REVIEW ARTICLE

UPI JOURNAL OF CHEMICAL AND LIFE SCIENCES (UPI-JCLS)

ISSN: 2581-4648 (An International online Peer Reviewed Open Access Journal)

www.uniquepubinternational.com Published by Unique Pub International (UPI)

A REVIEW ON HERBAL DRUG AND DRUG INTERACTIONS

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Received: 14 May 2025 Revised: 20 June 2025 Accepted: 16 JULY 2025

Abstract

Herbal medicines are increasingly popular worldwide, with an estimated one third of adults in developed nations and over 80% of people in developing countries using them for health promotion and to manage conditions like colds, inflammation, heart disease, diabetes, and central nervous system disorders. Despite their popularity, the mechanisms of action of many herbal medicines remain largely unknown, and their efficacy and toxicity are often inadequately supported by evidence. There are more than 11,000 medicinal plant species, with around 500 commonly used in Asia and other regions. Drug interactions with herbal medicines pose significant safety risks, especially with drugs that have narrow therapeutic windows, such as warfarin and digoxin. Combining herbal remedies with pharmaceuticals can alter their pharmacokinetics and pharmacodynamics, leading to potentially severe adverse reactions. A review of the top-selling herbal medicines, including St. John's wort, ginkgo, ginseng, garlic, echinacea, saw palmetto, and kava, identified interactions with several prescribed drugs. For example, St. John's wort lowers blood concentrations of warfarin, while ginkgo increases bleeding risks with warfarin. Ginseng affects alcohol and warfarin levels, and garlic alters the pharmacokinetics of paracetamol and warfarin. It is essential for healthcare providers to be aware of these interactions to avoid serious clinical consequences.

Keywords: Herbal drugs, Herbal medicines, Drug Interactions.

INTRODUCTION

Herbal therapies are plants or plant-based products that are used to treat or prevent illness. They can be referred to as herbs, herbal supplements, botanicals or biomedicines. Many plants have medicinal properties; in fact, numerous pharmaceutical drugs were originally derived from plants. Herbal therapies are usually prepared by grinding or steeping the parts of a plant that are believed to contain medicinal properties.

Herbal medicines have become a popular option in healthcare. The seven best-selling herbal medicines in 1998 were ginkgo, St John's wort, ginseng, garlic, echinacea, saw palmetto, and kava. There is growing evidence for the efficacy of these herbal medicines. However, safety issues associated with these treatments remain under-researched. The fact that herbal medicines are associated with adverse events is widely appreciated. Another area destined to gain importance is that of herb-drug interactions.

All herbal medicines are mixtures of more than one active ingredient. On one hand, the multitude of active ingredients obviously increases the likelihood of interactions. On the other hand, this multitude combined with the fact that herbal medicines are of variable and often undefined composition renders any analysis of interactions a complex and difficult task. Because users of herbal medicines tend to have chronic conditions for which they often take prescribed drugs concomitantly, interactions are likely. Thus, a review of this area is timely and relevant.

The aim of this article is to systematically review the existing clinical data on suspected interactions between the above-named herbal medicines and conventional drugs [1].

Introduction to herb drug interactions

Herbal medicines are becoming popular worldwide, despite their mechanisms of action being generally unknown, the lack of evidence of efficacy, and inadequate toxicological data. The population in many developing countries use herbal medicines in the hope of promoting health and to manage common maladies such as colds, inflammation, heart disease, diabetes and central nervous system diseases [2]. They are commonly used in Asian and other countries. These herbs are often co-administered with therapeutic drugs raising the potential of drug–herb interactions, which may have important clinical significance based on an increasing number of [3]. Clinical reports of such interactions. The

interaction of drugs with herbal medicines is a significant safety concern, especially for drugs with narrow therapeutic indices (e.g. warfarin and digoxin). Because the pharmacokinetics and/or pharmacodynamics of the drug may be altered by combination with herbal remedies, potentially severe and perhaps even life- threatening adverse reactions may occur. Timely identification of such drugs using proper in vitro and in vivo approaches may have important implications for drug development.

