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A Review on Herbal Drug Interaction

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A B S T R A C T

Herbal medicines are becoming popular worldwide, despite their mechanisms of action being generally unknown, the lack of evidence of efficacy, and inadequate toxicological data. An estimated one third of adults in developed nations and more than 80% of 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. To date, there are more than 11 000 species of herbal plants that are in use medicinally and, of these, about 500 species 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 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. Because of the clinical significance of drug interactions with herbs, it is important to identify drugs and compounds in development that may interact with herbal medicines. Timely identification of such drugs using proper in vitro and in vivo approaches may have important implications for drug development.

Keywords: Herbal medicines, pharmacokinetic interactions, 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. The resulting therapies come several forms, including oral tablets, capsules, extracts and infusions. They are eaten, swallowed, inhaled or applied to the skin[1].

Introduction to herb drug interactions

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based on an increasing number of clinical reports of such interactions[2].

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. Because of the clinical significance of drug interactions with herbs, it is important to identify drugs and compounds in development that may interact with herbal medicines. Timely identification of such drugs using proper in vitro and in vivo approaches may have important implications for drug development[1].

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 (Figure 1).

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[24-27]. Of the components of St. John's wort, hyperforin is purported to be the active constituent and it is the most potent agonist for PXR with a Ki of 27 nM. Because of the important role of P-gp in drug transport and excretion, modulation of P-gp by herbal medicines may have significant pharmacokinetic consequences[4]. St John's wort induces intestinal P-gp in vitro and in vivo[5-6]. Oral administration of St John's wort for 14 days in healthy volunteers resulted in a 1.4-fold increase in P-gp expression[7].

The substrates of P-gp, fexofenadine and digoxin, which are often used as probes for examining P-gp activity in vivo, were found to have increased clearance in healthy subjects treated with St John's wort[8].

However, there is rare clinical evidence for altered protein binding of drugs by herbal medicines. Given that many herbal

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. Alterations in absorption, metabolism, distribution or excretion of drugs are the cause for pharmacokinetic interactions. Inhibition and induction of drug-metabolizing enzymes (e.g. cytochrome P450 3A4) and drug transporters (e.g. Pglycoprotein) 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[2].

Herbal medicines are often administered orally and they can attain moderate to high concentrations in the gut lumen (the primary site of absorption for most orally-administered drugs) and liver, and may exert a significant effect on enterocytes and hepatocytes [9]. 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[32] . Thus, the modulation of intestinal and hepatic P-gp and CYP3A4 by herbal medicines represents a potentially important mechanism by which the bioavailability of co-administered drugs can be modulated.

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)[10]. If the effect of the drug in combination with the herbal medicine is enhanced (e.g. synergistic or additive effect), unfavourable on-target toxicity may occur. 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[11] .

Drugs That Interact With Herbal Medicines In Humans

Literature searches were performed using the following databases: Medline (via Pubmed), Biological Abstracts, Cochrane Library, and Embase (all from their inception to March 2007). 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. Only articles in English were included. Human studies
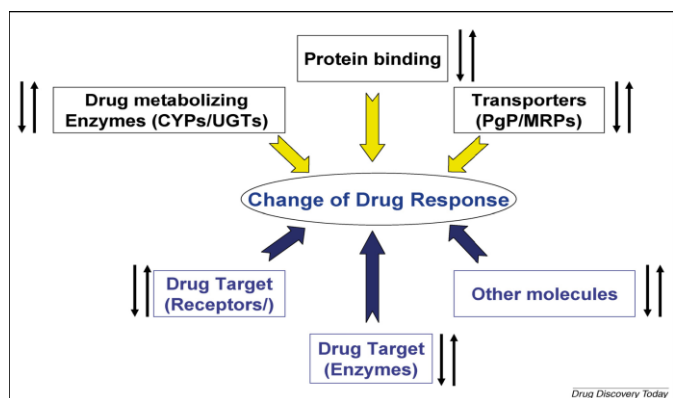
included case reports, case series, clinical trials or other types of studies.

