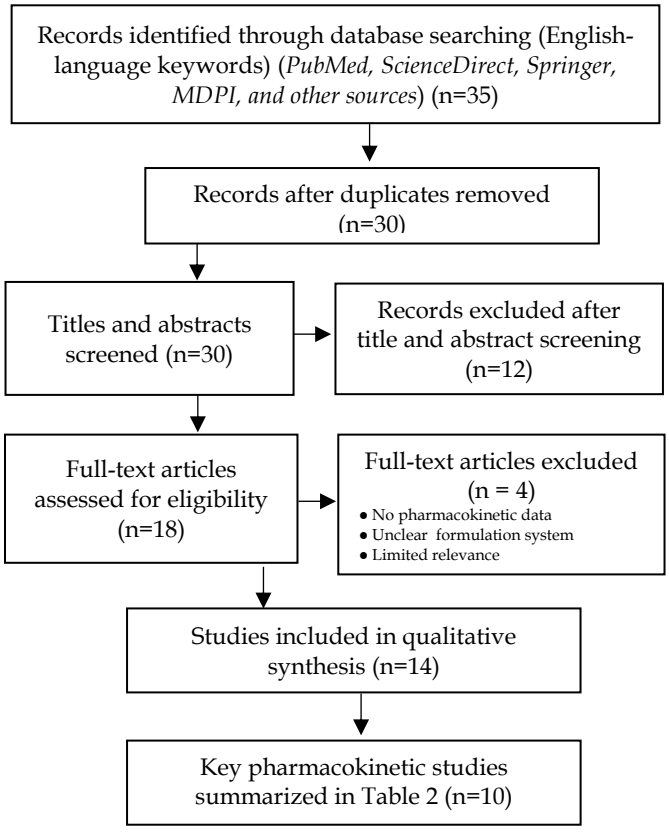

Figure 1. Article screening workflow for the literature review.

Result and Discussion

Pharmacokinetic Barriers of Natural Product-Derived Secondary Metabolites

Natural product-derived secondary metabolites often show promising biological activity, but their clinical use is frequently restricted by pharmacokinetic limitations. These barriers include poor aqueous solubility, limited dissolution, low gastrointestinal absorption, extensive first-pass metabolism, rapid systemic elimination, and low bioavailability. Such limitations are clinically important because favorable in vitro pharmacological activity does not necessarily translate into therapeutic efficacy if sufficient plasma or tissue concentrations cannot be achieved in vivo.

Curcumin, for example, is a polyphenolic compound from *Curcuma longa* with broad anti-inflammatory, antioxidant, and anticancer potential. However, its low water solubility, poor intestinal absorption, extensive metabolism, and rapid elimination substantially limit systemic exposure after oral administration (Arozal et al., 2021; Jabur et al., 2025). Berberine also has broad pharmacological activity, including antidiabetic, anti-inflammatory, antimicrobial, and anticancer effects, but its oral bioavailability is very low because of poor solubility, limited intestinal absorption, P-glycoprotein efflux, first-pass metabolism, and pre-systemic degradation (Mir et al., 2023; Amalraj et al., 2025). Quercetin and resveratrol face similar problems, particularly poor solubility, extensive metabolism, and limited systemic retention, which reduce their practical value as orally administered therapeutic candidates (Gujjula & Parameswari, 2023; Li et al., 2017).

These limitations indicate that the major challenge of natural product-derived compounds is not only related to pharmacodynamic potential, but also to whether the compound can achieve adequate exposure in the body. In this context, pharmacokinetic optimization becomes a crucial step before clinical translation. The compounds summarized in **Table 1** share a common pattern: they have relevant biological potential, but their therapeutic application is constrained by poor systemic exposure. Therefore, formulation strategies should not be viewed merely as pharmaceutical modifications, but as pharmacokinetic interventions designed to improve systemic exposure and increase the likelihood of successful clinical translation.

