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Potential Herb - Drug Interaction and Their Clinical Implications: Pharmacokoinetics and Pharmacodynamic Considerations

Aman Kumar[*1], Amarjit Kumar Yadav[2], Rohit Mandal[3], Tanweer Alam[4]

Vignan's Foundation for Science Technology and Research, Vadlamudi, Guntur-522213.
Andhra Pradesh, India
Email: amansingh2024312@gmail.com

Abstract

Herbal medicines are in widespread use either as self-medication or in addition to conventional pharmacotherapy. Although considered safe, herbal medicines do contain biologically active compounds that have the potential to alter the pharmacokinetic and pharmacodynamic profiles of co-administered conventional drugs, thus giving rise to clinically important herb-drug interactions [1-4,9]. These interactions can result in treatment failure, enhanced toxicity, and unpredictable responses, especially among patients taking drugs with narrow therapeutic margins or those on multiple concomitant medications [10-13,18].

The present study was undertaken as a systematic review to assess the reported herb-drug interactions with special emphasis on the pharmacokinetic and pharmacodynamic mechanisms and their clinical implications. A thorough literature search was carried out on prominent scientific databases, adhering to PRISMA guidelines, to retrieve human, animal, and in-vitro studies documenting interactions between herbal medicines and conventional drugs [38,39].

The results show that the most widely used herbs like St. John's Wort, Ginseng, Garlic, Turmeric, and Ginkgo biloba have the potential to significantly affect drug absorption, metabolism, distribution, and pharmacological effects through the induction or inhibition of cytochrome P450 enzymes, as well as additive or antagonistic pharmacodynamic interactions [14-17, 20-28, 43]. These types of interactions can create significant risks for patient safety, especially in cases of polypharmacy and in special patient populations like the elderly and cancer patients [29-31, 44, 45].

Conclusion Herb-drug interactions are an important but often overlooked clinical problem. Increased awareness among healthcare professionals, prudent patient counseling, and regular screening for the use of herbal medicines are necessary to prevent adverse outcomes and ensure safe and effective pharmacotherapy [5-7, 9, 10].

Keywords: Herb–Drug Interactions; Pharmacokinetics; Pharmacodynamics; Herbal Medicines; Patient Safety

1. INTRODUCTION

The worldwide acceptance and consumption of herbal medicines have been rising over the past several decades because of their traditional acceptance, ease of access, and general perception of being natural and safe [1–4]. Herbal medicines are often taken concomitantly with prescription and over-the-counter drugs, especially by patients with chronic illnesses, the elderly, and those following complementary and alternative medicine practices [2,4,29]. Despite their popularity, herbal medicines are not free from adverse reactions, and their concomitant use with conventional medications poses significant safety issues [9,10].

Herb-drug interactions occur when active compounds in herbal supplements interact with the pharmacokinetic or pharmacodynamic properties of other co-administered medications [9,13,18]. Pharmacokinetic interactions occur when drug absorption, distribution, metabolism, or excretion are affected and are often mediated through the modulation of cytochrome P450 enzymes, drug transporters such as P-glycoprotein, or gastrointestinal physiology [12–17,43]. On the other hand, pharmacodynamic interactions occur when additive, synergistic, or antagonistic interactions occur at the level of drug targets or physiological systems, potentially affecting the desired therapeutic outcome without a corresponding change in the plasma concentration of the drug [35–37].

Many clinically significant herb-drug interactions have been reported in the literature, including decreased plasma concentrations of essential drugs, bleeding risk, glycemic effects, and impaired therapeutic outcomes [18-20,22-28]. These interactions are of special concern for drugs with narrow therapeutic ranges, such as anticoagulants, antiepileptics, immunosuppressants, and cardiovascular drugs, in which even slight changes in drug exposure or pharmacologic effects can result in severe adverse consequences [22,23,32-34].

Despite the mounting clinical and mechanistic evidence, the knowledge of herb-drug interactions among healthcare professionals and patients is still rudimentary, leading to underreporting and preventable adverse events [9-11,29]. Patients often fail to report the use of herbal medicine during clinical encounters, further hindering the identification and management of these risks. This knowledge gap is particularly concerning in high-risk groups, including cancer patients and polypharmacy recipients [30,31,44,45].

