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Review Article

Effect of herbs for treating coronary heart disease on the CYP450 enzyme system and transporters

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Abstract: The incidence and mortality of coronary heart disease (CHD) continue to increase every year in China. It has become a serious public health concern, threatening people's health. The combination of herbs and drugs has become a common mode of treatment for various chronic diseases such as CHD and chronic lung disease. Clinical studies have shown that the combination of herbs and drugs can bring more clinical benefits in the treatment of CHD. However, safety issues caused by the interaction between herbs and drugs deserve attention. Recent findings indicate that many herbs and their active ingredients can affect the activities of cytochrome P450 enzyme system (CYP450s) and transporters related to drug metabolism, thus changing the metabolic process of combined drugs, leading to an increase or a decrease in plasma drug concentrations, finally increasing the uncertainty of clinical efficacy and the possibility of adverse events. This review aimed to discuss in detail the effect of herbs on CYP450s and/or transporters in the treatment of CHD and the potential herb-drugs interaction, thus providing the basis for the clinical rational combination of drugs.

Keywords: CHD, CYP450s, herb, herb-drug interaction, metabolism, transporters

Introduction

The total costs of health care have increased with the rapid increase in the incidence, prevalence, and case fatality rates of coronary heart disease (CHD) in China, threatening people's health [1]. Therefore, CHD has become a major public health concern. Herbs have been used for treating various diseases for thousands of years. In China, the combined use of herbs and drugs is a commonly used treatment model for CHD. Compared with monotherapy, the combination of herbs and drugs can improve clinical efficacy and the quality of life of patients with CHD [2-4]. However, safety issues caused by the combination of herbs and drugs have received increasing attention.

Many conventional drugs, such as verapamil, diltiazem, and rifampin, can affect the activity of cytochrome P450 enzyme system (CYP450s) or transporters, increase or decrease the plasma concentration of the substrate, and eventually lead to the occurrence of drug pharmacokinetic interactions. Drug pharmacokinetic interactions may reduce the efficacy of drugs, lead to treatment failure, and potentially increase the occurrence of adverse drug reactions. Recent studies have shown that many herbs and their active ingredients can also affect the metabolism of combined drugs through CYP450s and transporters.

For example, dachaihu decoction is composed of bupleuri radix (*Bupleurum falcatum* L., 6 g), pinnelliae tuber (*Pinellia ternata Breit*, 4 g), scutellariae radix (*Scutellaria baicalensis Georgi*, 3 g), paeoniae radix (*Paeonia lactiflora Pallas*, 3 g), zizyphi fructus (*Zizyphus jujuba Mill.* var. *inermis Rehder*, 3 g), aurantii fructus immaturus (*Citrus aurantium* L. var. *daidai Makino*, 2 g), zingiberis rhizoma (*Zingiber officinale Roscoe*, 1 g), and rhei rhizoma (*Rheum palmatum* L., 1 g). And it is often used in patients with hypertension and accessory symptoms or hyperlipidaemia and may be taken together with nifedipine. By inhibiting CYP3A2, dachaihu decoction can significantly increase the bioavail-

ability of nifedipine in rats, leading to dangerous consequences, such as drowsiness, bradycardia, significant hypotension, and loss of consciousness [5]. The standard *Ginkgo biloba* extract (EGb 761) contained 24% ginkgo flavone glycosides and 6% terpene lactones. When combined with the CYP1A2 substrate propranolol, it reduced the plasma concentration of propranolol by inducing CYP1A2, thus weakening the efficacy of the drug and affecting the therapeutic effect on patients [6]. Therefore, the pharmacokinetic interactions between herbs and conventional drugs through CYP450s and transporters cannot be ignored while treating CHD using integrative medicine [7].

CYP450 is a superfamily of enzymes catalyzing the phase I metabolism of many endogenous substrates, such as steroids, fatty acids, bile acids, and prostaglandins, as well as exogenous substrates such as drugs. Although CYP450 has been detected in the liver, kidney, intestine, brain, lung, and other tissues, liver CYP450 plays an important role in drug metabolism [8]. CYP450 is grouped into 17 families and many subfamilies; of these, CYP1, CYP2, and CYP3 account for about 70% of CYP450s in human liver microsomes. A drug can induce, inhibit, or be a substrate for the enzyme involved. By inducing or inhibiting CYP450s, the drug changes the activity of the enzyme, accelerates or slows down the metabolism of the enzyme substrate, and causes the drug concentrations to increase or decrease. The inhibition of CYP450s by most of these drugs is likely to cause the accumulation of drugs in the body, which is the most common cause of adverse drug reactions [9]. CYP3A4-catalyzed drug metabolism occurs for nearly 50% of drugs on the market because CYP3A4 is expressed in both the liver and the small bowel. The change in CYP3A4 activity can easily cause clinical adverse events [8, 10].

It is generally believed that the CYP450s are the main factor affecting drug interactions *in vivo*. However, a large number of studies showed that membrane transporters were also important targets of drug interactions [11]. Transporters are important functional membrane proteins or polypeptides located on the cell membrane in organisms. Based on the transport direction of the substrate, the transporters are divided into uptake and efflux transporters [12]. Uptake transporters are responsible for the uptake of exogenous substances into cells, including organic anion transporters (OATs), organic cation transporters (OCTs), organic anion transporting polypeptides (OATPs), and so on [12]. Efflux transporters belong to the ATP-binding cassette family, including mainly multidrug resistance (MDR, also known as P-gp) proteins, MDR-associated proteins (MRPs), breast cancer resistance proteins (BCRP), and so on [13]. These transporters can transport drugs and endogenous substances using the energy of ATP hydrolysis. Their main function is to transport drugs, limiting the uptake and absorption of drugs. Drugs can induce or inhibit transporters, affect the uptake and efflux of the transporter substrate, and lead to an increase or decrease in drug concentrations.

Herbs contain many biologically active ingredients. By inducing or inhibiting CYP450s and transporters, these ingredients may change the absorption, distribution, metabolism, and excretion of the combined conventional drugs, affecting the clinical efficacy and safety of the combined drugs [14-16]. Herbs are often used in combination with conventional drugs to treat CHD; however, herb-drug interaction has attracted enormous attention. This study involved a discussion on the current research progress on the metabolic interaction between herbs and drugs commonly used in the treatment of CHD through CYP450s and/or transporters, thus providing a theoretical basis for the occurrence of adverse reactions caused by metabolic interactions (**Figure 1**).

