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Metabolism-involved drug interactions with traditional Chinese medicines in cardiovascular diseases

Metabolism-involved drug interactions with traditional Chinese medicines in cardiovascular diseases

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Abstract

Herbal medicines have been widely used for the past millennia. Traditional Chinese medicine (TCM) is a major modality in Chinese medical care and has garnered global attention owing to its pharmacological effects and multi-targeted actions. The increased incidence of sequential or concurrent use of herbs and drugs in patients forces us to consider herb−drug interactions (HDIs) in this modern era. One of the main causes of HDIs is modulation of drug metabolism, in which cytochrome P450 (CYP), UDP-glucuronosyltransferase (UGT), and transporters play primary roles. In this review, we focus on *in vivo* studies of HDIs, particularly in the treatment of cardiovascular disease (CVD), which is currently the leading cause of disease-related mortality worldwide. A total of 55 HDIs are summarized, and their potential underlying mechanisms are examined. The pharmacokinetic (PK) and pharmacodynamic (PD) effects of three single herbs (Danshen, Ginseng, and Ginkgo) and four compound prescriptions (Shenmai injection, Shengmai-San, Shu-Jing-Hwo-Shiee-Tang, and Wu-Chu-Yu-Tang) are discussed. Due to the complex compositions and PK/PD profiles of TCMs, the determinants of significant HDIs have been listed to further define the pros and cons of HDIs in medical care.

Keywords: Cytochrome P450, Herb-drug interaction, Traditional Chinese medicine, Transporter, UDP-Glucuronosyltransferase

1. Introduction

Herbal products used as dietary supplements or complementary medicines have greatly expanded in the past few decades to meet health needs and for disease treatments [1]. Both the economic marketing and clinical applications of herbal medicines have increased worldwide [1,2]. In the US alone, the number of individuals using herbal medicines or dietary supplements increased from 12% in 1997 to 35% in 2015, representing 6.4 billion US dollars of marketing in 2015 [1,2]. Approximately 14% of these medicinal herbs are derived from plant species used in traditional Chinese medicine (TCM) [3]. The history of TCM applications in disease therapies has been recorded for millennia. Since nearly 20% of the world's population uses TCM as

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the main or auxiliary treatment for diseases ranging from acute to chronic and mild to severe [4], the safety of TCM use should be considered [3,5], particularly with cardiovascular diseases (CVDs) exhibiting high mortality rates.

Over the past 20 years, heart disease has remained the leading cause of death worldwide. In 2019, 17.9 million deaths due to CVDs represented 32% of deaths from all causes [6]. In addition to conventional Western drugs, 80% of patients with hypertension in Taiwan have used TCMs at least once during the course of the disease [7]. This situation is particularly likely to occur in patients who are elderly and those with chronic diseases such as CVD [8], cancer, and diabetes, because these patients generally require long-term treatment with synthetic drugs, and they are highly likely and willing to use herbal medicines for health improvement [9].

The term "herb-drug interactions" (HDIs) has appeared in the literature since the 1980s [10]. Possibly because "natural plants" are believed to be safe, the interactions between herbal medicines and prescription drugs are under-reported [11]. It was not until 2000, when Dr. Fugh-Berman's highly cited report was published, that HDI discussions became more widespread [12]. Some published reports subsequently evaluated the curative effects of the combined use of herbal and prescription drugs, and many have investigated the mechanisms involved in HDIs. One such mechanism is herb-elicited alterations of drug metabolism, in which cytochrome P450s (CYPs), UDP-glucuronosyltransferases (UGTs), and membrane transporters are the main contributors [13–16]. Research on HDIs driven by CYP regulation is the most extensive and in-depth [17], while the understanding of HDIs involving UGTs and transporters has only improved in recent years [18,19]. The importance of UGTs and transporters in HDIs has gradually increased, and some of their effects are discussed in this review.

The present report reviews the CYP/UGT/transporter-mediated interactions between TCMs and drugs that are highly prescribed for ameliorating CVD-related symptoms. The drugs discussed in this report include anticoagulants, calcium channel blockers, hypolipidemics, and therapeutic agents for bradycardia and migraine. The potential mechanisms underlying the modulation of CYPs, UGTs, and transporters are summarized. In addition, any inconsistent data on HDIs that may result from inter-study differences are presented and discussed in this review. Finally, a scheme of influencing factors is provided for further studies to establish appropriate herbal use when herbs and drugs interact.

Abbreviations

AUC	area under the plasma concentration versus time curve
CAR	constitutive androstane receptor
CVD	cardiovascular disease
CYP	cytochrome P450
HDI	herb–drug interaction
HLMs	human liver microsomes
OATP	organic anion transporting polypeptide
PD	pharmacodynamic
P-gp	P-glycoprotein
PK	pharmacokinetic
PXR	pregnane X receptor
SJHST	Shu-Jing-Hwo-Shiee-Tang
SMI	Shenmai injection
SMS	Shengmai San
TCM	traditional Chinese medicine
UGT	UDP-glucuronosyltransferase
WCYT	Wu-Chu-Yu-Tang

2. Metabolic process-mediated herb-drug interactions (HDIs)

Pharmacokinetic (PK) and pharmacodynamic (PD) interactions are the primary mechanisms underlying HDIs. Modulation of CYPs, UGTs, and transporters appears to be the key pathway in PK interactions. Here, we briefly introduce these membrane-bound enzymes/transporters and present some mechanisms that dominate HDIs.

