Identification of Drugs That Interact with Herbs in Drug Development

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Teaser: Due to the clinical significance of drug interactions with herbs, there is a strong necessity to identify drugs that may interact with herbal medicines in drug development.

Abstract

To date, a number of clinically important drugs have been identified that interact with commonly-used herbs. These drugs include (amongst others) warfarin, midazolam, digoxin, amitriptyline, indinavir, cyclosporine, tacrolimus and irinotecan. Importantly, many of these drugs have very narrow therapeutic indices. Most of them are substrates for cytochrome P450s (CYPs) and/or P-glycoprotein (P-gp). Because drug-herb interactions can significantly affect circulating levels of drug and, hence, alter the clinical outcome, the identification of drugs that interact with commonly-used herbal medicines has important implications in drug development. *In silico, in vitro*, animal and human studies are often used to identify drug interactions with herbs. We propose that drug-herb and herb-CYP interaction studies should be incorporated into drug development.

1 Introduction

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. Due to 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.

2 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 literatures in English were included. Human studies included case reports, case series, clinical trials or other types of studies.

A total of 34 drugs were identified that interacted with herbal medicines in humans (

Table 1). These drugs 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 [1-3].

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Of the drugs identified as interacting with herbal medicines, most were administered orally in long term regimens. There are a number of 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 [4], statins [5], and levofloxacin [6]. Additionally, a number of drugs such as ezetimibe [7] and carvedilol [8] can alter the pharmacokinetics and/or pharmacodynamics of cyclosporine.

Many of the drugs in

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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) [9]. 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, Dong quai, ginseng and ginkgo in patients on constant warfarin therapy [1,10]. Pharmacokinetic modulation of warfarin is common, but severe toxicity, such as postoperative bleeding, have been reported [1,10]. Combination of digoxin with St John's wort, or Siberian ginseng significantly affects its plasma concentration [1,10].

Of the 34 drugs that were found 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 [11]. In addition to warfarin, alprazolam, imatinib, midazolam and amitriptyline are also substrates for CYP3A4. CYP3A4 is the most abundance 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 [12,13]. 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 [12,14-16]. A number of drug-drug interactions have been found to be mediated by CYP modulation, resulting in altered drug clearance and effect [17].

Ten of the 34 drugs (29.4%) 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, 8 of the 34 drugs are dual substrates (23.5%) for both CYP3A4 and P-gp. P-gp 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 a number of xenobiotics, including drugs and herbal medicines [18] and it is also regulated by PXR. [19,20] Theoretically, a drug which 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 [21], but it is not a substrate of P-gp [22]. This reduces its potential for herbal interaction and as shown in Table 1, it appears not to interact with herbal medicines.

3 Mechanisms for 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 for pharmacokinetic interactions. Altered drug

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metabolism by herbal medicines is often a result of CYP induction and/or inhibition [17]. The most well-studied and understood example of this is the induction of CYP3A4 and CYP2B6 by St John's wort in humans [23-26]. 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 K_i of 27 nM [23]. Due to the important role of P-gp in drug transport and excretion, modulation of P-gp by herbal medicines may have significant pharmacokinetic consequences [18]. St John's wort induces intestinal PgP *in vitro* and *in vivo* [27-29]. Oral administration of St John's wort for 14 days in healthy volunteers resulted in a 1.4-fold increase in P-gp expression [27]. 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 [30]. However, there is rare clinical evidence for altered protein binding of drugs by herbal medicines. Given that many herbal components are highly bound by plasma proteins, they may displace the drugs from the binding sites [1].

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. Both P-gp and CYP3A4 are abundantly expressed in the villus tip of enterocytes and hepatocytes [31]. 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 [31]. Thus, the modulation of intestinal and hepatic P-gp and CYP3A4 by herbal

medicines represents a potentially important mechanism by which the bioavailability of coadministered drugs can be modulated.

Altered pharmacokinetics almost inevitably leads to a significant change in response to drugs that have a 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. In 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 coadministered herbal constituents at the same drug targets [10].