Table 1. Clinical Pharmacokinetic Barriers of Selected Natural Product-Derived Secondary Metabolites

Secondary Metabolite/ Study	Class and Source	Main Pharmacokinetic Barrier	Clinical relevance
Curcumin Arozal et al., 2021; Jabur et al., 2025	Polyphenol/diarylheptanoid; *Curcuma longa*	Poor aqueous solubility, low gastrointestinal absorption, rapid metabolism, and low systemic bioavailability	Low systemic exposure may limit predictable therapeutic effects in humans; nano-sized and nanoparticle-based formulations may improve bioavailability and support clinical translation, although patient-based efficacy still requires validation
Berberine Mir et al., 2023; Amalraj et al., 2025	Alkaloid; *Berberis* spp., *Coptis* spp., and *Hydrastis* spp.	Low solubility, poor intestinal absorption, P-glycoprotein efflux, presystemic degradation by gut microbiota, extensive hepatic metabolism, and renal excretion	Low systemic exposure may require higher doses and increase gastrointestinal intolerance; formulation-based delivery systems have shown improved absorption in human pharmacokinetic studies, but clinical efficacy in target patient populations remains to be confirmed
Quercetin Gujjula & Parameswari, 2023; Li et al., 2017	Flavonoid; fruits, onions, tomatoes, broccoli, lettuce, and tea	Poor water solubility, low oral absorption, extensive intestinal and hepatic metabolism, and low bioavailability	Limited absorption reduces its clinical utility despite broad pharmacological potential; lecithin-based phytosome delivery has shown improved human systemic exposure, supporting further clinical evaluation
Resveratrol Li et al., 2017	Polyphenol/stilbene; grapes, berries, mulberries, and *Polygonum cuspidatum*	Poor water solubility, low stability, rapid intestinal and hepatic metabolism, short systemic retention, and low oral bioavailability	Rapid metabolism may prevent sustained therapeutic plasma concentrations; micellar or other nano-based delivery systems may prolong systemic exposure, but human extrapolation from preclinical evidence remains limited
Naringenin Rajamani et al., 2018	Flavonoid; citrus fruits	Poor aqueous solubility, limited dissolution rate, low oral absorption, and low systemic bioavailability	Limited oral exposure may restrict its therapeutic application; nanosuspension-based formulation may improve dissolution, absorption, and systemic availability, but human pharmacokinetic confirmation is still needed
Baicalin Riadi et al., 2023	Flavonoid glycoside; *Scutellaria baicalensis*	Poor membrane permeability, gastrointestinal degradation, metabolic instability, and limited systemic bioavailability	Systemic exposure may be limited after oral administration; lipid-polymer hybrid nanoparticles may be more relevant for controlled release and colon-targeted delivery than for systemic bioavailability enhancement, requiring further human validation

The clinical relevance of these barriers is also important when considering patient populations. In real-world clinical practice, patients may have variable

gastrointestinal function, hepatic metabolism, renal clearance, comorbidities, and concomitant drug use, all of which may further influence the absorption and disposition of natural product-derived compounds. Therefore, improving pharmacokinetic behavior may contribute to more predictable systemic exposure across diverse patient populations. However, overcoming pharmacokinetic barriers should be considered a prerequisite rather than a guarantee of clinical efficacy, emphasizing that enhanced systemic exposure must ultimately be confirmed through pharmacodynamic and well-designed clinical studies.

Nanoparticle- and Formulation-Based Strategies for Pharmacokinetic Enhancement

Nanoparticle- and formulation-based delivery systems are designed to improve the pharmacokinetic performance of compounds with poor physicochemical properties. In natural product-derived secondary metabolites, these systems may enhance dissolution, protect active compounds from degradation, improve intestinal absorption, support controlled release, prolong systemic circulation, and modify tissue distribution. These mechanisms are particularly important for hydrophobic or unstable compounds because improving solubility, protecting against degradation, and facilitating intestinal transport may collectively increase systemic exposure and reduce pharmacokinetic variability following oral administration.