Effect of herbs on CYP450s

Effect of single herbs and their active ingredients on CYP450s

Danshen (Salvia miltiorrhiza Bge.): Danshen, a crude herb isolated from the dried root or rhizome of *salvia miltiorrhiza* bunge, is commonly used in combination with other medications such as losartan to treat cardiovascular diseases. Tanshinone IIA and salvianolic acid B are major active compounds of danshen exerting a cardioprotective effect by improving cardiac function [17].

Losartan can be metabolized into EXP3174 by CYP3A4 and CYP2C9 enzymes. The combined

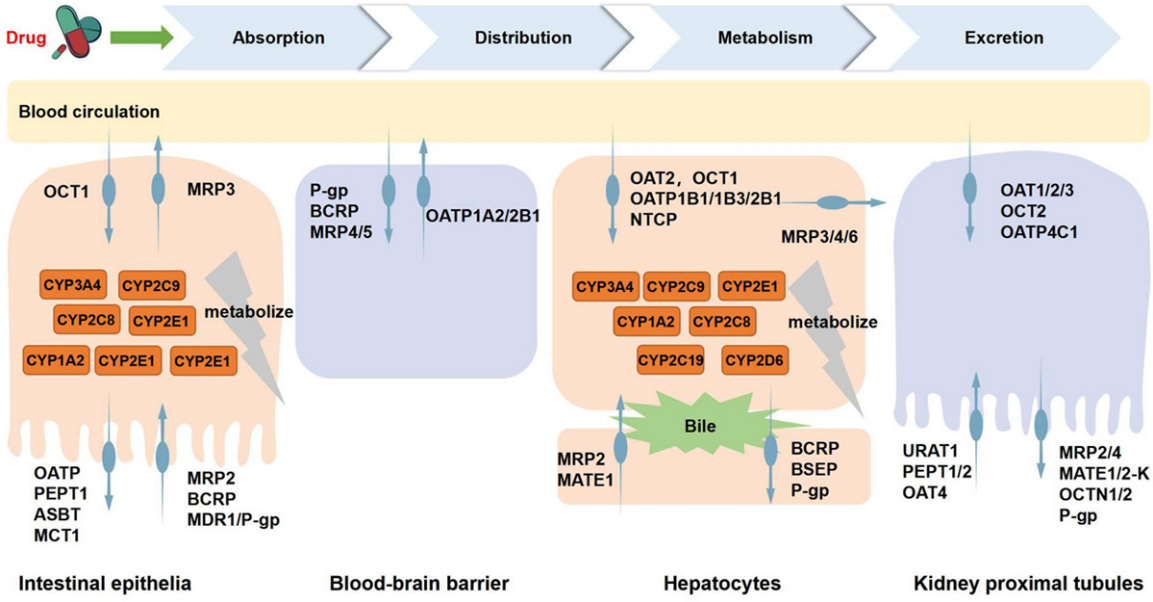

Figure 1. Pharmacokinetics of drugs in the human body involves cytochrome P450 enzyme system (CYP450s) and transporters. The enzymes involved in human drug metabolism are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. The transporters involved in human drug metabolism are divided into uptake and efflux transporters. Uptake transporters are responsible for the uptake of exogenous substances into cells, including organic anion transporters (OATs), organic cation transporters (OCTs), organic anion transporting polypeptides (OATPs), urate transporters, Na-taurocholate cotransporting polypeptide (NTCP), and peptide transporter. Efflux transporters belong to the ATP-binding cassette family, including mainly multidrug resistance (MDR, also known as P-gp) proteins, MDR-associated proteins (MRPs), breast cancer resistance proteins (BCRP), monocarboxylate transporter (MCT), bile salt export pump (BSEP), and multidrug and toxic compound extrusion.

use of 30 mg/kg salvianolic acid B or 2 mg/kg of tanshinone IIA significantly changed the oral exposure of losartan in rats compared with the control given losartan alone. The maximum plasma concentration (C_{max}), the area under the plasma concentration-time curve (AUC), the elimination half-life ($t_{1/2}$), and the mean residence time of losartan decreased from 1.4 ± 0.47 μg/mL, 7.7 ± 0.44 μg/(mL × h), 5.69 ± 2.67 h, and 5.97 ± 1.46 h to 1.22 ± 0.25 μg/mL, 5.84 ± 1.8 μg/mL h, 3.41 ± 0.61 h, and 4.11 ± 1.17 h in the presence of salvianolic acid B, and increased to 1.59 ± 0.39 μg/mL, 12.41 ± 2.29 μg/(mL × h), 8.46 ± 1.64 h, and 6.54 ± 0.98 h, respectively, in the presence of tanshinone IIA. Further studies showed that the $t_{1/2}$ change trend of losartan in rat microsomes *in vitro* was similar to that in rats. Hence, the two components of danshen, salvianolic acid B and tanshinone IIA, had different influences on the metabolism of losartan. Salvianolic acid B obviously speeded up the metabolism of losartan by inducing CYP3A4/CYP2C9 activities and expression. However, tanshinone IIA slowed down the metabolism of losartan by inhibiting CYP3A4/CYP2C9 activities [18].

Ginkgo biloba extract: Ginkgo biloba extract (GBE) exerted protective effects on the myocardial tissue by reducing the generation of oxygen-free radicals and increasing the antioxidant capacity of myocardial cells. It also had positive effects on vasodilation through endothelium-derived nitric oxide in patients with coronary artery disease [19, 20]. The administration of 4 mg/kg, 20 mg/kg, and 100 mg/kg GBE all significantly decreased the C_{max} and AUC of clopidogrel. However, pretreatment with only 100 mg/kg GBE significantly increased the C_{max} and AUC of the active metabolite of clopidogrel from 29.3 ± 2.4 ng/mL to 64.6 ± 3.8 ng/mL and 19.2 ± 4.7 ng/(mL × h) to 46.1 ± 6.2 ng/(mL × h), respectively [15]. The metabolism of clopidogrel requires the participation of CYP2C19, CYP3A4, CYP3A5 [21]. Hence, it is suggested that GBE may induce related metabolic enzymes.