2.1. Background of CYPs, UGTs, and transporters

2.1.1. Cytochrome P450 (CYP)

In a 2015 report on the oxidations of marketed drugs and those under development, CYPs participated in ~96% of drug oxidations [16]. In addition to drugs, CYPs catalyze ~94% of the oxidation of physiologically occurring substances and natural products. Drug-metabolizing CYP isoforms are mainly localized in cellular endoplasmic reticulum, which is the microsomal fraction after differential centrifugation of the tissue homogenate. Drug oxidation catalyzed by the microsomal CYP-dependent monooxygenase system requires the transfer of two electrons with the aid of a flavoprotein NADPH-CYP reductase (CPR) (Fig. 1). The hemoprotein cytochrome b_5 assists in the second electron transfer in the catalytic cycle of CYP [20]. In some instances, the presence of cytochrome b_5 stimulates the oxidation velocity in a reconstituted human CYP-dependent monooxygenase system

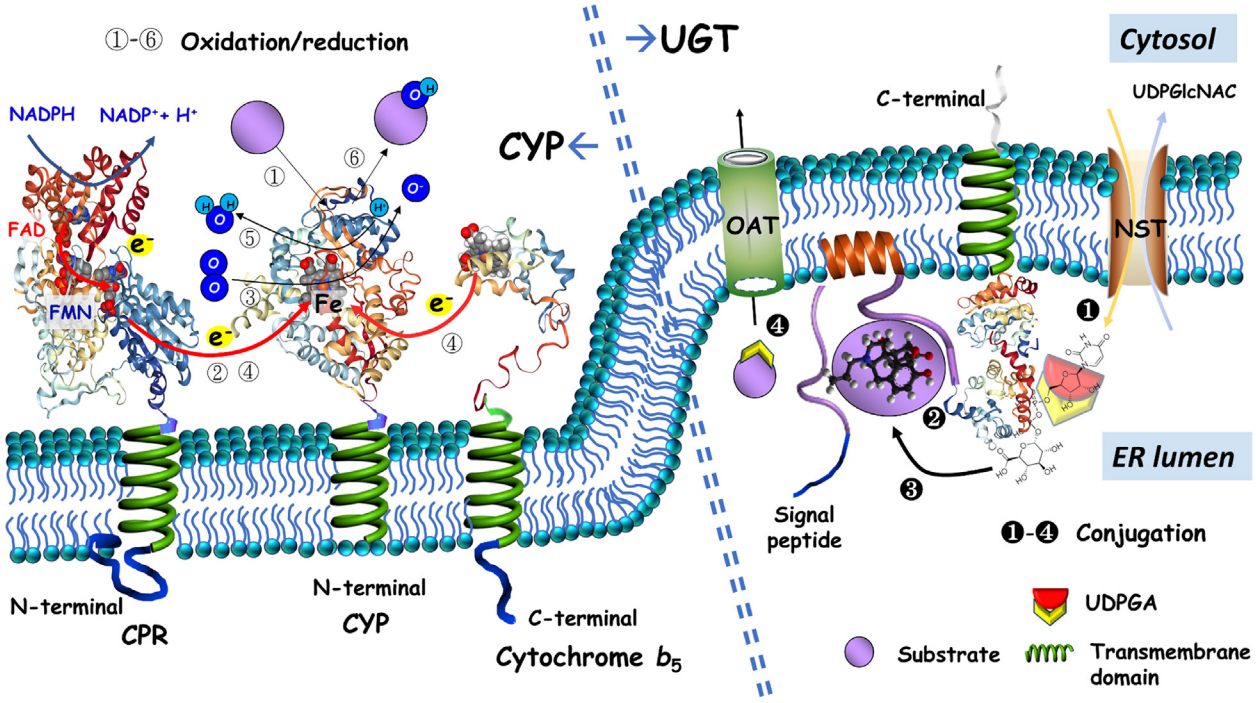

Fig. 1. The CYP- and UGT-catalyzed metabolic reactions, using the hydroxylation and naloxone glucuronidation as the representative, respectively. The hydroxylation and glucuronidation were separated by a dash line. CYP (represented by the proposed structure of CYP3A4 based on Protein Data Bank (PDB) ID: 1W0E) and UGT (represented by the proposed structure of UGT2B7) are anchored in the endoplasmic reticulum (ER) membrane with the active sites facing to the cytosolic and lumen sites, respectively. The principal features of the consensus mechanism of CYP oxidation and UGT conjugation are as demonstrated in the topologic diagrams. On the left, the representative hydroxylation catalyzed by CYP-dependent monooxygenase is divided into six steps (①–⑥). They are ① substrate binding; ② electron transfer from NADPH via CPR (the proposed structure based on PDB ID: 5FA6) to reduce ferric heme; ③ oxygen insertion; ④ a second electron transfer via CPR and cytochrome b_5 (the proposed structure based on PDB ID: 2I96) ⑤ dioxygen bond splitting and the formation of a reactive iron-oxo intermediate and release one molecule of water; ⑥ oxygen-atom transfer to the bound substrate and product dissociation [31]. On the right is the process of naloxone glucuronidation, which is divided into four steps (❶–❹). ❶ a cofactor UDP-glucuronic acid (UDPGA) is recognized by the signature motif of UGT in highly conserved C-terminal domain (the proposed structure based on PDB ID: 2O6L); ❷ aglycone substrate is attached to least conserved N-terminal domain, and UGT catalyze substrate when both UDPGA and substrate are bound at the active site; ❸ α-D-glucuronic acid is substituted to substrate by SN_2 nucleophilic reaction to form a hydrophilic β-D-glucuronide; ❹ the conjugated metabolite is pumped out from inner endoplasmic reticulum via OAT_{ER} [32].

[20,21] and in mice expressing human CYPs [22]. CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A are the main human CYP isoforms known to be important for the oxidations of cardiovascular drugs (Table 1) [23,24]. Among human tissues, the liver has the highest total CYP content and is primarily responsible for the systemic metabolism of drugs and natural products. However, intestinal first-pass metabolism is a determining factor in the restricted bioavailability of drugs, such as nifedipine and felodipine [24].

