



## Pharmacokinetics, Absorption, Distribution, Metabolism, and Bioavailability Challenges of Plant-Based Therapeutic Agents: Implications for Formulation and Clinical Translation

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### Abstract

Plant-based therapeutic agents have garnered increasing attention as potential sources of novel drug candidates and complementary medicines, yet their clinical translation remains hindered by significant pharmacokinetic challenges and unpredictable bioavailability profiles. The complexity of phytochemical mixtures, variability in plant material composition, and inherent physicochemical properties such as poor aqueous solubility and extensive metabolism contribute to suboptimal systemic exposure following oral administration. This article examines the pharmacokinetic principles governing the absorption, distribution, metabolism, and excretion of plant-derived drugs, with particular emphasis on factors that influence bioavailability including first-pass hepatic metabolism, efflux transporter activity, and physicochemical characteristics. Critical evaluation of formulation strategies designed to enhance systemic availability, such as nanoparticle-based delivery systems, liposomal encapsulation, solid dispersions, and structural modifications, is presented alongside preclinical and clinical evidence demonstrating their efficacy. The interplay between herb-drug interactions, safety considerations, and the necessity for rigorous standardization in phytopharmaceutical development is discussed within the context of regulatory requirements. Emerging technologies including precision dosing approaches, pharmacokinetic modeling, and personalized phytotherapy represent promising avenues for optimizing therapeutic outcomes. This comprehensive review synthesizes current knowledge on the pharmacokinetic challenges inherent to plant-based drugs and proposes future directions for advancing formulation science and clinical application of phytopharmaceuticals in evidence-based medicine.

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### Introduction

The utilization of plant-based therapeutic agents in modern medicine represents a convergence of traditional knowledge and contemporary pharmaceutical science. Natural products derived from botanical sources have historically served as the foundation for drug discovery, with estimates suggesting that approximately 25 to 50 percent of currently approved pharmaceutical compounds originate from or are inspired by plant constituents <sup>[1]</sup>. Despite this rich heritage and ongoing interest in phytopharmaceuticals, the translation of plant-based drugs from traditional use or laboratory investigation to clinically validated therapeutics faces substantial obstacles, particularly concerning pharmacokinetic characterization and bioavailability optimization <sup>[2]</sup>.

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The term bioavailability refers to the fraction of an administered dose that reaches the systemic circulation in unchanged form and is available at the site of action. For orally administered plant-based drugs, bioavailability is frequently compromised by multiple factors including poor aqueous solubility, limited permeability across intestinal epithelium, extensive first-pass metabolism, and active efflux by intestinal and hepatic transporters<sup>[3]</sup>. These challenges are compounded by the inherent chemical complexity of botanical extracts, which typically contain multiple bioactive constituents with diverse physicochemical properties, potentially leading to variable absorption kinetics and unpredictable pharmacological responses<sup>[4]</sup>.

Pharmacokinetic studies of plant-derived compounds have revealed considerable interindividual variability in absorption and disposition, influenced by genetic polymorphisms in metabolic enzymes, differences in gut microbiota composition, concomitant food intake, and formulation-dependent factors<sup>[5]</sup>. The absorption, distribution, metabolism, and excretion profiles of phytochemicals are governed by the same principles that apply to synthetic drugs, yet the structural diversity and complexity of natural product scaffolds introduce unique challenges in predicting their *in vivo* behavior<sup>[6]</sup>. Understanding these pharmacokinetic principles is essential for rational formulation development and dose optimization. Contemporary pharmaceutical research has increasingly focused on developing innovative formulation strategies to overcome the bioavailability limitations of plant-based drugs. Approaches such as nanoparticle encapsulation, liposomal delivery systems, solid dispersions, complexation with cyclodextrins, and self-emulsifying drug delivery systems have demonstrated promise in enhancing the systemic exposure of poorly bioavailable phytochemicals<sup>[7]</sup>. These technological advances, combined with improved analytical methodologies for pharmacokinetic assessment, have facilitated more rigorous evaluation of plant-based therapeutics in both preclinical models and clinical settings<sup>[8]</sup>.

The objective of this article is to provide a comprehensive examination of the pharmacokinetic challenges associated with plant-based therapeutic agents and to critically evaluate current strategies for addressing bioavailability limitations. The discussion encompasses fundamental pharmacokinetic principles, factors influencing absorption and disposition, formulation technologies, preclinical and clinical evidence, safety considerations including herb-drug interactions, regulatory aspects, and future directions in phytopharmaceutical development. By synthesizing current knowledge in this domain, this review aims to inform researchers, formulators, and clinicians engaged in the development and application of evidence-based phytotherapy.

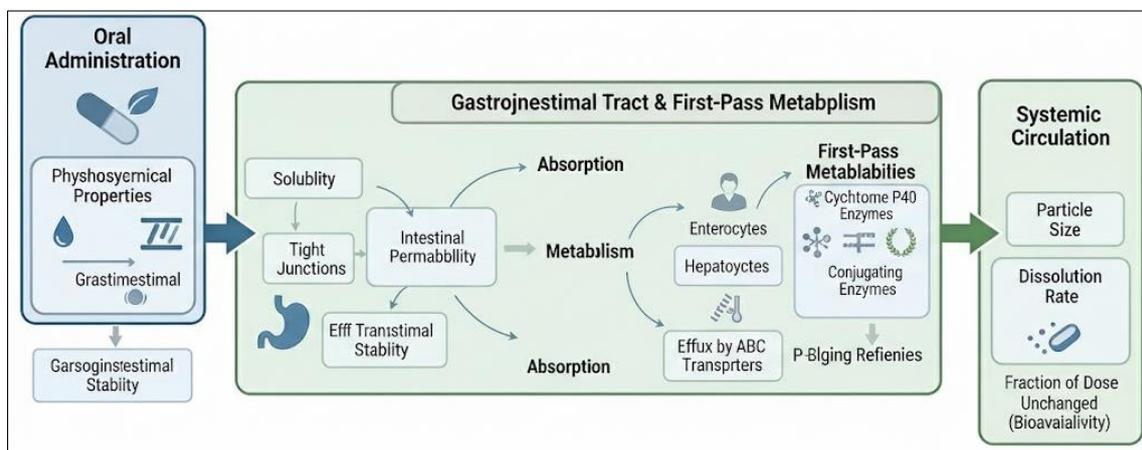
## Pharmacokinetic Principles Relevant to Plant-Based Drugs

The pharmacokinetic behavior of plant-based drugs is governed by fundamental principles that describe the time course of drug absorption, distribution, metabolism, and excretion within biological systems. These processes collectively determine the concentration of bioactive compounds at target sites and ultimately influence therapeutic efficacy and safety<sup>[9]</sup>. Understanding the pharmacokinetic profiles of phytochemicals requires consideration of both their physicochemical properties and their interactions with biological membranes, enzymes, and transporters.

