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"PHARMACOKINETIC AND PHARMACODYNAMIC HERB–DRUG INTERACTIONS: MECHANISM AND CLINICAL SIGNIFICANCE"

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Abstract
The use of herbal medicines has grown rapidly across the world, both as complementary therapies and in combination with conventional medicines. As a result, the possibility of clinically important herb–drug interactions has become an increasing concern. Although herbal products are often considered safe because they are derived from natural sources, they contain biologically active compounds that can influence the effectiveness and safety of prescription medications. These interactions may occur through pharmacokinetic or pharmacodynamic mechanisms. Pharmacokinetic interactions involve changes in the absorption, distribution, metabolism, or excretion of drugs, commonly through the modulation of cytochrome P450 (CYP450) enzymes and drug transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptides (OATPs). In contrast, pharmacodynamic interactions occur when herbal constituents alter the pharmacological response of a drug by producing additive, synergistic, antagonistic, or toxic effects without necessarily affecting drug concentrations. Such interactions may reduce therapeutic efficacy, increase toxicity, or lead to serious adverse clinical outcomes. Clinically significant interactions have been documented with commonly used herbal products, including Hypericum perforatum (St. John's wort), Ginkgo biloba, Allium sativum (garlic), green tea, grapefruit, valerian, chamomile, fenugreek, and licorice, particularly when used alongside anticoagulants, cardiovascular medications, central nervous system drugs, antidiabetic agents, immunosuppressants, and anticancer therapies. This review discusses the major pharmacokinetic and pharmacodynamic mechanisms responsible for herb–drug interactions, presents representative examples of clinical relevance, and examines their implications for patient safety. Greater awareness among healthcare professionals, routine documentation of herbal medicine use, stronger pharmacovigilance and herbovigilance practices, and well-designed clinical research are essential to reduce interaction-related risks and promote the safe integration of herbal medicines into modern healthcare.

Keywords: Herb–drug interactions; Herbal medicines; Pharmacokinetics; Pharmacodynamics; Cytochrome P450; P-glycoprotein; Drug transporters; ADME; Drug metabolism; Patient safety; Herbovigilance; Clinical significance.

1. Introduction

Herbal medicines and botanical supplements are increasingly used worldwide, often in combination with conventional drugs, raising significant concerns regarding potential herb–drug interactions that may influence therapeutic outcomes. According to the World Health Organization, around 80% of the global population uses traditional medicine — including herbal products — for various health

needs, highlighting the widespread reliance on these therapies. Contrary to the common perception that natural products are inherently safe, herbal medicines can substantially modify drug metabolism and transport, sometimes resulting in clinically significant adverse effects (Gupta et al., 2025). As the global use and market share of herbal medicines continue to rise across all age groups, safety concerns related to their concurrent use with conventional therapies have become increasingly prominent (Choi and Song, 2026). Herbal medicines typically contain complex mixtures of bioactive constituents capable of altering the absorption, distribution, metabolism, and excretion of co-administered drugs, thereby giving rise to clinically relevant pharmacokinetic and pharmacodynamic interactions (Czigle et al., 2023). Pharmacokinetic herb–drug interactions most commonly occur through the modulation of drug-metabolizing enzymes and transporters, particularly cytochrome P450 (CYP) isoforms and P-glycoprotein (P-gp). Such modulation can lead to altered systemic exposure of conventional drugs, affecting their efficacy and safety profiles (Cho and Yoon, 2015). Evidence suggests that these interactions may result in reduced therapeutic efficacy, enhanced toxicity, or unexpected adverse effects when herbal constituents influence the pharmacokinetics or pharmacodynamics of prescription medicines (Jogi et al., 2025). A well-documented example of a clinically significant herb–drug interaction is St. John's wort (Hypericum perforatum), which induces CYP3A4 and P-glycoprotein activity, leading to reduced plasma concentrations of drugs metabolized via these pathways. Scholz et al. (2021) demonstrated that concomitant administration of St. John's wort significantly decreased rivaroxaban exposure in healthy volunteers, highlighting the potential clinical consequences of unrecognized herb–drug interactions. The risk of adverse interactions is particularly pronounced in patients receiving multiple medications or drugs with a narrow therapeutic index. Vallepu Divya et al. (2025) reported that herbal–conventional drug combinations may lead to altered therapeutic responses, increased toxicity, or unpredictable side effects in such populations. Similarly, in oncology settings, herbal medicines have been shown to interact with anticancer agents through both pharmacokinetic and pharmacodynamic mechanisms, potentially compromising treatment efficacy or increasing toxicity (Duan et al., 2025). Despite the growing incidence of herb–drug interactions, their detection, documentation, and management remain challenging. Behare et al. (2025) highlighted that the widespread and often undocumented use of herbal medicines complicates safety monitoring within existing pharmacovigilance systems, underscoring the need for specialized herbovigilance frameworks. Rasheed et al. (2024) further emphasized the rising prevalence of herb–drug interactions and the urgent need to improve awareness among healthcare professionals and patients, although systematic assessment approaches remain limited. Therefore, a comprehensive understanding of the molecular mechanisms and clinical significance of pharmacokinetic and pharmacodynamic herb–drug interactions is essential for the safe integration of herbal medicines into modern healthcare systems and for optimizing patient safety and therapeutic outcomes (Choi and Song, 2026).