2.1.2. UDP-glucuronosyltransferase (UGT)

Glucuronidation catalyzed by UGTs is the most prevalent metabolic process in phase II reactions, and approximately 40–70% of clinical drugs and herbal medicines are metabolized by UGTs [18]. UGTs are mainly distributed in the liver and gastrointestinal tract [25] and participate in the glucuronidation of endogenous substances, such as steroids and bilirubin, as well as xenobiotics, including medicinal herbal ingredients and drugs [18,26]. The gastrointestinal tract is the main area exposed to extraneous substances after ingestion. As most TCMs are administered to patients orally, there is a considerable opportunity for TCMs to regulate intestinal UGTs under high exposure concentrations. Previous reports revealed that natural products, such as schisantherin A and schisandrin B, were present at higher levels in the intestine than in the liver and altered nifedipine bioavailability after oral administration [27,28]. In addition to changes in the liver with abundant UGT levels, the potential effects of natural products on intestinal UGT cannot be ignored in HDI assessments.

UGTs are mainly anchored to the endoplasmic reticulum on the luminal side and are partly localized to the nuclear envelope (Fig. 1). Unlike CYPs, conjugation reactions of UGTs occur in the lumen of the endoplasmic reticulum rather than on the

Table 1. CVD drug substrates of human main hepatic CYPs and the nuclear receptor/factor involved in the regulation of CYP expression.

Isoform	Drug substrate	Nuclear receptor/factor	SNP of nuclear receptor
CYP1A2	Caffeine Propranolol Theophylline Ticlopidine	AhR	Yes [47,48]
CYP2C9	Azilsartan Fluvastatin Losartan Pitavastatin Rosuvastatin Warfarin	CAR, PXR	Yes [49,50]
CYP2C19	Cilostazol Clopidogrel Phenytoin Ticlopidine	CAR, PXR	Yes [49,50]
CYP2D6	Mexiletine Metoprolol Propranolol Ticlopidine	HNF-4α	Yes [49–51]
CYP3A4	Amlodipine Apixaban Atorvastatin Cilostazol Cyclosporine A Felodipine Losartan Lovastatin Nifedipine Rivaroxaban Simvastatin Ticlopidine	PXR	Yes [49,50]

AhR, aryl hydrocarbon receptor; CAR, constitutive androstane receptor; HNF-4α, hepatocyte nuclear factor 4α; PXR, pregnane X receptor; SNP: single nucleotide polymorphism.

cytosolic side. Therefore, it is believed that glucuronidation exhibits a lag time, and the substrate must wait to pass through the cell membrane and enter the endoplasmic reticulum before conjugation can proceed [29]. Among human UGTs, UGT1 and UGT2 are the main families, containing 9 and 10 members, respectively [30]. Compared to UGT1 and UGT2, UGT3 and UGT8 were discovered later and are rarely involved in drug metabolism.

2.1.3. Transporters

Transporter-based interactions are sometimes referred to as phase III reactions, which are responsible for the absorption, distribution, and elimination of consumed substances, including drugs and herbal ingredients [33,34]. In addition to the well-known phase I and II metabolizing enzymes, transporters have been recognized to play an essential role in HDIs, resulting in significant clinical impacts [35,36]. Transporters are clusters of membrane-bound proteins that mediate the movement of endogenous and exogenous substances across biological membranes. They are broadly distributed in the body (e.g., intestines, liver, kidneys, brain, and placenta) and are divided into two superfamilies: ATP-binding cassette (ABC) and solute carrier (SLC) transporters. The ABC transporters, such as P-glycoprotein (P-gp), breast cancer resistance protein, and multidrug resistance-associated protein 2, direct substances outward from the inside to the outside of the cell using the energy derived from ATP hydrolysis [37]. In contrast, SLC proteins (e.g., organic anion transporter, organic cation transporter, and organic anion transporting polypeptide (OATP)) transport substrates in the reverse direction [35,38]. Generally, in the intestines and liver, ABC transporters are localized on the apical/canalicular side of the epithelium to minimize xenobiotic threats by pumping toxic substances out. Conversely, SLC transporters are located on the basolateral/sinusoidal side and are primarily responsible for substance uptake (Fig. 2).

2.2. Mechanisms of HDIs

2.2.1. Modulation of CYPs

Modulation of CYPs can reveal tissue specificity, species differences, and individual differences among people [23]. Increased CYP activity can be attributed to multiple regulatory mechanisms including nuclear receptor-triggered transcriptional upregulation, post-transcriptional induction, and decreased protein degradation. For example, St John's wort (*Hypericum perforatum*) stimulated