Propranolol is widely used for treating cardiovascular disorders. CYP1A2 is the major enzyme metabolizing propranolol to *N*-desisopropylpropranolol [22]. When propranolol was given to rats after 10 days of continuously admin-

istered EGb 761 at 100 mg/kg, the AUC and C_{max} of propranolol significantly decreased by 38.2% and 44.4%, but the values of *N*-desisopropylpropranolol significantly increased by 128.5% and 219.6%, respectively. Studies showed that pretreatment with EGb 761 at 10 and 100 mg/kg increased the expression of CYP1A2 by 24% and 160% in the liver, and 32% and 63% in the hepatic microsomes, respectively. In summary, this study indicated that EGb 761 pretreatment decreased plasma concentrations of propranolol by its accelerated conversion to *N*-desisopropylpropranolol due to the induction of CYP1A2. In addition, it significantly induced CYP2B1/2 and CYP3A1 in a dose-dependent manner, suggesting potential interactions with substrate drugs for these two enzymes [6].

Simvastatin is lipophilic statin with a short half-life that is primarily metabolized by CYP3A4 [23]. Meanwhile, GBE administration also reduced mean simvastatin AUC_{0-24}, $AUC_{0-\infty}$, and C_{max} by 39%, 36%, and 32%, respectively, but did not cause any significant differences in the pharmacokinetics or cholesterol-lowering efficacy of simvastatin acid. However, the possibility of pharmacodynamic interaction between GBE and simvastatin *in vivo* cannot be ruled out [24].

Safflower (Carthamus tinctorius L.): Safflower is widely used in traditional Chinese medicine for treating cardiovascular disease; its main active components are hydroxysafflor yellow A, quercetin, and so on. Hydroxysafflor yellow A has been demonstrated to have good antioxidant and neuroprotective effects on myocardial and cerebral tissues [25]. Hydroxysafflor yellow A had significant inhibitory effects on CYP1A2 and CYP2C11 in rats, as evident from the pharmacokinetic profiles of the probe drugs. Furthermore, CYP3A1 enzyme activity was induced by hydroxysafflor yellow A, and the mRNA expression results were in accordance with the pharmacokinetic results. However, hydroxysafflor yellow A had no effects on rat CYP2D4 [26].

Quercetin is one of the most common plant flavonoids exhibiting a broad spectrum of properties. Most of the flavonoids can bind to serum albumin with high affinity [27]. The present study demonstrated that quercetin bound to human serum albumin with high affinity and strongly displaced warfarin from human serum albumin, suggesting that a high dose of quercetin strongly interfered with warfarin therapy. On the contrary, quercetin showed no or weaker inhibition of CYP2C9 compared with warfarin, making it very unlikely that quercetin or its metabolites could significantly inhibit the CYP2C9-mediated inactivation of warfarin [28].

N-acetyl-*p*-benzoquinoneimine (NAPQI) is a toxic metabolite of paracetamol formed primarily via the CYP2E1 metabolic pathway when administered at therapeutic doses or an overdose [29]. The co-administration of paracetamol with quercetin in rats significantly decreased the C_{max} of NAPQI: from 0.579 ± 0.134 μg/mL to 0.432 ± 0.071 μg/mL with 10 mg/kg quercetin and to 0.335 ± 0.083 μg/mL with 20 mg/kg quercetin. Quercetin (20 mg/kg) significantly decreased the AUC_{0-12} of NAPQI from 4.089 ± 0.521 to 2.452 ± 0.239 μg/(mL × h). Also, the $AUC_{0-\infty}$ of NAPQI decreased from 7.892 ± 4.262 μg/mL to 5.146 ± 1.231 μg/mL with 10 mg/kg quercetin and 4.715 ± 0.803 μg/(mL × h) with 20 mg/kg quercetin. Quercetin decreased the $t_{1/2}$ of NAPQI from 9.927 ± 8.190 h to 10.064 ± 3.132 h with 20 mg/kg quercetin. This finding suggested that quercetin might inhibit the CYP2E1-mediated metabolism of paracetamol, thereby decreasing the formation of NAPQI and protecting the liver and kidney [30]. Therefore, when safflower is combined with the CYP450 enzyme substrate, attention should be paid to the drug interaction to avoid the effect of combination on the clinical efficacy of drugs.

Silybum [Silybum marianum (L.) Gaertn.]: Modern pharmacological studies have proved that silybum has anti-inflammatory, antioxidant, and hypolipidemic effects [31]. The fruit of silybum comprises a large number of flavonoids represented by silymarin. Nifedipine was administered as a CYP3A4 test drug either alone or with silymarin to 16 healthy male volunteers. Nifedipine AUC was found to be 1.13-fold higher (90% CI, 0.97- to 1.32-fold) after administering silymarin, and C_{max} values were 0.70-fold (90% CI, 0.39- to 1.27-fold) of those of the controls, with a trend to delayed absorption after silymarin administration. However, the combined administration of silymarin did not significantly change the absorption or metabolism of nifedipine, indicating that silymarin was not an effective CYP3A4 inhibitor [32].

A standardized dry extract of *silybum marianum* at concentrations of 15 and 150 μg/mL significantly inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 activities in primary human hepatocytes and liver microsomes [33].

Silybum comprises mainly silymarin, *iso*-silymarin, and other flavonols, besides some unknown polyphenols. Silybin B was the most potent inhibitor in human liver microsomes, followed by silybin A, isosilybin B, and isosilybin A. As with human liver microsomes, silybin B was more potent than silybin A toward recombinant CYP2C9*1, recombinant CYP2C9*2, and recombinant CYP2C9*3 [34]. The inhibitory effect of monomethyl and dimethyl analogs on CYP2C9 was enhanced after the methylation of silibinin B, which was six times that of silibinin B [35].

Huangqi (Astragalus radix): Astragalus radix is a well-known herbal medicine with various biological functions. Previous studies showed that *Astragalus propinquus* inhibited CYP3A4, CYP2B6, and CYP2E1 [36, 37]. Astragaloside IV, calycosin, and formononetin are the three main bioactive compounds of *Astragalus radix* responsible for its pharmacological activities and therapeutic efficacy. Astragaloside IV not only improved the energy metabolism of cardiomyocytes but also reduced the apoptosis induced by ischemia-reperfusion [38, 39]. It had inhibitory effects on CYP3A4 and CYP2B6 in HepG2 cells [37]. Formononetin and calycosin with anti-inflammatory and antioxidant properties induced CYP3A4 in human HepG2 cells. Formononetin also induced CYP2B6 expression and inhibited CYP2E1 protein expression [37].