Despite widespread use of herbal medicines, systematic understanding of their pharmacokinetic and pharmacodynamic interactions with conventional drugs remains limited. This review aims to provide a comprehensive synthesis of current evidence, highlighting clinically relevant interactions and strategies to enhance patient safety in modern healthcare.

2.Pharmacokinetic Herb–Drug Interactions

Herbal medicines may interact with conventional drugs by influencing key pharmacokinetic processes, including absorption, distribution, metabolism, and excretion. Such interactions commonly arise from the ability of herbal constituents to induce or inhibit drug-metabolizing enzymes and transport proteins, which can alter systemic drug exposure. These changes may compromise treatment effectiveness or increase the risk of adverse effects, highlighting the importance of clinician awareness of herb–drug interaction mechanisms (Awortwe et al., 2019). Pharmacokinetic herb–drug interactions can lead to alterations in drug plasma concentrations and pharmacodynamic effects. Clinical studies have reported changes in pharmacokinetic parameters in some cases, though the overall evidence is limited and often inconclusive. Awareness of these

potential interactions is important for clinicians to monitor and manage therapy effectively (Choi S et al.,2017)

2.1Modulation of Drug-Metabolizing Enzymes (CYP450)

Herbal products and dietary constituents can substantially influence drug disposition by modulating cytochrome P450 enzymes, particularly CYP3A4. St. John's wort (Hypericum perforatum) is one of the most clinically relevant herbal inducers; its bioactive constituent, hyperforin, activates the pregnane X receptor (PXR), leading to increased expression of CYP3A4 and P-glycoprotein, which accelerates the clearance of susceptible drugs (Scholz et al., 2021; Nicolussi & Drewe, 2020). Human pharmacokinetic studies have demonstrated a significant reduction in rivaroxaban exposure following co-administration with St. John's wort, and comparable decreases have been reported for other CYP3A4 substrates, including immunosuppressants and hormonal contraceptives (Scholz et al., 2021). Grapefruit (Citrus paradisi) juice contains natural compounds called furanocoumarins that can inactivate CYP3A4 enzymes in the intestinal wall. This inhibition reduces the metabolism of drugs taken orally, allowing higher amounts of the active drug to enter the bloodstream. Research indicates that this effect can last for several days after consuming the juice, making it a clinically significant factor for medications that rely heavily on CYP3A4 for metabolism (Abu Dayyih et al., 2024). Thus, modulation of CYP450 enzymes by herbal products can either accelerate or delay drug metabolism, resulting in clinically relevant changes in drug exposure and therapeutic outcomes.

Emerging evidence highlights the role of phase II enzymes, particularly UDP-glucuronosyltransferases (UGTs), in drug conjugation, and certain plant alkaloids have been reported to influence UGT-mediated glucuronidation, thereby affecting drug elimination and plasma concentrations (Gunasaykaran et al., 2025).

2.2 Influence on Drug Transporters

Drug transporters regulate cellular uptake and efflux, impacting drug bioavailability, tissue distribution, and elimination. Key transporters include:

Efflux transporters: P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP)

Uptake transporters: Organic anion transporting polypeptides (OATPs) (Sandoval et al., 2025).

