

# Herbal-Drug Interactions: Clinical Implications

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## ABSTRACT

Herbal medicines are widely consumed worldwide as complementary or alternative therapies, often in combination with conventional drugs. While generally perceived as safe, concurrent use of herbs and pharmaceuticals may lead to significant herbal drug interactions (HDIs) with clinical consequences. These interactions occur primarily through pharmacokinetic mechanisms such as alterations in drug absorption, metabolism, distribution, or excretion, often mediated by cytochrome P450 enzymes and P-glycoprotein transporters, and pharmacodynamic mechanisms, where herbal constituents synergize or antagonize drug actions. Notable examples include *St. John's wort*, which induces CYP3A4 and reduces the effectiveness of oral contraceptives and immunosuppressants; *Ginkgo biloba*, which increases bleeding risk when combined with anticoagulants; and *Garlic*, *Ginseng*, and *Echinacea*, which may interfere with cardiovascular, antidiabetic, and immunosuppressive drugs. The risk of HDIs is heightened in vulnerable populations such as the elderly, polypharmacy patients, and individuals with chronic illnesses. Despite growing recognition, many HDIs remain underreported due to inadequate patient disclosure and a lack of standardized monitoring. This review highlights the pharmacological basis, clinical relevance, and regulatory considerations of HDIs, underscoring the urgent need for patient education, healthcare provider vigilance, and more robust clinical trials to ensure safe integration of herbal remedies with conventional therapeutics.

**Keywords:** Herbal drug interactions; Cytochrome P450; *Ginkgo biloba*; Polypharmacy and *St. John's wort* (*Hypericum perforatum*).

## INTRODUCTION

Herbal drug interactions are defined as the pharmacological or clinical response to the administration of a herbal product in the presence of a drug [1]. The use of herbal products is becoming more widespread, with approximately 25% of prescribed medications containing at least one ingredient derived from herbs. This increase in herbal product consumption carries a consequent rise in the potential for interactions between these products and prescribed drugs. Herbal products may be categorized as either traditional or modern in origin. Plants such as *St. John's wort*, *Echinacea*, *Ginkgo biloba*, *garlic*, *ginseng*, *kava*, *valerian*, and *ginger* have a long history of use in traditional medicine. Modern herbal products include concentrated extracts derived from herbs incorporated into a wide range of formulations. These are promoted for various medicinal purposes [1]. Interactions between drugs have been the subject of extensive research, resulting in well-established guidelines. However, the potential for adverse reactions as a consequence of coadministration of drugs and herbal products is comparatively less understood. Herbal-medicine interactions are generally classified as either pharmacokinetic or pharmacodynamic in nature.

### Types of Herbal Products

Herbal products are generally used for various purposes: to maintain health and well-being, to prevent disease, to improve symptoms, or to counter the side effects of drugs [1]. Herbal products are sold in pharmacies, health food stores, and over the Internet, and they are used without medical supervision in many countries. Two types of products are available on the market. The first are those produced according to the traditional herbal medicine concept, which originated widely in Asia, especially in Chinese and Japanese societies, more than 2000 years ago. In the United States and Europe, this represents the medicinal practice of complementary and alternative medicine (CAM). ANA and EMEA have defined a herbal remedy as "a preparation derived from herbal substances or

combinations of herbal substances, usually with a long history of use, whose origin is so far restricted to Botany. The second type of herbal product is the modern herbal (botanical) [5, 7]. It is generally defined as a combination of herbs or a mixture of active compounds prepared for a specific health concern. These products are widely used as over-the-counter medications and are sold as dietary supplements. In the United States, a botanical is defined by the Food and Drug Administration (FDA) as "a finished, labeled product that contains as ingredients vegetable materials, which may include herbs, parts of herbs, and finished herbal products, other naturally occurring ingredients, or combinations. They are usually sold as tablets, powders, teas, or capsules, and some synthetic compounds may be added to the formulation to enhance the product [1].

#### **Traditional Herbal Remedies**

Traditional herbal remedies differ significantly from dietary supplements. Traditional remedies have often been used for centuries in many cultures with supportive evidence for their beneficial effect on health and longevity. Many of these remedies that have succeeded over time have become integrated into established systems of medicine, for example, Traditional Chinese Medicine, Indian Ayurveda, and Western Herbal Medicine. Additionally, individual herbs have remained in use despite a relatively narrow or single indication, for example, Senna (*cassia angustifolia*) and Evening Primrose (*Oenothera biennis*) [1, 5]. Both traditional remedies and modern supplements may cause adverse drug reactions and negatively affect the beneficial therapeutic effect of concomitantly used medicinal drugs. Some interactions can be life-threatening and may therefore be avoided where possible. Pharmacodynamic or pharmacokinetic mechanisms of interactions are responsible for such effects. The clinical significance of herb-drug interactions depends on specific patient and herbal product risk factors. Both patient groups and individual patients who are at special risk of experiencing such interactions should be identified to prevent negative clinical consequences. Differential assessment of the clinical relevance of herb-drug interactions is necessary to provide informed clinical advice to patients and consumers [1, 3].