Ginseng (Panax ginseng C. A. Mey.): Ginseng belongs to the genus *panax* in the family araliaceae and has a long history of use in Chinese medicine. The pharmacological activities of ginseng can be attributed primarily to ginsenosides among its diverse constituents. In recent years, the effects of ginsenosides on cardiovascular disease have been explored extensively because of their intrinsic properties of controlling the production of reactive oxygen species and nitric oxide and the ability to activate various receptors in endothelial cells [40].

Total ginsenosides in the ginseng extract exhibited a concentration-dependent suppressive effect on CYP1A2 mRNA and protein levels in both mice and primary mouse hepatocytes [41]. The bacterial lipopolysaccharide (LPS) inhibited the expression of CYP450 in different species. Notably, the inhibitory effects of total ginsenosides on CYP1A2 mRNA and protein expression were further enhanced following LPS treatment [42]. Moreover, ginsenosides reversed the decrease in CYP3A11/3A4 expression in the liver of LPS-injured mice and LPS-treated HepG2 cells. In another study, γ-ray irradiation upregulated the expression of CYP1A2, CYP2B1, CYP2E1, and CYP3A4, whereas ginsenoside total saponins had an inverse agonistic action against the expression of CYP450 of rats on irradiation and decreased the expression of CYP1A2, CYP2B1, CYP2E1, and CYP3A4 [43].

Ginsenoside compound K is a rare ginsenoside from *P. ginseng*. The present study showed that ginsenoside compound K inhibited the activities of CYP2C9 and CYP3A4 in human liver microsomes (**Table 1**) [44].

Effect of compound prescription of herbs on the CYP450 enzyme system

Compound danshen dripping pill: Compound danshen dripping pill is widely used for treating CHD. A clinical study found that compound danshen dripping pill combined with clopidogrel effectively reduced the platelet aggregation rate and improved blood lipid levels and clinical symptoms in patients with CHD [45]. Clopidogrel is an inactive prodrug, and only 15% of clopidogrel is biotransformed into an active thiol metabolite. CYP3A4 and CYP2C9 in humans (CYP3A1 and CYP2C11 in rats) are involved in the biotransformation process. The combined use of compound danshen dripping pill and clopidogrel causes a substantial decrease in systemic exposure to clopidogrel in rats, with C_{max} and AUC decreasing from 464.41 to 197.31 g/L and from 1989.77 to 1441.90 hg/L, respectively, and the CL value increasing from 11.95 to 16.33 L/h/kg. At the same time, the mRNA expression and protein level of CES1 significantly decreased, and the CYP2C11 and CYP3A1 mRNA expression and protein levels significantly increased. Pharmacokinetic interactions may be the result of the induction of CYP3A1 and CYP2C11 and inhibition of CES1 by the compound danshen dripping pill [46].

Compound danshen capsule and compound danshen dropping pill have the same composi-

tion. The co-administration of multiple doses of danshen capsule increased CL/F of clopidogrel and its metabolite by 96.5% and 73.7% and Vd/F by 94.2% and 75.1%, respectively. Besides, the co-administration decreased C_{max} by 41.7% and 32.9%, respectively. The AUC decreased by 50.3% and 41.8% for clopidogrel and its active metabolite, respectively, in human volunteers. These findings suggested potential interactions for drugs that were the substrates for CYP2C9 and/or CYP3A4 when co-administered with danshen, thus providing rigorous evidence to support the recommendation that close monitoring of the International Normalized Ratio should be done in patients receiving this herb-drug combination [14]. Further studies showed that cryptotanshinone and tanshinone IIA induced the expression of CYP3A4.

CYP2C19 is one of the main metabolic enzymes of warfarin. After administration of compound danshen dripping pill in CYP4F2 C/C patients, the peak concentration of S-warfarin changed from 403.5 (161.3) ng/mL to 467.1 (216.8) ng/mL and that of total warfarin changed from 1213.2 (363.7) ng/mL to 1379.4 (459.8) ng/mL. However, no significant difference was found in VKORC1, CYP2C9*3, EPHX1, and PROC genetic groups, and no bleeding occurred. Moreover, the monitored INR values were all < 3.0 [47].

Shexiang baoxin pill: Shexiang baoxin pill can promote angiogenesis, reduce the area of myocardial infarction, and exert a protective effect on the myocardium [48, 49]. Shexiang baoxin pill promoted the enzyme activity and gene and protein expression levels of CYP3A4 in human HepG2 cells; it also enhanced the enzyme activity and gene expression levels of CYP3A1 and CYP3A2 in rats [50]. Shen [51] found that shexiang baoxin pill competitively inhibited the enzyme activities of CYP2B6 and CYP2C19 in human liver microsomes, with the IC_{50} value of 260.4 and 302.2 μg/mL, respectively, but had no induction effect on CYP3A4. The former study proved that shexiang baoxin pill had an induction effect on CYP3A4, which might be caused by the different cell types used in the study.

Danhong injection: Danhong injection is a herb injection commonly used in the treatment of cardiovascular and cerebrovascular diseases; it has shown synergistic effects when often combined with other drugs [52]. It intensively inhibits CYP2A6 with an IC_{50} value of 0.262% in human liver microsomes. In addition, it showed moderate inhibitory effects on CYP1A2, CYP2B6, CYP2B8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 with IC_{50} values of 0.793%, 0.665%, 0.445%, 1.181%, 0.649%, 0.676%, 0.917%, and 0.538%, respectively [53].

Shenmai injection: Shenmai injection, a mixture of ginseng and ophiopogonis, is one of the most popular herbal medicinal products widely used for treating cardiovascular diseases [54]. The single and multiple shenmai injection pretreatment to rats resulted in a rise of 33.8% ($P < 0.01$) and 25.6% ($P < 0.01$) in AUC for midazolam and an increase in AUC for diclofenac by 14.7% ($P < 0.05$) and 31.2% ($P < 0.01$), respectively. However, the pharmacokinetics of chlorzoxazone and theophylline in rats was not altered markedly. In addition, in rat liver microsomes, a linear mixed-type inhibitory effect of shenmai injection on the enzyme activities of CYP3A1/2, CYP2C6, and CYP1A2 was observed, with IC_{50} values of 3.3%, 2.0%, and 3.1% and K_i values of 3.8%, 1.5%, and 1.9%, respectively. These *in vivo* and *in vitro* results indicated that shenmai injection had the potential to inhibit the activities of hepatic CYP3A1/2 and CYP2C6, but might not significantly affect CYP1A2- and CYP2E1-mediated metabolism in rats [55].