Absorption following oral administration constitutes the initial and often rate-limiting step in the pharmacokinetic cascade for plant-based drugs. The extent and rate of absorption are influenced by multiple factors including aqueous solubility, dissolution rate in gastrointestinal fluids, permeability across the intestinal epithelium, stability in the gastrointestinal environment, and presystemic metabolism<sup>[10]</sup>. The Biopharmaceutics Classification System, which categorizes drugs based on solubility and permeability characteristics, provides a useful framework for predicting absorption challenges, with many phytochemicals falling into Class II (low solubility, high permeability) or Class IV (low solubility, low permeability) categories<sup>[11]</sup>.

Distribution of plant-derived compounds throughout body tissues is determined by factors such as blood flow to various organs, tissue binding, plasma protein binding, and the ability to cross biological barriers including the blood-brain barrier and placental barrier<sup>[12]</sup>. The volume of distribution, a pharmacokinetic parameter that relates the amount of drug in the body to the plasma concentration, varies widely among phytochemicals depending on their lipophilicity, molecular size, and affinity for tissue components. Compounds with extensive tissue distribution typically exhibit large volumes of distribution, whereas those primarily confined to the vascular compartment demonstrate smaller distribution volumes<sup>[13]</sup>.

Metabolism represents a critical determinant of systemic bioavailability and clearance for most plant-based drugs. Phase I metabolic reactions, primarily mediated by cytochrome P450 enzymes, introduce or expose functional groups through oxidation, reduction, or hydrolysis, while Phase II conjugation reactions involve glucuronidation, sulfation, methylation, or acetylation to enhance hydrophilicity and facilitate excretion<sup>[14]</sup>. Many phytochemicals undergo extensive first-pass metabolism in the intestinal mucosa and liver before reaching the systemic circulation, substantially reducing oral bioavailability. The activity of metabolic enzymes exhibits considerable interindividual variation due to genetic polymorphisms, age, disease states, and environmental factors<sup>[15]</sup>.



**Fig 1:** Factors influencing oral absorption and systemic bioavailability of plant-derived drugs

Excretion of plant-derived compounds and their metabolites occurs primarily through renal and biliary pathways. Renal excretion involves glomerular filtration, active tubular secretion, and passive tubular reabsorption, with the relative contribution of each process depending on molecular characteristics and protein binding [16]. Biliary excretion is particularly important for larger molecules and conjugated metabolites, which may undergo enterohepatic recirculation if deconjugated by intestinal bacteria, potentially prolonging systemic exposure [17]. The terminal elimination half-life, determined by the balance between distribution volume and clearance, provides important information for dosing interval selection.

Pharmacokinetic modeling approaches, including compartmental and physiologically-based pharmacokinetic models, have been increasingly applied to characterize the disposition of plant-based drugs and predict their behavior under various conditions [18]. These models facilitate the estimation of key parameters such as clearance, volume of distribution, absorption rate constant, and bioavailability, enabling rational dose selection and prediction of drug-drug interactions. Population pharmacokinetic analyses can identify sources of variability and guide individualized dosing strategies, which is particularly relevant given the heterogeneity observed in responses to phytopharmaceuticals [19].

The application of pharmacokinetic principles to plant-based drugs is complicated by the multicomponent nature of botanical extracts, where interactions among constituents may alter absorption, metabolism, or elimination of individual compounds. Synergistic or antagonistic effects on bioavailability have been reported, highlighting the need for comprehensive pharmacokinetic assessment of both individual phytochemicals and complex mixtures [20]. Advanced analytical techniques including liquid chromatography-mass spectrometry have enabled simultaneous quantification of multiple constituents, facilitating more complete characterization of the pharmacokinetic behavior of botanical preparations [21].

### Factors Affecting Bioavailability of Phytopharmaceuticals

The bioavailability of plant-based therapeutic agents is influenced by a complex interplay of physicochemical, physiological, and formulation-dependent factors that collectively determine the extent and rate at which active constituents reach the systemic circulation. Poor oral bioavailability remains one of the most significant obstacles to the clinical development and therapeutic application of phytochemicals, with many promising compounds exhibiting systemic exposure levels insufficient for pharmacological activity despite adequate *in vitro* potency [22].

Physicochemical properties constitute primary determinants of bioavailability, with aqueous solubility and lipophilicity being particularly critical. Many plant-derived compounds exhibit poor water solubility due to extensive hydrophobic regions in their molecular structures, leading to incomplete dissolution in gastrointestinal fluids and limited availability for absorption [23]. According to the Noyes-Whitney equation, dissolution rate is directly proportional to surface area and saturation solubility, implying that compounds with extremely low solubility will dissolve slowly regardless of particle size reduction. Conversely, excessive lipophilicity can impair permeation through the aqueous boundary layer adjacent to intestinal epithelium, creating a barrier to absorption [24].

Intestinal permeability represents another crucial factor governing bioavailability. The intestinal epithelium presents both a physical barrier composed of tight junctions between enterocytes and a metabolic barrier involving brush border enzymes and intracellular metabolic systems [25]. Transcellular absorption, the predominant pathway for lipophilic compounds, depends on passive diffusion driven by concentration gradients and is influenced by molecular size, hydrogen bonding capacity, and degree of ionization at physiological pH. Paracellular absorption through tight junctions is generally limited to small hydrophilic molecules and is restricted by the size selectivity of these intercellular channels [26].

**Table 1:** Key pharmacokinetic parameters of representative plant-based drugs from preclinical and clinical studies

Phytochemical	Source	Cmax (ng/mL)	Tmax (h)	AUC (ng·h/mL)	t1/2 (h)	F (%)	Study Type	Reference
Curcumin	Curcuma longa	6.3	1.0	35.3	3.2	<1	Human	[27]
Resveratrol	Vitis vinifera	491.6	0.5	2890	1.9	0.5	Human	[28]
Quercetin	Various plants	254.3	0.7	1690	2.4	2.0	Human	[29]
Berberine	Berberis species	0.4	4.0	7.5	5.5	0.68	Human	[30]
Silymarin	Silybum marianum	140.2	4.0	820	6.0	23-47	Human	[31]
Ginsenosides	Panax ginseng	15.8	3.5	125	7.8	Variable	Human	[32]
Epigallocatechin gallate	Camellia sinensis	126.8	1.6	420	3.4	13.7	Human	[33]

**Note:** Cmax, maximum plasma concentration; Tmax, time to maximum concentration; AUC, area under the plasma concentration-time curve; t1/2, elimination half-life; F, oral bioavailability. Values represent typical findings and may vary based on dose and formulation.