Mechanisms of Drug Interactions with Herbal Medicines

The underlying mechanisms for most reported drug interactions with herbal medicines have not been fully elucidated. As with drug–drug interactions, both pharmacokinetic and pharmacodynamic mechanisms are implicated in these interactions.

Alterations in absorption, metabolism, distribution or excretion of drugs are the cause of pharmacokinetic interactions. Altered drug metabolism by herbal medicines is often a result of CYP induction and/or inhibition [3]. The most well studied and understood example of this is the induction of CYP3A4 and CYP2B6 by St John's wort in humans.

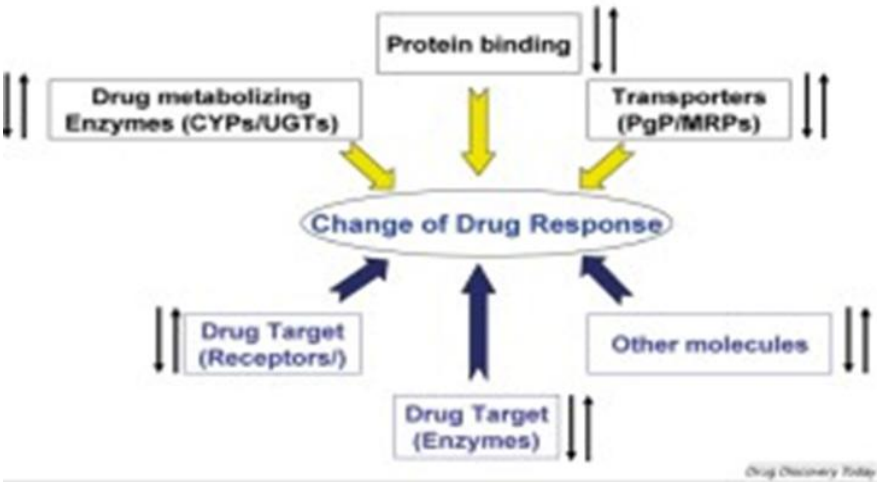

Figure 1: Possible mechanisms for drug interactions with combined herbal medicines.

As for drug–drug interactions, both pharmacokinetic and pharmacodynamic components may play important roles in herbal interactions with prescribed drugs [4]. Inhibition and induction of drug-metabolizing enzymes (e.g. cytochrome P450 3A4) and drug transporters (e.g. P glycoprotein) are the major mechanism underlying many pharmacokinetic drug–herb interactions. Furthermore, a herb may potentially mimic, increase, or reduce the effects of co-administered drugs through simultaneous effects on the same drug targets (e.g. enzymes or receptors). MRP = multidrug resistance associated protein; UGT=uridine diphosphate-glucuronosyltransferase. Components are highly bound by plasma proteins, they may displace the drugs from the binding sites. Both P-gp and CYP3A4 are abundantly expressed in the villus tip of enterocytes and hepatocytes. The interplay of both intestinal P-Gp and CYP3A4 has a strong effect on the bioavailability of most orally administered drugs including cyclosporine, midazolam, talinolol, statins, HIV protease inhibitors and verapamil.

Altered pharmacokinetics almost inevitably leads to a significant change in response to drugs that have narrow therapeutic indices; however, given that a single herbal preparation may contain more than 100 components, all of which may have unknown biological activities, a herb can potentially mimic, increase, or reduce the effects of co administered drugs through simultaneous effects on the same drug targets (figure 1).

By contrast, some herbal remedies may contain compounds with antagonistic properties, which are likely to reduce drug efficacy and produce therapeutic failure. The synergistic or antagonistic effects between herbs and drugs often result from the competitive or complementary effect of the drug and the co-administered herbal constituents at the same drug targets [5].

Drugs That Interact With Herbal Medicines In Humans

All human in vivo studies relating to drug–herb interactions were included, whereas data from animal and in vitro drug interaction studies were generally excluded, except for those exploring mechanisms for drug-herb interactions. Drugs that interact with herbal medicines mainly include anticoagulants (warfarin, aspirin and phenprocoumon), sedatives and antidepressants (midazolam, alprazolam, amitriptyline and trazodone), anti-HIV agents (indinavir and saquinavir), cardiovascular drugs (digoxin, nifedipine and propranolol), immunosuppressants (cyclosporine and tacrolimus) and anticancer drugs (irinotecan and imatinib). However, several other drugs, including ibuprofen, cilostazol, clopidogrel, acetaminophen, carbamazepine, mycophenolic acid, ritonavir and pravastatin are reported not to interact with herbal medicines.