Several nanoparticle- and formulation-based delivery approaches have been developed to address these limitations. Nanosuspensions may improve dissolution by reducing particle size and increasing surface area, while polymeric nanoparticles can protect active compounds and provide sustained release. Lipid-polymer hybrid nanoparticles combine the stability of polymeric systems with the biocompatibility of lipid-based carriers. Micelles and cyclodextrin-based nanosponges are useful for improving solubilization and controlled release of hydrophobic compounds, whereas phytosome-based systems and nano-sized water-soluble formulations may enhance absorption through better dispersion and interaction with biological membranes. The pharmacokinetic advantages of these systems are largely determined by their physicochemical characteristics particularly particle size, carrier composition, and drug encapsulation properties. For instance, reducing particle size increases the surface area available for dissolution, while lipid- or polymer-based carriers may enhance membrane interaction, reduce premature drug degradation, and prolong systemic circulation, thereby contributing to improvements in pharmacokinetic parameters such as Cmax, Tmax, AUC, and half-life.

The use of nanotechnology in natural products has been reported to improve bioavailability, targeting ability, controlled release, and clinical applicability (Lv et al., 2024). Lipid-based nanoparticles, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and related systems, have also been described as promising platforms for improving stability, entrapment, bioavailability, and therapeutic performance of bioactive compounds (Patel et al., 2024). Similarly, nanotechnology-based herbal formulations have been recognized as promising strategies for improving the clinical feasibility of poorly soluble, poorly absorbed, or unstable phytochemicals (Dewi et al., 2022). Collectively, these formulation strategies demonstrate that improvements in pharmacokinetic behavior arise from different mechanisms depending on the carrier system, including enhanced solubilization, improved membrane interaction, prolonged drug release, and protection against premature degradation.

From a clinical translation perspective, these systems may help bridge the gap between pharmacological potential and therapeutic feasibility. Improvements in pharmacokinetic parameters such as AUC, Cmax, Tmax, half-life, clearance, and tissue distribution may indicate enhanced systemic exposure or more favorable drug disposition resulting from improved formulation performance rather than alterations in the intrinsic pharmacodynamic properties of the active compound. However, these pharmacokinetic improvements should still be interpreted cautiously, as enhanced exposure alone does not confirm clinical efficacy without further validation in patient-based studies. These considerations provide the rationale for evaluating specific formulation systems through pharmacokinetic parameters, as discussed in the following section.

Clinical and Preclinical Pharmacokinetic Evidence

Clinical and preclinical pharmacokinetic evidence should be interpreted together to understand how nanoparticle- and formulation-based delivery systems may support the translation of natural product-derived compounds into human use. Clinical pharmacokinetic studies provide direct information on systemic exposure in humans, while preclinical studies remain the main foundation for explaining formulation behavior, pharmacokinetic mechanisms, and potential delivery advantages. Pharmacokinetic evaluation commonly includes changes in AUC, Cmax, Tmax, half-life, clearance, mean residence time, bioavailability, and tissue distribution after formulation modification. Such parameters are important because they indicate whether a delivery system can improve absorption, prolong systemic exposure, reduce elimination, or enhance localization to specific tissues.

Although clinical evidence is more directly relevant to human translation, the available data in this review are still largely supported by preclinical studies. Therefore, preclinical findings remain important as early translational evidence before broader clinical application is considered. Differences between animal models and humans, including gastrointestinal physiology, metabolic activity, transporter expression, and tissue distribution, may influence clinical outcomes. Table 2 summarizes selected clinical and preclinical studies on nanoparticle- or formulation-based natural product delivery systems, with emphasis on pharmacokinetic improvement and translational relevance.

Table 2. Pharmacokinetic Enhancement and Translational Relevance of Nanoparticle- or Formulation-Based Natural Product Delivery Systems