Active efflux transporters, particularly P-glycoprotein and breast cancer resistance protein located on the apical membrane of enterocytes, actively pump absorbed compounds back into the intestinal lumen, reducing net absorption and bioavailability [34]. Many phytochemicals serve as substrates for these efflux transporters, and their bioavailability can be significantly enhanced by co-administration with transporter inhibitors or through formulation strategies that saturate or bypass efflux mechanisms. The expression and activity of intestinal efflux transporters exhibit regional variation along the gastrointestinal tract and are subject to induction or inhibition by dietary components and drugs [35].

First-pass metabolism in the intestinal mucosa and liver substantially reduces the bioavailability of many plant-based drugs. Cytochrome P450 enzymes, particularly CYP3A4 which is abundantly expressed in both enterocytes and hepatocytes, catalyze oxidative metabolism of numerous phytochemicals [36]. Phase II enzymes including UDP-glucuronosyltransferases and sulfotransferases further contribute to presystemic elimination through conjugation reactions. The extent of first-pass metabolism varies among individuals due to genetic polymorphisms, with some populations exhibiting particularly rapid or slow metabolizer phenotypes that influence systemic exposure.

Food effects on bioavailability represent an important consideration for plant-based drugs, as concurrent food intake can either enhance or reduce absorption depending on the specific compound and meal composition. High-fat meals generally increase the bioavailability of lipophilic phytochemicals by stimulating bile secretion, prolonging gastric emptying, and enhancing solubilization in mixed micelles. Conversely, dietary fiber and certain food components may bind phytochemicals or alter gastrointestinal pH, potentially reducing absorption. The timing of administration relative to meals can substantially impact pharmacokinetic profiles and should be standardized in clinical studies.

Gut microbiota play an increasingly recognized role in modulating the bioavailability of plant-based drugs through biotransformation of parent compounds and metabolism of conjugated metabolites excreted in bile. Bacterial enzymes can cleave glycosidic bonds, reduce aromatic rings, and perform various other transformations that may activate prodrugs, generate active metabolites, or facilitate absorption of otherwise poorly bioavailable compounds. Interindividual variation in microbiome composition contributes to pharmacokinetic variability and may partially explain differential responses to phytopharmaceuticals among individuals.

### Absorption, Distribution, Metabolism, and Excretion (ADME) Profiles

The ADME profiles of plant-based therapeutic agents exhibit considerable diversity reflecting the wide range of chemical structures and functional groups present in phytochemicals. Comprehensive characterization of these profiles is essential for understanding the disposition of bioactive compounds *in vivo* and for predicting potential safety issues, drug interactions, and optimal dosing strategies. The application of modern analytical and imaging technologies has substantially advanced our ability to trace the fate of plant-derived compounds throughout the body.

Absorption mechanisms for phytochemicals vary depending on molecular characteristics and formulation. Passive diffusion represents the primary absorption pathway for small lipophilic molecules, with the rate of absorption governed by Fick's law of diffusion. Carrier-mediated transport plays an important role for certain classes of phytochemicals, including flavonoid glycosides that may be substrates for glucose transporters and phenolic acids that utilize monocarboxylic acid transporters. Active transport can result in saturable absorption kinetics, where increasing doses do not proportionally increase systemic exposure due to transporter capacity limitations.

The absorption of glycosylated phytochemicals presents unique considerations, as the sugar moieties generally must be removed before the aglycone can be absorbed. This deglycosylation can occur through the action of lactase phlorizin hydrolase and cytosolic beta-glucosidase in enterocytes, or through bacterial glycosidases in the colon. The site of glycoside hydrolysis influences the absorption profile, with enterocyte-mediated deglycosylation leading to more rapid systemic appearance compared to colonic bacterial metabolism. Some glycosides may be absorbed intact via glucose transporters and subsequently undergo intracellular or hepatic hydrolysis.

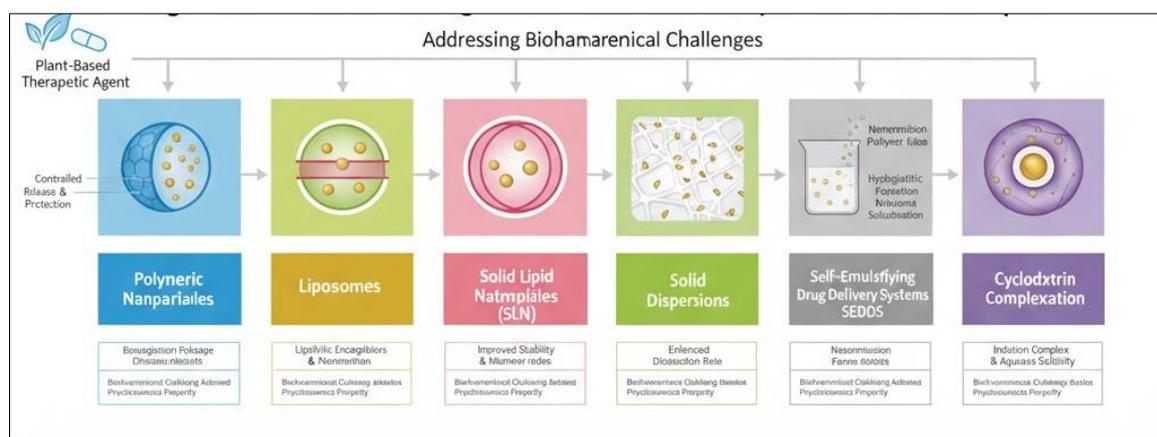
Distribution of plant-based drugs following absorption is influenced by plasma protein binding, tissue perfusion, and the presence of specific uptake or efflux transporters in various organs. Plasma protein binding, primarily to albumin and alpha-1-acid glycoprotein, can exceed 95 percent for highly lipophilic phytochemicals, resulting in a low free fraction available for tissue distribution and pharmacological activity. The extent of protein binding affects not only distribution but also hepatic extraction and renal clearance. Displacement interactions may occur when multiple highly protein-bound compounds are co-administered, potentially leading to transient increases in free drug concentrations.



enzymatic degradation. Surface modification with polyethylene glycol or other hydrophilic polymers enhances circulation time and reduces opsonization and clearance by the reticuloendothelial system.