#### **Modern Herbal Supplements**

Herbal-drug interactions are defined as alterations in the clinical effect of a drug by the concurrent intake of herbal supplements, and they have important clinical implications for drug safety and efficacy. The use of medicinal plants can be traced back at least 5,000 years; these plants can be categorized into traditional preparations and modern supplements [1]. Traditional herbal remedies, often referred to as folk medicines, are usually prepared by experts in unrefined and ready-to-use forms. Unlike traditional herbal remedies, modern herbal supplements are made mostly by pharmaceutical companies and often contain a relatively concentrated amount of active ingredients [8]. Modern herbal supplements were classified by the US Food and Drug Administration (USFDA) as dietary supplements in 1994. These products may be capable of producing herbal-drug interactions. There are two mechanisms behind herbal drug interactions. The first is a pharmacodynamic interaction that may be additive, synergistic, or antagonistic. The second is a pharmacokinetic interaction, which usually alters the pharmacokinetic parameters of drugs and thus changes their plasma concentrations [1, 8]. Interactions mediated by metabolic enzymes or P-glycoprotein mainly decrease rather than increase drug concentrations because of the simultaneous involvement of multiple enzymes in the metabolic pathways of the drugs. This phenomenon is due to the ability of herbs to modulate both metabolic enzymes and P-glycoprotein. Pharmacokinetic interactions usually produce serious adverse reactions and impair the therapeutic efficiency of drugs [1].

#### **Mechanisms of Interaction**

Mechanisms of Herbal Drug Interactions, Clinical implications often arise due to pharmacokinetic interactions that involve alterations in metabolizing enzymes and transport proteins or pharmacodynamic interactions that affect drug tolerance and the combined therapeutic effects of herbal products and conventional drugs. The use of herbal products is widespread throughout human history [1]. Traditional and ancient uses of herbs to relieve or treat disease symptoms can be distinguished from the modern usage of herbs for well-being and health maintenance, including dietary products, listed according to their different functions. Pharmacodynamic interactions relate to the actions and effects of the combined use of both drugs and herbs. Toxic or adverse drug reactions (ADRs) may be generated by drug interactions [6, 7]. Even if these products have known beneficial effects, they may also lead to toxicity or reduced clinical therapeutic efficacy when consumed concurrently with conventional drugs. Adverse drug effects should be taken into account, but in some cases, it is possible to envisage beneficial or positive effects that are the consequence of selected combinations of drugs and herbs. Finally, pharmacokinetics, which is the metabolic modification of these herbal products and metabolites in the human body that affects their clinical application, should be carefully examined [1].

#### **Pharmacokinetic Interactions**

Pharmacokinetic interaction of herbal constituents may result in alteration of the four stages of pharmacokinetics of prescribed drug p [1]. These stages can be summarized as absorption, distribution, metabolism, and

excretion. Herb-mediated alteration in these stages changes the prescribed drug plasma concentration, causing a change in the therapeutic action. A herbal constituent that alters the plasma concentration of a prescribed drug could be an inhibitor or inducer of respective stages of drug pharmacokinetics. Alteration in the absorption phase is mostly due to alteration in pH at the stomach or intestinal level. Herbal constituents capable of altering the HCl pH of the stomach may alter the absorption of the drug at the stomach level. Similarly, the effect of the herb on the excretion of the drug at the intestinal level disturbs the pharmacokinetics at the absorption level [5]. The unabsorbed drug may be eliminated from the body by excretion or may be absorbed by colonic mucosa, resulting in reabsorption of the drug. P-glycoprotein inhibitor herbal constituents influence the reabsorption of the drug and thus alter the plasma concentration of the drug. Herbal constituents affecting the plasma protein binding influence the distribution of the drug to the site of action in the body. Hepatic and renal clearance of the drug is most commonly affected by herbal constituents that may act as CYP enzymes or P-glycoprotein inhibitors or inducers [2, 3].

### **Pharmacodynamic Interactions**

Herbal drug interaction (HDI) is defined as the pharmacological or clinical response to the administration of a herbal product in combination with a conventional Western drug, which results in interference with the clinical activity or safety of one or both agents [1]. HDIs may involve non-metabolized therapeutic drugs with herbal medicines or vitamin/mineral supplements, or they may involve metabolites of drugs that are altered through the induction or inhibition of cytochrome P450 by herbal medicines. Such interactions may be either pharmacokinetic or pharmacodynamic in nature, and both traditional herbal medicines and modern herbal dietary supplements have been implicated [2]. In addition to increasing the incidence of adverse drug reactions, herbal drug interactions may attenuate the therapeutic effect of the prescribed drugs and render treatment ineffective. Cross-referenced to the detailed discussion above and related aspects, including clinical assessment, risk estimation, specific herbs of concern, clinical significance, adverse effects, and safe management of herb drug combinations. Because of the incomplete pharmacokinetic and pharmacodynamic database on herbal preparations, predictions, detection, and evaluation of the extent of these interactions remain a substantial challenge in clinical practice and patient safety. Awareness of the potential for adverse HDIs and active herbal product use among patients is critical. Thorough clinical history-taking, routine inquiries about herbal use, and prescription of drugs with low interaction potential, when indicated, are paramount during clinical assessment and prescribing to minimize the risk of harmful HDIs [2, 3].

