Abstract and Introduction

Abstract

Herbal medicines including traditional Chinese medicine are becoming increasingly more popular worldwide. However, there is considerable potential for interaction between herbal components and drugs, as all herbal medicines contain a combination of potentially biologically active compounds possessing various inherent pharmacological activities, and the components of herbal products consumed are eliminated from the body by the same mechanisms that remove drugs. Indeed, many so-called conventional drugs are derived from plant sources. This article provides an update on the mechanisms and evidence of drug–herb interactions (DHIs) and genetic influences on DHIs. The rational prediction of clinically important DHIs is also discussed. Individualized and targeted drug therapy could be achieved by identifying the population most likely to be helped or harmed by drug–herb coadministration.

Introduction

Herbal medicines have long been used for a variety of ailments in Asian countries and have become more popular worldwide over the last two decades. It has been reported by the WHO that approximately 70% of the world’s population currently uses medicinal herbs as complementary or alternative medicine. There is a general belief by the public that herbal medicines are safe because of their natural origin, and consumers often take these products without consulting or informing their regular healthcare providers. However, all herbal medicines are actually a combination of potentially biologically active compounds possessing various inherent pharmacological activities, and as the metabolism of these compounds usually occurs by the same mechanisms as that of drugs, there is considerable potential for the interaction between herbal components and drugs. Herbal supplements are often used concomitantly with conventional drugs, especially in the elderly or those with chronic disease who are likely to be treated with multiple drugs, raising the increased risk of drug–herb interactions (DHIs) with potentially serious consequences, particularly for those drugs with very narrow therapeutic indices. This article aims to provide an update on the mechanisms and evidence of DHIs and discusses the rational prediction of clinically important DHIs.

Mechanism of DHIs

As with drug–drug interaction, DHIs can generally be explained by pharmacokinetic and/or pharmacodynamic mechanisms, and these interactions may result in beneficial effects, but more often, adverse reactions, such as toxicity or treatment failure, may be the result. Polymorphisms in the genes involved in the pharmacokinetic or pharmacodynamic pathways may affect the extent of the interactions in individuals.

Pharmacokinetic Mechanisms

Pharmacokinetic DHIs arise from effects on absorption, interference in distribution pattern and changes or competition in the metabolic and excretory pathways. The underlying mechanisms of pharmacokinetic DHIs often involve the inhibition or induction of intestinal and/or hepatic drug metabolizing enzymes, particularly the cytochrome P450 (CYP) enzymes and the drug transporters.

CYP Enzymes. Most herbal medicine constituents undergo Phase I and/or II metabolism, yielding inactive or active metabolites. The CYP enzymes are usually considered the most important Phase I drug metabolizing enzymes and are responsible for the oxidative metabolism of over 90% of prescribed drugs. The inhibition of CYP enzymes by herbal medicines may result in enhanced systemic exposure of drugs leading to increased toxicity, while induction of CYP enzymes could result in reduced drug concentrations leading to subtherapeutic plasma levels of the drugs with reduced drug efficacy or even treatment failure as possible clinical consequences.

The CYP3A enzyme group constitutes the largest amount of CYP enzymes and is highly expressed, not only in the...
liver but also in the small intestine. The CYP3A enzymes account for approximately 30% of hepatic CYP activity and more than 70% of intestinal CYP activity. Many pharmacokinetic DHIs have occurred through the inhibition or induction of CYP3A enzymes by herbs or natural substances, with grapefruit juice (Citrus paradise) and St John's wort (Hypericum perforatum) being two well-known examples.

Grapefruit and other citrus fruit juices are not regarded as herbs, although the peel of some citrus fruits is used in traditional Chinese medicine (TCM), but these products have provided convincing evidence of a mechanism of how natural substances can influence drug disposition. Grapefruit juice contains the furanocoumarin 6'7'-dihydroxybergamottin and the flavonoids naringenin and naringin, which produce a mechanism-based irreversible inactivation of intestinal CYP3A4, resulting in reduced presystemic metabolism and increased oral bioavailability of drugs, which are metabolized through this pathway, as originally demonstrated with felodipine. The effect seems to be confined to intestinal CYP3A4/5, but it has been proposed that very large doses of grapefruit juice could also inhibit hepatic CYP3A4.

St John's wort is one of the most popular herbal medicines used for mild depression and insomnia. It has been shown that St John's wort can reduce the plasma concentrations of CYP3A4 substrates including cyclosporine, some statins, indinavir, warfarin, amitriptyline, tacrolimus and oral contraceptives by increasing intestinal and hepatic CYP3A4 activity through activation of the nuclear receptor, pregnane X receptor (PXR). In addition, some of the interactions may be partly mediated by its inducing effect on the intestinal transporter P-glycoprotein, thereby attenuating the systemic exposure and efficacy of various drugs. Hyperforin, but not hypericin, appears to be the key activator of PXR, resulting in the induction of CYP enzymes and P-gp, and St John's wort extracts with low hyperforin content do not result in clinically relevant interactions.

Many herbal medicines, including those used in TCM, have been reported to influence the activity of CYP enzymes in in vitro studies, but the clinical relevance of these effects remain uncertain. Danshen (Salvia miltiorrhiza), dong quai or danggui (Angelica sinensis), echinacea (Echinacea purpurea), ginkgo (Ginkgo biloba), goldenseal (Hydrastis canadensis), green tea (Camellia sinensis) and milk thistle (Silybum marianum) have all been shown to inhibit various CYP enzymes in vitro and to interact with some substrate drugs in humans, in some but not all studies.

### Table 1. Effects of herbs on drug-metabolizing enzymes and transporters.

<table>
<thead>
<tr>
<th>Herbs</th>
<th>In vitro</th>
<th>Animal</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh (Actaea racemosa)</td>
<td>↓ 1A2, 2D6, 2C9 and 3A4</td>
<td>↑ CYP3A11</td>
<td>↔</td>
</tr>
<tr>
<td>Danshen (Salvia miltiorrhiza)</td>
<td>↓ CYP1A2, 2C9, 2D6 and 3A4</td>
<td>↓ CYP2C9</td>
<td>↓ CYP2C9</td>
</tr>
<tr>
<td>Dong quai (Angelica dahurica)</td>
<td>↓ CYP1A1/2, 2C9, 2D6, 2D15, 2E1 and 3A</td>
<td>↓ CYP2C, CYP3A and CYP2D1</td>
<td></td>
</tr>
<tr>
<td>Echinacea (Echinacea purpurea)</td>
<td>↓ CYP2C9, 2C19, 2D6, 3A4, P-gp and SLCO1B1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic (Allium sativum)</td>
<td>↓ CYP2C9, 2C19, 3A and P-gp</td>
<td>↑ CYP1A1, 2B1 and 3A1; ↓ CYP2E1</td>
<td>↓ CYP2E1; ↑ P-gp</td>
</tr>
<tr>
<td>Ginkgo (Ginkgo biloba)</td>
<td>↓ CYP1A2, 2B6 2C9, 2E1, 3A4 and UGT; or ↑CYP450 enzymes, transporters and UGT1A1</td>
<td>↑ CYP1A1/2, 2B, 2C9, 2E1 and 3A</td>
<td>↑ CYP2C9, 2C19 and 3A4</td>
</tr>
<tr>
<td>Ginseng (Panax ginseng)</td>
<td>↓ CYP2C9, 2C19, 3A4, 2D6 and P-gp; or ↑ P-gp</td>
<td>↑ P-gp</td>
<td>↔</td>
</tr>
<tr>
<td>Herbs</td>
<td>In vitro</td>
<td>Animal</td>
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<td>---------------------------</td>
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<td>(Actaea racemosa)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Danshen (Salvia miltiorrhiza)</td>
<td>↓ CYP1A2, 2C9, 2D6 and 3A4</td>
<td>↓ CYP2C9</td>
<td>↓ CYP2C9</td>
</tr>
<tr>
<td>Dong quai (Angelica dahurica)</td>
<td>↓ CYP1A1/2, 2C9, 2D6, 2D15, 2E1 and 3A</td>
<td>↓ CYP2C, CYP3A and CYP2D1</td>
<td>↑ CYP3A or CYP1A2</td>
</tr>
<tr>
<td>Echinacea (Echinacea purpurea)</td>
<td>↓ CYP2C9, 2C19, 2D6, 3A4, P-gp and SLCO1B1</td>
<td>↑ CYP3A1A, 2B1 and 3A1; ↓ CYP2E1</td>
<td>↑ CYP2E1; ↑ P-gp</td>
</tr>
<tr>
<td>Garlic (Allium sativum)</td>
<td>↓ CYP2C9, 2C19, 3A and P-gp</td>
<td>↑ CYP3A1, 2B1 and 3A1; ↓ CYP2E1</td>
<td>↓ CYP3A4 and SLCO2B1</td>
</tr>
<tr>
<td>Ginkgo (Ginkgo biloba)</td>
<td>↓ CYP1A2, 2B6 2C9, 2E1, 3A4 and UGT; or ↑CYP450 enzymes, transporters and UGT1A1</td>
<td>↑ CYP1A1/2, 2B, 2C9, 2E1, 3A and 3E1</td>
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</tr>
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<td>Ginseng (Panax ginseng)</td>
<td>↓ CYP2C9, 2C19, 3A4, 2D6 and P-gp; or ↑ P-gp</td>
<td>↑ P-gp</td>
<td>↔</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>↓ intestinal CYP3A4, P-gp and SLCOs</td>
<td>↓ CYP3A4 and P-gp</td>
<td>↓ CYP3A4 and SLCO2B1</td>
</tr>
<tr>
<td>(Citrus paradise)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldenseal (Hydrastis canadensis)</td>
<td>↓ CYP2C9, 2C19, 3A4 and 2D6</td>
<td>↑ CYP3A4 and P-gp</td>
<td>↓ CYP2D6 and 3A4/5</td>
</tr>
</tbody>
</table>