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4 Clinical significance of identification of drugs that may interact with herbs

When a drug's clearance is significantly altered, or its drug targets are the same as the herbal components, a clinically important drug interaction with herbs may occur (Figure 2). Herbal medicines that are able to modulate intestinal and hepatic CYPs and P-gp often alter the bioavailability and clearance of coadministered drugs [1]. Many commonly-used herbal medicines have been shown to alter the plasma clearance of therapeutic drugs. For example, long-term treatment of St John's wort reduces the plasma levels of co-administered cyclosporin, amitriptyline, digoxin, indinavir, nevirapine, oral contraceptives, warfarin, phenprocoumon, theophylline or

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simvastatin [32]. Garlic preparations decrease the plasma concentrations of saquinavir, but not ritonavir [1,10,33]. Consequently, drug efficacy and toxicity may be changed. Decreased blood trough concentrations of cyclosporine have been observed in patients also taking St John's wort and this was associated with transplant graft rejection observed in all of these cases [1,10].

There are few clinical studies addressing the effect of combined herbal medicines on drug efficacy due to pharmacodynamic mechanisms. Patient cases have been reported where the combined use of St John's wort and selective serotonin re-uptake inhibitors (*e.g.* sertraline and nefazodone) caused symptoms characteristic of central serotonergic syndrome in the elderly [34-38]. This syndrome is characterized by a combination of any of the following symptoms: confusion, agitation, tremor, diaphoresis, hyperreflexia, nausea, diarrhoea, lack of co-ordination, coma, flushing or rhabdomyolysis [39]. This is mainly caused by inhibitory effect of St John's wort on serotonin transporters in the central nervous system [39].

This may lead to adverse reactions that are sometimes life-threatening or lethal [40]. For example, when St John's wort was combined with oral contraceptives (ethinylestradiol/desogestrel), loperamide, or selective serotonin-reuptake inhibitors (*e.g*. sertraline, paroxetine, and nefazodone), it caused intermenstrual bleeding, delirium, or mild serotonin syndrome in some patients [41-43]. Ginseng induced mania when used concomitantly with phenelzine [44]. Ginkgo raised blood pressure when combined with a thiazide diuretic and coma when combined with trazodone [45,46]. Garlic may also enhance the effect of hypoglycaemic drugs. A woman taking a curry containing garlic and karela (*Momordica charantia*) while on

chlorpropamide therapy experienced enhanced hypoglycemic response. [47] Kava caused a semicomatose state when given concomitantly with alprazolam [48].

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The clinical importance of drug interactions with herbs depends on factors that are related to coadministered drugs (dose, dosing regimen, administration route, pharmacokinetic and therapeutic range), herbs (species, dose, dosing regimen, and administration route) and patients (genetic polymorphism, age, gender and pathological conditions) [49]. Generally, a doubling or more in drug plasma concentration has the potential for enhanced drug effects and/or appearance of adverse effects [1]. However, less marked changes may still be clinically important for drugs with a steep concentration-response relationship or a narrow therapeutic index. In most cases, the extent of drug interactions with herbs varies markedly among individuals, depending on inter-individual differences in drug metabolizing enzymes and transporters, co-medication with other drugs, age and many of other factors [18,50].

5 Approaches to identifying drugs that may interact with herbal medicines

To avoid or minimize toxic drug-herb interactions, it is important to identify drugs that can interact with herbs using proper *in vitro* and *in vivo* models in the early stages of drug development (Figure 3). Such models have very different cost, reliability and possibility for high throughput studies. Thus, these models may be used in combination to obtain enough information that is useful for providing warning and proper advice to patients in clinical practice.