Study/ Compound	Nanoparticle system and model	Main pharmacokinetic improvement	Clinical and translational relevance
Rajamani et al., 2018; naringenin	Nanosuspension; in vivo oral pharmacokinetic study	Improved solubility and oral bioavailability; increased systemic exposure compared with non-nano naringenin	May improve oral delivery of poorly soluble flavonoids; human pharmacokinetic confirmation is still required
Riadi et al., 2023; baicalin	Lipid-polymer hybrid nanoparticles; rat pharmacokinetic and organ distribution study	Prolonged Tmax and MRT, reduced early systemic plasma exposure, and increased colon localization compared with baicalin suspension	More relevant as a colon-targeted delivery strategy than as a systemic bioavailability enhancer; clinical relevance requires human validation
Mir et al., 2023; berberine	Folic acid-grafted alginate/chitosan nanoparticles; in vivo oral pharmacokinetic study	Increased oral bioavailability compared with conventional berberine formulation	May improve the feasibility of berberine as an orally delivered therapeutic compound; safety and human PK data are needed
Riva et al., 2019; quercetin	Quercetin Phytosome, lecithin-based delivery system; human pharmacokinetic study in healthy volunteers	Increased oral absorption, with approximately 20-fold higher Cmax and 18-fold higher AUC compared with unformulated quercetin	Provides direct human pharmacokinetic evidence that formulation-based delivery can improve systemic exposure of poorly bioavailable flavonoids; further clinical outcome studies are needed
Li et al., 2017; resveratrol	Self-assembling lecithin-based mixed polymeric micelles; oral and intravenous pharmacokinetic study	Increased Cmax and AUC, prolonged half-life, reduced elimination rate, and decreased clearance	May overcome rapid elimination and improve systemic exposure; extrapolation to humans remains limited
Arozal et al., 2021; curcumin	Chitosan-sodium tripolyphosphate nanoparticles; rat oral pharmacokinetic study	Markedly increased Cmax, 16-fold higher AUC, faster Tmax, prolonged half-life, and lower clearance compared with non-nano curcumin	Strong preclinical evidence for improving oral curcumin exposure; clinical outcome studies are still needed
Petrangolini et al., 2021: berberine	Berberine Phytosome/ BBR-PP, food-grade lecithin-based delivery system; randomized double-blind crossover human PK study	Improved solubility and intestinal bioaccessibility; increased total berberine AUClast from 1217 ± 129 to 4952 ± 647 pg/mL·h with one BBR-PP tablet and 8212 ± 893 pg/mL·h with two BBR-PP tablets; Cmax increased from	Provides direct human pharmacokinetic evidence that formulation-based delivery can improve berberine absorption and systemic exposure; further clinical studies in patients with

		76.70 ± 14.04 to 316.88 ± 26.60 and 572.14 ± 64.26 pg/mL, respectively	metabolic or gastrointestinal disorders are needed
Jabur et al., 2025; curcumin	AQUATURM, nano-sized water-soluble curcumin formulation; randomized double-blind crossover human PK study	Curcumin AUC0–12h increased 7.33-fold and Cmax increased 6.76-fold; total curcuminoid AUC increased 7.12-fold vs conventional tablet	Supports human translational relevance of nano-sized curcumin formulation; clinical efficacy and long-term safety require further validation
Gujjula & Paramesswari, 2023; quercetin	Cyclodextrin-based nanosponges; in vivo pharmacokinetic study	Increased Cmax and AUC compared with pure drug suspension; provided more controlled release	May support improved oral or mucosal delivery of quercetin; human absorption data are needed
Amalraj et al., 2025; berberine	BerbiQ formulation; in vivo oral bioavailability study	Increased AUC and Cmax compared with conventional formulation; prolonged systemic exposure	Supports enhanced systemic exposure of berberine; clinical validation is required

Based on the clinical and preclinical studies summarized in **Table 2**, nanoparticle- and formulation-based delivery systems generally improved the pharmacokinetic profile of natural product-derived compounds by increasing systemic exposure, prolonging retention, reducing elimination, or enhancing tissue localization. Human pharmacokinetic studies on quercetin phytosome, berberine phytosome, and nano-sized curcumin formulation provide important clinical signals that formulation strategies can improve systemic exposure in humans. At the same time, preclinical studies on naringenin nanosuspension, berberine polymeric nanoparticles, resveratrol mixed polymeric micelles, curcumin chitosan-sodium tripolyphosphate nanoparticles, and quercetin nanosponges provide broader mechanistic support for pharmacokinetic enhancement. These findings support the role of nanoparticle systems as pharmacokinetic modifiers, particularly for compounds with poor solubility, limited absorption, rapid metabolism, or low oral bioavailability. Although both clinical and preclinical studies consistently demonstrated pharmacokinetic improvement, the magnitude of pharmacokinetic improvement differed considerably among studies. For example, human studies on quercetin phytosome reported approximately 20-fold increases in Cmax, whereas nano-sized curcumin formulations produced more moderate improvements in systemic exposure. These differences likely reflect variations in formulation design, carrier characteristics, study conditions, and the intrinsic physicochemical properties of each active compound rather than the superiority of a particular delivery system.