### **Clinical Significance of Herbal-Drug Interactions**

Herbal drug interactions refer to the pharmacological activities that occur when co-administered herbs affect the pharmacokinetic properties of drugs (absorption, distribution, metabolism, and elimination) or alter the pharmacodynamic activity of drugs. Herbs can be traditional remedies or modern supplements containing extracts, often with multiple active ingredients. Interactions can be pharmacokinetic, frequently caused by the inhibition or induction of p-glycoprotein or cytochrome P450 enzymes, or pharmacodynamic, involving synergistic or antagonistic actions. Such interactions have important clinical implications [1, 2]. They can produce adverse drug reactions or cause treatment failure, thereby affecting the safety and therapeutic efficacy of drugs. Patients undergoing medicinal regimens are particularly at risk, highlighting the need for awareness among physicians and healthcare providers, especially when patient use of herbal products is underreported. St John's wort and Ginkgo biloba display distinct interaction profiles [1, 2]. St John's wort induces metabolizing enzymes and p-glycoprotein, leading to reduced systemic exposure to substrates. Ginkgo biloba exhibits a moderate interaction profile with less pronounced effects on systemic exposure. Both have been documented to interact with widely prescribed drugs. Other herbs such as Allium sativum, Hydrastis canadensis, Psyllium, Panax ginseng, and Echinacea share the potential to produce clinically significant interactions. Risk factors include advanced age, polypharmacy, and underlying comorbidities. Clinical evaluation of patients for potential interactions and laboratory screening of herbal products can mitigate related risks [1].

### **Adverse Drug Reactions**

Adverse drug reactions are undesirable effects caused by the intake of a pharmaceutical or other exogenous substance [1]. Herbal drug interactions can lead to both mild and severe adverse reactions. Even more importantly, an interaction can severely impair the efficacy of the co-administered drug, which may impact the clinical outcome of therapy. Differential effects can be seen with the different herbal products, depending on whether the herbal product is a traditional herb or a supplement with isolated and standardized extracts, and also on the active constituents of the products being used. St. John's Wort and Ginkgo biloba are two of the most widely used herbal medicines [1,3]. St. John's Wort has been implicated most frequently and widely with interactions. Ginkgo biloba also shows certain potential to induce interactions, but of a lesser magnitude. Despite the widespread concern regarding the widespread use of herbal products and their potential interactions, current reports indicate that, apart from St. John's Wort, the majority of the herbal products seem to be free from any

significant interactions with prescribed drugs. However, such effects need to be balanced against the efficacy or health benefits associated with the herbal medicines or supplements. The various risk factors related to the affected patient and the co-administered drug can influence the clinical profile and safety of the combination and thereby modulate the extent and severity of potential adverse reactions [2, 3].

### Therapeutic Efficacy

The concomitant use of medicinal herbs with pharmaceuticals may lead to a variety of herb-drug interactions that severely disrupt therapeutic regimens [1]. Of particular concern are those interactions that reduce the therapeutic efficacy of drugs. A decline in therapeutic efficacy can result in inadequate responses to standard therapies, disease progression, an increase in the risk of complications, and eventually an increase in mortality and morbidity. In addition, a decrease in therapeutic efficacy may explain the paradoxical increase in deaths without an associated increase in liver failure during the hepatitis E outbreak in 2004, where indigenous herbal treatment was widely used. Several pharmacokinetic processes may be involved when medicinal herbs alter the therapeutic efficacy of drugs [3]. An increase in the rate or extent of drug metabolism often results in sub-therapeutic plasma drug concentrations, thus reducing therapeutic efficacy [2]. St. John's Wort actively induces CYP3A4 expression in human hepatocytes and increases first-pass metabolism of drugs metabolised by CYP3A4, such as indinavir, cyclosporine, tacrolimus, and nifedipine. Other inducers of drug metabolism include ginseng and ginkgo, which modulate the pharmacokinetics of warfarin, fexofenadine, and midazolam. Induction of CYP450 isoenzymes by fennel, schizandra, B-glucan, and ginger has also been demonstrated in rats. Pharmacodynamic interactions can also compromise therapeutic efficacy when drugs and herbs produce opposing pharmacological effects. An in vitro test is useful to provide a preliminary indication of any potential pharmacodynamic interactions between herbal products and drugs. Pharmacodynamic interaction studies show that eugenol, a major component of clove, ginger, sweet basil, wild ginger, holy basil, star anise, and cinnamon, antagonised the inhibitory effects of aspirin (1 mM) on platelet aggregation [4]. The antagonistic effects were comparable to those seen with some analgesic drugs such as mefenamic acid and ibuprofen; a finding that may explain the increased risk of cardiovascular accidents during concurrent therapy of aspirin and these medicinal herbs. Other examples of herbs having opposing effects on the cardiovascular system include vitex (prohypertensive) and feverfew (hypotensive) [2, 3].