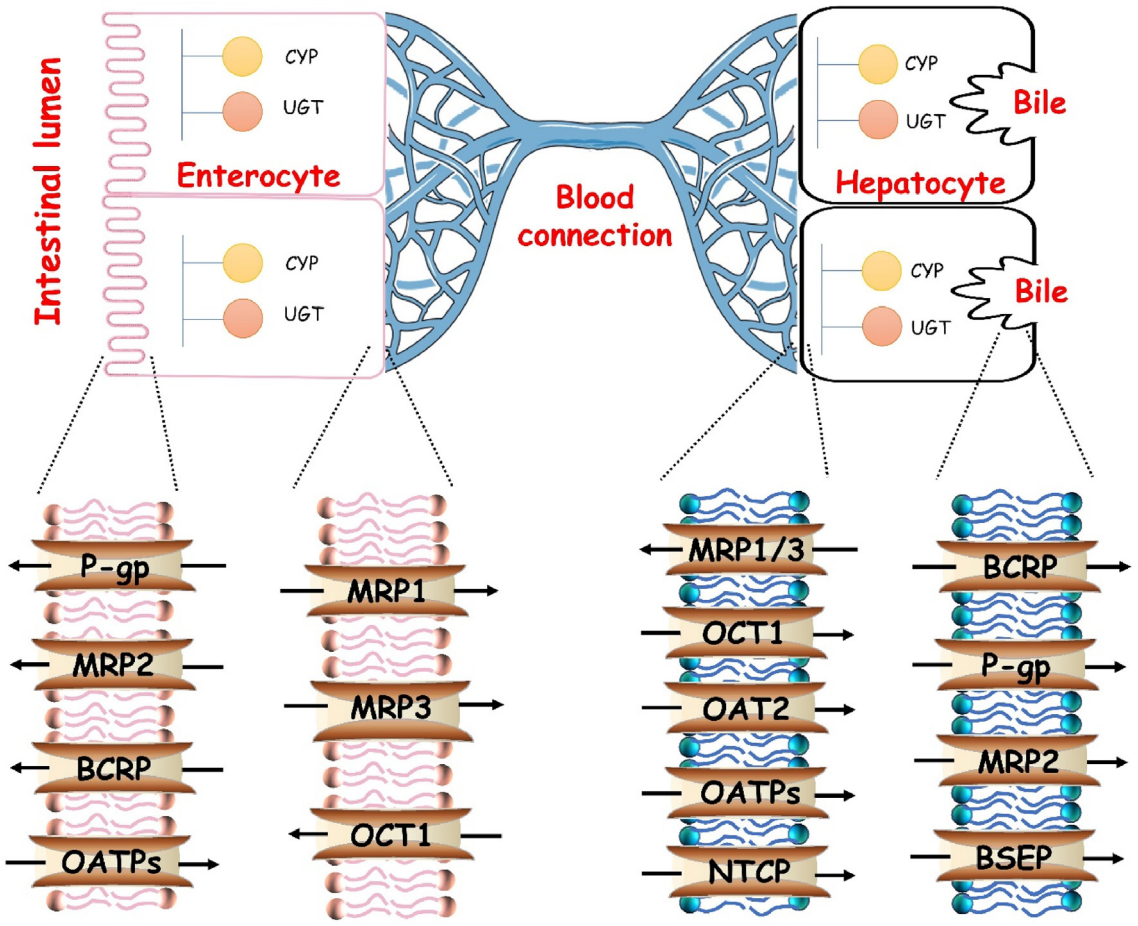

Fig. 2. Localization of transporters in enterocyte and hepatocyte and their direction of flux on drugs. The membrane transporters involved in drug intestinal absorption and hepatobiliary disposition can be divided into influx (uptake) and efflux proteins. The amount of drug systemic exposure mediated by the membrane pumps depend on the distribution and acting direction of the transporters on the cell apical/sinusoidal or basolateral/canalicular side. CYP, cytochrome P450; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; MRP, multidrug resistance associated protein; NTCP, sodium taurocholate co-transporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; UGT, UDP-glucuronosyltransferase.

CYP3A expression through pregnane X receptor (PXR)-triggered transcriptional induction, and its ingredient hyperforin was the main contributor to this induction [39]. Reduced CYP activity could be attributed to the decreased activities or expression levels of CYP and/or its electron-transfer partners (Fig. 1). Decreased activity is mostly attributed to reversible inhibition through different types of competitive inhibition [23,40]. Compared to reversible inhibition, time-dependent (mechanism-based) CYP inhibitors cause a more potent inhibitory effect, and the impaired function can only be restored through *de novo* protein synthesis of CYP. Time-dependent inhibitors cause suicidal inactivation through CYP-mediated oxidization to generate an active metabolite that irreversibly binds to CYP itself, leading to functional inactivation [41]. Irreversible inactivation and detection of a significant functional defect require time for drug oxidation and the accumulation of inactivated CYP. Grapefruit ingredients decreased intestinal, but not hepatic CYP3A4 function, through time-dependent inhibition [42]. In healthy participants, ingestion of grapefruit juice 2 h prior to oral administration of the CYP3A4 substrate midazolam significantly increased the area under the plasma drug concentration–time curve (AUC) of midazolam [43]. Recovery of the AUC to the level before grapefruit juice ingestion required 3 days.

Single nucleotide polymorphisms (SNPs) are one of the factors that influence CYP induction and inhibition [44–50]. SNPs exist in both CYPs and nuclear receptors (Table 1), resulting in individual differences not only in CYP function, but also in CYP inducibility and susceptibility to inhibition. SNPs represent one class of crucial factors that

influence drug dosing regimens in patients with CVD [44]. The genetic variants of CYPs and their influence on changes in amino acid residues and CYP function can be found on the PharmVar web site (https://www.pharmvar.org) [45,46].

2.2.2. Herb-mediated modulation of UGTs

Various natural products have been reported to alter the expression or function of UGTs through receptor activation-elicited induction [52] or functional suppression [18]. Flavonoids are a group of phenolic antioxidants commonly found in various herbal medicines (e.g., *Ginkgo biloba*) and have been shown to act as UGT substrates or strongly inhibit UGT activity [18]. The Japanese Kampo medicine Hange-Shashin-To (TJ-14) contains baicalin, the main flavonoid in *Scutellaria baicalensis*, and potently inhibits the glucuronidation of SN-38 (main active metabolite of irinotecan) in human liver microsomes (HLMs) [53]. β-Glucuronidase treatment enhanced the UGT inhibitory effect of TJ-14. The conjugated glucuronic acid of baicalin can be removed by intestinal glucuronidase to generate baicalein, which potently inhibited UGT activity in a competitive manner with an inhibition constant (K_i) of 8.7 μM. The simultaneous use of other flavonoid-rich herbal medicines may produce HDIs with CVD drugs that are also UGT substrates, such as aspirin, telmisartan, and coumarin derivatives [54–56]. Other plant ingredients that regulate UGTs have also been reported [18]. Since most HDI studies related to UGTs have been conducted *in vitro*, further PK/PD studies are urgently needed to evaluate the safety of concurrent uses of herbal medicines and UGT drug substrates.