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[2-4].

Of the drugs identified as interacting with herbal medicines, most were administered orally in long term regimens. 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 repaglinide[5], statins[6], and levofloxacin[7]. Additionally, several drugs such as ezetimibe[8] and carvedilol[9] can alter the pharmacokinetics and/or pharmacodynamics of cyclosporine.

Many of the drugs in Table 1, including warfarin, digoxin, theophylline and cyclosporine, have narrow therapeutic indices (warfarin: 2.0–3.0 of target international normalized ratio for most indications; digoxin: 0.5–2.0 ng/ml; theophylline: 10–20 μg/ml; and cyclosporine: 150–400 ng/ml)[10] Thus, a small change in their plasma concentration could lead to a marked alteration in their therapeutic effect and/or toxicity[2,11]. 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,

Dong quai, ginseng and ginkgo in patients on constant warfarin therapy . Pharmacokinetic modulation of warfarin is common but severe toxicity, such as postoperative bleeding, has been reported[2,11]. Combination of digoxin with St John's wort, or Siberian ginseng, significantly affects its plasma concentration .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 S-enantiomer) is compromised by combination with herbal remedies that are capable of modulating these enzymes[12]. In addition to warfarin, alprazolam, imatinib, midazolam and amitriptyline are also substrates for CYP3A4. CYP3A4 is the most abundant isozyme in the human liver, representing approximately 40% of total hepatic CYP contents and is responsible for the metabolism of more than 50% of all prescribed drugs[13,14].

All CYPs are subject to inhibition or induction by a variety of xenobiotics, including drugs and herbal medicines. Importantly, the expression of CYP3A4, CYP3A5, CYP2B6 and CYP2C8 is tightly regulated by the nuclear factor pregnane X receptor (PXR/NR1I2), which is activated by a variety of structurally distinct ligands, including certain herbal components such as hyperforin from St John's wort[13,15-17]. Several drug–drug interactions have been found to be mediated by CYP modulation, resulting in altered drug clearance and effect[18].

Some drugs that interact with herbs have been identified as substrates for P-glycoprotein (P-gp), a well-known drug transporter. These include cyclosporine, digoxin, fexofenadine, imatinib, indinavir, irinotecan, simvastatin, saquinavir and tacrolimus. Interestingly, these 10 drugs, except digoxin and fexofenadine, are also substrates for CYP3A4. Thus, these eight drugs are dual substrates for both CYP3A4 and P-gp. Pgp in the intestine, liver and kidney plays important roles in the absorption, distribution, or excretion of drugs. In common with CYP3A4, P-gp can be induced and inhibited by several xenobiotics, including drugs and herbal medicines and it is also regulated by PXR[20,21]. Theoretically, a drug that is a dual substrate for CYP3A4 and P-gp has a much higher potential for interaction with herbs that also modulate CYP3A4 and P-gp. For example, carbamazepine is metabolized by multiple CYPs[22], but it is not a substrate of P-gp[23]. This reduces its potential for herbal interaction and, as shown in Table 1, it appears not to interact with herbal medicines.

Interaction of Herbal Drugs with Some Commonly Used Drugs

Interaction of herbs with antibiotics

Table: 1 Interactions of herbs with antibiotics

Sno.	Antibiotic	Herb	Interaction outcome
1.	Monomycin ,kanamycin	Eleuthero	↑Effects of antibiotics
2.	Doxorubicin	Milk thistle, ubiquinone (co-enzyme Q_{10})	↓Kidney toxicity herb may ↓cardiac side effects from these medications
3.	Adriamycin	Schizandra	↓ cardiotoxicity
4.	Penicillin V	Guar gum	Herb slows the absorption in the stomach
5.	Tacrolimus	St. John's wort	↓ AUC by 57.8%
6.	Erythromycin	Digitalis	Erythromycin can ↑ the serum levels of digitalis glycosides increasing the therapeutic effects and risk of side effects.