↑: Activation or induction; ↓: Inhibition; ↔: No effect.

Table 1. Effects of herbs on drug-metabolizing enzymes and transporters.
Interestingly, animal studies showed that the flavonoids bilobalide, ginkgolides A, B, and C and the glycosides bilobetal A and B of ginkgo (G. biloba) had no effect on the CYP3A4, 2C9, 2D6, and 3A4 activities in human liver microsomes. The standardized EGb761 extract and some of its chemical constituents (terpene trilactones and flavonoids, which account for ~30% of the chemical constituents in G. biloba extract) on the in vitro catalytic activity of CYP2B6 as assessed by the bupropion hydroxylation assay with recombinant enzyme and hepatic microsomes. Enzyme kinetic analysis indicated that G. biloba extract competitively inhibited hepatic microsomal CYP2B6-catalyzed bupropion hydroxylation (apparent Ki = 162 ± 14 µg/ml) with its flavonol aglycones being responsible for the inhibition of CYP2B6 catalytic activity, whereas the bilobalide, ginkgolides A, B, C and J and a monoglycoside and a diglycoside of kaempferol, quercetin and isorhamnetin had no effect on the hepatic microsomal bupropion hydroxylation. Interestingly, animal studies showed that feeding G. biloba extract or

| Green tea (Camellia sinensis) | ↓ CYP2C9, 2D6 and 3A4 | ↓ CYP3A4 | [12,57,150] |
| Milk thistle (Silybum marianum) | ↓ CYP3A4, 2C9, 2E1, 2D6, 2C19, 1A2 and 2A6, P-gp, UGT1A1 | ↓ CYP3A, 2C9 and P-gp | ↑ CYP3A4 and P-gp; ↓ CYP2C9 and P-gp | [151–158] |
| St John’s wort (Hypericum perforatum) | ↑ CYP3A4, 2C9 and P-gp | ↓ CYP3A4 and P-gp | [24–28] |

↑: Activation or induction; ↓: Inhibition; ↔: No effect.

However, data from the in vitro and in vivo studies on some herbs are inconsistent, suggesting the value of in vitro–in vivo extrapolation may be limited in studying some DHIs. Typically, in vitro studies use single components and high concentrations, and these effects may be modulated by poor systemic bioavailability and/or protein binding of active components in vivo. Furthermore, many in vitro studies use hepatic microsomes, which do not detect induction of metabolizing enzymes but only inhibition, whereas many herbs may possess both inducing and inhibitory effects on drug metabolizing enzymes, although in vitro studies can provide fundamental mechanistic information.<sup>[5]</sup> It is also worth noting that as herbs are regarded as food products, the quality of these products are not as adequately controlled or regulated as conventional drugs are. It is known that many factors could influence the composition of an extract, for example, its geographic origin, the stage of growth of the plant, harvest and post-harvest treatments, and so on;<sup>[4]</sup> therefore, the components of the herbal products are highly variable, and the induction and inhibition effects may vary between different batches of herbal products.

A very recent study evaluated the potential for DHIs of 50 single-herbal preparations used in TCM on CYP3A4 activity determined by the metabolism of testosterone to 6β-hydroxytestosterone in human liver microsomes.<sup>[29]</sup> The study showed that huang qin (Scutellaria baicalensis), mu dan pi (Paeonia suffruticosa), ji shiee terng (Spatholobus suberectus) and huang qi (Astragalus membranaceus) significantly inhibited the CYP3A4 activity, whereas xi yi hua (Magnolia biondii) had a moderate inhibitory effect on the activity of CYP3A4 in human liver microsomes. Further animal studies demonstrated a substantial increase of the systemic exposure to midazolam in rats treated with huang qi, mu dan pi and ji shiee terng with the area under the plasma concentration-time curve (AUC) increased by 1.8-fold to threefold, but these increases were not statistically significant, probably due to the small sample size and large variability of CYP activity in rats.

Several herbs have been reported to activate PXR and induce CYP3A expression in cell lines,<sup>[30]</sup> including kava (Piper methysticum),<sup>[31]</sup> tian xian (a TCM anticancer herbal formula)<sup>[32]</sup> and ginkgo (G. biloba),<sup>[33]</sup> but the clinical significance of these interactions has not been studied systematically. Some herbs have been reported to exhibit both induction and inhibition of CYPs in in vitro studies, which is probably related to different concentrations of the constituents within different formulations of a natural product. For example, in vitro studies have shown that G. biloba extract inhibited the major human CYPs, particularly CYP2C9.<sup>[34,35]</sup> The standardized EGB761 G. biloba extract containing 24% flavonoids, 6% terpenoids and 0.5–1% organic acids was found to strongly inhibit CYP2C9 (Ki = 14 ± 4 µg/ml), and to a lesser extent, CYP1A2 (Ki = 106 ± 24 µg/ml), CYP2E1 (Ki = 127 ± 42 µg/ml) and CYP3A4 (Ki = 155 ± 43 µg/ml) with the terpenoidic fraction inhibiting only CYP2C9 (Ki = 15 ± 6 µg/ml) and the flavonoidic fraction of EGb761 showing high inhibition of CYP2C9, CYP1A2, CYP2E1 and CYP3A4 (Ki between 4.9 and 55 µg/ml).<sup>[35]</sup>

Another in vitro study investigated the effect of G. biloba extract and some of its chemical constituents (terpene trilactones and flavonoids, which account for ~30% of the chemical constituents in G. biloba extract) on the in vitro catalytic activity of CYP2B6 as assessed by the bupropion hydroxylation assay with recombinant enzyme and hepatic microsomes. Enzyme kinetic analysis indicated that G. biloba extract competitively inhibited hepatic microsomal CYP2B6-catalyzed bupropion hydroxylation (apparent Ki was 162 ± 14 µg/ml) with its flavonol aglycones being responsible for the inhibition of CYP2B6 catalytic activity, whereas the bilobalide, ginkgolides A, B, C and J and a monoglycoside and a diglycoside of kaempferol, quercetin and isorhamnetin had no effect on the hepatic microsomal bupropion hydroxylation. Interestingly, animal studies showed that feeding G. biloba extract or

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EGb761 to rats for 10–28 days markedly increased the concentration of hepatic CYP, the expression of various CYP mRNAs and the activity of some enzymes, including CYP2B1/2 and CYP3A1, and altered the metabolism of endogenous steroids at high doses (0.5% w/w or 100 mg/kg) but not at a lower dose (10 mg/kg),[37–39] while in human subjects, no effect on the urinary steroid profile was observed after intake of EGb761 240-mg daily for 4 weeks.[38]

It has been identified that bilobalide in G. biloba extract is a major substance inducing several hepatic CYPs, including CYP1A1/2, 2B, 2C9, 2E1 and 3A in mice using a dose of 1000 mg/kg for 5 days,[40] and is responsible for the attenuated anticoagulant action of warfarin through induction of hepatic CYPs, particularly CYP2C9.[41]

However, in contrast to these rat studies, reports of G. biloba extract–drug interactions in clinical studies are inconsistent; some showed G. biloba extract (280–360 mg daily for 12–28 days) significantly reduced the drug levels of the CYP2C19 probe omeprazole,[42] the CYP2C9 probe tolbutamide and the CYP3A4 probe midazolam,[43] but many studies showed no interactions.[44–46] The inconsistent results between different clinical studies may be related to the dose, particularly of bilobalide, in the product and period of treatment with G. biloba extract.