There are several drug–drug interactions in humans that were associated with combinations of these drugs. For example, cyclosporine has been reported to alter the pharmacokinetics and/or pharmacodynamics of a series of drugs, including repaglinide5, statins 6, and levofloxacin. Many of the drugs in Table 1, including warfarin, digoxin, theophylline

and cyclosporine, have narrow therapeutic indices; Thus, a small change in their plasma concentration could lead to a marked alteration in their therapeutic effect and/or toxicity. Warfarin is one of the most frequently used oral anticoagulants for prevention of blood clotting. There are some reports of interactions between warfarin and herbs such as St John's wort, danshen. Of the 34 drugs that were reported to interact with herbs, 28 (82.4%) are substrates for various cytochrome P450s (CYPs), in particular, CYP3A4 and CYP2C9. Warfarin is extensively metabolized by CYP3A4 and CYP2C9, thus the anticoagulant effect of warfarin is likely to be affected when its metabolism (in particular, that of its Senantiomer) is compromised by combination with herbal remedies that are capable of modulating these enzymes [6].

Other herbs that interact with Antihypertensive Medicines

Ephedra

A powerful decongestant. Contains ephedrine, which can open up bronchial passages. It's controversial because it's a powerful stimulant that can raise blood pressure, cause insomnia and high blood pressure. Do not mix with heart medications or if you are being treated for high blood pressure, glaucoma or thyroid problems.

Ginseng

Used to help reduce stress, boost energy and improve stamina, and may also help lower cholesterol. Can cause nervousness and excitation, and overuse can lead to headaches, insomnia and heart palpitations. Can increase blood pressure. Should not be used if you are taking prescriptions for high blood pressure or Coumarin.

Lico rice

Used to treat coughs, colds and peptic ulcers. High doses can lead to increased blood pressure, water retention and potassium loss. Do not use with diuretics or digoxin because it could lead to further loss of potassium, essential for heart function.

Cayenne Pepper

Reports of possible interaction with MAO inhibitors and antihypertensive therapy (used to lower blood pressure). In large quantities, may cause damage to liver and kidneys. Interaction of herbs with cardiac glycosides

Sno.	Herb	Interaction outcome
1.	St. John's Wort	↓ AUC by 25% ,C_{max} by 33% ,C_{trough} by 26% (through P-gp induction)
2.	Siberian Ginseng	↑ digoxin concentration
3.	Licorice	↓ efficacy and ↑ side effects of digoxin (large doses ↓ K, low K and hence risk for digitalis toxicity)
4.	Guar gum (Cyamopsis tetragonolobus)	Slows absorption of digoxin in the stomach
5.	Indian Snakeroot	Herb can ↑effect
6.	Plantain (Black Psyllium)	Herb may interfere with absorption dynamics/monitoring
7.	Senna (Cassia senna)	Herb may potentiate hypokalemia

Discussion

Garlic (Allium sativum) is being promoted to lower cholesterol and blood pressure, delay atherosclerotic processes and improve circulation. Two case reports suggested that concomitant use of warfarin and garlic was followed by an increase in INR (international normalised ratio). Other case reports highlighted its potential for increasing the risk of postoperative bleeding. A clinical trial suggested that garlic changes some pharmacokinetic variables of paracetamol (acetaminophen) after 1 to 3 months' treatment. The precise mechanism of this interaction is presently not known.[7]

Ginkgo

Ginkgo (Ginkgo biloba) is used mainly for memory loss, Alzheimer's disease and circulatory disorders. Its constituents (ginkgolides, bilobalides and others) have antiplatelet activity and are platelet activating factor receptor antagonists. s. Two case reports demonstrate that patients taking warfarin or aspirin have experienced severe spontaneous bleeding after self- prescribing ginkgo at recommended doses. Spontaneous bilateral subdural haematomas associated with long term ginkgo ingestion have been reported [8].