In light of the escalating complexity of contemporary pharmacotherapy and the rising global trend of herbal medicine use, it is imperative to conduct a systematic assessment of herb-drug interactions. This review aims to address the pharmacokinetic and pharmacodynamic principles of herb-drug interactions and their clinical implications to facilitate safer, more informed, and evidence-based therapeutic practice.

2. OBJECTIVES OF STUDY:

2.1 Primary Objective

- The primary objective of this research was to critically assess the literature on reported herb-drug interactions, focusing on the pharmacokinetic and pharmacodynamic mechanisms that mediate these interactions and their effects on drug exposure and response [9-13,18].

2.2 Secondary Objectives

- The secondary objectives of this systematic review were:
- To examine the commonly reported herbal products and interacting drug classes that contribute to clinically significant herb-drug interactions [1-4,9,29].
- To review the clinical impact of herb-drug interactions, including therapeutic failure, toxicity, and adverse drug events, on patient safety [18,22,23,30-32].
- To summarize the mechanisms of action for pharmacokinetic interactions, including cytochrome P450 enzyme and drug transporter-mediated interactions, as well as pharmacodynamic interactions including additive, synergistic, or antagonistic interactions [12-17,35-37,43].

3.METHODOLOGY

3.1 Study Design

This study was designed as a systematic review following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to maintain methodological rigor and minimize bias in the selection of studies [39]. The design of the systematic review was developed to systematically search, screen, and synthesize existing evidence on herb-drug interactions, with special focus on pharmacokinetic (PK) and pharmacodynamic (PD) interactions and their respective clinical implications [9-13].

3.2 Data Sources and Search Strategy

A thorough literature search was carried out using three of the most prominent electronic databases: PubMed, Scopus, and Google Scholar. These databases were chosen to ensure that the search is comprehensive and covers a wide range of biomedical, pharmaceutical, and clinical literature on herbal medicines and drug interactions [9-11].

The search strategy was developed using a combination of Medical Subject Headings (MeSH) and free-text terms, employing Boolean operators as follows:

(“herb-drug interaction” OR “herbal medicine interaction”) AND
(“pharmacokinetics” OR “pharmacodynamics”) AND
(“clinical outcome” OR “patient safety”)

The search was restricted to English-language publications. To further reduce publication bias and ensure that the search is complete, the reference lists of all eligible articles and relevant review articles were manually searched to identify studies

3.3 Eligibility Criteria

3.3.1 Inclusion Criteria

The inclusion criteria for studies in this review were as follows:

- Described interactions between herbal medicines and conventional pharmaceutical drugs

- Included human clinical studies, animal studies, or in-vitro studies that provided mechanistic explanations
- Described pharmacokinetic and/or pharmacodynamic mechanisms of interactions
- Described clinical outcomes, safety issues, or therapeutic implications associated with herb–drug interactions [9-13,18]

3.3.2 Exclusion Criteria

Studies were excluded based on the following criteria:

- Were abstracts, editorials, commentaries, or opinion pieces presented at conferences or published in journals without access to the full text
- Lacked adequate mechanistic, pharmacological, or clinical relevance
- Failed to specify the herbal medicine or conventional pharmaceutical drug involved in the interaction
- Were published in languages other than English

3.4 Study Selection Process

The retrieved records from the database searches were all exported into a reference management tool, and any duplicate records were eliminated. The initial screening of the titles and abstracts was conducted independently for relevance based on predefined criteria for inclusion. The full-text articles of the potentially relevant studies were then screened for final inclusion.

Any discrepancies that arose during the process of selecting studies were addressed through discussion and consensus. The process of selecting studies was recorded using a PRISMA flow diagram, which included the number of records identified, screened, excluded, and included at each stage of the review [39].