Baoyuan decoction: Baoyuan decoction is a herbs prescription composed of *Astragalus*, ginseng, cinnamon, and liquorice. It has anti-inflammatory and anti-fibrotic effects [56]. It improves cardiac energy production and antioxidant capacity, and may become a treatment for myocardial hypertrophy [57]. It inhibited the gene and protein expression of CYP2C9, CYP2E1, and CYP3A4 in rats, induced the gene and protein expression of CYP1A2 and CYP2D6, but had no significant effect on the activity of CYP2C19 enzyme. Further, low-dose baoyuan decoction could inhibit the gene and protein expression of CYP2B6, while a high dose had the opposite effect. This finding provided the basis for the safe and effective use of baoyuan decoction in clinic [58].

Table 1. Effect of single herbs and their active ingredients on CYP450s

Single herbs	Active ingredients	Conventional drug	Clinical outcomes of interactions	Possible mechanism	References
Danshen	Salvianolic acid B	Losartan	C_{max}: from 1.4 ± 0.47 to 1.22 ± 0.25 μg/mL AUC: from 7.7 ± 0.44 to 5.84 ± 1.8 μg/mL h $t_{1/2}$: from 5.69 ± 2.67 to 3.41 ± 0.61 h MRT: from 5.97 ± 1.46 to 4.11 ± 1.17 h	Induction of CYP2C9, CYP3A4	[18]
	Tanshinone IIA	Losartan	C_{max}: from 1.4 ± 0.47 to 1.59 ± 0.39 μg/mL AUC: from 7.7 ± 0.44 to 12.41 ± 2.29 μg/mL h $t_{1/2}$: from 5.69 ± 2.67 to 8.46 ± 1.64 h MRT: from 5.97 ± 1.46 to 6.54 ± 0.98 h	Inhibition of CYP2C9, CYP3A4	[18]
Ginkgo biloba extract	24% Ginkgo flavone glycosides and 6% terpene lactones	Clopidogrel	C_{max}: from 29.3 ± 2.4 to 64.6 ± 3.8 ng/mL AUC: from 19.2 ± 4.7 ng/mL h to 46.1 ± 6.2 ng/mL h	Induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4	[15]
		Propranolol	C_{max}: decreased 44.4% AUC: decreased 38.2%	Induction of CYP1A2	[6]
		Simvastatin	C_{max}: decreased 32% AUC_{0-24}: decreased39% $AUC_{0-\infty}$: decreased 36%	Induction of CYP3A4	[24]
Safflower	Quercetin	warfarin	–	No or weaker inhibition of CYP2C9	[28]
		N-acetyl-p-benzoquinoneimine	C_{max}: from 0.579 ± 0.134 to 0.432 ± 0.071 μg/ml (10 mg/kg), to 0.335 ± 0.083 μg/ml (20 mg/kg) $AUC_{0-\infty}$: from 7.892 ± 4.262 to 5.146 ± 1.231 μg/ml × hr (10 mg/kg), to 4.715 ± 0.803 μg/ml × hr (20 mg/kg)	Inhibition of CYP2E1	[30]
Silybum	Silymarin	Nifedipine	C_{max}: 0.70-fold; AUC: 1.13-fold higher	Not an effective CYP3A4 Inhibitor	[32]

Table 2. Effect of compound prescription of herbs on the CYP450 enzyme system

Compound prescription of herbs	Conventional drug	Clinical outcomes of interactions	Possible mechanism	References
Compound danshen dripping pill	Clopidogrel	C_{max}: from 464.41 to 197.31 g/L AUC: from 1989.77 to 1441.90 hg/L CL: from 11.95 to 16.33 L/h/kg	Induction of CYP2C11 and CYP3A1	[46]
	Warfarin	The peak concentration: from 1213.2 to 1379.4 ng/mL	Induction of CYP2C19	[47]
Compound danshen capsule	clopidogrel	C_{max}: decreased 41.7%; AUC: decreased 50.3%	Induction of CYP2C9 and CYP3A4	[14]
Shexiang baoxin pill	–	–	Induction of CYP3A1, CYP3A2 and CYP3A4	[50]
		IC_{50}: 260.4, 302.2 μg/mL	Inhibition of CYP2B6 and CYP2C19	[51]
Danhong injection	–	IC_{50}: 0.793%, 0.262%, 0.665%, 0.445%, 1.181%, 0.649%, 0.676%, 0.917% and 0.538%	Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2B8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4	[53]
Shenmai injection	Midazolam	AUC: increased 33.8% and 25.6%	Inhibition of CYP3A1/2	[55]
	Diclofenac	AUC: increased 14.7% and 31.2%	Inhibition of CYP2C6	
Baoyuan decoction	–	–	Inhibition of CYP2C9, CYP2E1, CYP3A4 and CYP2B6 Induction of CYP1A2, CYP2D6 and CYP2B6	[58]
Dachaihu decoction	Nifedipine	AUC: increased 160.9%	Inhibition of CYP3A2	[5]

Dachaihu decoction: Dachaihu decoction is a herbal medicine preparation with an inhibitory effect on atherosclerotic plaque formation in rabbits with spontaneous familial hypercholesterolemia [59]. It is often used in combination with nifedipine to treat hypertension and accessory symptoms. When a single dose of dachaihu decoction was administered simultaneously with nifedipine in rats, the AUC of nifedipine increased to approximately 160.9% of the controls. The result demonstrated that the increase in the AUC of nifedipine was attributed to the inhibitory effect of dachaihu decoction on the intestinal and hepatic metabolism of nifedipine. However, when dachaihu decoction was administered 2 h earlier, the pharmacokinetic fates of nifedipine were similar to those in the controls, suggesting that a time gap of more than 30 min between the administration of dachaihu decoction and nifedipine might be appropriate for avoiding their interactions [5].