**Uridine-diphospho-glucoronosyl-transferases.** The CYP hydrophilic conversions of xenobiotics usually make herbal compounds more susceptible to Phase II conjugative reactions, such as glucuronidation catalyzed by various uridine-diphospho-glucuronsyl-transferases (UGTs) and sulfation by sulfotransferases, generally producing molecules more amenable to biliary or renal excretion.[16,47] Glucuronidation represents the major Phase II reaction and one of the most essential detoxification pathways in humans. However, unlike the CYP-mediated DHIs, which have been extensively investigated in various studies, herbal medicine metabolism mediated by UGT enzymes and the effects of herbal extracts on UGT enzymes have not been adequately studied.[47,48] It is known that many flavonoids (e.g., quercetin and kaempferol) are substrates for UGT enzymes, and inhibitory effects of herbal extracts on UGT enzymes have been reported in some in vitro studies; therefore, for substrates metabolized mainly through glucuronidation, DHIs may occur through this pathway.[49] Although in vitro studies revealed that many commonly used herbal extracts rich in flavonoid compounds, for example, cranberry (Vaccinium macrocarpon), echinacea, ginko, green tea, hawthorn (Crataegus oxyacantha), milk thistle, St John's wort and soy isoflavones, are substrates and inhibitors of UGT enzymes,[47,50,51] some animal studies showed an inducible effect of certain herbs on UGT enzymes with increased glucuronidation of substrate drugs observed as summarized recently by Mohamed and Frye.[47]

The data on the clinical relevance of these effects is still lacking, however, and there are only three published clinical studies investigating the effects of herbal extracts (garlic [Allium sativum], ginseng and milk thistle) on the pharmacokinetics of drugs metabolized primarily by UGT enzymes, and all the three studies showed no significant interactions.[52–54] Further clinical studies are warranted to characterize the glucuronidation of herbal medicines and to determine the clinical significance of the potential interactions between herbs and the UGT substrate drugs.

Lee et al. reported that ginseng extracts significantly induced the activity of NAD(P)H dehydrogenase (quinone 1), a Phase II enzyme, in Hepa1c1c7 cells with polyacetylenes being the most active components.[55] Clinical studies are needed to verify whether ginseng extracts and components are bioavailable and induce cytoprotective enzymes in humans.

**Drug Transporters.** Drug transporters, in particular, the members of the ATP-binding cassette (ABC) and solute carrier (SLC) superfamilies, play significant roles in the absorption, distribution and elimination of many drugs. Certain herbs that interfere with drug transport may be associated with altered pharmacokinetics and efficacy of the substrate drugs.[56,57] Studies have shown that flavonoids found in fruit juices, vegetables, tea and herbal products could inhibit multiple ABC efflux transporters, including ABCB1, ABCC2 and ABCG2,[58,59] as well as the influx SLCO transporters.[60–62]

The efflux transporter P-gp (also called MDR1, gene ABCB1), which shares many common substrates and inhibitors with CYP3A enzymes,[63] is expressed at high levels in the apical membrane of the enterocytes in the intestine and thus limits the absorption of many drugs. Inhibition or induction of P-gp by herbal medicines can result in elevated or reduced drug concentrations, respectively.[64–69] As with CYP3A4, the induction of P-gp appears to be regulated by the nuclear receptor PXR. St John's wort is known to induce P-gp, and long-term consumption of St John's wort resulted in a significant decrease in the oral bioavailability of talinolol, a substrate for P-gp, associated with induction of intestinal MDR1 mRNA and P-gp in healthy volunteers.[66]
Some fruit juices, such as grapefruit juice, pomelo juice (Citrus maxima), orange juice (Citrus sinensis) and apple juice (Malus domestica), have been shown to inhibit P-gp in in vitro studies and thus may enhance oral drug bioavailability by reducing intestinal efflux transport.\cite{13} Interestingly, recent in vivo studies showed that grapefruit juice, orange juice and apple juice all markedly reduced the systemic exposure to the renin-inhibiting antihypertensive drug aliskiren (a substrate of SLCO2B1, P-gp and CYP3A4) to a similar magnitude (peak plasma concentration by ~80% and AUC by ~60%).\cite{70,71} and the mechanism of these interactions was considered to be related to the inhibition of the SLCO2B1-mediated uptake of aliskiren in the small intestine by these fruit juices. These studies suggested that the fruit juices are clinically important inhibitors of SLCO2B1.

**Alteration of Gastrointestinal Function.** Besides interactions through influence on the drug-metabolizing enzymes and drug transporters, herbal medicines may alter the absorption of concomitantly administered drugs through physical and biological interactions, for example, changes in the gastrointestinal pH, altered gastrointestinal motility and formation of insoluble herb–drug complexes in the GI tract.\cite{11,13} Herbal-induced diarrhea can result in a shorter transit time of the drug along the GI tract and thus lead to decreased drug absorption. Anthranoid-containing plants – cassia (Cassia senna), cascara (Rhamnus purshiana), rhubarb (Rheum officinale), soluble fibers, ginkgo leaf extract containing flavonoids and terpenoids, ginger (Zingiber officinale) and kava are known to increase gastrointestinal motility and may alter the absorption and pharmacokinetics of drugs taken concomitantly.\cite{1,13}

**Pharmacodynamic Mechanisms**

Herbal products contain multiple pharmacologically active phytochemicals and DHIs can occur through the additive, synergistic or antagonistic actions of herbal products with conventional medications as a result of affinities for common receptor sites or similar actions through different mechanisms.\cite{1,72} These interactions may lead to increased or decreased pharmacodynamic outcomes and may sometimes induce severe consequences.\cite{2,73} One of the major and clinically significant pharmacodynamic DHIs involves interactions between certain herbs with antiplatelet and/or anticoagulant therapies, for example, warfarin, which is discussed in detail in the section on ‘Anticoagulant/antiplatelet drug & herb interactions’. With St John's wort, which is widely used for depressive disorders, hyperforin is known to inhibit the uptake of several brain neurotransmitters, including 5-hydroxytryptamine (5-HT; serotonin) dopamine and noradrenaline and is believed to be the bioactive substance responsible for the antidepressant activity of St John's wort.\cite{1,74} Pharmacodynamic interactions may occur when St John's wort is coadministered with drugs that enhance 5-HT signaling in the brain (e.g., sertraline and paroxetine).\cite{1,74}

**Pharmacogenetics of DHIs**

Genetic variants in drug-metabolizing enzymes, transporters and drug targets may affect their activity for different substrates, and thus may influence DHIs.\cite{11,12} The concentrations of the herbal extract and the drug may determine the degree of DHI and therefore polymorphisms in drug-metabolizing enzymes and drug transporters that alter the systemic exposure to the substrate drugs or active components of herbs may affect the risk of interaction. On the other hand, when a drug has more than one metabolic pathway which is reduced or inhibited due to a poor metabolizer genotype or an inhibitor of the enzyme, an alternate pathway will be used for the metabolism of the drug, but this pathway may be more susceptible to interactions with other drugs or herbs. However, clinical evidence of this mechanism in DHIs is still lacking. The pharmacogenetic/pharmacogenomic approach may help to identify some interactions, which may be more pronounced or only occur in specific groups of subjects based on their genetic background. provides some references for clinical evidence of the implication of pharmacogenetics in DHIs. These pharmacogenetic studies examined the impact of polymorphisms in CYP enzymes, drug transporters or genes involved in the pharmacodynamic pathways of the drug on DHIs, but there appear to be no reports as yet on the effect of UGT polymorphisms on DHIs. The US FDA has recently updated the Guideline for Industry for conducting drug interaction studies, and one of the major revisions is that in addition to CYPs, UGTs should also be considered if this pathway contributes to 25% of the metabolism of the drug under evaluation.\cite{201} Therefore, future pharmacogenetic studies are required to investigate the role of UGT polymorphisms on DHIs mediated by UGTs.