Gingko is also a peripheral vasodilator. Surprisingly, an elderly patient was found to have a further increase in blood pressure after taking ginko while receiving a thiazide diuretic (not specified in the original paper) for hypertension. There is no rational pharmacological mechanism to explain this unusual interaction.

A patient with Alzheimer's disease fell into a coma after taking a combination of trazodone and ginkgo.[35] Ginkgo flavonoids increase the production of 1-(m-chlorophenyl) piperazine (mCPP), an active metabolite of trazodone, which releases γ-aminobutyric acid (GABA) through an agonistic action on presynaptic serotonin 5-HT2 and α2-adrenergic receptors located on GABA nergic nerve terminals.[9]

Ginseng

Ginseng (Panax ginseng) is marketed for a wide range of indications with tentative evidence in support of its efficacy. Case reports of suspected interactions with warfarin and the monoamine oxidase inhibitor (MAOI) phenelzine have been reported.

In the latter cases, the patients experienced insomnia, headache, tremulousness and mania; causality is likely because inadvertent rechallenge resulted in similar symptoms [10]. Three years later, one of these patients again ingested ginseng capsules (2 capsules for three days). She again experienced sleeplessness, tremors and headaches. Ginsenosides, one active ingredient of ginseng, inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase and thus increase cAMP levels. This effect may account partly for its psychoactive central effect both alone or in combination with MAOIs. However, the exact mechanism requires further study. Ginseng decreased plasma alcohol concentrations in mice by delaying gastric emptying with ginsenosides being responsible for this phenomenon. The effect could explain the ginsenginduced enhancement of blood alcohol clearance noted in one clinical study. The authors also hypothesise that the effect could be due to induction of the essential components of the microsomal alcohol oxidising system, CYP system and nicotinamide adenine dinucleotide phosphate (NADPH)- cytochrome reductase[11].

Kava

Kava (Piper methysticum) is an effective herbal anxiolytic. An interaction with alprazolam apparently caused a semicomatos state in one patient. Kava might have additive effects with benzodiazepines; both act on the same receptors and on the same areas of the CNS with increased GABA receptors. Kava possesses dopamine antagonistic properties, and cases of patients developing clinical signs suggestive of central dopaminergic antagonism have been described. The dopamine antagonistic properties of kava could explain the increase in the duration and number of 'off' periods in a patient with Parkinson's treated concomitantly with levodopa. The hypnotic action of both alcohol and kava has been shown to increase when administered in combination to mice. It is generally recommended not to take kava in conjunction with alcohol [12].

John's Wort

St John's wort (Hypericum perforatum) is effective for mild to moderate depression. As a monotherapy, St John's wort has a most encouraging safety profile. However, numerous reports indicate the possibility of important interactions, particularly with drugs metabolised by the CYmonoxygenase enzyme system and with selective serotonin-reuptake inhibitors (SSRIs). The enzyme-inducing properties of St John's wort were investigated in five trials using either internal (6β-hydroxycortisol/cortisol ratio) or external probe substrates (dextromethorphan, alprazolam,caffeine). Although an experimental study in vitro and a clinical study did not yield the same results, four clinical studies showed an increase or a trend to increase the metabolic capacity of CYP enzymes [13]. In addition to the enzyme-inducing properties of St John's wort, other evidence indicates that flavonoids contained in St John's wort raise the activity of P- glycoprotein, which, in turn, increases the elimination of drugs. Probably via these mechanisms it has been shown to reduce the plasma concentrations of warfarin, phenprocoumon, oral contraceptives, cyclosporin, amitriptyline, theophylline, and the protease inhibitor indinavir. When given in parallel with other SSRIs (sertraline, paroxetine) or serotonin nonadrenaline reuptake inhibitors (nefazodone), St John's wort can cause symptoms of central serotonin excess as suggested by seven case reports.

Echinacea

Echinacea (Echinacea augustifolia, Echinacea pallida, Echinacea purpurea) is used for stimulating the immune system. The clinical evidence in support is promising but not fully conclusive. Theoretically, echinacea extracts might decrease the effects of immunosuppressants. However, no clinical cases of interactions have been reported [14].