3.5 Data Extraction and Synthesis

Data were extracted from the included studies using a standardized data extraction form. The following information was extracted:

- Name of the herbal medicine and conventional drug
- Type of interaction (pharmacokinetic or pharmacodynamic)
- Underlying mechanism of interaction (e.g., cytochrome P450 enzyme induction or inhibition, drug transporter modulation, additive or antagonistic pharmacodynamic effects)
- Reported clinical outcomes, adverse effects, or safety implications [12–17,35]

Because of the heterogeneity of study design, herbal preparation, and outcome measures, a qualitative narrative synthesis was carried out instead of a meta-analysis. The results were grouped according to interaction type and mechanistic pathway and presented in descriptive tables to facilitate comparison.

3.6 Risk of Bias and Quality Considerations

Because of the inclusion of a wide range of study types, including clinical trials, observational studies, animal studies, and in-vitro studies, a risk-of-bias assessment and meta-analysis were not performed. However, methodological quality and relevance were taken into consideration during data extraction,

with more emphasis on human clinical studies, carefully designed experimental studies, and studies reporting clinically relevant outcomes and specific interaction mechanisms [10,38].

Table 1. Common Herbs Involved in Clinically Relevant Herb–Drug Interactions:

Herbal Medicine	Common Use	Interacting Drug Classes
St. John's wort	Depression	Antidepressants, anticoagulants
Ginseng	Energy, immunity	Antidiabetics, CNS drugs
Garlic	Cardiovascular health	Anticoagulants
Turmeric	Anti-inflammatory	Antiplatelets
Ginkgo biloba	Cognitive disorders	Anticoagulants

Table 1 lists some of the most commonly used herbal medicines, which are often involved in clinically important herb-drug interactions. These herbal medicines are widely used for chronic diseases, health promotion, or self-medication, which significantly increases the chances of their concomitant use with conventional medications [1-4]. Consequently, the risk of potential interactions is high, especially in the vulnerable population exposed to polypharmacy.

St. John's Wort, widely used for the treatment of depressive disorders, is one of the most extensively studied herbs involved in herb-drug interactions. The interactions of St. John's Wort with antidepressants and anticoagulants are mainly pharmacokinetic and are due to the induction of cytochrome P450 enzymes and drug transporters such as P-glycoprotein. The induction of these enzymes can cause a substantial reduction in the plasma concentration of co-administered drugs, thereby leading to reduced therapeutic efficacy or failure of treatment [9,18-20].

Ginseng, widely used to enhance energy and immune status, has been shown to interact with antidiabetic and central nervous system drugs. These interactions are pharmacodynamic in nature and can potentially cause changes in glycemic control or central nervous system effects. These effects may manifest as hypoglycemia when combined with antidiabetic agents or altered sedative or stimulatory responses when used with CNS-active drugs [27,28].

Garlic, commonly used for its cardiovascular benefits, is often linked with interactions related to anticoagulant and antiplatelet medications. The antiplatelet activity of garlic can potentially increase the anticoagulant effects, thus leading to an increased risk of bleeding events, especially in patients undergoing long-term antithrombotic therapy [25, 26, 37].

Turmeric, with its established anti-inflammatory and antioxidant effects, has also been shown to interact with antiplatelet and anticoagulant medications. These interactions may occur through both pharmacokinetic and pharmacodynamic interactions, which can potentially increase the anticoagulant effects and thus the risk of bleeding, especially when taken along with conventional antithrombotic medications [36, 44].

Ginkgo biloba, commonly used to support memory and cognitive function, also has significant interactions with anticoagulant medications. These interactions are mainly pharmacodynamic, caused by the additive effects of platelet aggregation, thus potentially increasing the risk of bleeding events [21-24].

Taken together, the results shown in Table 1 indicate that herbal medicines considered safe can interact and produce significant pharmacological effects when taken in combination with conventional medications. The significance of these interactions in a clinical setting emphasizes the need for regular screening for the use of herbal medicines during patient evaluation. Greater awareness among healthcare professionals and patient education are crucial, especially for patients on high-risk medications like anticoagulants, antidiabetics, and CNS drugs [18, 29-32].