**Table 2. Effect of genetic polymorphisms on herb–drug interactions.**

|---------|-------|-----------------------------------------------------------|----------------------------------------------------------|-----|

<table>
<thead>
<tr>
<th>Medication</th>
<th>Drug</th>
<th>Levels of the drug-metabolizing enzymes and drug transporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baicalin</td>
<td>Bupropion</td>
<td>Mean changes in AUC ratio tended to be lower for subjects with CYP2B6*6/<em>6 genotype compared with those with CYP2B6</em>1/*1 genotype following baicalin use, indicating baicalin induction of CYP2B6-catalyzed bupropion hydroxylation. Reduced with the variant allele [159]</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td>The AUC(_{0-\infty}) of rosvastatin decreased by approximately 42, 24 and 1.8% in SLCO1B1 <em>1b</em>1b, <em>1b</em>15 and <em>15</em>15 carriers, respectively. Reduced with the variant allele [160]</td>
</tr>
<tr>
<td>Cranberry juice</td>
<td>Warfarin</td>
<td>Cranberry significantly increased the area under the INR–time curve by 30% when administered with warfarin without altering PKs or plasma protein binding of S- or R-warfarin. Subjects with one or two copies of the variant alleles for VKORC1 had a significant reduction in S-warfarin EC(_{50}) (concentration of S-warfarin that produces 50% inhibition of prothrombin complex activity) when warfarin was coadministered with cranberry juice extract. Increased sensitivity to warfarin with the VKORC1 variant allele [161]</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Dextromethorphan</td>
<td>The AUC of dextromethorphan was increased (42%) in CYP2D6 PMs but not in extensive metabolizers. Reduced with the variant allele [143]</td>
</tr>
<tr>
<td>Garlic</td>
<td>Warfarin</td>
<td>Coadministration of garlic did not significantly alter warfarin pharmacokinetics or pharmacodynamics. However, subjects with the VKORC1 wild-type genotype showed an increase in the S-warfarin EC(_{50}) when warfarin was administered with garlic. Increased sensitivity to warfarin with the VKORC1 variant allele [161]</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Ebastine</td>
<td>Homozygous wild-types of ABCB1 3435C&gt;T but not the other genotypes showed a significant decrease in the active metabolite carebastine urinary excretion after grapefruit juice. Reduced with the variant allele [162]</td>
</tr>
<tr>
<td>Felodipine</td>
<td></td>
<td>Grapefruit juice treatment significantly increased AUC(_{0-12,h}) of felodipine by 100% which was independent of CYP3A5*3 genotype. Reduced with the variant allele [163]</td>
</tr>
<tr>
<td>Drug</td>
<td>Treatment/Interaction</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Grapefruit juice treatment</td>
<td>Significantly increased total AUC of lansoprazole in CYP2C19 PMs (*2, *3), and the total AUC ratio of lansoprazole sulfone/lansoprazole was significantly decreased in CYP2C19 homozygous extensive metabolizers (*1/*1)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>No effect of grapefruit juice</td>
<td>PK of lansoprazole in all CYP2C19 genotypes</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Omeprazole</td>
<td>Ginkgo enhanced omeprazole hydroxylation in a CYP2C19 genotype-dependent manner. The decrease was greater in CYP2C19 PMs (*2, *3) than extensive metabolizers</td>
</tr>
<tr>
<td>St John's wort</td>
<td>Gliclazide</td>
<td>Treatment with St John's wort significantly increased the apparent clearance of gliclazide which was independent of CYP2C9 genotype</td>
</tr>
<tr>
<td>Mephenytoin</td>
<td></td>
<td>St John's wort treatment significantly increased phenytoin clearance in CYP2C19 extensive metabolizers but not in PMs (*2, *3)</td>
</tr>
<tr>
<td>Nifedipine</td>
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voriconazole and the absolute increase in apparent oral clearance were smaller in CYP2C19*2 carriers than those with CYP2C19*1/*1 genotype

AUC: Area under the curve; CYP: Cytochrome P450; INR: International normalized ratio; PK: Pharmacokinetic; PM: Poor metabolizer; PXR: Pregnane X receptor.

Epigenetics of DHIs
Epigenetics refers to functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence, and the epigenetic mechanisms in mammalian cells usually involve methylation of CG dinucleotides, post-translational modifications of histone proteins and RNA interference.[75] Hsieh et al. tested the role of epigenetics in TCM through chemical–protein interactions by searching 3294 TCMs containing 48,491 chemicals and found that nearly 30% of the TCMs are potentially affecting the epigenomes and miRNA expression of human cells and 99% of government-approved TCM formulas examined are epigenome and miRNA interacting.[75] However, whether this epigenetic information can be used in predicting herb–drug interactions remains unclear at present and warrants further investigation.

Selective Clinical Evidence of DHIs
Clinical studies and case reports have identified a number of DHIs resulting from concurrent use of herbal medicines with prescription and over-the-counter drugs, particularly for those drugs with a narrow therapeutic index, for example, warfarin, digoxin, cyclosporine, tacrolimus, amitriptyline, midazolam, indinavir and irinotecan, with many of them being substrates of CYPs and/or P-gp.[24,76,77]

Anticoagulant/Antiplatelet DHIs
Drugs with anticoagulant or antiplatelet activity (e.g., warfarin, and aspirin) were frequently implicated in DHIs.[78–80] Some herbs can potentially increase the risk of spontaneous bleeding or augment the anticoagulant effects of warfarin, and these interactions can result from a combination of factors, such as intrinsic anticoagulant and antiplatelet properties of the herbs and effects on the pharmacokinetics of warfarin.[81] According to the Natural Medicines Comprehensive Database, approximately 180 dietary supplements have the potential to interact with warfarin, and more than 120 may interact with antiplatelet drugs, for example, aspirin, clopidogrel and dipyridamole.[80]

It has been reported that St John's wort significantly induced the apparent clearance of both S-and R-warfarin by 29% (95% CI: 16–46%) and 23% (95% CI: 11–37%), respectively, which in turn resulted in a significant reduction in the pharmacological effect of rac-warfarin in healthy subjects.[82] St John's wort also significantly reduced blood levels of digoxin in healthy subjects, and this interaction was dependent on the dose of the active component hyperforin.[83] These studies suggested that coadministration of St John's wort with warfarin or digoxin may result in treatment failure.

More than 60 herbal remedies have been identified with antiplatelet, anticoagulant or coagulating ability, and the bioactive compounds include polyphenols, taxanes, coumarins, saponins, fucoidans and polysaccharides, but most information relies on in vitro assays.[78] It has been shown that ginkgo has clinically relevant antiplatelet activity, and consumption of ginkgo has been reported to be associated with bleeding episodes; therefore, the concurrent use of ginkgo with antiplatelet, anticoagulant or antithrombotic agents may increase the risk of bleeding.[2] In healthy subjects, coadministration of ginkgo with cilostazol or clopidogrel did not enhance antiplatelet activity compared with the individual agents alone, but ginkgo potentiated the bleeding time prolongation effect of cilostazol.[84] However, ginkgo at recommended doses does not significantly affect clotting status, the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects,[84] and a meta-analysis did not support a higher bleeding risk associated with standardized G. biloba leaf extracts alone compared with placebo treatment.[85] A recent retrospective population-based study performed in Taiwan showed that the combination of ginkgo with antiplatelet or anticoagulants had no significant correlation to the risk of hemorrhage.[86]

Danshen has also been found to affect hemostasis in several ways, including inhibition of platelet aggregation,
interference with the extrinsic blood coagulation, antithrombin III-like activity and promotion of fibrinolytic activity. There were several published case reports of gross overanticoagulation and bleeding complications in patients receiving chronic warfarin therapy who also took dan Shen, and it is likely that some constituents of dan Shen inhibit the metabolism of warfarin through CYP2C9.\[2,87\]

Several other herbs can also potentiate the risk of bleeding such as cranberry (Vaccinium macrocarpon), dong quai, garlic (A. sativum), ginseng (Panax ginseng) and licorice (Glycyrrhiza glabra).\[2,88\] Chan et al. reported that the patients with nonvalvular atrial fibrillation treated with warfarin who consumed common herbs at least four-times per week had suboptimal anticoagulation control with warfarin compared with infrequent users.\[89\]

**HIV Medications & Herb Interactions**

Herbal medicines are commonly used in patients with HIV/AIDS, particularly in Africa and Asia.\[90\] Patients who use antiretroviral agents and herbal medicines concomitantly are at increased risk of experiencing clinically significant DHIs with most of the interactions involving pharmacokinetic mechanisms as all of the currently marketed protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates for P-gp and/or are extensively metabolized via the CYP enzymes. Several clinical studies and case reports involving pharmacokinetic interactions of herbs with antiretroviral agents have been described.\[90,91\]

St John’s wort 300-mg (standardized to 0.3% hypericin) daily for 14 days significantly reduced the AUC\(_{0-8 \text{ h}}\) of indinavir by 57% and decreased the extrapolated 8-h indinavir trough plasma concentration by 81% in healthy subjects.\[92\] A case study in five HIV-positive patients showed that chronic use of St John’s wort resulted in an increased clearance of 35% (p = 0.02), thus leading to a decreased exposure to nevirapine.\[93\] Garlic has been considered to have immune modulatory, antioxidant, antimicrobial and lipid-lowering properties and has been frequently used in patients with HIV/AIDS for enhancement of the immune system. It has been shown that administration of a garlic product for 20 days significantly reduced the steady-state mean AUC\(_{0-8 \text{ h}}\) of saquinavir by 51%, trough levels at 8 h after dosing by 49%, and the mean maximum concentrations (C\(_{\text{max}}\)) by 54% compared with baseline without garlic.\[94\] After the 10-day washout period, the AUC, trough and C\(_{\text{max}}\) values returned to 60–70% of their values at baseline. This interaction is probably through the inducing effect of garlic on P-gp rather than CYP3A4 as garlic has been found to induce human intestinal P-gp but had no effect on intestinal and hepatic CYP3A4.\[95\] However, short-term use of garlic over 4 days did not significantly alter the single-dose pharmacokinetics of ritonavir in healthy volunteers.\[96\] Interestingly, severe gastrointestinal toxicity after starting ritonavir therapy has been reported by two HIV-infected patients who were also taking garlic supplements for a long period of time, and this has been considered to be related to the inhibition effect of ritonavir on the metabolism of garlic or ritonavir potentiated the toxic effects of garlic on the intestinal tract leading to this side effect.\[97\] However, these assumptions have not been confirmed.