The interpretation of each finding should consider the study model, formulation type, and intended pharmacokinetic purpose. Clinical pharmacokinetic studies are important for supporting clinical translation because systemic exposure is evaluated directly in human subjects; however, preclinical evidence remains the larger part of the available data in this review. Therefore, preclinical studies are still essential for identifying formulation behavior, pharmacokinetic mechanisms, and potential delivery advantages before patient-based studies are conducted. Several formulation systems are primarily designed to increase systemic exposure, as demonstrated by curcumin, naringenin, berberine, resveratrol, and quercetin formulations. Arozal et al. (2021) reported that curcumin-loaded chitosan-sodium tripolyphosphate nanoparticles increased AUC and Cmax, shortened Tmax, prolonged half-life, and lowered clearance in rats, indicating improved plasma exposure and systemic retention. Li et al. (2017) reported that self-assembling lecithin-based mixed polymeric micelles improved the pharmacokinetic behavior of trans-resveratrol by increasing Cmax and AUC, prolonging half-life, and reducing elimination. Mir et al. (2023) demonstrated that folic acid-grafted alginate/chitosan nanoparticles increased berberine oral bioavailability compared with conventional berberine formulation. Taken together, these studies suggest that formulation-dependent pharmacokinetic enhancement is achieved through different mechanisms. Polymeric and lipid-based nanoparticles primarily prolong systemic retention and reduce elimination, whereas nanosuspensions and micellar systems mainly improve dissolution and absorption, leading to higher systemic exposure.

In contrast, not all formulation improvements should be interpreted only as increased plasma concentration. Baicalin-loaded lipid-polymer hybrid nanoparticles, for instance, appear more relevant as a

controlled-release and colon-targeted delivery system than as a systemic bioavailability enhancer. This distinction is clinically important because, for some diseases, improved local tissue exposure may be more meaningful than higher systemic exposure. These findings therefore support nanoparticle-based formulations as promising pharmacokinetic optimization strategies rather than definitive indicators of therapeutic success. Therefore, pharmacokinetic improvement should be interpreted according to the therapeutic target, route of administration, intended site of action, and level of clinical evidence available.

Overall, the available clinical and preclinical evidence supports the potential of nanoparticle- and formulation-based delivery systems to modify the pharmacokinetic profile of natural product-derived compounds. Clinical pharmacokinetic studies strengthen the translational direction of this approach by showing improved systemic exposure in humans, while preclinical studies provide the broader mechanistic basis for further development. Nevertheless, improved AUC or Cmax, especially in animal models, does not automatically confirm therapeutic efficacy in humans. Further patient-based clinical trials are required to determine whether these pharmacokinetic improvements can be translated into meaningful clinical benefit.

Human Pharmacokinetic Evidence and Clinical Translation

Human pharmacokinetic evidence provides a stronger basis for evaluating the translational potential of nanoparticle- and formulation-based delivery systems. In this review, human pharmacokinetic data were identified for quercetin phytosome, berberine phytosome, and a nano-sized water-soluble curcumin formulation. These studies are important because they directly demonstrate that formulation strategies can improve systemic exposure in humans, not only in animal models.

Riva et al. (2019) evaluated quercetin phytosome, a lecithin-based delivery system, in healthy volunteers. The formulation increased oral absorption, with approximately 20-fold higher Cmax and 18-fold higher AUC compared with unformulated quercetin. This result is clinically relevant because quercetin has poor water solubility, limited absorption, and extensive intestinal and hepatic metabolism. Improved systemic exposure in humans suggests that phytosome-based delivery may support further clinical evaluation of quercetin, particularly in conditions related to inflammation, oxidative stress, or metabolic dysfunction.