There is an increasing use of *in silico* methods to study CYPs, Phase II enzymes, P-gp and their interactions with xenobiotics, including herbs [51,52]. The *in silico* methods mainly include simple rule-based modelling, structure-activity relationships, three-dimensional quantitative structure-activity relationships (QSAR) and pharmacophore modelling [51]. Knowledge of substrate specificity and regulation of the CYPs is important, as this will provide information on the possible drug interactions with herbal medicines. A structure-activity relationship analysis has indicated that a furano-*O*-naphthoquinone in tanshinone analogues isolated from the roots of *Salvia Miltiorrhiza* is essential for cytotoxicity towards cancer cells [53]. A number of *in vitro* systems are available to investigate the potential for drug interactions with herbal medicines. For metabolic interactions, the major models include subcellular fractions (liver microsomes, cytosols and homogenates), precision-cut liver slices, isolated and cultured hepatocytes or liver cell lines, and cDNA-expressed enzymes [54,55]. For transport studies, Caco-2, MDCKII cells, oocytes with highly expressed drug transporters, membrane vesicles and cDNA-expressed drug transporters are widely used. Each of these systems has advantages and limitations, and a combination of these methods will provide the most accurate information on how herbal medicines affect CYPs and P-gp. For example, cultured human hepatocytes provide cellular integrity with respect to enzyme architecture, and allow the study of Phase I and II reactions and transport [23-25]; however, some transporters and enzymes are rapidly down-regulated after isolation of hepatocytes [56].

A guidance entitled “Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro” was published by the Food and Drug Administration (FDA) of the United States (see: http://www.fda.gov). We would

propose that in common with the *in vitro* drug-drug and drug-CYP interaction studies that have been incorporated into drug development, studies on drug-herb, herb-CYP and herb-P-gP interactions should also be included in the future. The application of high throughput approaches to the study of drug-herb, herb-CYP and herb-P-gP interactions is becoming possible [57]. They are capable of handling the great number of herbal constituents (*e.g*. a single herb usually contains dozens of biologically active constituents), and have the ability to provide in vitro inhibition data as a criterion for monitoring drug-herb interactions involving CYPs or P-gp.

Animal models are widely used for the evaluation of drug-herb interactions. When drug interactions with a herb are suspected to be likely or significant in animal studies, they should be confirmed by well-designed clinical studies. Selective and specific probes should be chosen for *in vivo* CYP and P-gp studies. In some cases, pharmacogenetic studies can be incorporated to explore the interplay of genetic mutations and combined use of herbal medicines.

6 Predicting a drug's potential for interaction with herbal medicines

It should be possible to predict drug-drug interactions assuming proper principles are followed. However, unlike the prediction of metabolic drug-drug interactions where there have been a number of successes with those drugs mainly metabolized by CYPs [58], the prediction of drug interactions with herbs appears to be more problematic. Prediction is hampered by the following factors associated with the drug, herb and/or patients: a) herb medicines often contain more than 100 constituents, with unknown amounts and inhibition/induction potency for CYPs and P-gp; b) the inhibitor/induction of CYPs and P-gp by herbal medicines may by temporally

distinguishable, depending on the herb's dosing, administration route and tissues and many other factors; c) many herbal medicines are used chronically; d) considerable variability in the active contents of herbal constituents due to quality control problems; e) drug-related factors such as presence of extra-hepatic metabolism; and active transport in liver; and f) patient-related factors including age, disease, renal and hepatic functions and genetic polymorphisms of *CYP3A4* and other relevant *CYPs* and *MDR1* that encodes P-gp. All these factors will contribute to the final outcome of drug interaction with herbal medicines.

A simple qualitative prediction of the potential for drug interactions with herbal medicines can be made based on the pharmacological properties of the drugs. If a drug is a substrate for CYP3A4 and P-gp, its potential for interaction with herbal medicines would be high, in particular when the combined herbal medicines contain potent inhibitory and/or inducing components for CYPs and P-gp. Generally, it can be anticipated that a herbal medicine such as St John's wort containing potent CYP3A4 and P-gp inducers would increase the clearance and decrease the bioavailability of coadministered drugs that are primarily metabolized by CYP3A4 and transported by P-gp.