2.2.1 Efflux Transporters:

Zhang et al. (2019) demonstrated that berberine can inhibit P-glycoprotein (P-gp) function and reduce its expression in in vitro and in situ models. This inhibition was associated with increased absorption and bioavailability of P-gp substrate drugs, such as digoxin in animal studies, suggesting that berberine has the potential to alter the pharmacokinetics of co-administered P-gp substrates.

2.2.2 Uptake transporters:

Kyriacou, Gross, and McLachlan (2025) reviewed evidence indicating that green tea catechins, including epigallocatechin-3-gallate (EGCG), can alter the pharmacokinetics of several orally administered drugs by reducing systemic exposure. These effects are thought to arise, at least in part, from decreased intestinal absorption potentially mediated by inhibition of organic anion transporting polypeptides (OATPs), particularly OATP1A2. The authors highlight that such interactions may have clinical implications, as co-consumption of green tea could influence the effectiveness of drugs whose absorption relies on these transporters.

2.3Effects on Absorption, Distribution, Metabolism, and Excretion (ADME)

Herbal constituents are capable of modifying intestinal physiological conditions, including gastrointestinal transit and luminal factors that govern drug dissolution and solubility. Such alterations can influence the extent of intestinal drug absorption and ultimately affect systemic drug exposure. Oyanna et al. (2024) describe green tea catechins and other botanical components as representative examples of natural products that exert these effects at the intestinal level. Anthranoid-containing herbal medicines, including Cassia and Cascara, act as stimulant laxatives that enhance gastrointestinal motility. This increase in intestinal transit may reduce the absorption of

co-administered drugs by limiting their residence time within the gastrointestinal tract, as described by Balkrishna et al. (2024). Tea-derived polyphenols, including catechins and tannins, are capable of binding iron within the intestinal lumen, leading to the formation of insoluble complexes that limit iron availability for absorption. Evidence from experimental models demonstrates that co-administration of polyphenol-rich preparations with dietary iron reduces non-heme iron absorption, confirming this interaction at the gastrointestinal level (Xu et al., 2025).

Herbal medicines can substantially alter drug distribution by modulating plasma protein binding and key drug transporters such as P-glycoprotein and uptake transporters. These changes can shift tissue exposure and systemic drug levels, leading to clinically meaningful alterations in drug efficacy or toxicity when herbs are used concomitantly with conventional medicines. (Li et al., 2022). Competition for plasma protein binding is a pharmacokinetic interaction that can affect drug distribution by increasing the unbound fraction of highly protein-bound drugs. Agents such as warfarin and phenytoin, which have narrow therapeutic indices, are particularly susceptible to clinically relevant changes in free drug concentration. Herbal products including garlic (Allium sativum) and ginkgo (Ginkgo biloba) have been associated with altered anticoagulant responses to warfarin, although these effects are likely multifactorial and may involve protein-binding displacement alongside metabolic or pharmacodynamic mechanisms (Cheng et al., 2023).

Herbal medicines have been shown to influence drug metabolism through their effects on both Phase I and Phase II metabolic enzymes, leading to clinically meaningful changes in pharmacokinetic behavior and therapeutic outcomes. According to Khan et al. (2025), numerous herbal extracts and their bioactive constituents are capable of modulating cytochrome P450 (CYP) enzymes by either inhibiting or inducing their activity, which may alter first-pass metabolism, oral bioavailability, systemic clearance, and drug half-life. Such modulation can result in elevated drug exposure with an increased risk of adverse effects or, alternatively, reduced plasma concentrations and diminished therapeutic efficacy. In addition to Phase I effects, herbal constituents also interact with Phase II conjugation pathways. Gunasaykaran et al. (2025) reported that plant-derived alkaloids from herbal medicines can affect UDP-glucuronosyltransferase (UGT) enzymes, thereby modifying glucuronidation processes that are critical for drug elimination. Altered UGT activity may lead to changes in drug clearance and, in some cases, accumulation of parent compounds or active metabolites. Collectively, these findings highlight the importance of considering herb-drug interactions mediated by metabolic enzyme regulation when herbal products are used concurrently with conventional pharmacotherapy.