2.2.3. Modulation of influx and efflux transporters

In addition to CYP induction, the PXR and constitutive androstane receptor (CAR) are well-known transcription factors related to the modulation of transporters [57]. CAR overlaps with PXR in many aspects, such as being regulated by herbal medicines and affecting gene expression of drug-metabolizing enzymes and transporters [58,59]. For example, hyperforin increased intestinal P-gp activity, thereby reducing the plasma level of the human immunodeficiency virus drug indinavir by 57% [60]. The extensively studied flavonoid quercetin is present in many herbal medicines and is rich in Ginkgo Folium. Rutin, the glycoside of quercetin, induces OATP2B1 expression, leading to a decrease in rosuvastatin uptake [61]. Due to its dual inductive effects on CYP3A4 and P-gp, quercetin has been shown to elicit significant HDIs [62,63]. However, other conflicting reports have indicated that quercetin elevates doxorubicin and etoposide levels in rats by attenuating the activities of CYP3A4 and P-gp [64,65]. The underlying reason for this discrepancy remains unclear. It is worth mentioning that another type of "enzyme-transporter" interplay may also exist in HDIs [66]. If perpetrators (herbs) act as enzyme/transporter inhibitors and PXR inducers, the fate of the victim drugs may depend on the relative potency of these two opposing actions [66]. Schisandrae Fructus (Wu-Wei-Zi), a common TCM used to treat CV disorders, is a typical example of this phenomenon [66].

Depending on the target proteins, affected sites, and influx/efflux directions, the modulation of transporters may significantly alter the PK profiles of concurrently used drugs. The commonly used *Panax ginseng* induces P-gp activity, which in turn increases the bioavailability of fexofenadine (an antihistamine) [67]. Glycyrrhiza showed potent inhibitory effects against breast cancer resistance proteins and P-gp, resulting in increased exposure to co-administered drugs [68]. However, it should be noted that contradictory HDIs between TCMs and transporters are not uncommon in the

Table 2. The main active ingredients of three single herbs potentially regulate drug-metabolizing enzymes and transporters.

Danshen (*Salvia miltiorrhiza*) [83,84]	Ginseng (*Panax ginseng*) [95]	Ginkgo (*Ginkgo biloba*) [124,129]
Lipophilic diterpenoids:	Ginsenosides	Flavonoids
Cryptotanshinone	Ginsenoside Rg1	Quercetin
Dihydrotanshinone	Ginsenoside Rc	Kaempferol
Tanshinone I	Ginsenoside Rd	Apigenin
Tanshinone IIA	Ginsenoside Re	Isorhamnetin
Hydrophilic depsides:	Ginsenoside Rb1	Terpene trilactones
Danshensu (salvianic acid A)	Ginsenoside Rb2	Ginkgolide A
Protocatechuic aldehyde	Flavonoids	Ginkgolide B
Rosmarinic acid	Sterols	Ginkgolide C
Salvianolic acid A	Polysaccharide	Ginkgolide J
Salvianolic acid B	Compound K	Ginkgolide K
		Ginkgolide M
		Bilobalide

literature. For example, silymarin (milk thistle) decreased systemic exposure (AUC_{0-48}) of the P-gp substrate metronidazole by 27.9% [69], whereas it increased the AUC_{0-36} of another P-gp substrate, talinolol, by 36.2% in participants [70]. Moreover, Danshen ingredients, cryptotanshinone and dihydrotanshinone, reduced P-gp expression and decreased the efflux ratio of digoxin in colon cancer cells [71], whereas tanshinone IIA and cryptotanshinone induced the expression of P-gp mRNA in cryopreserved human hepatocytes [72]. These contradictory results may be related to the complex and cell-type specific actions of herbal ingredients. Variations in the dosing regimens, enzyme-transporter interactions, and composition of herbal medicines are also potential causes [73–75].

HDIs between herbal medicines and uptake transporters are relatively rare compared with those between herbal medicines and efflux transporters. However, a growing body of evidence has shown that many TCMs (e.g., Danshen, Huanglian, and licorice) have significant effects on the function of uptake transporters [36]. The clinical impact of the changes in cellular drug-uptake by these TCMs cannot be ignored, particularly because they are often included in compound formulas.

3. Potential HDIs between single TCMs and prescribed CVD drugs

As mentioned above, driven by the culture of Chinese medicine and dietary habits, the consumption of TCMs is prevalent in Asia, especially in patients with chronic diseases such as CVD. The active ingredients of three herbs are indicated in Table 2, and the progress to date of the HDI-relevant *in vivo* studies of these herbs and the four compound formulas described in section 4 are summarized in Table 3. These herbs and formulas are included because they have been reported to be frequently used to ameliorate CVD-associated symptoms and have the potential to interact with CVD drugs by altering drug metabolism, as discussed in the following sub-sections.