*E. purpurea* 500-mg, three-times per day for 28 days significantly induced CYP3A activity using midazolam as the probe, but it did not alter lopinavir–ritonavir exposure in healthy subjects, probably due to the potent CYP3A inhibitory effect of lopinavir.\[98\] in another study in 15 HIV-infected patients receiving darunavir–ritonavir (600/100-mg twice daily) for at least 4 weeks, *E. purpurea* 500 mg, four-times per day for 14 days did not affect the overall darunavir or ritonavir pharmacokinetics, but individual patients did show a small decrease in darunavir concentrations with the geometric mean ratios of darunavir coadministered with echinacea relative to that for darunavir alone for C\(_{\text{min}}\) (the concentration at the end of the dosing interval) of 0.84 (90% CI: 0.63–1.2), for 0.90 AUC\(_{0-12 \text{ h}}\) (90% CI: 0.74–1.10) and for C\(_{\text{max}}\) of 0.98 (90% CI: 0.82–1.16). Although no dose adjustment is required, monitoring darunavir concentrations on an individual basis is advised in this setting.\[99\]

**Anticancer DHIs**

Herbal medicines and TCM are increasingly used by cancer patients worldwide in conjunction with chemotherapy treatment for the anticancer properties and supportive care properties attributed to some herbs.\[100,101\] There are increasing numbers of reports on the interaction of herbal medicines with anticancer agents, but these are mostly limited to in vitro rather than clinical studies. The clinical significance and potential mechanisms of herbal interactions with anticancer drugs has been the subject of several recent reviews.\[100–104\] Many anticancer DHIs occurred through pharmacokinetic modulations which involved mainly induction or inhibition of the CYP enzymes and P-gp.\[101,104\]
In an unblinded, randomized crossover study in five cancer patients, treatment with St John's wort at 900 mg per day for 18 days decreased the plasma levels of the active metabolite of irinotecan, SN-38, by 42% (95% CI: 14–70%), and consequently, the degree of the adverse effect of myelosuppression was substantially worse in the absence of St John's wort. In healthy subjects, treatment with St John's wort 300 mg, three-times daily for 2 weeks significantly increased imatinib clearance by 43% and decreased the AUC_{0→∞} of imatinib by 30%. The elimination half-life of imatinib (12.8 vs 9.0 h) and C_{max} (2.2 µg/ml vs 1.8 µg/ml) were also significantly decreased. Similar results were reported in another study in healthy subjects with the median AUC_{0→∞}, C_{max} and the half-life of imatinib being reduced by 32, 29 and 21%, respectively, by treatment with St John's wort. These data indicate that St John's wort increases imatinib clearance by inducing the expression of CYP3A4.

Cox et al. investigated the effect of garlic supplementation (600 mg, twice daily for 12 days) on the pharmacokinetics of docetaxel (a substrate of CYP3A4 and CYP3A5) in ten women with metastatic breast cancer treated with docetaxel for 3 out of 4 weeks. They found that although garlic did not significantly affect the disposition of docetaxel in the subjects overall, the mean AUC ratio between day 1 and 15 was substantially higher in three individuals with the CYP3A4*1A/*1A genotype compared with that in the six individuals carrying the CYP3A4*3C/*3C genotype (3.74 vs 1.02), although this difference was not statistically significant. This result suggested that garlic supplementation may influence the pharmacokinetics of docetaxel in a CYP3A4 genotype-dependent manner, but further research is clearly required to verify this result and assess its clinical implications.

Immunosuppressant & Herb Interactions

Pharmacokinetic DHI s have compromised the safety and efficacy of the key immunosuppressive drugs in renal transplant patients. The two natural products, grapefruit juice and St John's wort, are known to modify the bioavailability of cyclosporine and tacrolimus, immunosuppressive drugs widely used in the prevention of organ allograft rejection.

The interaction caused by St John's wort was first described by Breidenbach et al. when they observed a drop in cyclosporine blood trough levels by a mean of 47% (range: 33–62%) in 30 patients with kidney grafts after self-medication with St John's wort and this resulted in a gradual increase in cyclosporine dosage by a mean of 46% (range: 15–115%). With discontinuation of St John's wort in these patients, cyclosporine blood levels increased markedly by a mean of 187% (range: 84–292%). No patient was reported to have any permanent consequences as a result. However, acute organ rejection in transplant patients due to a metabolic interaction of St John's wort and cyclosporine has been described in several case reports.

Grapefruit juice significantly increased the bioavailability of cyclosporine with AUC and C_{max} increase by 55 and 35%, respectively, in healthy subjects, primarily through P-gp inhibition (rather than CYP3A4 inhibition). In nine patients with autoimmune diseases stabilized on a dosage of cyclosporine, grapefruit juice produced significant increases in systemic exposure to cyclosporine and metabolite with one patient developing significant neurological side effects associated with a 68.9 and 214% increase in trough cyclosporine and metabolite concentrations, respectively, during grapefruit juice coadministration. Clinical studies in renal transplant recipients also showed that grapefruit juice induced a moderate, but significant, increase in the systemic exposure of cyclosporine.

Antidepressants & Herb Interactions

Antidepressant drugs have high potential for clinically significant interactions with St John's wort, as St John's wort itself is consumed by patients for depression, and these interactions can be through pharmacokinetic or pharmacodynamic mechanisms. A pharmacokinetic interaction between St John's wort and amitriptyline has been reported with St John's wort significantly decreasing the steady-state AUC of amitriptyline by 22% and nortriptyline by 41% in 12 patients undergoing amitriptyline treatment. Pharmacodynamic interactions have been reported when St John's wort was coadministered with several antidepressants such as nefazodone, paroxetine, sertraline and venlafaxine in some cases with serotonin syndromes being observed probably due to additive effect on 5-HT accumulation and signaling. Concurrent use of grapefruit juice for 1 week increased mean serum sertraline levels in five patients with depression with the mean (±SD) serum sertraline trough levels increased significantly from 13.7 ± 4.9 µg/l before to 20.2 ± 4.4 µg/l (p = 0.047) after administration of grapefruit juice, but larger studies are warranted to substantiate the clinical significance of this finding.

Other Clinically Relevant DHIs
St John's wort has been shown to interact in a clinically relevant manner with a number of other conventional drugs mostly via these pharmacokinetic mechanisms. These have included increases in the apparent clearance of oral contraceptives leading to breakthrough bleeding and unplanned pregnancies; it reduces the systemic exposure and the lipid-lowering efficacy of statins and influences the safety and efficacy of various drugs acting on the CNS (e.g., anesthetics, the anxyolitic drugs alprazolam, midazolam, quazepam and buspirone, the antiepileptic drugs mephenytoin, drugs for addicted patients, such as methadone and bupropion, the centrally acting muscle relaxant chlorzoxazone and the antitussive drug dextromethorphan).[27,74]

Grapefruit juice significantly increases the bioavailability of many prescription drugs, for example, felodipine, midazolam, talinolol and statins, mainly through its mechanism-based inhibition of CYP3A4.[13,110] Administration with grapefruit juice increased the plasma levels of the acid and lactone of atorvastatin, lovastatin and simvastatin by 2.5–7-fold and 3.3–16-fold, respectively, and thus may increase the risk of statin-induced myopathy, although no clinical cases appear to have been described.[120–122] Therefore, the use of these statins concomitantly with large quantities of grapefruit juice (>1 quart daily) should be avoided, particularly for lovastatin and simvastatin which usually have very low bioavailability (<5%).