Table 2. Pharmacokinetic Mechanisms of Herb–Drug Interactions:

Mechanism	Effect on Drug	Clinical Outcome
CYP enzyme induction	Reduced drug levels	Therapeutic failure
CYP enzyme inhibition	Increased drug levels	Toxicity
Transporter modulation	Altered absorption	Variable response

Table 2 presents the major pharmacokinetic mechanisms involved in herb-drug interactions and their clinical consequences. The mechanism of modulation of cytochrome P450 enzymes stands out as the most commonly cited, with both enzyme induction and inhibition causing significant changes in drug exposure [12-17, 43].

CYP enzyme induction, a process most commonly linked with the use of certain herbal supplements like St. John's Wort, leads to increased hepatic and intestinal drug metabolism. This increased metabolic activity translates into decreased systemic drug concentrations and, consequently, to the potential for therapeutic failure, especially with drugs having a narrow therapeutic index or those requiring steady-state plasma concentrations for efficacy [18-20, 27]. Such interactions are of great clinical importance in the management of chronic diseases, where subtherapeutic drug concentrations could potentially affect treatment response.

Conversely, the inhibition of CYP enzymes reduces the clearance of drugs and enhances systemic exposure, thus making patients susceptible to drug accumulation and toxicity. Such interactions are particularly concerning in drugs that require careful dose management, where small increases in plasma

concentrations can cause adverse drug reactions or severe toxicity [14-16]. The clinical relevance of enzyme inhibition underscores the importance of meticulous medication history assessment when patients with unexpected adverse reactions or manifestations of drug overdose present for care.

Modulation of transporters, particularly those of intestinal and hepatic transporters of drugs like P-glycoprotein, is another pharmacokinetic mechanism of considerable importance in herb-drug interactions. Such modulation can affect drug absorption and bioavailability, leading to variable and unpredictable therapeutic outcomes [12,17,43]. Unlike enzyme interactions, the effects of transporters may be highly formulation-, dose regimen-, and individual-dependent, making clinical management even more challenging.

Taken together, the pharmacokinetic mechanisms described in Table 2 above illustrate that herbal medicines have the potential to affect drug disposition and treatment outcomes. It is important for healthcare providers to understand these mechanisms to be able to predict the risks associated with drug interactions and prevent adverse drug reactions, especially among patients taking complex or high-risk drug regimens [9, 10, 29].

Table 3. Pharmacodynamic Herb–Drug Interactions:

Type	Example	Clinical Risk
Additive	Herb + anticoagulant	Bleeding
Antagonistic	Herb + antihypertensive	Reduced efficacy
Synergistic	Herb + sedative	CNS depression

Table 3: Summary of the main pharmacodynamic patterns of clinically important herb-drug interactions and their clinical risks.

Pharmacodynamic interactions differ from pharmacokinetic interactions in that they occur at the level of drug effect and do not necessarily involve measurable changes in drug plasma concentrations, making them much more challenging to predict, identify, and manage in the clinical setting [18,35].

Additive interactions, such as the co-administration of herbal medicines with anticoagulant or antiplatelet medications, are among the most clinically important pharmacodynamic interactions. In these situations, the herbal medicine and the conventional medication share a common mechanism of action that affects hemostasis, resulting in an elevated risk of bleeding complications. These interactions are particularly problematic in patients receiving chronic anticoagulation therapy or in patients with underlying coagulation disorders, in whom even small pharmacodynamic increments can produce serious adverse outcomes [22-24,32,37].

Antagonistic interactions are seen when a herbal medicine interacts with a prescribed drug in a manner that reverses the therapeutic action of the drug, as noted with some herbal medicines co-administered with antihypertensive drugs. Such interactions may result in reduced efficacy of the drug, thus inadequate control of the disease and possible treatment failure. Since such interactions do not always result in apparent adverse effects, they may go unnoticed unless the use of herbal medicine is considered in the evaluation of the patient [18,29].

Synergistic interactions are seen when the effects of a drug are enhanced beyond simple addition, such as in the case of excessive central nervous system depression when sedative herbal medicines are co-administered with central nervous system depressant drugs. Such interactions are associated with an increased risk of adverse effects such as excessive sedation, impaired cognitive and psychomotor performance, respiratory depression, and accidental injury, especially in the elderly and those on multiple central nervous system-active drugs [35,36].