3.1. Danshen (*Salvia miltiorrhiza*)

Danshen (Salviae miltiorrhizae Radix et Rhizoma), the dried root and rhizome of *S. miltiorrhiza*, is a Chinese herbal drug widely used to treat CVDs [76]. Danshen can react directly with CVD drug targets relevant to antithrombotic effects, including thrombin, activated coagulation factor X, and cyclooxygenase 1 [77]. However, the clinical indications for Danshen are broad, including angina, coronary artery disease, hypertension, and many other CV-derived symptoms [76]. In Taiwan, Danshen was the most frequently prescribed herb used in patients with hypertension from 2003 to 2009 (17.1%), with an average daily dose of 2.3 g powdered decoction [7]. Danshen was also the most commonly used herbal medicine in the prescriptions for ischemic heart disease [7,78]. Danshen extract and Danshen-containing formula, such as Danhong injection and compound Danshen dripping pill (Danshen, Sanqi, and Borneol), are often used in combination with prescribed Western drugs to treat CVD.

The underlying mechanisms of the interplay between Danshen and drugs have been studied for a long time, and CYP-mediated interactions, although controversial, have been identified as the major causes of Danshen-induced interaction with CVD drugs. As shown in Table 3, potentially through CYP3A4 induction by either the hydrophilic ingredient (salvianolioc acid B) or the hydrophobic ingredients (cryptotanshinone and tanshinone IIA), repeated treatments with Danshen capsule/tablet decrease clopidogrel and atorvastatin exposures in humans and rats, respectively [79,80]. However, by using midazolam as a CYP3A marker substrate, another preparation of Danshen extract caused the opposite influence accompanied by a decreased CYP3A protein level in rats [81]. A mouse study of the aqueous decoction of Danshen and Gegen (the dried root of *Pueraria lobata*) (DG, 7:3 w/w) showed that 8-week co-treatment with atorvastatin and DG resulted in stronger hypolipidemic effects than treatment with atorvastatin or DG alone, potentially owing to CYP3A suppression [82]. One explanation for these discrepancies may be the differential herbal composition and CYP/transporter-modulatory effects of the hydrophilic and hydrophobic constitutes extracted from Danshen [83]. At least nine primary pharmacologically active ingredients found in Danshen (Table 2) play significant roles in altering CV functions [83,84]. It is believed that the hydrophobic ingredients in Danshen, rather than the water-extracted constituents, are much more potent in interfering with the activities of CYP enzymes. However, the hydrophilic ingredients (e.g. tanshinol and salvianolic acid B) may have some effects on transporters (especially SLC members), whose involvement can alter PK behaviors of CVD drugs [83]. Another possible reason for these controversial results is the difference between enzyme inhibition after short-term treatment and enzyme induction (mediated by PXR activation) after long-term administration and the effects of Danshen dosing frequency thereon [85]. Because of

Table 3. The metabolism-mediated HDIs associated CVD in the in vivo animal and clinical studies.

TCM	Interacted CVD Drug	Study design	TCM administration (dose, route, duration)	Ingredient mentioned	Possible underlying mechanism		Significant effect on PK of concurrent drug[a]	Physiological impact	Ref
					Phase I & II	Transporter			
Danshen (*Salvia miltiorrhiza*)	Amlodipine 1 mg/kg, po, single dose	SD rats, n = 6 in each group	Danshen tab, 100 mg/kg/d, po, 7 days	Salvianolic acid B	CYP3A (↑)	NA	C_{max} (↓) 26.5% AUC_t (↓) 52.4% $t_{1/2}$ (↓) 25.1% CL/F (↑) 135.8%	NA	[149]
	Atorvastatin 1 mg/kg, po, single dose	SD rats, n = 6 in each group	Danshen tab, 100 mg/kg, po, single dose	Salvianolic acid B	CYP3A (↑)	NA	C_{max} (↓) 38.7% AUC_t (↓) 46.9% $t_{1/2}$ (↓) 30.3% CL/F (↑) 98.7%	NA	[80]
	Atorvastatin 8 or 16 mg/kg/d, po, 8 weeks	C57BL/6 mice, n = 19–25 in all groups	Water extract of Danshen and Gegen (7:3, w/w), 600 mg/kg/d, po, 8 weeks	NA	CYP3A (↓)	NA	NA	Significant hypo-lipidemic effect: Body weight (↓) Liver weight (↓) Liver fat (↓) Adipose tissue (↓) Lipid profile (↓)	[82]
	Azilsartan 2 mg/kg, po, single dose	SD rats, n = 6 in each group	DDP (Danshen, Sanqi, Bingpian), 81, 405, 810 mg/kg/d, po, 7 days	Danshensu, salvianolic acid A and B, protocatechuic aldehyde and rosmarinic acid	CYP2B1 (↓) CYP2C6 (↓) CYP2C11 (↓)	NA	(1) DDP 81 mg/kg/d: C_{max} (↑) 96.1% AUC_t (↑) 77.9% CL/F (↓) 72.2% (2) DDP 405 mg/kg/d: C_{max} (↑) 97.3% AUC_t (↑) 88.8% CL/F (↓) 72.2% (3) DDP 810 mg/kg/d: C_{max} (↑) 113.3% AUC_t (↑) 103.0% CL/F (↓) 77.8%	NA	[150]
	Clopidogrel 300 mg, po, single dose	Human healthy subjects, cross-over n = 20	Danshen cap, 4's (0.56 g/cap), po, tid, 7 days before drug co-administration	Cryptotanshinone and tanshinone IIA	CYP3A4 (↑)	Induction of P-gp may also take part in the interactions	(1) Clopidogrel: C_{max} (↓) 41.7% AUC_t (↓) 50.3% CL/F (↑) 96.5% (2) Active thiol metabolite: C_{max} (↓) 32.9% AUC_t (↓) 41.8% CL/F (↑) 73.7%	IPA ↓ Reduction of the inhibitory effect of platelet aggregation	[79]
	Clopidogrel 30 mg/kg, po, single dose	SD rats, n = 4 in study and control groups	Danshen extract, 400 mg/kg, po, single dose	Tanshinone I, IIA, IIB, dihydrotanshinone, and cryptotanshinone	CYP3A (↔)	P-gp (↔)	Non-significant change	NA	[151]