Though it is difficult to predict precisely the potential of a drug to interact with herbal medicines, useful information may be obtained from *in vitro* models such as hepatic microsomes and hepatocytes. [59,60] Generally speaking, prediction is possible when the following criteria are met: a) the clearance of the drug is predominantly through hepatic metabolism (>80%); b) the drug is not subjected to substantial Phase II reactions (*e.g.* conjugation) or other non-CYP metabolism; c) the liver is the primary

organ of metabolic clearance and d) the drug does not possess physiochemical properties that are associated with absorption problems (*i.e.* limited water solubility and low intestinal permeability).

The effects of inhibition/induction of drug metabolism on *in vivo* pharmacokinetics are highly variable and depend on a number of factors associated with the drug and combined herbal medicine and patients. The following factors determine the degree of change in plasma concentration at steady-state caused by the drug-herb interaction *in vivo* [60,61]:

- Route of administration (intravenous or oral, *i.e.*, whether the drug and herb medicine undergo significant first-pass metabolism).
- Fraction of hepatic clearance in total clearance.
- Fraction of the metabolic process subjected to inhibition/induction in total hepatic clearance.
- Unbound intrahepatic concentrations of the inhibitory or inducing components existing in combined herbal medicines.
- Unbound concentrations of the drug (*i.e.* that concentration of drug available for the hepatocytes).
- The metabolic kinetics of the drug by hepatocytes (*e.g.* K_m and V_{max}).
- The extent of active transport of the drug by P-gp and other transporters.
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7 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 [62]. 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 [63]. As such, drug interactions with herbal medicine are highly likely to be significantly under-reported and underestimated, and are probably more frequently than drug-drug interactions.

Because CYP3A4 is involved in the oxidative metabolism of over 50% of current therapeutic drugs, herb remedies, such as St John's wort, that induce this enzyme is highly likely to interact with many more drugs than previously reported [62]. 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 critical 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.

The majority of clinical trials looking at efficacy excluded patients already taking prescribed drugs and therefore did not investigate the potential interactions with combined herbal remedies. Some clinical trials, however, did include patients taking medication for hypertension, circulatory disorders, bronchial asthma and menopausal symptoms with no evidence of any interactions between them and herbs [1]. The majority of interactions identified to date involve medicines that often require regular monitoring of blood levels. However, the interaction identified with oral contraceptives, without blood monitoring, is likely to effect a large population of individuals. Given that the number of medicines that currently require monitoring is low, compared with the number of medicines on the market that are metabolized by either CYP1A2, 2C9 and 3A4, it can be anticipated that more drug interactions with herbs will be identified and reported in the future.

Since drug-herb combinations are often encountered in clinical practice and drug-herb interactions have important clinical and toxicological implications, a proper design of drugs that have minimal potential for herbal interaction has important implications in drug development [62]. It appears that the chemical properties of a drug critical for herbal interaction include (i) being a CYP substrate, (ii) being a P-gp substrate, and (iii) preponderance of CYP inducers and/or inhibitors. Thus, any newly developed drugs which are identified to be CYP and/or P-gp substrates have a potential for interactions with commonly used herbs.

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 [62]. The concept of “hard drugs” was first proposed by Ariens [64]. These drugs are non-metabolizable, excreted through either the bile or kidney with simple kinetics. Thus, their pharmacokinetics is simplified and, usually, is predictable. When these drugs are administered, the potential for interactions with combined herbal remedies will be greatly reduced.

For new drug application, its potential for CYP interactions is needed by FDA and subsequently in vitro drug-drug and drug-CYP interaction studies have been incorporated into drug development. Given that drug-herb interactions in humans are increasingly reported and fatal events are possible, studies on drug-herb, herb-CYP and herb-P-gp interactions should also be included and implemented at the early stage of drug development. With the current techniques, it is increasingly possible to identify drugs that are highly likely to interact with herbs. By screening drug candidates for possible interactions with CYPs and P-gp, it is possible to identify and eliminate such chemicals at early stages of development.

If the 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.