Herbal products can influence drug excretion by altering renal processes and modulating transporters involved in renal and biliary elimination. Evidence indicates that herbal constituents regulate key transport proteins, including P-glycoprotein (ABCB1), organic anion transporters (OATs), organic cation transporters (OCTs), and other ATP-binding cassette transporters, thereby affecting the clearance of transporter-substrate drugs. As reported by Li et al., phytochemicals such as flavonoids and saponins may inhibit or induce these transporters, leading to either enhanced drug elimination or drug accumulation. These transporter-mediated herb–drug interactions are clinically relevant and may alter drug efficacy or increase toxicity, particularly for drugs with narrow therapeutic indices (Li et al., 2022). Wu et al. (2023) report that bioactive herbal constituents regulate transport proteins such as P-glycoprotein, organic anion transporters, organic cation transporters, and other ATP-binding cassette transporters, leading to changes in drug elimination. These transporter-mediated herb–drug interactions may increase drug accumulation or enhance clearance, thereby affecting therapeutic efficacy and toxicity.

3.Pharmacodynamic Herb–Drug Interactions

Narwal et al. (2025) described pharmacodynamic interactions as clinically significant effects in which one agent modifies the action of another through receptor-level mechanisms, modulation of enzymes or intracellular signaling pathways, or by influencing physiological systems such as coagulation, central nervous system function, glucose regulation, and immune responses, with particular importance for drugs having narrow therapeutic indices. In this context, Duan et al. (2025) reported that pharmacodynamic herb–drug interactions occur when herbal constituents alter a drug's

effect at its target site, leading to additive, synergistic, or antagonistic outcomes without changes in plasma drug concentrations, which may affect therapeutic efficacy or increase toxicity despite unchanged pharmacokinetics.

3.1Additive and Synergistic Effects

Several medicinal plants are known to affect haemostasis and may interact with oral anticoagulant therapy. According to Martins, Monteiro, and Duarte (2025), herbs such as Ginkgo biloba, Allium sativum (garlic), and Zingiber officinale (ginger) possess antiplatelet or anticoagulant properties and have been associated with an increased risk of bleeding when used concomitantly with oral anticoagulants, particularly warfarin. The authors highlight that these interactions may enhance anticoagulant effects and contribute to hemorrhagic complications, underscoring the need for caution and clinical monitoring when such combinations are used.

Czigle et al. (2023) report that the central nervous system effects of herbal medicines such as Valeriana officinalis, Humulus lupulus, and Hypericum perforatum arise from the additive or synergistic actions of multiple bioactive constituents. Due to these combined pharmacodynamic effects, such CNS-active plants may produce additive interactions with conventional sedative or anxiolytic drugs, potentially enhancing overall central nervous system effects. Chamomile contains flavonoids such as apigenin that interact with benzodiazepine binding sites, producing mild benzodiazepine-like effects, as further supported by the clinical findings summarized by Saadatmand et al. (2024). Due to these pharmacodynamic properties, the concomitant use of these herbal products with CNS depressant medications, including benzodiazepines, barbiturates, opioids, or alcohol, may result in additive or synergistic central nervous system depression, leading to excessive sedation, impaired cognition, psychomotor dysfunction, and potentially respiratory depression.

Several medicinal herbs demonstrate glucose-lowering effects through mechanisms involving improved insulin sensitivity or insulin-like activity. Fenugreek (Trigonella foenum-graecum) has been reported to enhance insulin sensitivity, whereas Gymnema sylvestre promotes insulin release from pancreatic β-cells. Bitter melon (Momordica charantia) contributes to glycemic control by increasing peripheral glucose uptake and utilization. The simultaneous use of these herbal agents with insulin or oral antidiabetic therapies, including metformin and sulfonylureas, may lead to an additive hypoglycemic effect. Such synergism can elevate the risk of hypoglycemia-related adverse events, such as dizziness, confusion, and, in severe cases, loss of consciousness (Chahrour et al., 2025; Bhatt & Sharma, 2025; Husak et al., 2026).