Clopidogrel 31 mg/kg, po on day 1 and 7.75 mg/kg for 13 days + Aspirin 8.3 mg/kg, po for 14 days	SD rats, n = 6 in each group	Danshen, 1.03 g/kg/d or 1.55 g/kg/d, po, 2 weeks	Salvianolic acid	CYP2C11 (↓)	NA	Non-significant change	No significant changes in PT	[152]
Losartan 10 mg/kg, po, single dose	SD rats, n = 6 in each group	Compound Danshen tab 1's, po, single dose	Salvianolic acid B (36.2 mg/kg) and tanshitone IIA (2.7 mg/kg)	Induction of CYP enzymes	Competition of transportation protein	(1) Losartan: AUC_t (↓) 9.8% C_{max} (↓) 6.1% $t_{1/2}$ (↓) 13.3% CL/F (↑) 7.4% (2) EXP3174: No significant change	NA	[153]
Theophylline 100 mg, po, single dose	Human healthy subjects, cross-over n = 12	Danshen tab 4's, po, tid for 14 days before drug co-administration	Cryptotanshinone, tanshinone I, tanshinone IIA, danshensu, and salvianolic acid B	CYP1A2 (↔) (Possibly due to the low oral BA of lipo-philic compo-nents of Danshen)	NA	No significant change	NA	[154]
Warfarin 1.0 mg/kg, po	Wistar rats, n = 6 in each group	Compound DDP (Danshen, Sanqi, Bingpian), 50 mg/kg or 250 mg/kg, po, bid, 7 days	Tanshinol, protocatechuic aldehyde, rosmarinic acid, salvianolic acid A, B, and D	NA	NA	No significant change	No significant change in PT	[88]
Warfarin 3.41−3.39 mg, po	Human CVD patients, sequential n = 59	Compound DDP (Danshen, Sanqi, Bingpian), 10 grains, po, tid, > 4 weeks	Danshensu, protocatechuic aldehyde, rosmarinic acid, and salvianolic acid A	NA	NA	No significant change, but the peak concentrations of S-warfarin (↑ 15.8%) and total warfarin (↑ 13.7%) significantly increased in CYP4F2 C/C patients	No significant change in INR	[89]
Warfarin 2−6.5 mg, po, 25 days	Human, healthy subjects, sequential n = 23	T89 (Danshen, Sanqi, Borneol), 225 mg, po, bid, 7 days	Tanshinone I, tanshinone IIA, cryptotanshinone, and salvianolic acids	No effects on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5	NA	No significant effect on steady-state PK of warfarin	No significant change in INR, the bleeding risk possibly pre-vented by Sanqi	[155]
(1) Warfarin 1 mg/d, po, 5 days	Human, healthy subjects, 5-ses-sion n = 12−14	Danshen-Gegen (7:3) 750 mg, po, bid, 5 days	Danshensu, protocatechuic aldehyde, salvianolic	CYP2C9 (↓)	NA	(1) 7-OH warfarin: AUC_t (↓) 53.5%	(1) Warfarin: plasma thrombo-modulin (↓)	[156]

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Table 3. (continued)

TCM	Interacted CVD Drug	Study design	TCM administration (dose, route, duration)	Ingredient mentioned	Possible underlying mechanism		Significant effect on PK of concurrent drug[a]	Physiological impact	Ref
					Phase I & II	Transporter			
	(2) Aspirin 100 mg/d, po, 5 days			acid B, cryptotanshinone, tanshinone I and tanshinone IIA			(2) Aspirin: AUC_t (↑) 242.2%	(2) Aspirin: thromboxane B2 formation (↓)	
	Warfarin 0.2 mg/kg, po, 5 days	SD rats, n = 6 in each group	Danshen 240 mg/kg/d or 480 mg/kg/d, po, 5 days	Danshensu, salvianolic acid B, and protocatechuic aldehyde	No effects on CYP2C11, 2C6, 1A1, and 2B1	NA	No significant change	No significant change	[157]
	(1) Warfarin 2 mg/kg, po, single dose (2) Warfarin 0.2 mg/kg/d, po, 8 days	SD rats, n = 6 in each group	(1) For single dose warfarin: DEAE, 50 or 200 mg/kg/d, ip, single dose or 3 days (2) For multiple dose warfarin: DEAE, 2 g/kg, po, bid, 4 days	DEAE: tanshinone I, tanshinone IIA, and cryptotanshinone	CYP1A1 (↓) CYP2C6 (↓) CYP2C11 (↓)	NA	(1) Single DEAE 50 mg/kg: AUC (↓) 21.4% $t^{1}/_{2}$ (↓) 35.8% CL/F (↑) 27.5% (2) Single DEAE 200 mg/kg: C_{max} (↓) 28.0% (3) Multiple DEAE 50 mg/kg/d: No significant change (4) Multiple DEAE 200 mg/kg/d: C_{max} (↓) 27.3% $AUC_{4'\text{-OH warfarin}}$ (↓) 47.1% $AUC_{7\text{-OH warfarin}}$ (↓) 33.1% (5) Multiple DEAE 2 g/kg: C_{ss} (↑) 23%	NA	[158]
Ginseng (*Panax ginseng*)	(1) Amlodipine 10 mg/kg, po, single dose (2) Amlodipine 2 mg/kg, iv, single dose	SD rats, n = 5–9	RG from 0.5 to 2 g/kg/d, po, 2 weeks	Ginsenosides Rg1, and Rb1	CYP3A4 (↔)	NA	No significant changes	NA	[159]
	Cocktail probe: Caffeine 200 mg, losartan 50 mg, dextromethorphan 30 mg, omeprazole 20 mg, midazolam 7.5 mg, and	Human healthy subjects, cross-over n = 14	RG solution, 10 mL/d (dried Ginseng 64%), po, qd, 2 weeks	Ginsenosides Rb1, Rb2, Rc, Re, F2, Rg1, 20(S)-Rg3, 20(R)-Rg3, 20(S)–Rh1, 20(S)/20(R)-Rh2, 20(R)-Rh1/Rd/F1, compound K,	CYP1A2 (↓) CYP2C9 (↓) CYP3A4 (↓) CYP2C19 (↔) CYP2D6 (↑)	P-gp (↔)	The metabolic GMR (90% CI): (1) 0.870 (0.805–0.940) for caffeine to para-xanthine (CYP1A2) (2) 0.871 (0.800	No clinically significant xrelevant	[160]