Saw Palmetto

Saw palmetto (Serenoa repens) is an effective symptomatic short-term treatment for benign prostate hyperplasia, possibly through hormonal effects. Therefore, it could interact with concomitant hormone therapies but no clinical evidence exists for this theoretical possibility. There are no suggestions of interactions with any other medicate[15].

Limitations

The data presented in section 2 also have obvious limitations. For many of the interactions listed, our understanding of the mechanisms involved is incomplete (tables I and II). Much of the literature on herbal medicine is limited by the fact that the authors of clinical reports fail to adequately define the botanicals used. All pharmacologically active herbal extracts are associated with varying degrees of toxicity in their own right. Often case reports do not allow a clear distinction between adverse events due to toxicity and those caused by herb-drug interactions. These limitations amount to a significant challenge for further research in this area[16].

Implications of Identification of Drugs That May Interact With Herbs in Drug Development:-

Interactions of drugs with herbal supplements are difficult to anticipate because of the general lack of information characterizing their pharmacologic actions and composition.
The dramatic rise in the use of herbal medicine worldwide means that many more patients on conventional medicines are being exposed to herbal medicines. Thus, timely identification of drugs capable of interacting with herbs is important to remind drug scientists of the possible safety concerns arising from combined use of herbs with any prescribed medicines 53. Existing knowledge advises us that many herbal preparations must not be taken at the same time with many other drugs that are substrates for CYP3A4 and Pgp. In many cases, patients think that herbal remedies are natural products and, thus, are safe. They are not willing, or do not think it is necessary, to mention the types and doses of herbal remedies being used to clinicians, so there is little knowledge of who is taking these products and for what indications 54. As such, drug
interactions with herbal medicine are highly likely to be significantly under-reported and underestimated, and are probably more frequent than drug–drug interactions. Because CYP3A4 is involved in the oxidative metabolism of over 50% of current therapeutic drugs, herb remedies that induce this enzyme are highly likely to interact with many more drugs than previously reported 53. To date, only a very small proportion of currently available drugs have been investigated for their potential interaction with herbs, such as St John's wort and ginkgo, in humans [17].
Thus, further well-designed clinical studies are certainly required to gain knowledge of drug interactions with herbs. The crucial examination of interactions between herbs and drugs requires the ability to accurately determine not only the presence of altered metabolism and transport but also the ability to quantitate the extent of the interaction and clinical consequences in drug development. A possible approach to overcoming unfavourable drug interactions with herbal remedies is to design new drugs that are so-called 'hard drugs' which are not metabolized by CYPs and/or not transported. Predicting the risks for potential drug–herb interactions following proper pharmacokinetic principles that are used for predicting drug–drug interactions and in vitro–in
vivo extrapolation is likely. A fourth approach for circumventing toxicity arising from drug– herb interactions is proper design of drugs with minimal potential for herbal interaction.

Conclusion

Herb-drug interactions are a significant concern in healthcare, as they can pose serious risks to human health. Healthcare professionals must remain vigilant about these potential interactions, particularly with drugs that have narrow therapeutic indices, such as warfarin and digoxin. These interactions can lead to adverse effects, sometimes resulting in life-threatening or fatal consequences. The complexity of these interactions highlights the need for greater awareness among clinicians and researchers. Identifying drugs that interact with herbal products is critical in drug development, especially for medications that are substrates for CYP3A4 and/or P-glycoprotein (P-gp), as they are more likely to cause herb-drug interactions.
To mitigate these risk s, drug development processes should integrate studies on herb- drug and herb-CYP interactions alongside traditional drug-drug interactions. This early identification is crucial in preventing harmful reactions and ensuring patient safety.
Clinicians must adopt strategies to minimize the potential for toxic herb-drug interactions, including awareness of the drugs that are more likely to interact with herbs. The incorporation of herb- drug interaction data into the early stages of drug development could significantly reduce the risk of adverse reactions, ultimately leading to safer pharmaceutical practices and better patient outcomes [20].

Author Contributions

All authors are contributed equally

Financial Support

None

Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

Acknowledgements

None

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