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, offer advantages for encapsulation of lipophilic phytochemicals and promotion of lymphatic absorption. Liposomes, composed of phospholipid bilayers surrounding an aqueous

core, can encapsulate both hydrophilic and lipophilic compounds depending on formulation design. The incorporation of plant-based drugs into the lipid bilayer or aqueous compartment protects them from degradation and can enhance intestinal permeation through interaction with enterocyte membranes. Long-circulating liposomes modified with polyethylene glycol demonstrate prolonged systemic exposure and potential for targeted delivery when conjugated with ligands specific for cellular receptors.



**Fig 3:** Strategies for enhancing bioavailability, including nanoparticles, liposomes, and solid dispersions

Self-emulsifying drug delivery systems and self-microemulsifying drug delivery systems have demonstrated considerable success in enhancing bioavailability of lipophilic plant-based drugs. These systems consist of oil, surfactant, and co-surfactant mixtures that spontaneously form fine emulsions or microemulsions upon contact with aqueous gastrointestinal fluids under gentle agitation. The resulting small droplet size (typically less than 200 nanometers for microemulsions) provides large interfacial area for drug dissolution and absorption. These systems also stimulate lymphatic transport, bypassing first-pass hepatic metabolism for compounds absorbed through this route. Solid dispersion technology, wherein crystalline drug is dispersed in a hydrophilic polymer matrix, represents an established approach for improving dissolution rate and apparent solubility of poorly water-soluble compounds. Common polymeric carriers include polyvinylpyrrolidone, polyethylene glycol, and various cellulose derivatives, which prevent crystallization and maintain the drug in an amorphous, high-energy state with enhanced dissolution characteristics. The preparation of solid dispersions employs various techniques including hot-melt extrusion, spray drying, freeze drying, and solvent evaporation, each offering specific advantages in terms of scalability, drug loading capacity, and physical stability. Amorphous solid dispersions can achieve bioavailability enhancements of several-fold compared to crystalline formulations.

Complexation with cyclodextrins provides another mechanism for solubility enhancement through formation of inclusion complexes between the hydrophobic cavity of cyclodextrin molecules and lipophilic phytochemicals. Alpha-cyclodextrin, beta-cyclodextrin, and gamma-cyclodextrin, containing six, seven, and eight glucose units respectively, accommodate guest molecules of different sizes. Chemically modified cyclodextrins such as hydroxypropyl-beta-cyclodextrin and sulfobutylether-beta-cyclodextrin demonstrate superior aqueous solubility and complexation efficiency compared to natural cyclodextrins. The resulting complexes exhibit increased dissolution rate and stability while maintaining the biological activity of the encapsulated compound.

Particle size reduction through micronization or nanosizing increases the surface area available for dissolution according to the Noyes-Whitney equation, potentially accelerating absorption. Wet milling, high-pressure homogenization, and supercritical fluid technology enable production of submicron particles with improved dissolution characteristics. However, the benefits of particle size reduction are limited for compounds with extremely poor aqueous solubility, where dissolution rate is not the rate-limiting step in absorption. Additionally, very small particles may exhibit stability challenges including aggregation and increased susceptibility to oxidation due to high surface energy.

**Table 2:** Formulation strategies, dosage forms, and their impact on bioavailability of selected phytochemicals

Phytochemical	Formulation Strategy	Technology/Excipient	Bioavailability Enhancement (Fold Increase)	Study Model
Curcumin	Solid lipid nanoparticles	Glyceryl monostearate, poloxamer 188	9.0	Rat
Quercetin	Self-emulsifying system	Capryol 90, Cremophor RH40	3.7	Rat
Resveratrol	Solid dispersion	Polyvinylpyrrolidone K30	5.2	Rat
Silymarin	Liposomes	Phospholipon 90G	2.8	Rabbit
Berberine	Nanostructured lipid carriers	Compritol ATO 888, oleic acid	4.3	Rat
Genistein	Cyclodextrin complex	Hydroxypropyl-beta-cyclodextrin	2.1	Human
Baicalein	Polymeric micelles	Poly(ethylene glycol)-poly(lactic acid)	6.5	Mouse

**Note:** Bioavailability enhancement is expressed as the ratio of area under the curve for the formulated product to that of the conventional formulation. Values are approximate and may vary based on dose and experimental conditions.

Permeation enhancers, which temporarily increase intestinal epithelial permeability through various mechanisms including tight junction modulation, membrane fluidization, or efflux transporter inhibition, have been incorporated into formulations to improve absorption of poorly permeable phytochemicals. Natural permeation enhancers such as medium-chain fatty acids, bile salts, and certain terpenes offer advantages of biocompatibility and GRAS (generally recognized as safe) status. However, concerns regarding potential mucosal damage and enhanced absorption of toxins necessitate careful evaluation of safety and reversibility of permeation enhancement effects. The use of permeation enhancers must be balanced against the need to maintain intestinal barrier integrity

Prodrug strategies involve chemical modification of parent phytochemicals to improve biopharmaceutical properties, with subsequent enzymatic or chemical conversion to the active form *in vivo*. Esterification, for instance, can increase lipophilicity and membrane permeability, with subsequent hydrolysis by esterases releasing the active compound. Prodrug approaches must consider the potential for incomplete conversion, individual variability in activating enzyme activity, and the formation of potentially toxic byproducts. The regulatory pathway for prodrugs may be more complex than for formulation-based bioavailability enhancement strategies.

### Preclinical and Clinical Evidence on Pharmacokinetics

The translation of plant-based therapeutic agents from traditional use or *in vitro* efficacy to clinical application requires rigorous pharmacokinetic evaluation in preclinical models and human subjects. Preclinical pharmacokinetic studies in rodents, rabbits, dogs, and non-human primates provide essential information regarding absorption profiles, tissue distribution, metabolic pathways, and elimination kinetics that inform formulation development and first-in-human dose selection. However, species differences in physiology, enzyme expression, and transporter function necessitate careful interpretation when extrapolating preclinical findings to human pharmacokinetics. Rodent models, particularly rats and mice, represent the most commonly employed species for preliminary pharmacokinetic assessment due to practical considerations including cost, availability, and established protocols. Comparative pharmacokinetic studies have demonstrated that while qualitative metabolic pathways are often conserved between rodents and humans, quantitative differences in metabolic rates, clearance, and bioavailability are frequently observed. The higher metabolic rate per unit body weight in rodents typically results in faster clearance and shorter half-

lives compared to humans. Allometric scaling approaches, which adjust for differences in body size and physiological parameters, can improve the accuracy of human pharmacokinetic predictions from preclinical data.

