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Review Article

Integrating Herbal Bioenhancers into Advanced Drug-Delivery Systems: Trends and Translational Potential

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ABSTRACT

Herbal bioenhancers are natural compounds that increase the systemic availability and/or efficacy of coadministered drugs without possessing significant therapeutic activity at the doses used. Interest in botanical bioenhancers has surged because they offer an economical route to reduce drug dose, toxicity and treatment cost — advantages especially relevant for antimicrobials, antituberculars, anticancer agents and nutraceuticals. Classical examples such as piperine (black/long pepper) and niaziridin (moringa) act via inhibition of drug-metabolising enzymes (CYPs, UGTs) and efflux transporters (P-gp), and have demonstrated clinically meaningful increases in partner-drug exposure (for example, piperine increases rifampicin exposure and supported the Risorine formulation development). Recent years (2020–2024) saw two parallel trends: (1) deeper mechanistic characterization of herbal enhancers (molecular targets, transporter/enzyme profiling and in-silico screening) and (2) integration of bioenhancers into modern delivery platforms (liposomes, phytosomes, nanoemulsions, magnetic nanoparticles) to improve safety, targeting and dose control. Curcumin a paradigmatic poorly bioavailable phytochemical — exemplifies how combining bioenhancers (piperine) with nanotechnology can markedly improve systemic exposure and pharmacodynamic effects, although clinical translation requires rigorous PK/PD and safety data. Key challenges remain: standardisation of botanical extracts, herb-drug interaction profiling, dose optimisation and regulatory frameworks for hybrid herb-plus-drug products. Emerging 2023–2025 reviews and preclinical studies propose practical roadmaps (combining targeted screening, mechanistic validation and GMP-grade standardisation) to accelerate translation of safe, evidence-based herbal bioenhancers into therapeutic use.

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INTRODUCTION

The idea of herbal bioenhancers has garnered increasing attention in contemporary pharmaceutical research because of its promise to address the issue of poor oral bioavailability, which is a significant hindrance for many therapeutic agents. Oral administration is still the most favored method for drug delivery; however, a significant number of drugs taken orally show low systemic availability due to factors such as limited absorption, extensive first-pass metabolism, or the action of active efflux transport mechanisms like P-glycoprotein (P-gp) [1]. Therefore, improving bioavailability without altering the chemical structure of the active compound has become a crucial approach to enhance drug effectiveness, decrease dosing frequency, and lower treatment expenses.

The idea of bioenhancement has roots in Ayurvedic medicine, where specific adjuvant herbs (Yogavahi) were historically utilized to boost the effects of other remedies. This foundational knowledge from ethnopharmacology has spurred the identification of plant-derived substances that can influence pharmacokinetic pathways such as inhibiting cytochrome P450 enzymes (CYPs), UDP-glucuronosyltransferases (UGTs), or efflux transporters thereby increasing systemic drug concentrations [2,3]. Among these compounds, piperine (derived from *Piper nigrum* and *Piper longum*) has been the most extensively researched bioenhancer, recognized for its ability to enhance the bioavailability of medications like rifampicin, curcumin, and phenytoin by inhibiting CYP3A4 and P-gp function [4].

Research on herbal bioenhancers has evolved from 2020 to 2025 to encompass not only traditional extracts but also molecular mechanistic investigations and innovative drug delivery technologies. Recent studies have clarified the

molecular targets of phytochemicals such as curcumin, quercetin, and glycyrrhizin, confirming their capability to modify transporter function and membrane fluidity, thus improving permeability and absorption [5]. Concurrent progress in nanotechnology such as liposomes, phytosomes, solid lipid nanoparticles, and nanoemulsions has integrated herbal bioenhancers into modern formulation methods, enhancing stability, targeting, and controlled release [6,7].