### Common Herbs and Their Interactions

The herbal products most commonly responsible for clinically significant herbal drug interactions are St John's wort, Ginkgo biloba, Kava, Valerian, Ginseng, Garlic, Grapefruit juice, and Goldenseal [1]. It is known that St John's wort induces cytochrome P450 enzymes (mainly CYP3A4) and P-glycoprotein (P-gp), which can reduce the effectiveness of a variety of drugs. Additionally, St John's wort may adversely interact with other central nervous system drugs such as synthetic antidepressants and oral contraceptives. The risk of bleeding is increased when St John's wort is consumed with anticoagulants. Ginkgo biloba has potential interactions with several classes of drugs, including anticoagulants, antiplatelets, non-steroidal anti-inflammatory drugs, antidepressants, and anticonvulsants [1]. Both Kava and Valerian may increase the sedative potential of benzodiazepines and other central nervous system depressants. Ginseng is known for immunomodulatory and/or anti-inflammatory effects and can adversely interact with immunosuppressants, anticancer agents, glucocorticoids, antidiabetic agents, and anticoagulants. Both Garlic and Grapefruit juice can elevate plasma concentrations of protease inhibitors, anticoagulants, statins, and calcium channel blockers, thereby increasing the risk of their adverse effects. Moreover, Goldenseal is considered an inhibitor of cytochrome P450 enzymes and may reduce the metabolism of various drugs [1, 2]. Advanced patient age and polypharmacy increase the risk of herbal drug interactions, particularly in patients with existing chronic diseases or those receiving medications with a narrow therapeutic window, such as anticoagulants, antineoplastics, and anti-HIV agents [1]. The assessment of potential herbal drug interactions is a vital component of clinical practice, especially in countries where herbal medicine use is widespread. Clinical or laboratory assessments for these interactions, either prospective or retrospective, can prevent serious adverse drug reactions or diminished therapeutic effectiveness. Moreover, patients should be advised that, despite their natural origin, herbal products are not devoid of potentially harmful interactions when combined with drugs, adjuvants, or other active ingredients [2].

### St. John's Wort

St. John's wort (*Hypericum perforatum*) is a popular herbal remedy used as an antidepressant in many countries. Numerous pharmacokinetic herbal drug interactions have been reported, mainly as a result of the induction of cytochrome (CYP) P450 enzymes, drug transporters, or a combination of both [2]. Adverse drug reactions, especially through a pharmacodynamic interaction mechanism, have also been reported because of the herbal product's own intrinsic pharmacologic activity. Both traditional herbal products and modern dietary supplements may cause these herb-drug interactions. Five classes of interacting drugs have been identified with St John's wort: immunosuppressants, protease inhibitors and non-nucleoside reverse transcriptase inhibitors, oral contraceptives,

anticoagulants and antiplatelets, and antidepressants. Besides St John's wort, other commonly seen pharmacokinetic and pharmacodynamic herbal drug interactions involve other drugs and herbs, including Ginkgo biloba, Allium sativum, and Panax ginseng. Many case reports link pharmacokinetic interactions with induction and/or inhibition of CYP enzymes or P-glycoprotein and pharmacodynamic interactions with a combined herbal and drug effect [5].

### Ginkgo Biloba

Ginkgo biloba is a tree native to China, and its leaf extracts have been used medicinally for thousands of years. The historical use of the plant is evident in illustrations found in ancient medicines such as Shen Nong Ben Cao Jing and Ben Cao Gang Mu, dating back more than 1,200 years. Today, G. biloba is one of the most widely used medicinal plants worldwide, with extracts like EGb 761 being common. The main pharmacologic activities of the leaf extracts are vasomodulatory and neuroprotective, achieved through their bioflavonoid and terpene lactone components [1]. Both neutral and acidic fractions of the leaf extracts also demonstrate antioxidant properties. Interest in the potential deleterious effects of Ginkgo biloba, especially its ability to potentiate bleeding, prompted investigations into its possible interactions with other drugs. Interactions with aspirin, warfarin, ticlopidine, and nifedipine, which are partially metabolised via both cytochrome P450 enzymes and platelet aggregation pathways, were first reported in published case studies. Subsequently, several trials reported that 240 mg/day doses of G [4] biloba extract did not significantly affect bleeding time in healthy subjects or patients undergoing various operations, nor did it influence the clearance of CYP-metabolised drugs. However, these studies were criticised for inadequately addressing the potential for Ginkgo to increase bleeding risk based on the pharmacodynamic effects of the aforementioned medications. A subsequent randomised, double-blind, controlled trial evaluated the effects of Ginkgo biloba on bleeding time in patients with intermittent claudication who concurrently received aspirin and clopidogrel since the early 1990s [2, 5]. The results indicated that Ginkgo biloba could intensify the blood-thinning effect of aspirin, increasing the risk of bleeding.

### Garlic

Garlic is widely used to prevent and treat major human diseases, including cardiovascular disease, cancer, hypertension, diabetes, and high cholesterol. Garlic may reduce cardiovascular risk through several mechanisms: stimulation of NO production causing vasodilatation, inhibition of platelet aggregation, reducing blood pressure, antioxidant properties, and reduction of serum total cholesterol and LDL-C [2]. A number of clinical studies demonstrated that garlic in capsule preparations at a dose of 600–3000 mg/day is effective in lowering blood cholesterol, and cholesterol is reduced by 6–15% after short-term treatment. Platelet aggregation activity may be reduced if garlic is administered together with anticoagulants/antiplatelets, potentially increasing the risk of bleeding [1, 2]. Notably, organs such as the liver and gastrointestinal tract are affected by modulation mechanisms of many garlic compounds, such as activation of cytochrome P450 enzymes and inhibition of blood clotting. Case reports of adverse hemorrhagic events during abdominal surgery and the use of garlic extract as prophylaxis for cardiovascular disease highlight clinically relevant interactions [2]. Moreover, several reports show the ability of garlic to modulate the activity of CYP enzymes (especially CYP2E1 and CYP3A4), UDP-glucuronosyltransferases (UGT), and P-glycoprotein, inducing changes in the metabolism of antiretroviral drugs and other drugs with a narrow therapeutic index, potentially causing sub-therapeutic or toxic drug concentrations.