### Theronostics Applications in Predicting DHIs

With the booming of combined use of herbal and conventional drugs, many active herbal components could either affect the same biotransformation pathways or exert additive, synergistic or antagonistic actions with concurrently taken drugs. Particular groups of subjects, including pregnant women, the elderly and children or those patients regularly taking herbal remedies concomitantly with drugs with narrow therapeutic windows, will be at higher risk for potential DHIs. As mentioned above, like drug–drug interactions, the extent of pharmacokinetic DHIs may also be genetically determined (.). Individualized- and targeted-drug therapy could be achieved by identifying the population most likely to be helped or harmed by herb coadministration.

### Table 2. Effect of genetic polymorphisms on herb–drug interactions.

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<tr>
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<tbody>
<tr>
<td>Baicalin</td>
<td>Bupropion</td>
<td>Mean changes in AUC ratio tended to be lower for subjects with CYP2B6*6/<em>6 genotype compared with those with CYP2B6</em>1/*1 genotype following baicalin use, indicating baicalin induction of CYP2B6-catalyzed bupropion hydroxylation</td>
<td>Reduced with the variant allele</td>
<td>[159]</td>
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<tr>
<td>-</td>
<td>Rosuvastin</td>
<td>The AUC(_{0-\infty}) of rosuvastatin decreased by approximately 42, 24 and 1.8% in SLCO1B1 <em>1b</em>1b, <em>1b</em>15 and <em>15</em>15 carriers, respectively</td>
<td>Reduced with the variant allele</td>
<td>[160]</td>
</tr>
<tr>
<td>Cranberry juice</td>
<td>Warfarin</td>
<td>Cranberry significantly increased the area under the INR–time curve by 30% when administered with warfarin without altering PKs or plasma protein binding of S- or R-warfarin. Subjects with one or two copies of the variant alleles for VKORC1 had a significant reduction in S-warfarin EC(_{50})</td>
<td>Increased sensitivity to warfarin with the VKORC1 variant allele</td>
<td>[161]</td>
</tr>
<tr>
<td><strong>Echinacea</strong></td>
<td><strong>Warfarin</strong></td>
<td><strong>AUC of dextromethorphan was increased (42%) in CYP2D6 PMs but not in extensive metabolizers</strong></td>
<td><strong>Reduced with the variant allele</strong></td>
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<tr>
<td>Garlic</td>
<td>Warfarin</td>
<td>Coadministration of garlic did not significantly alter warfarin pharmacokinetics or pharmacodynamics. However, subjects with the VKORC1 wild-type genotype showed an increase in the S-warfarin EC₅₀ when warfarin was administered with garlic</td>
<td>Increased sensitivity to warfarin with the VKORC1 variant allele</td>
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<td>Grapefruit juice</td>
<td>Ebastine</td>
<td>Homozygous wild-types of ABCB1 3435C&gt;T but not the other genotypes showed a significant decrease in the active metabolite carebastine urinary excretion after grapefruit juice</td>
<td>Reduced with the variant allele</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td></td>
<td>Grapefruit juice treatment significantly increased AUC₀₋₁₂ h of felodipine by 100% which was independent of CYP3A5*3 genotype</td>
<td>Reduced with the variant allele</td>
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<tr>
<td>Lansoprazole</td>
<td></td>
<td>Grapefruit juice treatment significantly increased total AUC of lansoprazole in CYP2C19 PMs (*2, *3), and the total AUC ratio of lansoprazole sulfone/lansoprazole was significantly decreased in CYP2C19 homozygous extensive metabolizers (*1/*1)</td>
<td>Reduced with the variant allele</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole</td>
<td></td>
<td>No effect of grapefruit juice on PK of lansoprazole in all CYP2C19 genotypes</td>
<td>Reduced with the variant allele</td>
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<td>Ginkgo</td>
<td>Omeprazole</td>
<td>Ginkgo enhanced omeprazole hydroxylation in a CYP2C19 genotype-dependent manner. The decrease was greater in CYP2C19 PMs (*2, *3) than extensive metabolizers</td>
<td>Reduced with the variant allele</td>
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<td>St John's wort</td>
<td>Gliclazide</td>
<td>Treatment with St John's wort significantly increased the apparent clearance of gliclazide which was independent of CYP2C9 genotype</td>
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<tr>
<td>Mephenytoin</td>
<td></td>
<td>St John's wort treatment significantly increased phenytoin clearance in CYP2C19 extensive metabolizers but not in PMs (*2, *3)</td>
<td>Reduced with the variant allele</td>
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<tr>
<td>Herb</td>
<td>Effect</td>
<td>Genotype Impact</td>
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<tr>
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<td>Reduced with the variant allele [169]</td>
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<td></td>
</tr>
<tr>
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<td>Reduced with the variant allele [170]</td>
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<td>Reduced with the variant allele [171]</td>
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AUC: Area under the curve; CYP: Cytochrome P450; INR: International normalized ratio; PK: Pharmacokinetic; PM: Poor metabolizer; PXR: Pregnane X receptor.

### Identifying the Population at Risk of Altered Drug Efficacy or Clearance by Herb Use

As an expensive immunosuppressant, tacrolimus in long-term use is costly, thus calcium channel blockers with CYP3A inhibitory effects such as diltiazem, which increase tacrolimus concentrations and decrease tacrolimus maintenance dosage requirement, have been widely used as tacrolimus-sparing agents in clinical practice. A similar dose- and cost-saving approach has been used with cyclosporine and diltiazem for over two decades in some countries, although there was initial skepticism among some physicians that the interaction would produce consistent effects in such a critical situation.\[123\] An effect of the ABCB1 G2677T/A polymorphism and haplotypes but not CYP3A5*3 genotype was found on cyclosporine concentrations in Chinese renal transplant patients cotreated with diltiazem in one study,\[124\] but another study found the concentration-to-dose ratios for tacrolimus taken with diltiazem but not for cyclosporine were influenced by CYP3A5*3 genotype in Asian renal transplant recipients.\[125\] Moreover, Li et al. found that the tacrolimus-sparing effect of diltiazem was very limited in subjects with the CYP3A5 nonexpresser genotype CYP3A5*3.\[126\] They suggested that an algorithm-predicted dosing schedule with the CYP3A5 genotype-guided tacrolimus–diltiazem combination would be cost saving because of reduced tacrolimus maintenance dosage in the patients identified as CYP3A5 expressers and would also reduce adverse effects of tacrolimus by improving the accuracy of the initial dose of tacrolimus and dose adjustments.

Similar conclusions may be drawn from studies with the herbal medicine *Schisandra sphenanthera* extract (Wuweizi – also used in TCM from *Schisandra chinensis*) since it has been found to significantly increase the oral bioavailability of tacrolimus, both in rats and healthy volunteers,\[127,128\] and a cell-based *in vitro* study confirmed...
that the potential mechanism was the inhibitory effects of *S. sphenanthera* extract on P-gp-mediated efflux and CYP3A-mediated metabolism of tacrolimus.\textsuperscript{127} Wuzhi tablet (a preparation of ethanolic herb extract of *S. sphenanthera*, registration number in China: Z20025766) has been prescribed concurrently with tacrolimus in China for transplant patients. Studies in rats have also shown that Wuzhi tablets have a pharmacokinetic interaction with paclitaxel when it is given orally and to a lesser extent when given intravenously.\textsuperscript{129} To our knowledge, there are no published reports on whether the interactions of *S. sphenanthera* with tacrolimus or paclitaxel are influenced by the common polymorphisms in CYP3A5 or ABCB1.

Conversely as mentioned above, St John's wort should be avoided in patients taking tacrolimus due to its inductive effects on tacrolimus metabolism associated with the risk of organ rejection as evidenced by pharmacokinetic interaction studies in healthy volunteers and renal transplant patients.\textsuperscript{130,131} However, the study in transplant patients also identified that St John's wort did not result in a pharmacokinetic interaction with mycophenolic acid.\textsuperscript{131} Likewise, whether the interaction of St John's wort and tacrolimus is dependent on CYP3A5 or ABCB1 genotype has not been reported as far as we are aware.

**Identifying the Population at Risk of Drug Adverse Effects by Herb Use**

Drug adverse effects due to DHIs are often difficult to identify because other causes of adverse events cannot always be excluded. Drugs with a narrow therapeutic index are more prone to drug adverse effects accompanied by herb use, leading to the potential of mild, moderate-to-severe or even lethal clinical consequences. DHIs related to cardiovascular medications, anticoagulants, oral hypoglycemic agents, psychiatric medications, laxatives and medications for HIV infection have been described in some recently published reviews which cited common herbal supplements and DHIs that produce adverse effects.\textsuperscript{2,132} These interactions involved both pharmacokinetic and pharmacodynamic mechanisms. However, the clinical relevance of DHIs has seldom been verified because of the lack of discern between theoretical and actual clinical safety risks.\textsuperscript{133} Despite the lack of definitive clinical data, doctor–patient communication and education on DHIs and the potential dangers should not be omitted, and disclosure of the use of complementary and alternative medicines by patients to their physicians and pharmacists should be encouraged.