Petrangolini et al. (2021) evaluated berberine phytosome, also known as BBR-PP, in a randomized double-blind crossover pharmacokinetic study in healthy volunteers. This formulation improved solubility and intestinal bioaccessibility and increased total berberine AUClast and Cmax compared with unformulated berberine. This finding is relevant because berberine has strong clinical interest in metabolic and gastrointestinal disorders but is limited by poor oral absorption and low systemic exposure. Improved pharmacokinetic exposure may help reduce dosing limitations and improve therapeutic feasibility, although clinical studies in target patient populations are still required.

Jabur et al. (2025) reported a randomized double-blind crossover human pharmacokinetic study of AQUATURM, a nano-sized water-soluble curcumin formulation. Compared with a conventional curcumin tablet, AQUATURM increased curcumin AUC0–12h by 7.33-fold and Cmax by 6.76-fold, while total curcuminoid AUC increased by 7.12-fold. This finding, provides direct human evidence that a nano-sized curcumin formulation can enhance systemic exposure. However, because the study was conducted in healthy adults, additional studies are needed to determine whether this improvement leads to better therapeutic outcomes in patients.

Although the magnitude of pharmacokinetic improvement differed among formulations, all three human studies consistently demonstrated enhanced systemic exposure following formulation optimization. Quercetin phytosome produced the greatest relative increase in Cmax and AUC, whereas nano-sized curcumin and berberine phytosome showed more moderate but clinically meaningful improvements. These differences likely reflect variations in carrier composition, formulation strategy, and the physicochemical characteristics of each active compound rather than the superiority of any single delivery platform.

Together, these human pharmacokinetic studies strengthen the translational argument of this review. They show that formulation-based delivery systems can improve systemic exposure in humans for compounds with poor intrinsic bioavailability. However, current evidence remains limited because most human studies focus on short-term pharmacokinetic endpoints in healthy volunteers. Therefore, future clinical trials should include target patient populations rather than only healthy volunteers, incorporate pharmacokinetic-pharmacodynamic correlations, evaluate long-term safety, establish optimal dosing strategies, and determine whether improved systemic exposure translates into meaningful clinical benefit.

Clinical Implications, Translational Limitations, and Future Perspectives

The clinical relevance of nanoparticle- and formulation-based delivery systems lies in their ability to improve the pharmacokinetic behavior of compounds that otherwise have limited therapeutic feasibility. Increased AUC may indicate greater systemic exposure, while increased Cmax reflects a higher peak plasma concentration. A shorter Tmax may suggest faster absorption, whereas prolonged half-life or mean residence time may indicate longer systemic retention. Reduced clearance may also support sustained exposure, while improved tissue distribution may be useful for compounds intended to act at specific organs or local disease sites.

These pharmacokinetic changes may have several implications for human clinical use. First, improved systemic exposure may increase the likelihood that the compound reaches concentrations associated with pharmacological activity. Second, better bioavailability may reduce the need for high oral doses, which is particularly important for compounds such as curcumin and berberine. Third, prolonged systemic retention may support more stable exposure over time. Fourth, improved tissue distribution or targeted localization may be useful in conditions where local therapeutic effects are needed, such as intestinal inflammation, cancer-related targets, or inflammatory tissue environments.

However, clinical interpretation should remain cautious. Higher systemic exposure is not always beneficial if it increases toxicity, drug interactions, or unpredictable exposure in vulnerable patients. Natural product-derived compounds may interact with drug-metabolizing enzymes, efflux transporters, or conventional medications. This issue is clinically important because many potential users of natural product-based therapies are patients with chronic diseases who may already be receiving multiple drugs. Therefore, pharmacokinetic enhancement should be viewed as an enabling step toward clinical translation, not as final evidence of therapeutic efficacy. While enhanced systemic exposure may improve therapeutic potential, excessive increases in Cmax or overall drug exposure could theoretically narrow the therapeutic window, underscoring the importance of dose optimization and careful pharmacokinetic evaluation during clinical development.