8 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 indexes (e.g. warfarin and digoxin) [65]. This may lead to adverse reactions that are sometimes life-threatening or lethal [40]. 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 a 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.

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.

Table 1. Drugs that interact with herbal medicines in humans.

Drugs	Interacting herb	Study type & subject No.	Interaction outcome	Possible mode of interaction	References
Acetaminophen	Garlic	BAC; 16 HV	Increased sulfation	Induction of enzyme	[66]
Alprazolam	SJW	BAC; 7 HV	↓AUC by 41%, $t_{1/2}$ by 24%; ↑ C_{max} by 15% ($P > 0.05$)	Minor induction of CYP3A4	[67]
Amitriptyline	SJW	Open BAC; 12 PTS	↓AUC (amitriptyline) by 22% and nortriptyline by 41%	Induction of CYP3A	[68]
Aspirin	Ginkgo	Case report	Spontaneous hyphema	Additive effect	[69]
Chlorpropamide	Garlic	Case report	Hypoglycemic response	Additive effect	[47]
Cyclosporine	SJW	Case report & series; 88 PT	↓blood concentration and rejection events	Induction of enzyme and PgP	[70-78]
	SJW	BAC; 11 PTS	↓AUC by 46%, C_{max} by 42%, C_{trough} by 41%, altered metabolite profiles	Induction of enzyme and PgP	[79]
Digoxin	SJW	Placebo-controlled parallel study; 25 HV	↓AUC by 25%, C_{max} by 33%, C_{trough} by 26%,	PgP induction	[80]
	Siberian ginseng	Case report; 1 PT	↑digoxin concentration	Interference with assay?	[81]
Fexofenadine	SJW	Open BAC; 12 HV	↓C_{max} by 45% and oral CL by 20% (single dose of herb)	PgP inhibition	[82]
Fluindione	Garlic	Case report	↓INR	Additive effect	[83]
Imatinib	SJW	Open crossover; 10 HV	↓AUC by 32%, C_{max} by 29%	CYP3A induction	[84]
	SJW	Open fixed-sequence; 12 HV	↓AUC by 30%, ↑CL by 42%	CYP3A induction	[85]
Indinavir	SJW	BAC; 8 HV	↓AUC by 57%, C_{trough} by 81%	Enzyme induction	[86]
	Milk Thistle	Open crossover, 10 HV	↓AUC by 9%, ↓ trough level (C_8) by 25%	Modulation of CYP3A and PgP	[87]
Irinotecan	SJW	Open BAC; 5 PTS	↓SN-38 by 42%,	Modulation of	[88]

			↓myelosuppression	PgP?	
Loperamide	SJW	Case report; 1PT	Acute delirium episode	MAO inhibition	[89]
Levodopa	Kava	Case report	↑ "off" period	Unknown	[90]
Methadone	SJW	Case series; 4 PTS	↓C_{trough} by 47%	Enzyme induction	[91]
Midazolam	SJW	BAC; 12 HV	↑oral CL by 108.9% and ↓oral bioavailability by 39.3%; ↓20% of AUC (i.v.)	Induction of CYP3A4	[92]
	SJW	BAC; 21 HV	↑1.5-fold (i.v.) and 2.7-fold (oral) of CL.	Induction of CYP3A4	[30]
Nefazodone	SJW	Case report; 1PT	Nausea, vomiting, headache	Additive effect on serotonin uptake inhibition, enzyme inhibition?	[34]
Nevirapine	SJW	Case report; 1 PT	↑CL	Induction of Enzyme and PgP	[93]
Nifedipine	SJW	BAC, 12 HV	Nifedipine: C_{max}↓38.5%, AUC↓44.9% Dehydronifedipine: C_{max}↑55.9%, AUC↑25.7%	Induction of CYP3A4	[94]
Omeprazole	SJW	12 HV, crossover	Induced metabolism	Induction of CYP2C9	[95]
Paroxetine	SJW	Case report; 1 PT	Nausea, weakness, lethargy	Additive effect on serotonin uptake inhibition, enzyme inhibition?	[35]
Oral contraceptives	SJW	Single-blind sequential, 16 HV	↓13-15% in norethindrone and ethinyl estradiol levels. ↑breakthrough bleeding	Enzyme induction	[96]
Phenelzine	SJW, ginseng	Case report	Serotonin syndrome	Additive effect	[44,66]
Phenprocoumon	SJW	Single-blind, placebo-controlled, crossover; 10 HV	↓AUC by 17.4%	Enzyme induction?	[97]
Procyclidine	Betel nut	Case reports	Severe extrapyramidal symptoms (rigidity, tremor,	Antagonism of procyclidine by	[98]