### Ginseng

Ginseng, particularly Panax ginseng, holds a prominent place in Asian medicinal culture and is also widely employed for various ailments, including hyperglycemia, hypertension, erectile dysfunction, and hiccups. Psychological applications include relaxation, memory improvement, and treatment of neurasthenia. However, due to insufficient information concerning the risks and benefits of ginseng extract in cancer patients, caution is advisable [1]. Loss of consciousness in a healthy young man with chronic ginseng use has been attributed to the ginseng caffeine interaction, highlighting the need for prudent consumption. A prospective study of 40 cancer patients receiving warfarin revealed significant increases in their international normalized ratio following Korean Panax ginseng intake [7]. Panax ginseng may induce cytochrome P450 (CYP) enzymes in vitro, notably CYP3A4, thereby accelerating the metabolism of numerous drugs, including calcium channel blockers, benzodiazepines, antidepressants, anticancer agents, HMG-CoA reductase inhibitors, immunosuppressants, antimicrobial agents, and protease inhibitors. Nevertheless, ginseng has also been reported to exhibit inhibitory effects on CYP enzymes. Such pharmacokinetic interactions could lead to subtherapeutic plasma concentrations of coadministered drugs, while pharmacodynamic interactions may cause additive effects [6].

### Echinacea

Echinacea, a popular medicinal plant, is reputed for its immunomodulating properties and is primarily employed for the prophylaxis of the common cold. The key constituents believed to be responsible for these effects include alkylamides, caffeic acid derivatives, and polysaccharides. Nonetheless, these active components have also been

linked to hepatotoxicity, attributable to their action on cytochrome P450 enzymes and inflammatory mediators [3]. The complexity of predicting possible interactions following the co-administration of Echinacea is compounded by the variability inherent in the sources of its bioactive compounds. However, the potential exists for interactions with either inducible or cotreatment drugs such as cyclosporine, statins, protease inhibitors, and tacrolimus during concomitant therapy [2]. Consequently, caution should be exercised when patients on therapy with Echinacea also receive agents with a low therapeutic index.

#### **Risk Factors for Interactions**

Hemorrhagic adverse effects and potential interactions have been associated with several herbs, including milk thistle, ginkgo, garlic, ginger, and ginseng. Ginkgo biloba, notable for platelet inhibition, can increase bleeding risk, especially when combined with aspirin or nonsteroidal anti-inflammatory drugs [1]. St. John's wort induces cytochrome P450 3A4 and/or P-glycoprotein in the intestine, liver, or both, which can markedly decrease plasma levels and clinical effects of numerous drugs such as cyclosporine, indinavir, and oral contraceptives [1]. Patients at increased risk of herbal-drug interactions include children and the elderly, particularly when prescribed multiple drugs, and individuals who are poor metabolizers of cytochrome P450 enzymes. The effects of herbal products on drug-metabolizing enzymes and transporters are typically dose-dependent, making large quantities potentially more hazardous. A combination of two or more herbs with overlapping toxicities may further increase the risk of adverse reactions [2]. Many herbs with a narrow therapeutic index, such as St. John's wort and ginger, pose significant risks if dose control is lost. Multiple herbs and components in traditional medicines lead to complex synergistic or antagonistic interactions. Concomitant use of other drugs that induce or inhibit cytochrome P450 enzymes, efflux transporters, or conjugating enzymes (e.g., phenytoin, rifampicin, or theophylline) similarly enhances the risk potential [2].

#### **Patient-Specific Factors**

Patient-specific factors that increase the risk of herbal drug interactions include age, sex, and comorbidities [1]. Elderly and very young patients may be at higher risk due to altered metabolism and elimination of drugs. Women, especially during pregnancy and lactation, represent vulnerable populations. Patients with liver or kidney dysfunctions may also experience alterations in pharmacokinetics [3]. Preexisting chronic diseases, such as diseases of the cardiovascular system, diabetes, hyperlipidemia, cancer, and immunodeficiency syndromes, may also influence pharmacokinetics and pharmacodynamics, regardless of whether the comorbidities require treatment. Other factors, including genetics, alcohol use, nutrition status, and pregnancy, can influence hospitalization risk [3].

#### **Drug-Specific Factors**

The likelihood of herb drug interactions depends upon drug- and patient-specific factors that include drug characteristics as well as patient-related factors [1, 2]. Drugs with a narrow therapeutic dose range or a low therapeutic index or potency are more inclined to interact with herbs; these include antiretrovirals, immunosuppressants, chemotherapeutic agents, antiepileptics and psychotropics, anti-arrhythmics, selective serotonin-reuptake inhibitors (SSRIs), anticoagulants, oral contraceptives, and hypoglycemics [1, 2]. Patient-related factors such as age, sex, and genetic polymorphisms can alter the herbal-interaction potential of a drug; elderly and pediatric groups are more at risk of interactions because of altered or reduced organ function and metabolic processes. Other factors that contribute to patient risk include disease characteristics that influence drug metabolism and comorbidities that include polypharmacy (multiple medications) and dietary restrictions (e.g., a low vitamin K diet in patients on warfarin); life stages such as pregnancy and lactation also alter drug metabolism and disposition [2].