The catalytic abilities of rat CYP3A2 and human CYP3A4 are generally considered to be similar because rat CYP3A2 exhibits a 73% homology of the amino acid sequence, some substrate preference, and functional analogies to human CYP3A4 [60]. The difference between the metabolic inhibition by dachaihu decoction in rats and that in humans needs to be clarified by further studies. However, caution should be exercised when using dachaihu decoction with nifedipine and other calcium channel blockers undergoing extensive first-pass metabolism [61] (**Table 2**).

Effect of herbs on transporters

Effect of single herbs and its active ingredients on transporters

Danshen: Danshensu is one of the main medicinal ingredients in the water-soluble active components of danshen. After co-administration of danshensu, the pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of rosuvastatin in rats increased by about 123%, 194%, and 195%, respectively, while the CLz/F value decreased by 60%. Danshensu at concentrations of 20, 40, and 80 μmol/L reduced the uptake of rosuvastatin in hepatocytes by 3.13%, 41.15%, and 74.62%, with IC_{50} 53.04 ± 2.43 μmol/L. Finally, the lentiviral vector technology was used to construct a HEK293T cell model stably expressing OATP1B1*1a and OATP1B1*5, and explore the effect of danshensu on the uptake of rosuvastatin by HEK293T cells expressing OATP1B1*1a and OATP1B1*5. The experiment demonstrated that the inhibitory effect of danshensu on OATP1B1-mediated rosuvastatin transport was related to the OATP1B1 genotype; danshensu exerted obvious competitive inhibitory effects on the transport of mutant OATP1B1*5. When the drug concentration was 1 and 10 μmol/L, the transport of rosuvastatin to OATP1B1*5 was reduced by (39.11 ± 4.94)% and (63.61 ± 3.94)%, respectively. For wild-type OATP1B1*1a, the inhibitory effect of danshensu was lighter. Danshensu at concentrations of 1 and 10 μmol/L reduced the transport of rosuvastatin by OATP1B1*1a by (8.22 ± 2.40)% and (11.56 ± 3.04)%, respectively. Danshensu significantly affected the pharmacokinetic characteristics of rosuvastatin in rats, and this was closely related to the competitive inhibition of OATP1B1 specifically expressed in hepatocyte-mediated rosuvastatin transport [62].

In addition, in the MCF-7/PTX model of human breast cancer anti-paclitaxel cell line, salvianolic acid A could reverse paclitaxel resistance by inhibiting the expression of P-gp, MRP1, and BCRP, thereby improving the sensitivity of chemotherapy for breast cancer [63]. In the Caco-2 cell monolayer model, cryptotanshinone and dihydrotanshinone at a concentration of 25 μM reduced the efflux ratio of digoxin bidirectional transport from 12.59 to 5.25 and 5.56, respectively. The results were similar to those for verapamil. Hence, cryptotanshinone and dihydrotanshinone had an inhibitory effect on P-gp, and the two tanshinones increased the intracellular accumulation of P-gp substrate anticancer drugs doxorubicin and irinotecan [64]. Taken together, these findings suggested that salvianolic acid A, cryptotanshinone, and dihydrotanshinone could be further used for sensitizing resistant cancer cells and as an adjuvant therapy with anticancer drugs to improve their therapeutic efficacies against cancer.

Safflower: Quercetin is an effective component of not only safflower but also other herbal medicines such as ginkgo biloba and wulingzhi. Everted intestinal sacs of rats were used to study the effect of quercetin on the intestinal transport of valsartan. Experiments demonstrated that the transport of valsartan from the

serosal side to the mucosal side decreased from 53.12 ± 1.27 to 40.15 ± 0.45 μg/mL in the presence of quercetin and 53.12 ± 1.27 to 28.68 ± 0.31 μg/mL in the presence of verapamil (standard P-gp inhibitor) in 120 min. At the same time, the concentration of valsartan increased from 67.27 ± 0.02 to 70.45 ± 0.02 μg/mL in rats, and AUC increased from 199.79 ± 0.29 to 278.93 ± 0.13 μg/(mL × h). Similarly, the C_{max} and AUC_{0-t} of losartan significantly increased after the co-administration of quercetin. These results suggested that quercetin might affect the metabolism of valsartan and losartan by inhibiting P-gp [65, 66]. The aforementioned results had positive clinical significance for the rational use of P-gp inhibitors (such as quercetin) to develop new oral valsartan and losartan preparations and improve the oral bioavailability.

Quercetin could inhibit the expression of P-gp, MRP1, and MRP2 in BEL-7402 cells. Furthermore, it could be developed into an efficient natural sensitizer for resistant human hepatocellular carcinoma [67]. Rosuvastatin is a common drug for cardiovascular disease. Quercetin induced the expression of OATP1B1 and OATP2B1 in the basement membrane of hepatocytes to a certain extent so as to reduce the plasma concentration of rosuvastatin [68].

Glycyrrhiza: Glycyrrhiza is a legume perennial herb widely used and indispensable in clinic. Modern pharmacological research shows that glycyrrhetinic acid is a metabolite of *glycyrrhiza.* Membrane vesicle transport experiments showed that glycyrrhetinic had a strong inhibitory effect on MRP4 and BCRP, with IC_{50} values of 6.05 and 13.79 μM, respectively, but it exerted a weak inhibitory effect on P-gp and MRP2, with IC_{50} values of 21.22 and 44.75 μM, respectively. Combining glycyrrhetinic acid with entecavir increased the AUC of entecavir by 1.4-fold. However, when BCRP or MRP4 was knocked down, the intracellular accumulation of entecavir was significantly elevated, and the enhancement of entecavir activity by glycyrrhetinic acid disappeared. These results indicated that glycyrrhetinic acid promoted the accumulation and subcellular distribution of entecavir in hepatocytes through inhibiting MRP4 and BCRP, thus augmenting the antiviral efficiency of entecavir [69]. It had almost tenfold stronger inhibitory activity on OATP2B1 (IC_{50} of 13.0 μM) compared with glycyrrhizic acid. Moreover, it inhibited more than 60% of the OATP-mediated uptake of statins, including atorvastatin, fluvastatin, and rosuvastatin [70], These results indicated that clinically relevant drug interactions could occur between glycyrrhetinic acid and OATP2B1 substrate drugs (**Table 3**).