			bradykinesis)	arecoline	
Propranolol	Piperine	Open crossover; 6 HV	time to C_{max}, ↑C_{max} and AUC	CYP1A2 inhibition	[99]
Saquinavir	Garlic	Open crossover, 10 HV	↓AUC by 51%, ↓C_{8h} by 49%, ↓C_{max} by 54%	Induction of CYP3A4 and PgP	[100]
Sertraline	SJW	Case series; 5 PTS	Nausea, vomiting, anxiety, confusion, restlessness, manic episode	Additive effect on serotonin uptake inhibition, enzyme inhibition?	[34,36]
Simvastatin	SJW	Double-blind, crossover; 16 HV	↓C_{max} & AUC of simvastatin hydroxy acid	Induction of enzyme and PgP	[101]
Tacrolimus	SJW	BAC; 10 PTS	↓AUC by 57.8%	Induction of enzyme and PgP	[102]
Theophylline	Piperine	Open crossover; 6 HV	↑C_{max}, $t_{1/2}$, AUC	Inihhition of enzymes	[99]
	SJW	Case report; 1 PT	↓blood level	Enzyme induction	[103]
Tolbutamide	SJW	BAC; 12 HV	⇔AUC, CL, C_{max}, V_d, $t_{1/2\beta}$, ↑hypoglycemia episode	Additive effect?	[92]
Trazodone	Ginkgo	Case report	Coma	Unknown	[46]
Voriconazole	SJW	Controlled, open-label, 16 HV	↓AUC by 59%; ↑oral CL by 144%	Enzyme induction	[104]
Warfarin	SJW, Matricaria chamomilla	Case series; 7PTS	↓INR	Enzyme induction	[77,105]
	Garlic	Case report; 1 PT	↑INR and clotting time	Additive effect	[106]
	Donggui	Case reports; 2 PTS	↑INR and bruise	Herb as COX inhibitor	[107,108]
	Ginkgo	Case report; 1 PT	PT16.9, PTT35.5, left parietal hemorrhage	Additive effect	[109]
	Ginseng	Case report; 1 PT	↓INR to 1.5	Additive effect	[110]
	Danshen	Case reports; 3 PTS	↑INR	Additive effect	[45,107,111]

AUC = area under the plasma concentration-time curve; BAC = before and after comparison; C_{max} = maximum plasma concentration; CL = clearance; HV = Healthy volunteers; INR = internationally normalized ratio; MAO = Monoamine oxidase; PTS = Patients; SJW = St John's wort; $t_{1/2\beta}$ = elimination half-life. ↑ = Increase; ↓ = Decrease; ⇔ = Unchanged.

Figure legends

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.* 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).

Figure 2. Possible clinical outcomes when a drug interacts with combined herbal medicines. When the clearance of a drug is significantly altered, or its drug targets are identical as the herbal components, a clinically important drug interaction with herbs may occur. Combined use of herbal medicines may alter drug efficacy, leading to over- or under-treatment. Moreover, a drug-herb interaction may cause adverse reactions that may be minor, moderate, life-threatening or lethal.

Figure 3. Various approaches to identifying drugs that may interact with herbal medicines. These approaches include *in silico*, *in vitro* and *in vivo* (animal and human) models. The hierarchy shows the increased cost but decreased ability of conducting high throughput studies from *in silico* to human studies. These models are

often used in combination to obtain enough information that is useful for providing warning and proper advice to patients in clinical practice.