3.2 Antagonistic Effects

Herbal products can sometimes reduce the effectiveness of prescribed medications through mechanisms such as increased drug metabolism, changes in drug transport, or opposing physiological effects. For instance, St. John's Wort (Hypericum perforatum) contains hyperforin, which activates the pregnane X receptor (PXR) and can induce CYP3A4 and P-glycoprotein, potentially lowering plasma concentrations of certain immunosuppressants and antidepressants (Gamil et al., 2025). Licorice (Glycyrrhiza spp.) may cause sodium and water retention and reduce potassium levels via glycyrrhizic acid, which could diminish the effects of diuretics and antihypertensive medications (Gamil et al., 2025). Products containing Ephedra have sympathomimetic properties, including increases in heart rate and blood pressure, which may interfere with antihypertensive therapy and elevate cardiovascular risk in vulnerable patients (Spanakis et al., 2025). These findings highlight the importance of healthcare providers routinely asking about herbal use and monitoring patient responses when managing therapy in chronic or cardiovascular conditions.

3.3 Toxicodynamic Interactions

Toxicodynamic herb–drug interactions are clinically significant because they can enhance drug toxicity through additive or synergistic effects at pharmacological sites of action, even when systemic drug concentrations remain unchanged. For example:

- Antiplatelet effects: Ginkgo biloba and Allium sativum (garlic) have been reported to influence platelet function and coagulation. When taken with anticoagulant or antiplatelet medications, these supplements may contribute to an increased risk of bleeding, reflecting a potential toxicodynamic interaction where both the supplement and drug affect similar pathways involved in hemostasis (Hatfield, Saad, & Housewright, 2022).
- Oncology drugs: Herbal medicines may interact with anticancer drugs through overlapping pharmacodynamic effects, potentially influencing both the efficacy and toxicity of chemotherapy by antagonism or synergy at shared biological targets (Duan et al., 2025).
- Hepatotoxicity: Ma et al. (2023) note that reports of herb-induced liver injury include cases associated with the combined use of certain herbs with other herbs or with non-herb components, suggesting that interactions among these agents may contribute to hepatotoxicity.

4. Conclusion

The use of herbal medicines alongside prescription and over-the-counter drugs has become increasingly common across the world. While many people choose herbal products because they believe they are natural and therefore safe, research has shown that these products can interact with conventional medicines in clinically significant ways. Herbal medicines contain biologically active compounds that can influence how drugs are absorbed, distributed, metabolized, and eliminated from the body. They may also alter the effects of medicines by producing additive, synergistic, or opposing pharmacological actions. As a result, these interactions can reduce treatment effectiveness, increase the risk of adverse effects, or lead to unexpected clinical outcomes. The risk is particularly high in patients taking multiple medications or drugs with a narrow therapeutic index, such as anticoagulants, immunosuppressants, anticancer agents, and antidiabetic medications.

Although knowledge about herb–drug interactions has expanded considerably, many uncertainties still remain. The composition of herbal products often varies because of differences in plant sources, cultivation methods, manufacturing processes, and product quality. In addition, inconsistencies in dosage and the limited availability of well-designed clinical studies make it difficult to accurately predict the likelihood and severity of many interactions. Another important challenge is that many patients do not inform healthcare providers about their use of herbal supplements, making it harder to identify and prevent potentially harmful interactions. The lack of comprehensive herbovigilance systems further limits the monitoring and reporting of adverse events associated with herbal medicines.

Ensuring the safe use of herbal medicines requires collaboration among healthcare professionals, researchers, regulatory agencies, and patients. Doctors and pharmacists should routinely ask patients about the use of herbal products as part of medication history taking and provide evidence-based advice regarding possible interactions with prescribed medicines. At the same time, greater efforts are needed to strengthen pharmacovigilance and herbovigilance programs, improve the standardization and quality control of herbal products, and support high-quality pharmacokinetic, pharmacodynamic, and clinical research. Emerging technologies, including pharmacogenomics, systems pharmacology, and artificial intelligence, also have the potential to improve the prediction and prevention of clinically important herb–drug interactions.

Overall, herbal medicines should not be considered harmless simply because they are derived from natural sources. Like conventional drugs, they contain active constituents that can influence therapeutic outcomes and patient safety. A clear understanding of the mechanisms, risk factors, and clinical consequences of herb–drug interactions is essential for minimizing adverse effects, improving treatment effectiveness, and promoting the safe integration of herbal medicines into modern healthcare. Continued research, increased awareness among healthcare professionals, and better patient education will play a vital role in ensuring that herbal and conventional medicines can be used together safely and effectively.

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