Despite their promising pharmacokinetic advantages, nanoparticle-based formulations also require careful safety evaluation. Enhanced systemic exposure may alter the pharmacokinetic profile of bioactive compounds, potentially affecting dose requirements, adverse effects, and drug-drug interaction risks. Consequently, comprehensive toxicological assessment, dose standardization, long-term safety evaluation, and post-marketing pharmacovigilance should be considered essential components of future clinical development before widespread implementation.

Several translational limitations remain. Many available studies are still preclinical, and human pharmacokinetic studies are mostly conducted in healthy volunteers. In addition, formulation characteristics such as particle size, carrier composition, surface charge, encapsulation efficiency, stability, release profile, and manufacturing reproducibility may influence pharmacokinetic behavior. Lv et al. (2024) noted that clinical translation of nano-drug delivery systems still faces challenges related to safety, nanotoxicity, carrier specificity, targeting efficiency, and evaluation methods. Additional challenges include large-scale manufacturing, batch-to-batch reproducibility, regulatory approval, and cost-effective production, all of which must be addressed before widespread clinical application can be achieved. Therefore, future development should prioritize biocompatible and reproducible carriers, long-term safety assessment, and patient-based validation.

Future research should move beyond pharmacokinetic comparison and evaluate whether improved exposure translates into clinically meaningful benefit. For natural product-derived compounds such as curcumin, berberine, quercetin, resveratrol, naringenin, and baicalin, further studies should assess dose-exposure-response relationships, optimal dosing regimens, long-term safety, potential drug interactions, and clinical efficacy in relevant disease populations. Future studies should also evaluate formulation performance in patient populations with altered pharmacokinetics, such as individuals with metabolic or hepatic disorders, rather than limiting evaluations to healthy volunteers. This direction is essential to determine whether nanoparticle- and formulation-based delivery systems can truly bridge pharmacokinetic optimization and human clinical application.

Limitations of This Review

This review has several limitations that should be considered when interpreting the findings. First, although human pharmacokinetic studies were included whenever available, the current evidence remains dominated by preclinical investigations (n=9), and only a limited number of clinical study (n=1) have evaluated nanoparticle- and formulation-based delivery systems for natural product-derived compounds. Second, the included studies exhibited substantial heterogeneity in formulation design, nanoparticle composition, carrier materials, particle size, pharmacokinetic endpoints, study models, and experimental conditions, making direct comparisons across studies difficult. Third, as with many narrative

literature reviews, publication bias cannot be excluded because studies reporting positive pharmacokinetic outcomes are more likely to be published than studies with neutral or negative findings. Finally, this review did not perform a formal meta-analysis because of the considerable methodological heterogeneity among the available studies, including differences in formulation strategies, pharmacokinetic parameters, animal models, and clinical study designs. Consequently, the conclusions presented here are based on qualitative synthesis rather than quantitative pooled analysis. Despite these limitations, the available evidence generally supports the potential of nanoparticle- and formulation-based delivery systems to improve the pharmacokinetic performance of natural product-derived secondary metabolites and provides a useful foundation for future well-designed clinical investigations.

Conclusion

Natural product-derived secondary metabolites have substantial therapeutic potential, but their clinical application is often limited by poor pharmacokinetic performance. Nanoparticle- and formulation-based delivery systems may address these limitations by improving solubility, absorption, systemic exposure, retention time, and tissue distribution. These improvements suggest that pharmacokinetic optimization is not merely a formulation objective but a prerequisite for facilitating the clinical translation of natural product-derived compounds.

Human pharmacokinetic evidence on quercetin phytosome, berberine phytosome, and nano-sized curcumin formulation further supports the translational promise of these delivery systems. Nevertheless, improved pharmacokinetic performance alone does not guarantee clinical efficacy. Their clinical value ultimately depends on patient-based validation, long-term safety assessment, dose-exposure-response evaluation, and confirmation of meaningful therapeutic outcomes. Therefore, nanoparticle- and formulation-based delivery systems represent promising translational platforms for improving the clinical feasibility of poorly bioavailable natural product-derived compounds, while emphasizing the need for robust clinical evidence before routine therapeutic application.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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