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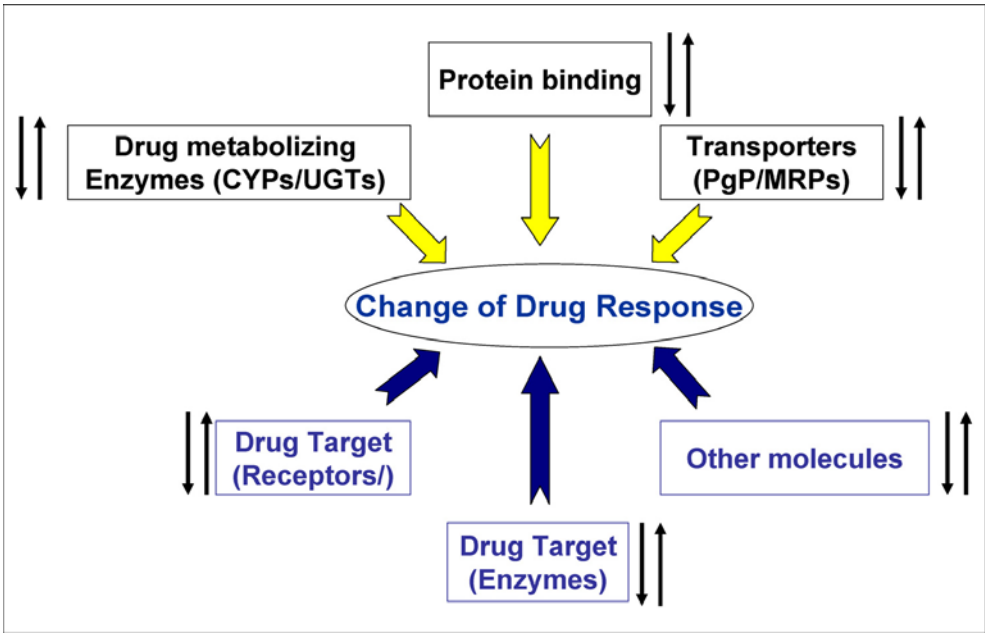
FIG 1


Protein binding
Drug metabolizing Enzymes (CYPs/UGTs)
Transporters (PgP/MRPs)
Change of Drug Response
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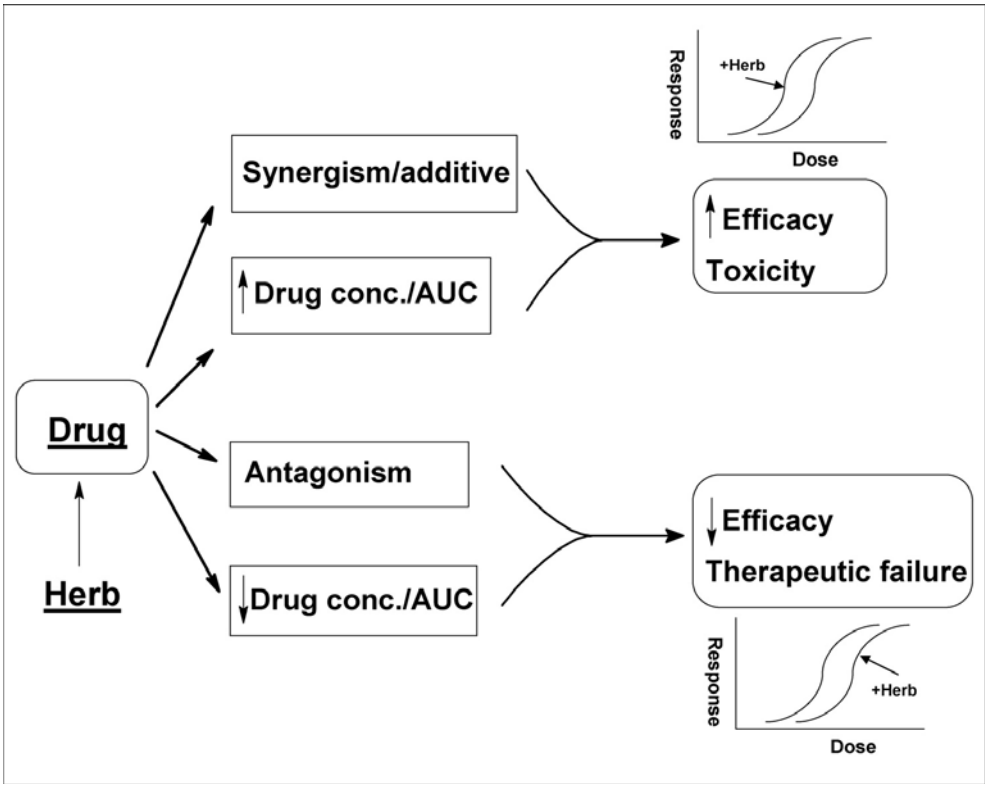
Other molecules
Drug Target (Enzymes)