*In vitro-in vivo* correlation studies utilize cell-based models including Caco-2 cell monolayers to predict intestinal permeability and liver microsomes or hepatocytes to assess metabolic stability. The correlation between *in vitro* permeability coefficients and *in vivo* absorption in humans has been well established for many conventional drugs, although predictions may be less accurate for compounds that are substrates for intestinal transporters or undergo extensive gut wall metabolism. Microsomes provide information on intrinsic clearance via specific enzyme systems, while hepatocyte models better reflect the integrated metabolic capacity including uptake, metabolism, and efflux processes. Clinical pharmacokinetic studies in healthy volunteers and patient populations provide definitive evidence regarding the absorption, disposition, and elimination of plant-based drugs in the target species. Phase I studies typically employ crossover or parallel designs to characterize dose-proportionality, food effects, and inter-individual variability under controlled conditions. The selection of appropriate doses for initial human studies draws on preclinical data, traditional usage patterns, and safety margins derived from toxicology studies. Single-dose pharmacokinetic studies elucidate absorption and elimination parameters, while multiple-dose studies reveal accumulation behavior and achievement of steady-state concentrations.

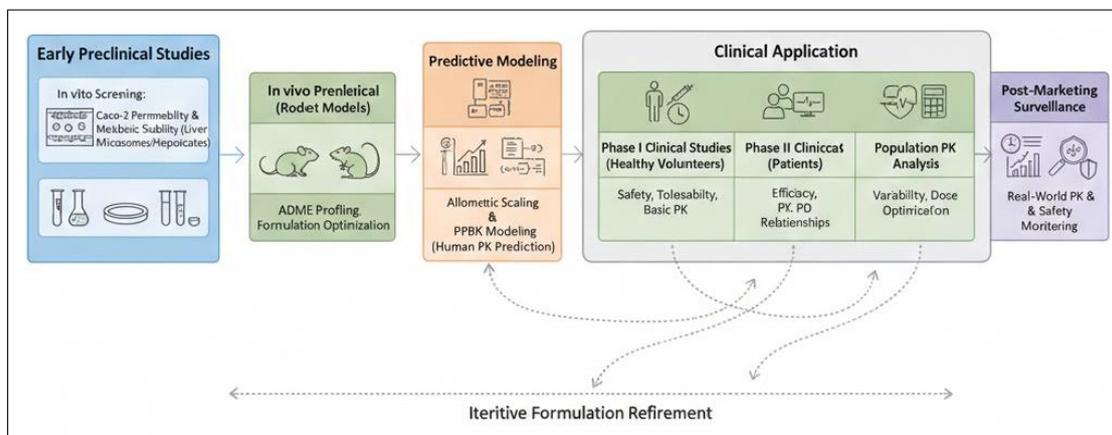
Population pharmacokinetic analyses, utilizing sparse sampling strategies and mixed-effects modeling, enable characterization of pharmacokinetic parameters and their variability in larger and more diverse patient populations than traditional intensive sampling studies. These analyses can identify demographic factors, genetic polymorphisms, disease states, and concomitant medications that influence pharmacokinetics, facilitating development of individualized dosing algorithms. Covariate analysis within population pharmacokinetic models has revealed significant effects of age, body weight, renal function, hepatic function, and CYP polymorphisms on the disposition of various plant-based drugs.

Pharmacokinetic-pharmacodynamic modeling establishes quantitative relationships between systemic exposure or tissue concentrations and therapeutic or toxic effects, providing a scientific basis for dose selection and regimen optimization. For plant-based drugs, this approach can elucidate whether efficacy correlates with peak concentrations, trough concentrations, area under the curve, or time above a threshold concentration. The characterization

of exposure-response relationships enables rational dose adjustment to achieve target pharmacodynamic endpoints while minimizing adverse effects. Integration of pharmacogenomic information into pharmacokinetic-pharmacodynamic models further refines predictions and supports precision medicine applications.

Bioanalytical methodology development represents a critical prerequisite for pharmacokinetic studies of plant-based drugs. Liquid chromatography coupled with tandem mass spectrometry has become the gold standard analytical technique, offering sensitivity in the picogram per milliliter

range, specificity through selected reaction monitoring, and capability for simultaneous quantification of parent compounds and multiple metabolites. Method validation according to regulatory guidelines ensures accuracy, precision, sensitivity, specificity, and stability of analytes under relevant storage and processing conditions. Special considerations for plant-based drugs include potential interference from endogenous compounds in matrices such as plasma and urine, and the need to account for protein binding when correlating total versus free concentrations with activity.



**Fig 4:** Translational pathway from preclinical pharmacokinetic studies to clinical application

Bioequivalence studies comparing different formulations or products containing the same phytochemical provide evidence regarding the interchangeability of products. Regulatory guidelines typically require demonstration that the 90 percent confidence interval for the ratio of test to reference product area under the curve and maximum concentration falls within 80 to 125 percent. For plant-based drugs, additional challenges arise from batch-to-batch variability in botanical raw materials and the complex mixture of constituents in whole extracts. Some regulatory authorities require bioequivalence testing on multiple marker compounds representative of different chemical classes present in the extract.

Tissue distribution studies employing radiotracer techniques or mass spectrometry imaging provide valuable information regarding the accumulation of plant-based drugs and their metabolites in various organs and their ability to reach target sites. Whole-body autoradiography in rodents enables visualization of distribution patterns, although this technique cannot distinguish parent compound from metabolites unless combined with chromatographic separation. Microdialysis techniques allow measurement of free drug concentrations in extracellular fluid of specific tissues, providing more pharmacologically relevant information than total tissue homogenate concentrations.

#### **Safety, Herb-Drug Interactions, and Toxicity Considerations**

The evaluation of safety, potential herb-drug interactions, and toxicity is integral to the development and appropriate clinical use of plant-based therapeutic agents. Despite the common perception that natural products are inherently safe, plant-based drugs can elicit adverse effects, interact with conventional medications, and produce toxicity under certain circumstances. Comprehensive safety assessment requires

consideration of direct toxic effects, immunological reactions, contamination issues, and pharmacokinetic or pharmacodynamic interactions with co-administered drugs. Herb-drug interactions can occur through pharmacokinetic mechanisms, wherein the plant-based drug alters the absorption, distribution, metabolism, or excretion of the conventional medication, or through pharmacodynamic mechanisms, involving additive, synergistic, or antagonistic effects at the site of action. Pharmacokinetic interactions mediated by enzyme induction or inhibition represent a particularly important class, as many phytochemicals modulate the expression or activity of cytochrome P450 enzymes. St. John's wort, for instance, is a potent inducer of CYP3A4 and P-glycoprotein, leading to reduced plasma concentrations and diminished efficacy of numerous drugs including immunosuppressants, anticoagulants, and oral contraceptives.