AUC: Area under the plasma concentration curve, ↓ : decrease; ↑ increase

Interaction of herbs with antihypertensive medicines

Table: 2 Interaction of herbs with antihypertensive medicines

Sno.	Name/class of antihypertensive drugs	Herb	Interaction
1.	Nifedipine (Calcium channel blocker)	St. John's wort	Nifedipine : C_{max} ↓ 38.5%, AUC ↓44.9%, Dehydronifedine :C_{max} ↑ 55.9%, AUC ↑ 25.7%
2.	Propranolol	Piperine	↑C_{max} and AUC
3.	B-blockers and calcium channels	Guggul	↓ efficacy of beta blockers and calcium

Sno.			
	blocker		channel blocker
4.	Diuretics	Licorice	↓efficacy and ↑ toxicity of diuretics (large doses ↓ K)
5.	Thiazide diuretics	Aloe	↑ cardiac toxicity due to electrolyte imbalance
		Senna	Herb may↓ K levels

AUC : Area under the plasma concentration curve ↓ : decrease ; ↑ increase ; C_{max} : Maximum plasma concentration ;K : Potassium

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[64].

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[64].

Licorice: 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[64].

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[64].

Interaction of herbs with cardiac glycosides

Table: 3 Interaction of herbs with cardiac glycosides (digoxin)

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

Interaction of herbs with corticosteroids:

Table: 4 Interaction of herbs with corticosteroids

Sno.	Herb	Interaction outcome
1.	Licorice	Potentiates corticosteroids
2.	Echinaceae	Combination should be avoided
3.	Ginseng (American)	Herb may effect steroid concentration or may have possible additive effect
4.	Saiboku-to (Asian herb mixture)	Herb may ↑ prednisolone levels

Interaction of herbs with NSAIDs

Table: 5 Interaction of herbs with NSAIDs

Sno.	Drug/Class	Herb	Interaction outcome
1.	Indomethacin	Garlic	↑indomethacin level
2.	Sulindac and /or tamoxifen	Green Tea	Synergistic effect
3.	NSAIDs	Feverfew	May ↓ therapeutic effect of feverfew.
4.	Acetaminophen	Garlic	Increased sulfation through induction of enzyme
5.	Aspirin	Ginkgo	Spontaneous hyphema

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 P-gp. 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.

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 by P-gp[53]. The concept of 'hard drugs' was first proposed by Ariens [54]. These drugs are non-metabolizable, and excreted through either the bile or kidney with simple kinetics. Thus, their pharmacokinetics are simplified and, usually predictable. When these drugs are administered, the potential for interactions with combined herbal remedies will be greatly reduced. If drugs have to be used in combination with herbal remedies, in some instances rational use of such drugs becomes necessary, including the use of a safe drug combination regimen, dose adjustment and discontinuation of therapy when toxic drug–herb interactions occur. When herbs are combined with drugs with narrow therapeutic indices, the monitoring of plasma drug concentrations and observing of potential toxicities should be conducted.

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.

CONCLUSIONS AND FUTURE PERSPECTIVES

A major safety concern is the potential for interactions of herbal products with prescribed drugs. This issue is especially important with respect to drugs with narrow therapeutic indices (e.g. warfarin and digoxin)[55]. This may lead to adverse reactions that are sometimes life threatening or lethal [36]. The identification of drugs that interact with herbs has important implications in drug development. It appears that any new drugs that are substrates for CYP3A4 and/or P-gp have the potential to cause herb–drug interactions. Thus, caution should be taken when these drugs are coadministered with herbs. Since in vitro drug–drug and drug–CYP interaction studies have been incorporated into drug development, drug–herb and herb–CYP interactions should also be

included to identify drugs that interact with herbs in the early stage of drug development[1].

Clinicians should adopt proper strategies to minimize toxic drug–herb interactions. Early identification of drugs that interact with herbs and the mechanism involved is important. Identification of drugs that interact with herbs can be incorporated into the early stages of drug development[1]

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