Effect of compound prescription of herbs on transporters

Compound danshen dripping pill: Compared with carbamazepine alone, the concentration of carbamazepine in the brain tissue of rats with refractory epilepsy was significantly lower when used alone compared with the combined use of compound danshen dripping pill and carbamazepine, indicating that compound danshen dripping pill reduced the clearance rate of carbamazepine. This change trend was basically the same as that of carbamazepine combined with verapamil, with no statistically significant difference. In rats with refractory epilepsy, the effect of compound danshen dripping pill on the concentration of carbamazepine brain drugs might be similar to that of verapamil in inhibiting P-gp. Compound danshen dripping pill improved the permeability of blood-brain barrier in rats with refractory epilepsy to carbamazepine and increased the distribution of carbamazepine in the brain [71].

Danhong injection: The network analysis showed that the t active components of danhong injection were involved in the regulation of *cyclooxygenase-1/2* and *nitric oxide synthase-2/3* target genes, and also in the regulation of platelet IIIa to improve the platelet activation process [72]. Danhong injection combined with aspirin significantly inhibited the expression of renal transporters OAT1 and OAT3 (the inhibition effect on OAT3 was stronger than that on OAT1), decreased the renal salicylic acid uptake rate, and reduced the secretion of salicylic acid in renal tubules, eventually leading to a decrease in salicylic acid excretion and an increase in drug concentrations [73]. The effect of danhong injection on OATP, NTCP, and OCT1 activity was also evaluated. Danhong injection inhibited OATP, NTCP, and OCT1 with IC_{50} of 0.85%, ≥2%, and >2%, suggesting that danhong injection had a stronger inhibitory effect on OATP in human primary hepatocytes compared with NTCP and OCT1. In addition, the

danhong injection had a concentration-dependent inhibitory effect on OATP; the effect at 2% was most remarkable [74].

Shaoyaogancao decoction: Shaoyaogancao decoction has anti-inflammatory and antioxidant effects [75]. Shaoyaogancao decoction and its main components-shaoyao (*Paeonia lactiflora* Pall.) and liquorice (*Glycyrrhiza uralensis* Fisch.)-enhanced the activity of the MDR1 promoter *in vitro* in a concentration-dependent manner and upregulated the expression of MDR1 mRNA in hPXR-transfected LS174T cells [76]. Verapamil is an effective inhibitor of P-gp. The addition of verapamil into 3H digoxin, a substrate of P-gp transport media, increased the apparent permeability of digoxin from the intestinal cavity side to the basal side by 382.1% in a Caco-2 cell monolayer of the positive absorption mode. The apparent permeability of 3H digoxin from the intestinal cavity side to the basal side decreased by 159.83%, 217.95%, and 160.26% when shaoyaogancao decoction was administered at concentrations of 50 mg/L, 250 mg/L, and 1250 mg/L, respectively, indicating that shaoyaogancao decoction inhibited P-gp, but the inhibition was less than that by verapamil [77].

Shexiang baoxin pill: Hek293-OATP1B cells, MDR1 vesicles, and BCRP vesicles were incubated with 0.5, 5, 50, and 500 μg/mL of shexiang baoxin pill. When the concentration of shexiang baoxin pill was 50 μg/mL, the uptake rate of Hek293-OATP1B cells decreased to 8.22%. The average relative uptake rate of *n*-methyl-quinidine-the probe substrate of MDR1-was not significantly reduced. Only when the concentration of shexiang baoxin pill was 500 μg/L, the uptake activity of fluorescein of BCRP probe substrate significantly reduced. This finding indicated that shexiang baoxin pill had moderate and weak inhibitory effects on human OATP1B1 and BCRP with IC_{50} of 179 μg/mL, but no significant inhibitory effect on MDRI [51].

Siwu decoction: Siwu decoction, a traditional Chinese medicinal formula with more than 1000 years of clinical history, is used to promote blood circulation and treat cardiovascular disease. The incubation of Caco-2 cells with siwu decoction induced the gene and protein expression of P-gp and enhanced the P-gp efflux function of Caco-2 cells after long-term application [78]. Furthermore, siwu decoction downregulated the protein levels of uric anionic exchanger1 and glucose transporter 9 and upregulated the protein levels of OAT1, ABCG2 (BCRP), OCT1, OCT2, OCTN1, and OCTN2 in the kidney of hyperuricemic mice [79] (**Figure 2** and **Table 4**).

Summary and prospects

Pharmacokinetic interaction involves absorption, distribution, metabolism and excretion, among which drug-drug metabolic interaction mediated by CYP450s and transporters plays a major role. With the wide application of herbs and its active ingredients in disease prevention and treatment, the herb-drug interaction deserves more consideration. These herbs, which are used to keep healthy, had been proven their safety in thousands of years of clinical use. Based on this, there is a tendency to believe that even if they were used together with conventional drugs, it should be safe. However, findings of herb-drug interaction experiments indicates that some herbs and their active ingredients can affect the metabolism of drugs by inhibiting or inducing the activity of CYP450s and transporters, thus potentially affecting the clinical efficacy and safety. Herb-drug interaction, compared with drug-drug interaction, is lacked of awareness.

The incidence and mortality of CHD continue to increase every year in China. The combination of herbs and drugs has become a common mode of treatment for CHD. In this paper, we reviewed the researches on the activities of CYP450s and transporter of herbs and their active components in the treatment of CHD in recent years, and discussed the potential herb-drug metabolic interactions, so as to provide more evidence for the rational combination of herbs and drugs in clinical use and the avoidance of adverse drug reactions.

Drug metabolic interaction is a double-edged sword. On one hand, it could be used to increase the bioavailability of drugs in order to improve clinical efficacy. On the other hand, it could lead to adverse drug reactions. The process of drug-drug metabolic interaction is quite complicated. By inducing or inhibiting CYP450s and transporters, one drug may change the absorption, distribution, metabolism, and ex-