#### **Assessment of Herbal Drug Interactions**

Herbal-drug interactions are an important consideration in the clinical setting, where the pervasive use of complementary and alternative medicine poses an additional challenge to clinicians in choosing safe and effective drug therapies. Herbal products consist of herbal remedies or plant materials used for their purported curative or preventive benefits, as well as modern nutrition- or dietary-type supplements, which are concentrated extracts or components of the original herb [1]. Herb drug interactions may involve pharmacokinetic and pharmacodynamic processes. With herbal remedies, the principal concern is pharmacodynamic synergism or antagonism causing adverse effects [4], whereas for supplements, the primary influence is on metabolism and transport pathways that affect the disposition of either agent. Herbal drug interactions may result in adverse drug reactions or changes in therapeutic efficacy. Adverse drug reactions may arise from unexpected or exaggerated effects when a herb causes an increase in drug levels or activity. Changes in therapeutic efficacy may result from diminished activity or altered action. Patients consuming herbal products in addition to conventional medications for other ailments are thereby exposed to a risk of adverse herb-drug interactions, unless adequate clinical support and counseling are available to ensure safe and effective usage [1,4].

### Clinical Evaluation

The evaluation of herbal drug interactions involves identifying the herbal product, the prescription drug whose activity is altered, and the clinical consequences of the interaction. When ethnopharmacological usage information is unavailable, recommendations in reference works may be applied [1]. Methods used to evaluate the clinical significance of the interaction, together with approaches employed to detect and quantify the interaction, are reviewed. Assessment strategies involve physiological studies, clinical investigation, and laboratory testing [1].

### Laboratory Testing

Standard determination of herbal compounds is mostly achieved using chromatography/spectroscopy and immunoassays; a few have been evaluated electrochemically [1]. Laboratory testing plays a vital role in assessing herb-drug interactions by considering multiple factors that contribute to synergistic or antagonistic effects [5].

### Guidelines for Safe Use of Herbal Products

Herbal medicine enjoys widespread popularity and use both in many less-developed countries and also by an increasing number of patients in the developed world. Since many patients taking prescribed medications also consume herbal medicines, there is concern about the increased risk of their interaction. Herbal medicines can modify the pharmacokinetic and pharmacodynamic profiles of many drugs and thus increase the potential risk for unwanted effects or reduced therapeutic efficacy [1]. Herbal products can, therefore, induce toxic or subtherapeutic effects when administered concomitantly with prescribed medications. A wide variety of medicinal plants have been reported to interact with commonly prescribed drugs, but the large majority of observations are based on in vitro assays or case reports; few interactions are supported by controlled clinical trials. Therefore, the clinical significance of many possible interactions remains speculative [6]. Many environmental and patient factors must also be taken into account when assessing the potential risk of injury. However, the enormous amount of information now available allows the development of a solid platform of knowledge from which patients and healthcare professionals can obtain guidance. As a rule, patients should follow simple rules if they decide to consume herbal products while on medication [1]. All healthcare workers, and especially pharmacists, should provide the necessary information and instructions on the safe use of herbal products for their patients and staff members [6]. Because recent evidence indicates that herbal products are implicated in an increasing number of serious interactions during the preoperative period, it is now recommended that all medicinal plant products should be withdrawn 2 to 3 weeks before elective surgery.

### Patient Education

Patients have been observed to show reluctance in reporting the use of herbal products to healthcare professionals, largely because of their perception that these substances are safe due to their natural origin and frequent marketing as dietary supplements [6]. The fact that herbal products do not require a prescription can further encourage self-medication, particularly among patients with chronic, incurable health conditions who may resort to alternative or complementary medicine to better manage their symptoms [1]. Evaluation of recent drug withdrawals, both from the market and clinical trials, reveals that side effects and severe toxicity have been among the main reasons for these decisions [1, 6]. These observations underscore the significance of patient education about adverse effects and the possibility of serious reactions associated with herbal medicines. Patient counselling, therefore, plays a crucial role in helping patients understand the chemical relevance of herbal medicines, thereby facilitating their optimal use [1, 6].

### Healthcare Provider Recommendations

Herbal medicines have multiple active ingredients, and the likelihood of an interaction increases in proportion to the number of chemicals involved [1]. Herb drug interactions thus occur more commonly than drug interactions. They may be pharmacokinetic or pharmacodynamic, but the majority of the documented examples involve pharmacokinetic processes. Many of these reflect the inhibition of cytochrome P-450 3A4 (CYP3A4) in the small intestine, which causes reduced metabolism and a corresponding increase in the plasma concentrations of the affected drugs [1, 6]. If the drug has a narrow therapeutic index, toxicity may result. There are scarcely any herbs that can be recommended routinely for use with drug treatments, the sole exceptions being the traditional Chinese “essences of chicken (or other meat)” that are used in chronic fatigue states. Even herbs such as St. John’s wort, which might have been thought to lower the risk of depression in vulnerable individuals, should not be used in combination with either monoamine oxidase (MAO) inhibitors or selective serotonin reuptake inhibitors (SSRIs) because of the danger of a serious and potentially fatal “serotonin syndrome”. It is safer to follow the recommendation that all herbs be avoided during drug treatment if there is doubt regarding an interaction [1, 6].