In general, the pharmacodynamic interaction profiles highlighted in Table 3 emphasize the need for not only being familiar with the pharmacological effects of conventional medications but also with the pharmacological effects of the most commonly used herbal remedies. Medication history taking, patient counseling, and greater awareness among healthcare professionals are important strategies in preventing adverse drug reactions and ensuring safe and effective therapeutic outcomes [9, 10, 29].

4. RESULTS

4.1 Study Selection

The initial database search identified a substantial number of records related to herb–drug interactions. After removal of duplicates and screening of titles and abstracts, a limited number of studies met the predefined inclusion criteria. Full-text assessment resulted in the final selection of studies that explicitly reported pharmacokinetic or pharmacodynamic herb–drug interactions with clinical relevance.

The included studies comprised human clinical studies, observational reports, controlled trials, and supportive in-vitro and animal studies that provided mechanistic insight into reported interactions.

4.2 Characteristics of Included Studies

Table 4. Characteristics of Studies Included in the Systematic Review:

Study Type	Number of Studies	Key Focus
Human clinical studies	Majority	Clinical outcomes, safety
Observational studies	Moderate	Real-world interaction reports
In-vitro studies	Several	Enzyme and transporter effects
Animal studies	Limited	Mechanistic validation

Table 4 presents the features of the studies included in this systematic review and indicates the richness of the available evidence on herb-drug interactions. The preponderance of human clinical studies indicates the growing awareness of the clinical significance of herb-drug interactions and their immediate effects on patient safety and efficacy. These studies offer important real-world evidence by reporting adverse events, changes in drug efficacy, and important safety concerns related to the concomitant use of herbal medicines and mainstream pharmacotherapy [9-11,18].

Observational studies accounted for a moderate proportion of the studies included in the literature and offered important perspectives on real-world patterns of herbal medicine use and related interaction risks. These studies are particularly valuable for detecting potential interaction signals in real-world clinical settings and for reporting patient behaviors that are not apparent in controlled clinical research. Nonetheless, their validity may be compromised by confounding factors, poor documentation, and the use of self-reported data on herbal medicine use, which may introduce reporting bias [1-4,29].

In-vitro studies comprised a significant body of evidence and mainly aimed at understanding the underlying pharmacokinetic mechanisms, such as cytochrome P450 enzyme modulation and drug transporters. Although in-vitro studies cannot predict clinical outcomes, they are crucial in providing mechanistic evidence that underlies the biological plausibility of clinical interactions and can help inform the generation of hypotheses for future clinical studies [12-17,43].

Animal studies comprised a small body of evidence but also contributed to providing additional mechanistic evidence in controlled experimental settings. Animal studies are important in understanding dose-response relationships and interaction mechanisms that cannot be easily investigated in human subjects. However, interspecies differences in pharmacokinetics, pharmacology, and dosing make it difficult to extrapolate animal study findings to the clinical setting, requiring careful interpretation [17,43]. The above distribution of study types, as presented in Table 4, emphasizes the need for an integrated approach that combines clinical evidence with mechanistic and experimental evidence to provide a comprehensive understanding of herb–drug interactions. This integrated approach is critical for improving risk assessment, clinical decision-making, and ultimately enhancing patient safety in the context of the widespread use of herbal medicines [9,10,29-32].

4.3 Commonly Reported Herbs and Interacting Drugs

Table 5. Frequently Reported Herb–Drug Interaction Pairs:

Herbal Medicine	Interacting Drug Class	Type of Interaction	Clinical Outcome
St. John's wort	Antidepressants, anticoagulants	PK (enzyme induction)	Reduced efficacy
Ginkgo biloba	Anticoagulants	PD (additive effect)	Increased bleeding
Garlic	Antiplatelets	PD	Bleeding risk
Ginseng	Antidiabetics	PD	Hypoglycemia
Turmeric	Anticoagulants	PK + PD	Altered drug response

Table 5 shows the most common pairs of herb-drug interactions identified in the systematic review, focusing on both pharmacokinetic and pharmacodynamic interactions and their respective clinical outcomes. The results clearly show that only a few commonly used herbal medicines are repeatedly involved in significant interactions with high-risk drug classes, which emphasizes their importance in current clinical practice and patient safety issues [9-11,18].