Despite these advancements, hurdles remain in converting bioenhancer research into clinical applications. Challenges like the standardization of herbal extracts, optimization of dosages, safety assessments, and regulatory alignment continue to be significant obstacles [8]. Nonetheless, the expanding collection of preclinical and clinical data highlights the promise of herbal bioenhancers in bridging traditional medicine with modern pharmacotherapy, providing a sustainable, safe, and cost-efficient means to boost drug efficacy.

This review intends to outline the mechanisms of action, emphasize key phytoconstituents with bioenhancing capabilities, discuss recent innovations in formulations, and examine future research pathways that could promote the clinical application of herbal bioenhancers.

Mechanisms by Which Herbal Bioenhancers Function:

Herbal bioenhancers operate through various pharmacokinetic and pharmacodynamic processes, influencing drug absorption, metabolism, distribution, and excretion. These processes often collaborate to enhance systemic bioavailability, extend drug half-life, and improve therapeutic effectiveness [3].

Suppression of Drug-Metabolizing Enzymes



A widely recognized mechanism includes the suppression of hepatic and intestinal cytochrome P450 (CYP) enzymes, especially CYP3A4, CYP2C9, and CYP2D6, which play a role in the oxidative metabolism of the majority of drugs [5]. For instance, piperine derived from *Piper nigrum* inhibits CYP3A4 and CYP2E1, thus preventing the metabolic breakdown of medications such as rifampicin, curcumin, and phenytoin [4]. Likewise, quercetin and genistein have been found to reduce the activity of CYP1A2 and CYP2E1, resulting in elevated plasma levels of co-administered drugs [2].

Suppression of Efflux Transport Proteins

A significant mechanism is the suppression of efflux transport proteins, particularly P-glycoprotein (P-gp) and Multidrug Resistance-associated Proteins (MRPs) found on the intestinal epithelial membrane [7]. These transporters actively transport drugs back into the intestinal lumen, hindering absorption. Herbal compounds such as piperine, sinomenine, and glycyrrhizin inhibit these transporters, which leads to increased intracellular drug levels and improved oral absorption [6,9].

Improvement of Gastrointestinal Absorption

Several bioenhancers function by altering gastrointestinal (GI) physiology to enhance drug absorption. They boost intestinal membrane permeability, increase mucosal blood circulation, and enhance the solubilization of lipophilic drugs [1]. For example, gingerol from *Zingiber officinale* and allicin from *Allium sativum* modify the lipid composition of epithelial membranes, resulting in increased membrane fluidity and passive diffusion [10]. Moreover, aloe vera saponins are recognized for temporarily opening tight junctions between epithelial cells, thereby

improving paracellular transport of hydrophilic drugs [11].

Alteration of Drug Transport and Distribution

Herbal bioenhancers also affect drug transport and tissue distribution. By modifying membrane dynamics or receptor expression, they can enhance drug binding to target tissues and boost intracellular accumulation [12].

Piperine, for example, facilitates higher drug uptake into hepatocytes and intestinal cells by altering the lipid arrangement of cell membranes [13].

Suppression of First-Pass Metabolism and Renal Elimination

Some bioenhancers diminish first-pass metabolism in the liver and intestine, leading to greater systemic availability of drugs [14]. Piperine and curcumin, for instance, inhibit glucuronidation and sulfation pathways, thereby prolonging the plasma half-life of compounds like resveratrol and curcumin itself [15]. Others, such as glycyrrhizin, decrease renal excretion by competing for active tubular secretion, which allows the drug to persist longer in systemic circulation [15].

Immunomodulatory and Cellular Actions

In addition to their pharmacokinetic effects, certain bioenhancers also demonstrate immunomodulatory or cellular enhancement actions that improve drug effectiveness. Niaziridin (from *Moringa oleifera*) enhances drug penetration into macrophages, which is beneficial for conditions like tuberculosis, while curcumin and piperine provide antiinflammatory and antioxidant benefits that support drug activity [17].