Table 3. Effect of single herbs and their active ingredients on transporters

Single herbs	Active ingredients	Conventional drug	Clinical outcomes of interactions	Possible mechanism	References
Danshen	Danshensu	Rosuvastatin	C_{max}: increased 123%	Induction of OATP1B1	[62]
			AUC_{0-t}: increased 194%; $AUC_{0-\infty}$: increased 195%		
			CLz/F: decreased 60%		
	Salvianolic acid A	–	–	Inhibition of P-gp, MRP1 and BCRP	[63]
	Cryptotanshinone	Digoxin	The efflux ratio of digoxin bi-directional transport: from 12.59 to 5.25	Inhibition of P-gp	[64]
	Dihydrotanshinone	Digoxin	The efflux ratio of digoxin bi-directional transport: from 12.59 to 5.56	Inhibition of P-gp	
Safflower	Quercetin	Valsartan	The transport of valsartan from serosal side to mucosal side: from 53.12 ± 1.27 to 40.15 ± 0.45 μg/mL	Inhibition of P-gp	[65]
			The concentration: from 67.27 ± 0.02 to 70.45 ± 0.02 μg/mL		
			AUC: from 199.79 ± 0.29 to 278.93 ± 0.13 μg/mL/h		
		Losartan	Increased C_{max} and AUC_{0-t}	Inhibition of P-gp	[66]
		Rosuvastatin	Reduced the plasma concentration	Induction of OATP1B1 and OATP2B1	[68]
				Inhibition of P-gp, MRP1, and MRP2	[67]
Glycyrrhiza	Glycyrrhetic	Entecavir	IC_{50}: 6.05, 13.79, 21.22 and 44.75 μM AUC: increased 1.4-fold	Inhibition of MRP4, BCRP, P-gp and MRP2	[69]
		Statin	IC_{50}: 13.0 μM	Inhibition of OATP2B1	[70]

Table 4. Effect of compound prescription of herbs on the CYP450 enzyme system

Compound prescription of herbs	Conventional drug	Clinical outcomes of interactions	Possible mechanism	References
Compound danshen dripping pill	Carbamazepine	Increased the concentration and reduced the clearance rate	Inhibition of P-gp	[71]
Danhong injection	Aspirin	Increased drug concentrations	Inhibition of OAT1 and OAT3	[73]
		IC_{50}: 0.85%, ≥2% and >2%	Inhibition of OATP, NTCP and OTC1	[74]
Shaoyaogancao decoction	Digoxin	The apparent permeabilities of from the intestinal cavity side to the basal side: discreased 159.83% (50 mg/L), 217.95% (250 mg/L) and 160.26% (1250 mg/L)	Inhibition of P-gp	[77]
Shexiang baoxin pill	–	Decreased the uptake rate of Hek293-OATP1B cells to 8.22%, and IC_{50} 179 μg/mL	Inhibition of OATP1B1 and BCRP	[51]
Siwu decoction	–	Induced the gene and protein expression of P-gp and enhanced the P-gp efflux function of Caco-2 cells through long-term application	Induction of P-gp, OAT1, ABCG2, OCT1, OCT2 and OCTN1/2	[78, 79]

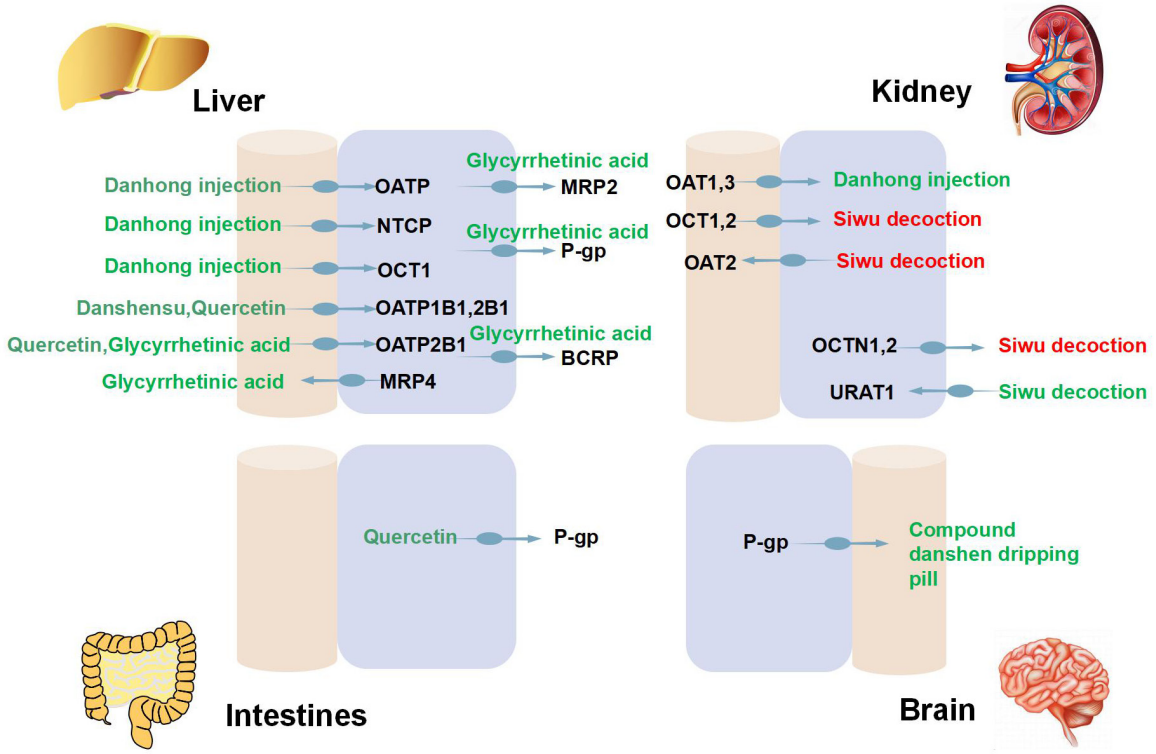

Figure 2. Effect of herbal medicines on transporters. Danshensu had an inhibitory effect on rat liver OATP1B1. Quercetin had an inhibitory effect on rat intestinal P-gp and liver OATP1B1/2B1. Glycyrrhetinic acid inhibited mouse liver MRP4, BCRP, P-gp, and MRP2. Compound Danshen dripping pills had an inhibitory effect on rat brain P-gp. Danhong injection had inhibitory effects on kidney OAT1 and OAT3 of HEK293 cells and OATP, NTCP, and OCT1 of human primary hepatocytes. Siwu decoction exerted an inhibitory effect on mouse kidney URAT1 and induced OAT2, OCT1/2, and OCTN1/2 in the kidney.

cretion of the other one, vice versa. What's more, the degree of induction or inhibition, CYP450s and transporters gene polymorphism and some other factors influence the pharmacokinetic parameters between drugs. However, due to the complexity of herbal ingredients, the herb-drug interaction is more difficult to predict. In view of the increasing use of herbs, in-depth study of herb-drug metabolic interaction is meaningful but challenging.

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Disclosure of conflict of interest

None.

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