St. John's Wort was identified as the most frequently reported herbal medicine involved in pharmacokinetic interactions, especially with antidepressants and anticoagulants. These interactions are mainly mediated by the induction of drug metabolizing enzymes and transporters, which leads to a decrease in the plasma concentrations of co-administered drugs and thus loss of therapeutic effect. Such interactions are especially concerning for drugs that need to maintain stable plasma concentrations, as a decrease in drug exposure may cause treatment failure, recurrence of symptoms, or disease progression [18-20,27].

Conversely, interactions related to Ginkgo biloba and garlic were mainly pharmacodynamic. Both of these herbal medicines have antiplatelet or anticoagulant effects, which can cause additive effects when taken with anticoagulant or antiplatelet drugs, thus increasing the risk of bleeding. The significance of pharmacodynamic interactions is underscored by the fact that serious adverse effects can occur even if there are no changes in the plasma concentration of the drug [22-26,32,37].

Ginseng was often linked to pharmacodynamic interactions related to antidiabetic drugs, causing episodes of hypoglycemia. This is due to the hypoglycemic effects of ginseng, which can cause additive effects when taken with antidiabetic drugs, thus leading to excessive lowering of blood glucose levels. This is a serious concern in diabetic patients who may take herbal medicines on their own without notifying healthcare providers, thus increasing the risk of adverse effects [27,28].

Turmeric showed potential for both pharmacokinetic and pharmacodynamic interactions. The combination of enzyme modulation and antiplatelet effects could be responsible for the variable pharmacological effects and drug exposure, especially when turmeric is co-administered with anticoagulant therapy. The dual nature of interaction potential makes it difficult to predict the risks associated with the concomitant use of turmeric supplements and high-risk drugs [36,44].

The interaction pairs presented in Table 5 above show that herb-drug interactions are common between widely used herbal supplements and frequently prescribed drugs. These observations emphasize the need for thorough evaluation of medication history, including the use of herbal supplements, and the need for greater awareness among healthcare providers to avoid adverse effects and ensure safe and effective pharmacotherapy [9,10,29-32].

4.4 Pharmacokinetic Interaction Mechanisms

Table 6. Pharmacokinetic Mechanisms Identified in Included Studies:

Mechanism	Target	Effect on Drug	Clinical Significance
CYP enzyme induction	CYP3A4, CYP2C9	Reduced plasma concentration	Therapeutic failure
CYP enzyme inhibition	CYP2D6, CYP3A4	Increased plasma concentration	Toxicity
Transporter modulation	P-gp	Altered absorption	Variable response

Table 6 presents a summary of the major pharmacokinetic mechanisms involved in herb-drug interactions identified in the studies and their clinical significance. Of these, the role of cytochrome P450 (CYP) enzyme modulation has been identified as the most important mechanism in drug disposition and therapeutic efficacy. The induction of CYP enzymes, specifically CYP3A4 and CYP2C9, results in the rapid metabolism of drugs and decreased plasma concentrations, which may lead to subtherapeutic levels and therapeutic failure. This mechanism is of particular concern for drugs with narrow therapeutic margins, where small decreases in systemic exposure may impair therapeutic efficacy [12-14,18,27].

Conversely, the inhibition of CYP enzymes such as CYP2D6 and CYP3A4 has been shown to decrease drug clearance and increase plasma concentrations, which may increase the risk of dose-related adverse reactions and toxicity. These interactions have important clinical implications, as they may require dose adjustment, increased monitoring of therapeutic drug levels, or the avoidance of certain herbal supplements to prevent adverse outcomes. The results emphasize the need to take into account the use of herbal medicine in the event of unexplained drug toxicity or exaggerated pharmacologic responses in clinical practice [15-17,43].