Inhibition of metabolic enzymes by phytochemicals can result in elevated drug concentrations and increased risk of dose-dependent adverse effects or toxicity. Grapefruit juice, containing furanocoumarins that irreversibly inhibit intestinal CYP3A4, substantially increases the bioavailability of susceptible drugs and has been associated with serious adverse events. Other commonly consumed plant products including green tea, turmeric, and black pepper contain compounds with enzyme inhibitory activity, although the clinical significance depends on the potency of inhibition, concentrations achieved *in vivo*, and therapeutic index of the affected drug.

Transporter-mediated interactions represent an additional mechanism by which plant-based drugs can alter the pharmacokinetics of conventional medications. Inhibition of P-glycoprotein, organic anion transporting polypeptides, or organic cation transporters can increase the systemic or tissue exposure of transporter substrates, potentially leading to

toxicity. Conversely, induction of efflux transporters can reduce drug absorption or enhance elimination, compromising therapeutic efficacy. The clinical relevance of transporter interactions depends on whether the affected drug is a substrate for a single transporter or multiple redundant systems, with greater impact expected when a drug's disposition relies primarily on a single transporter pathway. Prediction of herb-drug interactions requires integration of information from *in vitro* mechanistic studies, preclinical models, and clinical interaction studies. *In vitro* studies employing recombinant enzymes or transporter-expressing cell lines enable screening for inhibitory or inducing potential and determination of inhibition constants or induction fold-change. Static and dynamic mechanistic models utilize these *in vitro* parameters along with pharmacokinetic data to predict the magnitude of clinical interactions.

Physiologically-based pharmacokinetic modeling represents a sophisticated approach for interaction prediction, incorporating anatomical and physiological parameters, drug-specific properties, and enzyme or transporter kinetics. Clinical drug interaction studies provide definitive evidence regarding the magnitude and clinical significance of interactions. These studies typically employ a crossover design wherein subjects receive the victim drug alone and in combination with the perpetrator plant-based drug, with comparison of pharmacokinetic parameters. The selection of appropriate victim drugs should consider those with narrow therapeutic indices or those commonly prescribed to populations likely to use plant-based therapies. Positive and negative controls may be included to verify the sensitivity of the study design to detect interactions. Evaluation of pharmacodynamic endpoints in addition to pharmacokinetics can provide a more complete assessment of interaction consequences.

Direct toxicity of plant-based drugs can result from excessive doses, prolonged use, individual susceptibility, or inherent toxicity of constituents. Hepatotoxicity represents a particular concern, with numerous cases of liver injury attributed to herbal products reported in the literature. Mechanisms of hepatotoxicity include direct mitochondrial damage, formation of reactive metabolites that bind to cellular macromolecules, immune-mediated reactions, and vascular injury. The temporal relationship between product use and onset of liver injury, resolution upon discontinuation, and recurrence upon rechallenge support causality assessment, although confirmation is often challenging due to polypharmacy and the multicomponent nature of botanical products.

Nephrotoxicity, cardiotoxicity, and neurotoxicity have been documented with specific plant-based drugs, particularly those containing pyrrolizidine alkaloids, aristolochic acids, or cardiac glycosides. Quality control issues including contamination with heavy metals, pesticides, or pharmaceutical adulterants contribute to toxicity risk, highlighting the importance of rigorous testing and standardization. Regulatory oversight varies substantially across jurisdictions, with some countries requiring premarket approval and others employing post-market surveillance approaches for botanical products.

Immunological reactions including allergic responses and autoimmune phenomena can occur with certain plant-based drugs, particularly those of the Asteraceae family which contains allergenic sesquiterpene lactones. Hypersensitivity reactions range from mild skin reactions to severe systemic

responses including anaphylaxis. Photosensitivity has been reported with products containing furocoumarins or hypericin, necessitating appropriate warnings regarding sun exposure. Idiosyncratic reactions, which are dose-independent and not predictable from pharmacology, pose particular challenges for risk assessment and mitigation. Pregnancy and lactation represent special populations requiring careful consideration of safety, as many plant-based drugs have not been adequately studied in these contexts. Some phytochemicals demonstrate uterotonic, hormonal, or teratogenic effects in preclinical models, raising concerns about use during pregnancy. The transfer of phytochemicals or their metabolites into breast milk and potential effects on nursing infants are largely unknown for most plant-based drugs. Conservative recommendations generally advise avoiding use during pregnancy and lactation unless clear benefit outweighs potential risk, or limiting use to products with extensive safety data.

### Regulatory and Standardization Considerations

The regulatory framework governing plant-based therapeutic agents varies considerably across jurisdictions, reflecting different historical traditions, healthcare systems, and approaches to risk-benefit assessment. These regulatory differences have significant implications for product quality, clinical evidence requirements, pharmacovigilance, and market access. Understanding the regulatory landscape is essential for developers of phytopharmaceuticals and for healthcare providers making evidence-based recommendations regarding their use.

In the United States, most plant-based products are regulated as dietary supplements under the Dietary Supplement Health and Education Act of 1994, which imposes less stringent requirements than those for conventional drugs regarding premarket approval, efficacy demonstration, and manufacturing standards. Manufacturers are responsible for ensuring safety and may not make disease claims, although structure-function claims are permitted. The FDA can take action against products found to be unsafe or misbranded through post-market surveillance. A limited number of plant-based drugs have been approved through the conventional drug development pathway, requiring demonstration of safety and efficacy through adequate and well-controlled clinical trials.

The European Union employs a tiered regulatory approach that includes well-established use registrations, traditional use registrations, and authorization as conventional medicinal products. Well-established use registration requires at least 10 years of documented medicinal use within the EU and scientific literature supporting efficacy and safety. Traditional use registration requires at least 30 years of use including 15 years within the EU, though efficacy may be based on long-standing use rather than clinical trials. This framework provides a regulatory pathway for plant-based medicines with historical use while maintaining quality and safety standards through Good Manufacturing Practice requirements.