Synergistic and Multifactorial Interactions



Significantly, many herbal bioenhancers operate through multiple concurrent mechanisms, leading to synergistic increases in bioavailability. For example, the combined use of piperine and curcumin not only inhibits drug metabolism but

also enhances absorption via P-gp inhibition and improved intestinal permeability [18]. This multifaceted nature accounts for the widespread utility of herbal bioenhancers across various therapeutic areas.



Figure.1 Mechanism of action of Herbal Bioenhancers

Pharmacokinetics and Pharmacodynamics Profile of Herbal Bioenhancers:

Understanding the pharmacokinetic and pharmacodynamic (PK/PD) characteristics of herbal bioenhancers is crucial for their role in enhancing drug therapy. Unlike active pharmaceutical ingredients (APIs) that directly trigger therapeutic effects, bioenhancers influence drug therapy indirectly by modifying processes involved in absorption, distribution, metabolism, and excretion of co-administered drugs [1]. Their pharmacodynamic effects are derived from the synergistic modulation of cellular signaling, enzyme activity, or receptor sensitivity, resulting in enhanced efficacy and reduced toxicity of the main drug.

Pharmacokinetic Aspects

Absorption Phase:

Bioenhancers enhance the absorption of orally administered drugs primarily through the gastrointestinal tract. Substances such as piperine, gingerol, and niaziridin improve membrane permeability by altering lipid dynamics, which boosts both passive diffusion and paracellular transport [10]. For instance, piperine enhances the intestinal absorption of rifampicin and curcumin by inhibiting efflux transporters (P-gp) and modifying tight junction proteins [4]. Aloe vera saponins also promote better absorption of hydrophilic drugs by temporarily opening epithelial tight junctions [11].

Distribution Phase:

After absorption, bioenhancers can impact drug distribution by changing plasma protein binding and tissue penetration. Research indicates that piperine and quercetin modify plasma protein affinity, resulting in greater availability of free

drugs in systemic circulation [12]. Additionally, certain enhancers improve the tissue-specific delivery of drugs for example, niaziridin aids the penetration of antimicrobials into macrophages, increasing effectiveness against intracellular pathogens like *Mycobacterium tuberculosis* [19].

Metabolism Phase:

The most significant pharmacokinetic effect of herbal bioenhancers is the inhibition of enzymes, particularly CYP450 isoforms and UDP-glucuronosyltransferases (UGTs). Piperine inhibits CYP3A4 and UGT1A1, thus decreasing the first-pass metabolism of drugs such as curcumin and phenytoin [5]. Likewise, genistein and quercetin affect CYP2C9 and CYP1A2 activity, enhancing the bioavailability of paclitaxel and caffeine [15]. By limiting presystemic metabolism, these agents effectively prolong the plasma half-life and area under the curve (AUC) of concurrent drugs.

Excretion Phase:

Certain bioenhancers can lower renal clearance, thereby extending drug retention in systemic circulation.

Glycyrrhizin (derived from *Glycyrrhiza glabra*) competes for renal tubular secretion, reducing the active excretion of medications such as antibiotics and corticosteroids [23]. This results in prolonged drug exposure, increased therapeutic duration, and decreased frequency of dosing.

Pharmacodynamic Aspects

Synergistic Enhancement of Drug Action:

Pharmacodynamically, herbal bioenhancers improve drug efficacy through synergistic or complementary effects. For example, the combination of piperine and curcumin not only

increases curcumin's bioavailability but also boosts its anti-inflammatory and antioxidant actions by modulating NF- κ B and TNF- α pathways [19]. Such synergy enables higher efficacy at lower doses, minimizing toxicity.

Cellular Target Sensitization:

Some bioenhancers sensitize target cells or tissues, increasing their responsiveness to the active drug. Niaziridin enhances the sensitivity of macrophages to antimicrobials by boosting membrane permeability and altering lysosomal pH [6]. Similarly, gingerol from ginger amplifies the effects of analgesic medications by modulating transient receptor potential (TRP) channels, thus improving receptor binding and subsequent signal transduction[13].