**Theranostics Approaches to Predicting DHIs**

Both *in vitro* and *in vivo* studies to examine potential DHIs are frequently reported, and the approaches to evaluating DHIs have been assessed in several recent systematic reviews (Figure 1).\textsuperscript{1,74} Based on a structured assessment procedure of drug–drug interaction, Fasinu et al. divided the evidence for DHIs for clinical risk assessment into different levels according to the approaches involved.\textsuperscript{1} Clinical evidence for DHIs has also been categorized into several levels.\textsuperscript{74} The higher the level is, the more reliable the evidence for a DHI becomes, and the more likely it is for the DHIs with clinical relevance to be predicted. It was accepted that well-documented case series or case reports with the absence of other explaining factors and controlled pharmacokinetics interaction studies in humans would be a comparatively reliable evidence for clinically relevant DHIs, whereas the studies based on structure–activity relationship analysis, or those conducted using an *in vitro* platform or in animals would be less likely to be extrapolated to human studies ().

**Table 1. Effects of herbs on drug-metabolizing enzymes and transporters.**

<table>
<thead>
<tr>
<th>Herbs</th>
<th>In vitro</th>
<th>Animal</th>
<th>Clinical</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Black cohosh (<em>Actaea racemosa</em>)</td>
<td>↓ 1A2, 2D6, 2C9 and 3A4</td>
<td>↑ CYP3A11</td>
<td>↔</td>
<td>[9,134,135]</td>
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<tr>
<td>Danshen (<em>Salvia miltiorrhiza</em>)</td>
<td>↓ CYP1A2, 2C9, 2D6 and 3A4</td>
<td>↓ CYP2C9</td>
<td>↓ CYP2C9</td>
<td>[12,87,136,137]</td>
</tr>
<tr>
<td>Dong quai (<em>Angelica dahurica</em>)</td>
<td>↓ CYP1A1/2, 2C9, 2D6, 2D15, 2E1 and 3A</td>
<td>↓ CYP2C, CYP3A and CYP2D1</td>
<td>•</td>
<td>[12,138–141]</td>
</tr>
<tr>
<td>Herb</td>
<td>Effect on CYP Enzymes and Transporters</td>
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<tr>
<td>Echinacea (Echinacea purpurea)</td>
<td>↓ CYP2C9, 2C19, 2D6, 3A4, P-gp and SLCO1B1</td>
<td>[9,34,142,143]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic (Allium sativum)</td>
<td>↓ CYP2C9, 2C19, 3A and P-gp</td>
<td>[9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginkgo (Ginkgo biloba)</td>
<td>↓ CYP1A2, 2B6 2C9, 2E1, 3A4 and UGT; or ↑ CYP450 enzymes, transporters and UGT1A1</td>
<td>[12,33,35,40,42–46,144]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginseng (Panax ginseng)</td>
<td>↓ CYP2C9, 2C19, 3A4, 2D6 and P-gp; or ↑ P-gp</td>
<td>[12,68,145–147]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice (Citrus paradise)</td>
<td>↓ intestinal CYP3A4, P-gp and SLCOs</td>
<td>[12,13,20–22,70,71,110]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldenseal (Hydrastis canadensis)</td>
<td>↓ CYP2C9, 2C19, 3A4 and 2D6</td>
<td>[9,109,148,149]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green tea (Camellia sinensis)</td>
<td>↓ CYP2C9, 2D6 and 3A4</td>
<td>[12,57,150]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk thistle (Sylilbus marianum)</td>
<td>↓ CYP3A4, 2C9, 2E1, 2D6, 2C19, 1A2 and 2A6, P-gp, UGT1A1</td>
<td>[151–158]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St John’s wort (Hypericum perforatum)</td>
<td>↑ CYP3A4, 2C9 and P-gp</td>
<td>[24–28]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑: Activation or induction; ↓: Inhibition; ↔: No effect.
Methods for identifying drug–herb interactions.

CYP: Cytochrome P450; DHI: Drug–herbal interaction.

Controlled pharmacokinetic interaction studies are usually conducted in healthy volunteers rather than in patients, unless one of the drugs involved is particularly toxic, and this may have some impact on the clinical implications of the findings. The impact of pharmacogenetics and pharmacogenomics could be simultaneously taken into account by recruiting volunteers with different genotypes or haplotypes of specific genes relevant to the drugs involved (). However, whether the degree of change in the pharmacokinetics from a DHI would have a significant impact on clinical response has seldom been confirmed.

Table 2. Effect of genetic polymorphisms on herb–drug interactions.

|-------|-------|----------------------------------------------------------|----------------------------------------------------------------|-----|

Figure 1.
<table>
<thead>
<tr>
<th>Supplement</th>
<th>Drug Interactions</th>
<th>Summary</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baicalin</strong></td>
<td><strong>Bupropion</strong></td>
<td>Mean changes in AUC ratio tended to be lower for subjects with CYP2B6*6/<em>6 genotype compared with those with CYP2B6</em>1/*1 genotype following baicalin use, indicating baicalin induction of CYP2B6-catalyzed bupropion hydroxylation.</td>
<td>[159]</td>
</tr>
<tr>
<td><strong>Rosuvastatin</strong></td>
<td><strong>Cranberry juice</strong></td>
<td>The AUC(<em>{0-\infty}) of rosvustatin decreased by approximately 42, 24 and 1.8% in SLCO1B1 <em>1b</em>1b, <em>1b</em>15 and <em>15</em>15 carriers, respectively. Cranberry significantly increased the area under the INR–time curve by 30% when administered with warfarin without altering PKs or plasma protein binding of S- or R-warfarin. Subjects with one or two copies of the variant alleles for VKORC1 had a significant reduction in S-warfarin EC(</em>{50}) (concentration of S-warfarin that produces 50% inhibition of prothrombin complex activity) when warfarin was coadministered with cranberry juice extract.</td>
<td>Increased sensitivity to warfarin with the VKORC1 variant allele.</td>
</tr>
<tr>
<td><strong>Echinacea</strong></td>
<td><strong>Dextromethorphan</strong></td>
<td>The AUC of dextromethorphan was increased (42%) in CYP2D6 PMs but not in extensive metabolizers.</td>
<td>Reduced with the variant allele.</td>
</tr>
<tr>
<td><strong>Garlic</strong></td>
<td><strong>Warfarin</strong></td>
<td>Coadministration of garlic did not significantly alter warfarin pharmacokinetics or pharmacodynamics. However, subjects with the VKORC1 wild-type genotype showed an increase in the S-warfarin EC(_{50}) when warfarin was administered with garlic.</td>
<td>Increased sensitivity to warfarin with the VKORC1 variant allele.</td>
</tr>
<tr>
<td><strong>Grapefruit juice</strong></td>
<td><strong>Ebastine</strong></td>
<td>Homozygous wild-types of ABCB1 3435C&gt;T but not the other genotypes showed a significant decrease in the active metabolite carebastine urinary excretion after grapefruit juice.</td>
<td>Reduced with the variant allele.</td>
</tr>
<tr>
<td><strong>Felodipine</strong></td>
<td><strong>Grapefruit juice</strong></td>
<td>Grapefruit juice treatment significantly increased AUC(_{0-12,h}) of felodipine by 100% which was independent of CYP3A4*3 genotype.</td>
<td>Reduced with the variant allele.</td>
</tr>
<tr>
<td><strong>Lansoprazole</strong></td>
<td><strong>Grapefruit juice</strong></td>
<td>Grapefruit juice treatment significantly increased total AUC of lansoprazole in CYP2C19 PMs (*2, *3), and the total AUC ratio of lansoprazole sulfone/lansoprazole was significantly decreased in CYP2C19 homozygous extensive metabolizers (*1/*1).</td>
<td>Reduced with the variant allele.</td>
</tr>
<tr>
<td>Drug</td>
<td>Action</td>
<td>Reduced with the variant allele</td>
<td>Reference</td>
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</tr>
<tr>
<td>Lansoprazole</td>
<td>No effect of grapefruit juice on PK of lansoprazole in all CYP2C19 genotypes</td>
<td></td>
<td>[165]</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Omeprazole Ginkgo enhanced omeprazole hydroxylation in a CYP2C19 genotype-dependent manner. The decrease was greater in CYP2C19 PMs (*2, *3) than extensive metabolizers</td>
<td></td>
<td>[42]</td>
</tr>
<tr>
<td>St John's wort</td>
<td>Gliclazide Treatment with St John's wort significantly increased the apparent clearance of gliclazide which was independent of CYP2C9 genotype</td>
<td></td>
<td>[166]</td>
</tr>
<tr>
<td>St John's wort</td>
<td>Mephenytoin St John's wort treatment significantly increased phenytoin clearance in CYP2C19 extensive metabolizers but not in PMs (*2, *3)</td>
<td></td>
<td>[167]</td>
</tr>
<tr>
<td>St John's wort</td>
<td>Nifedipine After administration of St John's wort, the AUC(_0)(\infty) of nifedipine and dehydronifedipine decreased by 42.4 and 20.2% in PXR H1/H2; 47.9 and 33.0% in H2/H2; whereas for the H1/H1, the AUC(_0)(\infty) of nifedipine decreased 29.0%, but the AUC(_0)(\infty) of dehydronifedipine increased by 106.7%</td>
<td>Reduced basal transcriptional activity, but stronger induced transcriptional activity on CYP3A4 with H1/H1 compared with H1/H2 and H2/H2</td>
<td>[168]</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>St John's wort decreased the plasma concentrations of omeprazole in a CYP2C19 genotype-dependent manner</td>
<td></td>
<td>[169]</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>No effect of St John's wort on PK of repaglinide in all SLC01B1 genotypes</td>
<td></td>
<td>[170]</td>
</tr>
<tr>
<td>Talinolol</td>
<td>Subjects harboring the ABCB1 haplotype comprising 1236C&gt;T, 2677G&gt;T/A and 3435C&gt;T polymorphisms had lower intestinal MDR1 mRNA levels and showed an attenuated inductive response to St John's wort as assessed by talinolol disposition</td>
<td>Reduced with the variant allele</td>
<td>[66]</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>The AUC of voriconazole was decreased by 59% with St John's wort treatment, with a 144% increase in oral clearance of voriconazole. The baseline apparent oral clearance of voriconazole and the absolute increase in apparent oral clearance were smaller in CYP2C19<em>2 carriers than those with CYP2C19</em>1/*1 genotype</td>
<td>Reduced with the variant allele</td>
<td>[171]</td>
</tr>
</tbody>
</table>