Standardization of botanical products represents a critical challenge due to the inherent variability in plant material composition arising from genetic factors, growing conditions, harvesting time, and post-harvest processing. The content of bioactive constituents can vary several-fold among batches of the same plant species, affecting both efficacy and safety. Standardization approaches include specification of

marker compounds (constituents with known or presumed activity), adjustment of extracts to contain defined levels of markers through addition of active or inactive plant material, or specification of total extract characteristics. The selection of appropriate markers requires chemical knowledge and understanding of the active principles responsible for therapeutic effects.

Analytical methods for quality control of plant-based drugs must be validated according to pharmacopeial or regulatory guidelines and must be capable of detecting relevant bioactive constituents as well as potential contaminants. High-performance liquid chromatography with various detection methods including ultraviolet, diode array, or mass spectrometry enables quantification of multiple constituents and assessment of chemical fingerprints characteristic of authentic material. DNA-based authentication methods complement chemical analysis by confirming botanical identity and detecting substitution or adulteration with related species. The combination of orthogonal analytical approaches provides greater assurance of product quality and consistency.

Good manufacturing practices for botanical products encompass appropriate sourcing and authentication of raw materials, validated analytical methods, in-process controls, stability testing, and documentation systems to ensure batch-to-batch consistency and traceability. The complexity of botanical manufacturing, involving extraction and concentration processes that can alter the chemical composition, requires particular attention to process validation and control. Environmental monitoring, cleaning validation, and prevention of cross-contamination are essential components of quality assurance programs. Third-party certification programs provide independent verification of manufacturing practices and product quality. Clinical trial design for plant-based drugs presents unique challenges related to the selection of appropriate formulations, standardization requirements, choice of comparators, and endpoint selection. Placebo-controlled designs remain the gold standard for efficacy demonstration, though active-controlled non-inferiority trials may be acceptable when placebo use would be unethical. The FDA and other regulatory authorities have issued guidance documents specific to botanical drugs, emphasizing the need for chemical characterization, reproducible manufacturing, and demonstration of batch-to-batch consistency of material used in clinical trials and proposed commercial products. Pharmacovigilance and post-market surveillance provide essential information regarding the safety of plant-based drugs in real-world use, where populations are more diverse and co-morbidities and concomitant medications are common. Spontaneous reporting systems collect adverse event reports from healthcare providers and consumers, though under-reporting is a significant limitation. Causality assessment for suspected adverse reactions is challenging due to polypharmacy, use of unstandardized products, and the long latency periods that may exist between exposure and certain adverse outcomes. Enhanced surveillance efforts including registry studies and electronic health record analyses can provide more complete safety data. Intellectual property considerations influence the development pathway for plant-based drugs, as naturally occurring compounds and traditional knowledge may not be patentable in many jurisdictions. Novel formulations, synthetic analogs, specific indications, or manufacturing

processes may be eligible for patent protection. The investment required for rigorous clinical development and regulatory approval may not be justified without intellectual property protection, creating challenges for the evidence-based advancement of traditional medicines. Public-private partnerships and alternative incentive structures have been proposed to address this translational gap.

### **Future Directions in Phytopharmaceutical Pharmacokinetics**

The field of phytopharmaceutical pharmacokinetics is poised for significant advancement through the application of emerging technologies and evolving scientific paradigms. Integration of systems biology approaches, artificial intelligence, personalized medicine concepts, and sophisticated delivery platforms promises to address current limitations and unlock the full therapeutic potential of plant-based drugs. These innovations will require interdisciplinary collaboration among botanists, chemists, pharmacologists, formulation scientists, clinicians, and data scientists. Physiologically-based pharmacokinetic modeling represents a powerful tool for predicting human pharmacokinetics from *in vitro* and preclinical data, optimizing formulations, and simulating the impact of physiological or pathological variations on drug exposure. These mechanistic models incorporate anatomical and physiological parameters, drug-specific physicochemical properties, and information on absorption, distribution, metabolism, and excretion processes. The application of PBPK modeling to plant-based drugs enables prediction of food effects, drug-drug interactions, and appropriate dosing in special populations including pediatric and geriatric patients, without requiring extensive clinical studies in each scenario. Regulatory authorities increasingly accept PBPK modeling as supporting evidence for labeling and dose selection. Pharmacometabolomics, the study of metabolic profiles associated with drug response, offers potential for identifying biomarkers that predict individual responses to plant-based drugs. This approach recognizes that pharmacokinetic variability is influenced by endogenous metabolic processes and that baseline metabolic phenotypes may predict absorption, metabolism, or elimination capacity. Integration of metabolomics data with pharmacokinetic measurements and clinical outcomes can reveal mechanistic insights and facilitate patient stratification. The identification of predictive biomarkers could enable precision dosing and improve the benefit-risk ratio of phytopharmaceuticals. Advances in drug delivery technology continue to expand possibilities for overcoming bioavailability limitations. Stimuli-responsive nanocarriers that release their cargo in response to pH, enzymes, or other triggers present in the gastrointestinal tract or diseased tissues enable targeted delivery and controlled release. Cell-penetrating peptides and receptor-targeting ligands conjugated to nanocarriers can enhance cellular uptake and specificity. Oral delivery systems capable of traversing the intestinal epithelium through transcytosis pathways or temporarily opening tight junctions represent active areas of investigation. The gut microbiome's role in modulating plant-based drug pharmacokinetics is increasingly recognized, and strategies to harness or manipulate microbial metabolism may enhance therapeutic outcomes. Probiotic co-administration, prebiotics that selectively stimulate beneficial microorganisms, or even engineered bacteria expressing specific enzymes represent

potential approaches for optimizing biotransformation and absorption. Conversely, understanding the impact of phytochemicals on microbiome composition may reveal additional mechanisms of therapeutic action or adverse effects. The integration of pharmacomicrobiomics with traditional pharmacokinetic assessment will provide a more holistic understanding of plant-based drug disposition. Artificial intelligence and machine learning algorithms are being applied to predict pharmacokinetic parameters, optimize formulations, and identify candidates likely to have favorable absorption properties. These computational approaches can analyze large datasets from *in vitro* assays, preclinical studies, and clinical trials to discern patterns and generate predictive models. Deep learning neural networks show promise for predicting complex phenomena such as drug-drug interactions or individual variability in metabolism. The integration of AI into drug development workflows may accelerate identification of lead compounds and reduce attrition rates during clinical development. Transdermal and other alternative delivery routes offer potential advantages for plant-based drugs by avoiding first-pass metabolism and providing sustained release. Microneedle patches, which create microscopic conduits through the stratum corneum, enable delivery of molecules that otherwise cannot penetrate skin. Sublingual and buccal formulations allow absorption through the oral mucosa directly into systemic circulation, though the surface area is limited compared to the small intestine. Pulmonary delivery via inhalation provides rapid absorption and high bioavailability for suitable compounds, with applications in both local and systemic therapy.