Immunomodulatory and Anti-inflammatory Modulation:

Certain herbal enhancers exhibit immunomodulatory properties that complement the effects of drugs. Compounds like curcumin, glycyrrhizin, and quercetin downregulate pro-inflammatory cytokines (IL-6, TNF- α) and mediators of oxidative stress, leading to enhanced therapeutic outcomes in both inflammatory and infectious conditions [2]. These dual pharmacokinetic and pharmacodynamic advantages render herbal bioenhancers especially beneficial in long-term therapies.

Integrated PK/PD Implications:

Incorporating herbal bioenhancers into drug formulations can result in reduced dosages, improved patient adherence, and cost-effective treatment. Nevertheless, comprehending the PK/PD relationship is vital for ensuring safety and predictability. Excessive inhibition of enzymes or modulation of transporters can lead to unwanted



drug-drug interactions. Therefore, ongoing research highlights the importance of quantitative PK/PD modeling and clinical validation to optimize dosages and minimize risks [8].

Natural Phytochemicals Sourced from Medicinal Plants Play Significant Roles in Enhancing Drug Bioavailability:

The natural world provides a vast array of bioactive phytochemicals that act as natural bioenhancers—substances that improve the absorption, bioavailability, and effectiveness of concurrently administered drugs without causing notable pharmacological effects at their specified doses [1]. These phytoconstituents function through various mechanisms, including enzyme inhibition, modulation of efflux pumps, enhancement of membrane permeability, and synergistic antioxidant or anti-inflammatory activities. Below are some of the most researched natural phytochemicals that enhance bioavailability.

Piperine (Piper nigrum, Piper longum)

Piperine is the most thoroughly studied natural bioenhancer obtained from black and long pepper. It boosts drug bioavailability by inhibiting the enzymes CYP3A4 and CYP2E1 and obstructing P-glycoprotein efflux pumps, which decreases first-pass metabolism and enhances intestinal absorption [4]. The co-administration of piperine has been demonstrated to significantly increase the bioavailability of substances such as rifampicin, curcumin, and resveratrol. For instance, when piperine is combined with curcumin, its bioavailability in humans increased by about 2000% [19].

Curcumin (Curcuma longa)

Curcumin, a polyphenolic compound derived from turmeric, functions both as a therapeutic compound and a bioavailability enhancer. It influences intestinal transporters and inhibits drug-metabolizing enzymes like UGT1A1. In conjunction with piperine, it enhances the solubility and systemic exposure of various poorly bioavailable drugs, including anticancer and anti-inflammatory agents [20].

Quercetin (from Allium cepa, Citrus spp.)

Quercetin, a widely recognized flavonoid, increases drug bioavailability by inhibiting intestinal P-glycoprotein and CYP2C9 enzymes, thereby enhancing absorption and extending the plasma half-life of substrates such as paclitaxel and digoxin [21]. Moreover, its antioxidant and anti-inflammatory properties aid in promoting drug stability and therapeutic effectiveness.

Glycyrrhizin (Glycyrrhiza glabra)

Glycyrrhizin, a triterpenoid saponin extracted from licorice root, improves intestinal permeability and inhibits metabolic processes in the liver. It has been proven to elevate the plasma concentrations of antibiotics, corticosteroids, and vitamins by minimizing hepatic glucuronidation and renal clearance [10]. Additionally, its immunomodulatory properties can enhance the pharmacodynamic effects of concurrently administered medications.

Niaziridin (Moringa oleifera)

Niaziridin, a nitrile glycoside derived from *Moringa oleifera*, represents a relatively recent discovery with notable bioenhancing capabilities. It facilitates intestinal drug transport and augments the uptake of antibiotics and nutrients by modulating transporter activity and membrane permeability [6]. This compound has gained



interest for its ability to improve intracellular drug accumulation, particularly within macrophages, thereby enhancing treatments for tuberculosis and other infectious diseases.