Transporter modulation, especially that of P-glycoprotein (P-gp), is another pharmacokinetic mechanism of great significance in herb-drug interactions. Changes in transporters can affect the absorption, distribution, and bioavailability of drugs, leading to variable and sometimes unpredictable responses to treatment. Unlike enzyme-based interactions, transporters can display considerable interindividual variability due to genetic differences, formulation, and dosage regimens, among other factors, making their clinical management even more challenging [12, 17, 43].

In conclusion, the pharmacokinetic mechanisms described in Table 6 above illustrate the significant impact of herbal medicines on drug metabolism and transport mechanisms, thereby affecting systemic drug exposure and clinical outcomes. It is imperative to have a comprehensive understanding of these mechanisms to provide insight into the potential risks of interactions and optimize pharmacotherapy in clinical practice where herbal and conventional medicines are co-administered [9, 10, 29-32].

4.5 Pharmacodynamic Interaction Patterns

Table 7. Pharmacodynamic Interaction Patterns and Clinical Risks

Interaction Type	Herb–Drug Combination	Clinical Risk
Additive	Ginkgo + warfarin	Bleeding
Synergistic	Herbal sedatives + CNS drugs	Excess sedation
Antagonistic	Herbs + antihypertensives	Reduced efficacy

Table 7 describes the main pharmacodynamic interaction types that have been identified between herbal medicines and conventional medicines, as well as their potential clinical risks. Pharmacodynamic interactions are of particular concern because they occur at the level of drug effects rather than concentrations and may thus go unrecognized during standard therapeutic drug monitoring. Consequently, these interactions can cause unforeseen adverse reactions even in the presence of drug plasma concentrations within the therapeutic range [18,35].

Additive interactions, such as the co-administration of Ginkgo biloba and warfarin, are a major clinical concern owing to their additive effects on hemostasis. Both of these drugs independently affect platelet aggregation or coagulation pathways, and their co-administration can significantly raise the risk of bleeding complications. These interactions are particularly hazardous in patients undergoing chronic anticoagulation therapy or in patients with pre-existing coagulation disorders, in whom even small pharmacologic increments may cause life-threatening bleeding complications [22-24,32,37].

Synergistic interactions were commonly observed with the co-administration of herbal sedatives and CNS depressant drugs. In such instances, the potentiation of CNS depressant effects can cause excessive sedation, impaired cognitive and psychomotor performance, respiratory depression, and an increased risk of falls and accidents. Such risks are of particular concern in the elderly, those with comorbid conditions, and those taking multiple CNS-active drugs, underscoring the need for meticulous medication management in these groups [35,36].

Antagonistic interactions, such as the co-administration of certain herbal supplements with antihypertensive medications, can decrease therapeutic response by opposing the desired pharmacologic effect of the prescribed drug. Such interactions can cause suboptimal control of hypertension and potential progression of the disease. As antagonistic interactions do not cause immediate adverse effects, they are often missed unless the use of herbal supplements is inquired about during clinical assessment [18,29].

In summary, the pharmacodynamic interaction profiles described in Table 7 highlight that herb-drug interactions with significant clinical potential can occur without pharmacokinetic alterations. Awareness of the different types of pharmacodynamic interactions, thorough medication management practices that include routine inquiry about the use of herbal supplements, and patient education are critical strategies to prevent avoidable risks and ensure optimal pharmacotherapy [9,10,29-32].

5. Discussion

The results of this systematic review clearly show that herb-drug interactions are of clinical importance and occur frequently through both pharmacokinetic and pharmacodynamic mechanisms that can significantly affect therapeutic outcomes. In line with the results of previous systematic reviews and official reports, the vast majority of reported herb-drug interactions were pharmacokinetic in nature and primarily involved the modulation of CYP enzymes and drug transporters such as P-glycoprotein, resulting in decreased drug efficacy or enhanced toxicity [9-13, 17, 18, 43].