Combination products containing multiple phytochemicals or combinations of plant-based and conventional drugs represent an emerging area with potential for synergistic pharmacological effects or pharmacokinetic enhancement. The concept of combination therapy is well established in modern medicine, and rational combinations of complementary mechanisms may achieve superior efficacy compared to monotherapy. However, the regulatory pathway for combination products is complex, requiring demonstration of the contribution of each component and characterization of potential interactions. Fixed-dose combinations must be formulated to ensure chemical and physical compatibility of the components. Pediatric formulation development for plant-based drugs requires special consideration of age-appropriate dosage forms, palatability, and dose flexibility. Liquid formulations, dispersible tablets, and chewable preparations facilitate administration and dose adjustment based on weight or age. Pharmacokinetic studies in pediatric populations are essential to establish appropriate dosing regimens, as developmental changes in absorption, distribution, metabolism, and excretion can substantially affect drug disposition. Extrapolation from adult data using allometric scaling or physiologically-based pharmacokinetic models may provide initial dose estimates, but pediatric clinical studies remain necessary for confirmation.

Personalized dosing strategies based on pharmacogenomic information, therapeutic drug monitoring, or predictive algorithms may optimize outcomes for plant-based drugs exhibiting high pharmacokinetic variability. Genotyping for polymorphisms in key metabolic enzymes or transporters could guide initial dose selection for compounds highly dependent on these pathways. Therapeutic drug monitoring,

involving measurement of plasma concentrations and dose adjustment to achieve target exposure, has been successfully applied to certain conventional drugs and could be adapted for phytopharmaceuticals with well-characterized exposure-response relationships and validated analytical methods. Sustainability and environmental considerations are increasingly important in the sourcing and production of plant-based drugs. Overharvesting of wild plants threatens biodiversity and sustainability of traditional medicine systems, necessitating development of cultivation practices or alternative sources. Biotechnology approaches including plant tissue culture, heterologous expression in microbial systems, and semi-synthetic production from precursors may provide sustainable alternatives to wild-harvested material while ensuring consistency and quality. Life cycle assessments can evaluate the environmental impact of different production methods and guide decision-making toward more sustainable practices.

## Conclusion

Plant-based therapeutic agents represent a valuable resource for drug discovery and development, offering chemical diversity and biological activities that complement synthetic drug portfolios. However, the clinical translation and optimal utilization of phytopharmaceuticals require comprehensive understanding and strategic management of pharmacokinetic challenges, particularly those related to bioavailability. The complex interplay of physicochemical properties, physiological barriers, metabolic processes, and formulation characteristics determines the systemic exposure achieved following administration and ultimately influences therapeutic outcomes.

This review has synthesized current knowledge regarding the absorption, distribution, metabolism, and excretion profiles of plant-based drugs, highlighting the multiple factors that contribute to poor and variable bioavailability. Inadequate aqueous solubility, limited intestinal permeability, extensive first-pass metabolism, and active efflux by intestinal and hepatic transporters emerge as recurring obstacles across diverse chemical classes of phytochemicals. Individual variability arising from genetic polymorphisms in metabolic enzymes and transporters, differences in gut microbiome composition, and physiological factors further complicates dose selection and prediction of therapeutic response.

Advances in formulation science have provided a sophisticated toolkit for addressing bioavailability limitations through rational design of drug delivery systems. Nanoparticle-based approaches, lipid carriers, solid dispersions, self-emulsifying systems, and cyclodextrin complexation have demonstrated substantial improvements in systemic exposure for numerous poorly bioavailable phytochemicals. The selection of appropriate formulation strategy must consider the specific biopharmaceutical challenges presented by individual compounds, scalability of manufacturing processes, stability of the finished product, and regulatory requirements. Integration of formulation development with pharmacokinetic assessment enables iterative optimization toward products with reproducible and adequate bioavailability.

The importance of rigorous preclinical and clinical pharmacokinetic evaluation cannot be overstated, as these studies provide essential data for dose selection, formulation optimization, prediction of drug interactions, and identification of safety concerns. Population pharmacokinetic

approaches and pharmacokinetic-pharmacodynamic modeling enhance understanding of exposure-response relationships and sources of variability, supporting evidence-based dosing recommendations. The application of physiologically-based pharmacokinetic modeling offers opportunities to predict human pharmacokinetics from preclinical data and to simulate scenarios not readily studied in clinical trials.

Safety considerations, particularly the potential for herb-drug interactions mediated through enzyme induction or inhibition, transporter modulation, or pharmacodynamic mechanisms, necessitate comprehensive assessment and clear communication to healthcare providers and patients. The widespread use of plant-based products in populations taking multiple conventional medications creates numerous opportunities for clinically significant interactions. Proactive identification of interaction potential through mechanistic studies and clinical interaction trials, combined with post-market surveillance, contributes to safer use of phytopharmaceuticals.

Regulatory frameworks and standardization practices vary across jurisdictions but share common goals of ensuring product quality, consistency, and appropriate evidence of safety and efficacy. The inherent variability of botanical materials requires robust quality control measures including validated analytical methods, appropriate selection of marker compounds, and adherence to good manufacturing practices. Harmonization of regulatory standards and mutual recognition of quality systems would facilitate global development and availability of high-quality phytopharmaceutical products.

Future directions in phytopharmaceutical pharmacokinetics will likely involve increased application of computational modeling, artificial intelligence, and systems biology approaches to predict and optimize pharmacokinetic behavior. Personalized medicine concepts incorporating pharmacogenomic information, therapeutic drug monitoring, and individual metabolic phenotyping may enable precision dosing and improved therapeutic outcomes. Sustainable sourcing practices and alternative production methods will become increasingly important as demand for plant-based medicines grows. Continued innovation in drug delivery technology promises further improvements in bioavailability and therapeutic performance.

The successful development and clinical application of plant-based therapeutic agents requires interdisciplinary collaboration, rigorous scientific methodology, and commitment to evidence-based practice. While challenges related to pharmacokinetics and bioavailability remain substantial, the tools and knowledge now available provide a clear path forward. Continued investment in pharmacokinetic research, formulation development, clinical evaluation, and post-market surveillance will advance the field of phytopharmaceuticals and contribute to their integration into modern healthcare as safe, effective, and scientifically validated therapeutic options.

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