### Regulatory Aspects of Herbal Products

Herbal drug interactions are potential effects arising when a drug interacts with a traditional or modern herbal product, influencing pharmacokinetic or pharmacodynamic processes during combined use. This interaction may induce adverse drug reactions or alter the therapeutic efficacy of involved substances [1, 4]. Clinical evaluation

and laboratory tests can help exclude specific interactions. Patients should be advised about the safe use of herbal products. Concerning regulation, in the United States of America, the Food and Drug Administration (FDA), through the Dietary Supplement Health and Education Act of 1994 (DSHEA), requires the inclusion of a trigger clause in all dietary supplements' labels concerning possible safety problems, such as side effects, drug interactions, and warnings [1, 2]. Among traditional herbal remedies commonly involved in clinically significant pharmacokinetic interactions with drugs, St. John's Wort, ginkgo, and garlic have been extensively studied. Numerous studies and clinical evaluations have documented their pharmacokinetic effects. St. John's Wort interacts frequently with cyclosporine, HIV protease inhibitors, indinavir, warfarin, oral contraceptives, theophylline, and digoxin [1, 2]. Similarly, ginkgo has been associated with bleeding effects during anticoagulant therapy and severe interactions during antiretroviral therapy. The pharmacodynamic interactions of traditional herbal remedies with prescribed drugs and their clinical implications remain an important issue warranting consideration. In addition to traditional herbal remedies, popularity has shifted toward commercial modern popular supplements such as Echinacea, kava, ginseng, and garlic [2, 5].

#### **FDA Regulations**

The term "herbal drug interaction" is not new. The labeling of the St. John's Wort (SJW) commercial products has highlighted the possibility and significance of interactions between prescribed and over-the-counter (OTC) medications [1, 2]. The United States Food and Drug Administration (FDA) generally defines herbal products as substances derived from botanicals either in their raw state or prepared as purified extracts containing active phytochemicals administered either orally or topically. Herbal supplements are defined by the Dietary Supplement Health and Education Act (DSHEA) of 1994 as dietary ingredients that supplement the diet by increasing total dietary intake. They include herbs or other botanicals; vitamins, such as folate; minerals such as magnesium; amino acids such as tryptophan; and dietary substances such as fiber [1]. However, although herbal supplements are manufactured and sold in bulk, the process often involves a large number of other substances, frequently of synthetic origin, added during the manufacturing process [4, 5]. The intent of DSHEA was to clarify in detail the distinction between foods, dietary supplements, and drugs, primarily for the protection of individual freedom to choose nutritional supplements.

#### **International Guidelines**

International guidelines aim to provide consistent regulatory frameworks and address the quality, safety, and efficacy of herbal medicines at the national level [3].

#### **Future Directions in Research**

Emerging research trends in herbal drug interactions involve clinical trials, pharmacogenomic studies, and patient case scenarios focusing on clinical implications. Controlled and uncontrolled clinical trials play a key role in evaluating the incidence and severity of adverse events associated with these interactions. Moreover, the pharmacogenomic approach may offer a reliable tool to predict individual susceptibility to altered drug responses during concomitant use of prescription drugs and herbal remedies [1, 2]. Herbal products encompass both traditional remedies and modern supplements. Interaction mechanisms operate at either the pharmacokinetic or pharmacodynamic level, influencing the incidence of adverse drug reactions or a loss in therapeutic effectiveness. Many commonly used plants, such as *Hypericum perforatum* (St John's Wort), *Panax ginseng*, *Ginkgo biloba*, *Allium sativum* (garlic), *Pausinystalia yohimbe* (yohimbe), and *Ginseng*, interact with prescription drugs, raising the risk of clinical adverse effects. Assessment of these interactions, grounded in clinical implications, guides strategies for the safe use of herbs [2, 3].

#### **Clinical Trials**

Clinical trials investigating herbal drug interactions are primarily designed to explore the pharmacokinetic and pharmacodynamic consequences of co-administration. Pharmacokinetic interactions are of greater clinical significance because variations in plasma concentrations, often resulting from cytochrome P450 induction or inhibition, can reduce a drug's efficacy or increase the risk of toxicity [3]. For example, St. John's wort induces cytochrome P450 enzymes and P-glycoprotein, thereby altering the metabolism of various drugs. On the other hand, herbs such as *Ginkgo biloba* and *Panax ginseng* have been implicated in pharmacodynamic interactions, exhibiting antiplatelet activity that may raise the risk of bleeding when used with anticoagulant or antiplatelet drugs [3, 4]. *Hypericum perforatum* (St. John's wort) is among the most thoroughly examined herbs concerning herb-drug interactions. Pharmaceutical companies often conduct clinical trials to assess the safety and efficacy of their products in healthy volunteers: these studies are exploratory, aiming to uncover potential adverse interactions. Concomitantly, randomized controlled clinical trials are conducted to investigate the adverse activity of herb-drug interactions, focusing on patient safety. Unlike pharmaceutical agents, herbal products are commonly administered without prior assessment of hepatic drug-metabolizing enzymes. Consequently, the inductive or

inhibitory effects of certain medicines on metabolizing enzymes can go unnoticed until a clinically meaningful drug interaction manifests [4, 5].