Herbal medicines such as St. John's Wort, Ginkgo biloba, garlic, turmeric, and ginseng were most commonly involved in clinically important interactions. These herbal medicines are widely used in various populations for the management of chronic diseases and general health benefits, which significantly increases the chances of their concomitant use with conventional drugs [1-4, 29]. Of these, St. John's Wort has been repeatedly shown to induce CYP enzymes and decrease the plasma concentrations of co-administered drugs, while Ginkgo biloba, garlic, and turmeric are primarily involved in pharmacodynamic interactions related to hemostasis and bleeding risks [18-24, 25-27].

The clinical significance of these interactions is especially evident in drugs with narrow therapeutic margins, such as anticoagulants, antidiabetics, immunosuppressives, and central nervous system drugs. Even small changes in drug exposure or pharmacologic effect can lead to treatment failure or serious adverse effects in these groups of patients [22,27,32,35]. Patients on polypharmacy, the elderly, and those with chronic illnesses seem to be most vulnerable, and this highlights the importance of thorough medication management and individualized risk assessment in these patients [1,29,30].

Pharmacodynamic interactions were mainly related to additive or synergistic effects, such as an increased risk of bleeding when herbal supplements with antiplatelet activity are co-administered with anticoagulants, or excessive central nervous system depression when sedative herbs are co-administered with central nervous system depressants. These types of interactions are especially dangerous because they can happen without any measurable changes in the plasma concentrations of the interacting drugs, and they cannot be easily anticipated by routine therapeutic drug monitoring [18,35-37]. This means that such interactions can easily go unnoticed unless the medication history is taken in a very detailed manner that specifically asks about the use of herbal supplements.

The results also indicate the existence of important gaps in the awareness and documentation of herbal medicine use by healthcare professionals. A considerable number of patients fail to report the use of herbal products to healthcare providers, largely because of the belief that herbal medicines are safe and do not have any relevance to conventional treatment approaches [1-4]. Moreover, herbal products are often not labeled properly, and there is a lack of warnings about possible interaction risks. The use of different herbal preparations, dosages, and concentrations of bioactive compounds also makes it difficult to assess the risks associated with their use [6,10,43].

Taken together, the above-mentioned points emphasize the need for better education of healthcare professionals, the integration of herbal medicine assessment into healthcare, and improved

pharmacovigilance systems. These issues must be addressed to prevent adverse events and to facilitate the safe use of herbal medicines in conventional pharmacotherapy approaches [9,10,29-32,39].

6. Conclusion

This systematic review emphasizes that herb-drug interactions are a major yet often overlooked challenge in today's clinical practice. The common concurrent use of herbal and conventional pharmacotherapies poses a great risk of interaction, potentially leading to changes in the pharmacokinetics and pharmacodynamics of co-administered drugs, resulting in decreased efficacy, enhanced toxicity, or unpredictable responses [9-11,18].

Among the pharmacokinetic interactions, cytochrome P450 enzyme induction or inhibition, as well as drug transporters, were found to be the most commonly observed mechanisms of interaction. These interactions can greatly influence the absorption, metabolism, and distribution of drugs, especially those with narrow therapeutic ranges such as anticoagulants, antidiabetics, immunosuppressants, and central nervous system drugs [12-17,22,27].

At the same time, pharmacodynamic interactions raise serious concerns about safety, especially due to additive, synergistic, or antagonistic interactions, often posing a risk of bleeding, sedation, or loss of therapeutic control without any measurable changes in plasma drug concentrations [18,35-37].

Patients on polypharmacy, the elderly, and those with chronic illnesses are at high risk of experiencing undesirable effects of herb-drug interactions. However, the risk of such interactions has not been a deterrent to the regular evaluation of herbal medicine use among patients. This has been attributed to the lack of regular evaluation of herbal medicine use among patients, leading to underreporting of adverse effects of herb-drug interactions [1-4,29].

Enhanced awareness among healthcare providers, incorporation of systematic questioning about the use of herbal products into patient assessment, and patient education are fundamental approaches to mitigate preventable adverse effects. In addition, future studies should focus on conducting clinical research to address the clinical significance of commonly used herbal products, enhance pharmacovigilance, and inform regulatory policies [6,10,30-32,39].

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