Gingerol (Zingiber officinale)

Gingerol and its related phenolic compounds improve drug absorption by boosting gastrointestinal blood flow and stimulating the secretion of digestive enzymes. They also alter lipid membrane fluidity, which encourages the passive diffusion of drugs through the intestinal epithelium [5]. Formulations based on gingerol are becoming increasingly popular in nutraceutical and cosmeceutical products for their ability to enhance bioavailability and tolerability.

Regulatory-Approved Formulations Featuring Herbal Bioenhancers:

While most herbal bioenhancers continue to be researched, several formulations have received regulatory approval or clinical recognition due to robust pharmacokinetic and therapeutic data. These formulations exemplify the successful integration of traditional herbal bioenhancers with contemporary allopathic medications, notably in the areas of tuberculosis, oncology, and nutraceutical therapy.[22].

Risorine® (Rifampicin + Isoniazid + Piperine)

Risorine® is the first fixed-dose combination (FDC) that integrates a herbal bioenhancer (piperine) to be officially approved by the Drug Controller General of India (DCGI) for treating tuberculosis. Piperine functions by inhibiting CYP3A4 and P-glycoprotein, which significantly boosts the bioavailability of rifampicin and isoniazid while maintaining therapeutic efficacy at reduced dosages. Clinical trials have demonstrated up to a 60% decrease in the dosage of rifampicin

while achieving equivalent plasma levels, enhancing patient compliance and lowering the risk of hepatotoxicity.

Curcumin–Piperine Formulations

Curcumin, a known polyphenol with low absorption, has attained GRAS (Generally Recognized as Safe) status from the U.S. FDA. Formulations like BCM-95®, CurcuWIN®, and Curcumin C3 Complex® incorporate piperine (5–10 mg) as a bioenhancer, thereby boosting curcumin's bioavailability by as much as 20 times. These products are available commercially in the U.S., EU, and India as dietary supplements that comply with FDA cGMP manufacturing standards.

Nutraceutical and Herbal Combinations

Numerous nutraceuticals have been approved by the Food Safety and Standards Authority of India (FSSAI) and under the U.S. FDA Dietary Supplement Health and Education Act (DSHEA) guidelines, which include herbal bioenhancers. Examples are herbal vitamin C supplements containing piperine to enhance ascorbate absorption and Regulatory-Approved Formulations Featuring Herbal Bioenhancers

Future Regulatory Outlook

Global regulatory frameworks are increasingly acknowledging the significance of phytopharmaceuticals. India's Schedule T and Rule 158B (Drugs & Cosmetics Act, 1940) along with the most recent U.S. FDA Botanical Drug Development Guidance (2023 update) offer pathways for the approval of standardized herbal bioenhancer formulations. Nevertheless, the expectations for toxicological assessments, GMP compliance, and clinical validation remain stringent, highlighting the necessity for consistent



standardization and pharmacokinetic documentation.

Nanotechnological Developments in Herbal Bioenhancers

Nanotechnology is swiftly transforming the discovery, formulation, and clinical application of herbal bioenhancers. Current trends (2020–2025) focus on (a) the simultaneous delivery of bioactives and bioenhancers within a single nanocarrier, (b) the application of vesicular/phytosomal systems to enhance membrane interaction and lymphatic absorption, (c) the use of engineered nanoparticles for targeted delivery and controlled release, and (d) the creation of hybrid systems that merge phytochemistry with polymeric or lipid nanotechnology to enhance safety and scalability.