### Pharmacogenomics

Clinical and observational studies surrounding herbal drug interactions have illuminated the role of genetic polymorphisms in associated risks. The focus has been on Phase I cytochrome P450 enzymes (CYP450), drug transporters encoded by ABC and SLC genes, and enzymes pivotal to choline uptake and metabolism like ChAT, SLC5A7, and BCHE in patients receiving treatment for cancer, cardiovascular, and central nervous system diseases [4, 5]. Animal models are also frequently employed to explore the effects of herbal products on CYP450 polymorphisms. The identification of variant gene alleles encoding P450 enzymes, including CYP2C9, CYP2D6, CYP2E1, CYP3A4/5, CYP2C19, and CYP1A2, is particularly pertinent to pharmacogenetics. Discovery of such polymorphisms has spurred in-depth investigations into therapeutic drug dosing and susceptibility to adverse drug reactions. Research into the effects of plant and herbal products on their clinical risk in combination with anticancer, cardiovascular, and central nervous system therapeutic drugs has gained attention, especially regarding the interactions of pomegranate, St. John's Wort, and Ginkgo biloba [4, 5].

### Case Studies

Herbal-drug interactions can increase the risk of adverse drug reactions, adversely affect the therapeutic outcome, especially for drugs with a narrow therapeutic index, affect the clinical assessment of a patient receiving therapy with a particular drug, lead to enrollment in a clinical trial, or be life-threatening. Both pharmacokinetic and pharmacodynamic interactions are possible [1, 6]. Therefore, it is important that the occurring interactions are detected early, evaluated, and managed properly to ensure maximum benefit for the patient receiving treatment. Herbal products are very diverse, ranging from traditional remedies or crude extracts to products containing isolated active compounds, and can be administered via a variety of routes, including intravenous, rectal, and oral. Pharmacodynamic interactions have been reported for the majority of traditional herbal medicines or crude extracts, while clinically significant pharmacokinetic interactions have been reported mostly for products containing St John's wort or its active components [6, 7]. The increased potential for an interaction can also be linked to the properties of the drug with which the herbal product is combined and the condition of the patient requiring treatment. Both the patient and the drug-related risk factors have to be taken into account when assessing the potential for an interaction. Following assessment, practical guidelines are suggested for patients using or considering self-administration of herbal products [1, 7].

### Successful Management of Interactions

Modern medicines and herbs have been used concomitantly by many people worldwide, despite the potential for harmful interactions. Unlike synthetic drugs, herbal products usually contain multiple active ingredients. When combined with conventional medications, they can affect both pharmacodynamics and pharmacokinetics [1]. Attempts to manage these interactions are both successful and unsuccessful in terms of clinical outcomes. By identifying and understanding the possible adverse effects, appropriate treatment can be provided [7]. A first step to ensure safe use of regulated herbal products is to communicate the risks associated with herbs and drugs. Established treatments may therefore be continued, with monitoring for therapeutic failure or increased adverse reactions [1, 7].

### Challenging Cases

The successful management of herbal drug interactions includes cases such as the appropriate administration of St. John's wort for photodynamic therapy or the deliberate induction of chemotherapeutic metabolism. However, some cases remain challenging, including the concomitant use of Ginkgo biloba and selective serotonin-reuptake inhibitors and the combined administration of warfarin and nonsteroidal anti-inflammatory drugs [1].

### Patient Case Scenarios

Clinical pharmacologists, pharmacists, and clinicians may consult drug-herb interaction database resources to guide decision-making. Several herbs and dietary supplements may interact with conventional drug therapies; the most common globally include *Hypericum perforatum* (St. John's Wort), *Panax ginseng*, *Ginkgo biloba*, *Allium sativum* (garlic), *Hydrastis canadensis* (goldenseal), and *Echinacea purpurea*. "Herbal-drug interactions" denotes clinically relevant modifications in drug pharmacokinetics or pharmacodynamics induced by herbal medication coadministration [1]. A multitude of herbs may alter clinical parameters governing drug efficacy or adverse event incidence when concomitantly administered with conventional pharmaceuticals; among the most prominent are St. John's Wort [8], *Ginkgo biloba*, and *Allium sativum*, which are sometimes deemed relatively safe. Conversely, several herbs pose severe toxic interaction risks or diminish the efficacy of treatments in autoimmune and cancer conditions, specifically *Astragalus membranaceus*, *Hydrastis canadensis*, *Panax ginseng*, *Silybum marianum*, and *Paullinia cupana*. Patient case scenarios illustrate clinical evaluation procedures, screening guidelines, counselling

### CONCLUSION

Herbal drug interactions represent an important yet often underestimated challenge in modern clinical practice. Although many herbal remedies provide therapeutic benefits, their concurrent use with conventional medicines can significantly alter drug efficacy and safety, leading to adverse events or treatment failure. Evidence indicates that HDIs occur mainly through modulation of drug-metabolizing enzymes and transport proteins, as well as through direct pharmacodynamic effects. Commonly used herbs such as St. John's wort, Ginkgo biloba, Garlic, Ginseng, and Echinacea illustrate both the therapeutic potential and risks associated with such interactions. A lack of standardized herbal formulations, poor regulation, and insufficient clinical trials further complicate risk assessment and safe use. To minimize harm, healthcare providers must proactively inquire about patients' use of herbal supplements, educate them on potential risks, and implement appropriate monitoring strategies. Moving forward, systematic pharmacological studies, toxicological profiling, and evidence-based regulatory policies are essential to guide the safe co-administration of herbal and conventional medicines. Effective collaboration between patients, clinicians, and regulatory bodies will be crucial in harnessing the benefits of herbal remedies while safeguarding against clinically significant interactions.

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