Response
+Herb
Dose
Synergism/additive
Drug conc./AUC
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Toxicity
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Herb
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Therapeutic failure
Response
+Herb
Dose
FIG 2

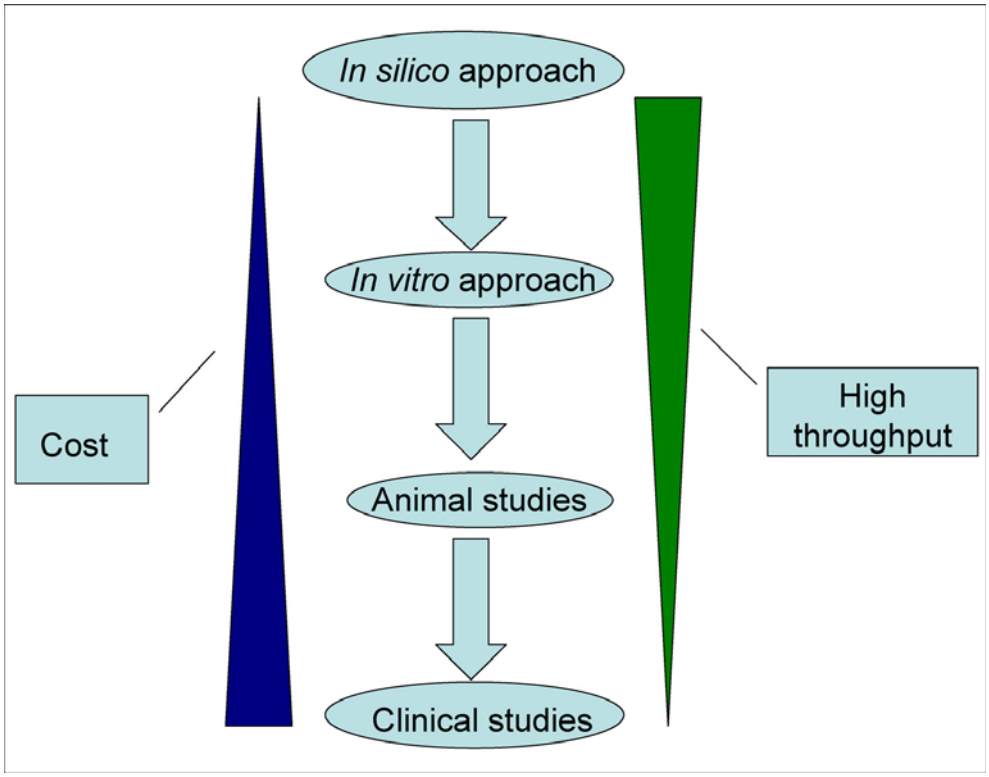
In silico approach
In vitro approach
Animal studies
Clinical studies
Cost
High throughput

FIG 3