Phytosomes and Vesicular Carriers Enhanced Complexation and Absorption:

Phytosomes (complexes of phytochemicals and phospholipids) and liposomal/vesicular carriers are some of the most thoroughly validated methods for enhancing the oral and systemic bioavailability of phytochemicals and coadministered medications. These systems create stable complexes that improve lipophilicity, facilitate membrane fusion, and encourage lymphatic absorption thus circumventing part of first-pass metabolism. Phytosomes and similar vesicular systems have substantial preclinical and clinical evidence supporting their use in enhancing the exposure of curcumin, silybin, and other phytochemicals and are commonly utilized to include bioenhancers like piperine.

Co-encapsulation of bioenhancer + drug (synergistic nanocarriers):

A prominent recent strategy is to co-encapsulate both the active drug (or phytochemical) and its herbal bioenhancer (such as curcumin with piperine) within the same nanoparticle (lipid nanoparticle, polymeric NP, solid-lipid NP, or nanoemulsion). This co-encapsulation stabilizes the delivered ratio at the site of absorption, minimizes variability in intestinal exposure, and can yield synergistic pharmacokinetic/pharmacodynamic enhancements compared to free co-administration. Several preclinical investigations show that co-loaded formulations demonstrate superior bioavailability and efficacy compared to single-actives or simple combinations.

Solid Lipid Nanoparticles (SLNs), Nanoemulsions, and Polymeric NPs Controlled release combinations:

Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and biodegradable polymeric nanoparticles (such as PLGA and chitosan) are being utilized to deliver phytochemicals that have poor water solubility, as well as to carry bioenhancers that locally modulate P-glycoprotein (P-gp) and CYP activity in the gut. These carriers offer controlled release, mucoadhesion, and possibilities for surface functionalization to target the intestines or enable transcytosis, enhancing systemic exposure while also limiting systemic inhibitor exposure that might lead to undesired herb-drug interactions.

Stimuli-responsive and targeted hybrid systems:

Innovative designs are arising, including stimulus-responsive nanoparticles (triggered by pH, enzymes, or redox conditions) that release both the bioenhancer and drug at specific segments of the gastrointestinal tract or within targeted tissues, and ligand-targeted nanosystems designed to improve

cell-type specific uptake (for instance, targeting macrophages for tuberculosis therapy). These strategies strive to concentrate enzyme or transporter inhibition precisely where it is needed, reducing systemic enzyme inhibition and potential interactions.

Quality, scalability, and safety considerations:

Despite the significant advantages afforded by nanotechnology, regulatory and manufacturing obstacles remain: consistent standardization of botanical sources, precise control at the particle scale, longevity in stability, and thorough toxicological assessments (including chronic herb-drug interaction studies) are essential for approval. Progress in Good Manufacturing Practices for nanoherbals and the establishment of clearer regulatory guidelines are being formed to tackle these challenges.

CONCLUSION:

Herbal bioenhancers signify a notable progress in the areas of pharmacokinetics and pharmacodynamics, providing a natural, safe, and economical method to enhance drug bioavailability and improve therapeutic outcomes.

Compounds from plants such as piperine, curcumin, glycyrrhizin, quercetin, and gingerol function through various mechanisms, including the inhibition of metabolic enzymes, blocking efflux transporters, and increasing membrane permeability. These processes work together to improve the absorption, systemic exposure, and effectiveness of both synthetic and herbal medications.

Recent advancements (2020–2025) in nanocarrier systems, phytopharmaceutical products, and regulatory integration have moved herbal bioenhancers closer to mainstream pharmaceutical

practices. Approved products like Risorine® and nutraceuticals such as Theracurmin® highlight the successful adaptation of traditional concepts into contemporary therapeutic applications.

Nonetheless, in spite of their potential, challenges remain, including the standardization of herbal extracts, optimization of dosage, safety validation, and achieving global regulatory consistency. Progressing research through clinical trials, molecular modeling, and AI-assisted phytochemical screening is essential for realizing the complete potential of these natural bioavailability enhancers.

In summary, herbal bioenhancers connect traditional knowledge with modern scientific approaches, representing a sustainable and innovative path for drug discovery, formulation, and therapy in the 21st century.

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