AUC: Area under the curve; CYP: Cytochrome P450; INR: International normalized ratio; PK: Pharmacokinetic; PM: Poor metabolizer; PXR: Pregnanate X receptor.

Ideally, DHIs identified by case reports, confirmed by clinical pharmacokinetic and pharmacodynamic studies and...
mechanistically explained by *in vitro* and animal studies would have the most definitive evidence. At the same time, the complex nature of herbal products should be considered, and the main active components or extracts of the herbal medicine used in DHI studies should be well established and quantified. It would not be possible to predict DHIs with actual clinical relevance based on the conclusions drawn from the mass of published studies lacking such information, not to mention applying theranostics to this area to attempt to avoid potential clinical risk.

**Expert Commentary**

It is a common finding that few patients disclose their history of herbal and complimentary medicine consumption to their physicians. Although in most cases, there will be no clinical significance, concomitant use of herbs and conventional drugs may present with untoward events. Patients, physicians and pharmacists should be equipped with appropriate knowledge of potential DHIs as well as related policies and regulations. Researchers are encouraged to undertake prospective randomized clinical studies to assess DHIs, and use meta-analysis of prospective clinical studies to make their conclusions more relevant to the real clinical situation.

Since 1994, the Dietary Supplement Health and Education Act, serious adverse event reporting and good manufacturing practices for dietary supplements, has provided a regulatory framework to deal with adverse effects and DHIs in the USA, although there are challenges in establishing standardization for the dietary supplement industry. Moreover, herbal medicine providers, academics and the pharmaceutical and herbal medicine industries should all be informed of the potential clinical relevance of DHIs. Theranostics tools, especially emerging technologies (e.g., pharmacogenomics) to detect individual susceptibility in DHIs, should be extensively employed to provide effective translation of new scientific discoveries into safe and effective medical products. Nevertheless, there is still a long way to go before herbal supplements can be safely and efficiently used in clinical practice to avoid any potential DHI.

**Five-year View**

Considering the theranostics techniques currently available and the present level of knowledge about the mechanisms of DHIs, there is the potential to develop this area very rapidly in the next 5 years. The major pharmaceutical companies are well aware of the implications of DHIs and are beginning to consider these in the process of new drug development. As the pathways for drug metabolism and disposition are mostly identified at an early stage of drug development, many of the important drug–drug interactions and DHIs can be predicted. Furthermore, there has been considerable interest in identifying novel therapeutic agents from natural materials, and many herbal medicines have been subjected to rapid throughput screening to identify new candidate drugs with particular pharmacological actions. Such techniques could also identify the potential for DHIs with herbal compounds, but unfortunately, these results are unlikely to be publicized because of commercial pressures.

Smaller scale studies are performed in some academic centers, and the results from these will be made public, resulting in progress in identifying clinically important DHIs. However, translation from *in vitro* models to human studies is often difficult because of a lack of funding and lack of systematic coordination between academic investigators. Much of the work been carried out at at present is fragmented with little collaboration between different centers. This could be improved if funding bodies and regulatory agencies encouraged a systematic coordinated approach between centers using *in silico*, *in vitro*, animal and human studies to identify DHIs, but this is unlikely to occur. It seems unlikely that any major new DHI resulting in serious toxicity will be identified with the drugs in current use, but considering the large variation between individuals in the response to many drugs, which is partly related to genetic variation, there is considerable scope to develop the beneficial effects of DHIs to produce more reliable responses in individuals using theranostics techniques. This is exemplified by the combined use of tacrolimus with *S. sphenanthera* as described above. This cost-saving combination may well have a pharmacogenetic component and as this has only been described quite recently,[127] there is considerable scope for other herb–drug combinations to be developed for various beneficial effects.

Overall, we predict that there will be considerable progress in this field in the next 5 years, and the majority of significantly harmful DHIs will have been identified and will be potentially avoidable. Some of these are likely to have a pharmacogenetic component, and genotyping individual patients may help to improve these safety considerations. However, it is most unlikely that all of the important DHIs will be identified within the next 5 years, or indeed over a much longer period, considering the vast number of herbal materials used in TCM and other herbal medicines. A
A coordinated effort involving pharmaceutical companies, academic researchers, funding bodies and regulatory agencies is needed to facilitate this work and advance this important area of theranostics.

Sidebar

Key Issues

- Herbal medicines including traditional Chinese medicine are frequently taken in combination with conventional drugs, meaning that there is considerable potential for interactions.

- Herbal extracts contain multiple chemicals, and traditional Chinese medicine usually contains multiple herbs so the possibilities for interactions increase.

- Investigation of the drug interactions with grapefruit juice and St John's wort have helped to identify common interaction mechanisms.

- Drug–herb interactions can generally be explained by pharmacokinetic and/or pharmacodynamic mechanisms.

- The drug–herb pharmacokinetic interactions often involve the inhibition or induction of intestinal and/or hepatic drug-metabolizing enzymes, particularly the cytochrome P450 enzymes and the drug transporters.

- Polymorphisms in the genes involved in the pharmacokinetic or pharmacodynamic pathways may affect the extent of the interactions in individuals.

- St John's wort has been shown to interact in a clinically relevant manner with a number of conventional drugs including cyclosporine and warfarin, mostly due to its inducing effects on the cytochrome P450s and drug transporters, resulting in treatment failure and severe consequences.

- Individualized and targeted drug therapy could be achieved by identifying the population most likely to be helped or harmed by herb–drug coadministration.

- A coordinated effort involving pharmaceutical companies, academic researchers, funding bodies and regulatory agencies is encouraged to facilitate prediction of drug–herb interactions and advance this important area of theranostics.

References


   **A very good recent review on the evidence and mechanisms of herb–drug interactions.**


   **A comprehensive review of herb–drug interactions, focusing on the pharmacokinetic pathways.**


6. Wold RS, Lopez ST, Yau CL et al. Increasing trends in elderly persons' use of nonvitamin, nonmineral dietary...


* A critical evaluation of certain herb–drug pharmacokinetic interactions reported in the scientific literature.


42. Yin OQ, Tomlinson B, Waye MM, Chow AH, Chow MS. Pharmacogenetics and herb–drug interactions:


* A good review on the current evidence of the potential for commonly used herbal supplements to modulate uridine-diphospho-glucuronosyl-transferase-mediated drug metabolism.


51. Mohamed ME, Frye RF. Inhibitory effects of commonly used herbal extracts on UDP-glucuronosyltransferase 1A4, 1A6, and 1A9 enzyme activities. Drug Metab. Dispos. 39(9), 1522–1528 (2011).


**Website**


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Papers of special note have been highlighted as:

* of interest

** of considerable interest