fexofenadine 30 mg, po, single dose			compound O, compound Y, Protopanaxadiol, and Protopanaxatriol			−0.947) for losartan to EXP3174 (CYP2C9) (3) 1.027 (0.938 −1.123) for omeprazole to 5-OH omeprazole (CYP2C19) (4) 1.373 (0.864 −2.180) for dextromethorphan to dextrorphan (CYP2D6) (5) 0.824 (0.658− 1.032) for midazolam to 1-OH midazolam (CYP3A4)		
Cocktail probe: caffeine 100 mg, losartan 50 mg, omeprazole 20 mg, dextromethorphan 30 mg, midazolam 2 mg, and atorvastatin 2 mg, po, single dose	Human healthy subjects, sequential n = 15	RGE (dried Ginseng >60%, Ginsenosides 85.1 mg/d), po, qd, 15 days	Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1, Rg3, and Rh1	CYP1A2 (↓) CYP2C19 (↓) CYP2D6 (↓) CYP2C9 (↔) CYP3A4 (↔)	OATP1B1 (↔)	The GMR of metabolite AUC (90% CI) for the probe drugs: (1) within 0.8−1.25 (CYP2C9, CYP3A4, and OATP1B1 probe substrates) (2) within 1.25−2 (CYP1A2, CYP2C19, and CYP2D6 probe substrates)	RG does not cause clinically relevant HDI	[161]
Cocktail probe: caffeine 2 mg/kg, bupropion 30 mg/kg, omeprazole 4 mg/kg, dextromethorphan 40 mg/kg, midazolam 2 mg/kg, po, single dose	C54BL/6N mice, n = 3	Korea RGE from 0.5 − 2.0 g/kg/d, po, 2 or 4 weeks	Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg3, Rh1, Rh2, F1, F2, Compound K, protopanaxadiol, and protopanaxatriol	CYP3A (↑) CYP2D (↓)	NA	The metabolic GMR of 4 weeks RGE administration: (1) RGE 0.5 g/kg: Midazolam (↑) 51.2% (2) RGE 1 g/kg: Midazolam (↑) 57.8% Dextromethorph (↓) 29.9% (3) RGE 2 g/kg: Midazolam (↑) 68.3%	NA	[162]

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Table 3. (continued)

TCM	Interacted CVD Drug	Study design	TCM administration (dose, route, duration)	Ingredient mentioned	Possible underlying mechanism		Significant effect on PK of concurrent drug[a]	Physiological impact	Ref
					Phase I & II	Transporter			
							Dextromethorph (↓) 53.6%		
	(1) Losartan 10 mg/kg, po, single dose (2) Losartan 10 mg/kg, iv, single dose	SD rats, n = 4–7	RG from 0.5 to 2 g/kg/d, po, 2 weeks	Ginsenosides Rg1 and Rb1	CYP3A4 (↔) CYP2C9 (↔)	NA	No significant changes	NA	[163]
	Nifedipine, 10 mg, po	Human healthy subjects, n = 22	Ginseng 200 mg/d, 18 days	NA	CYP3A4 (↓)	NA	C_{max} (↑) 53.4%	NA	[101] [b]
	Valsartan 1 mg/kg, iv, single dose	SD rats, n = 4	(1) RGE 1.5 g/kg/d, po, 7 days (2) Rc 3 mg/kg/d, iv, 5 days	Ginsenosides Rb1, Rb2, Rc, Rd, Rg3, compound K, and Rh2 (protopanaxadiol type, PPD-type)	NA	Oatps (↔)	May be due to high protein binding and limited liver distribution of GS, no effect on valsartan PK	NA	[164]
	PK: Warfarin 1 mg/kg, po, single dose PD: Warfarin 0.4 mg/kg, po, 7 days alone + 3 weeks GS co-administration	SD rats, n = 10 in each group	PK: Ginsenosides 300 mg/kg/d, po, 3 weeks pretreated PD: Ginsenosides 30, 100, and 300 mg/kg/d, po, 3 weeks	Ginsenosides Rg1, Re, Rd, Rf, Rb1, Rb2, Rc,	CYP3A (↑) CYP2C (↑)	NA	AUC (↓) 45.5% CL/F (↑) 84.0%	(1) The expression of factors II, VII and protein Z elevated (2) Repeated GS significantly decrease the INR	[99]
	(1) Warfarin 2 mg/kg, po, single dose (2) Warfarin 0.2 mg/kg/d, po, 6 days	SD rats, n = 6 in each group	Ginseng crude drug, 2 g/kg, po, bid, 5 days	NA	NA	NA	No significant changes in PK parameters	No significant change in PT	[100]
	Warfarin 0.25 –0.32 mg/kg, po, 7 days	Hyperlipidemia rats, n = 5 in each group	Ginsenosides from 50, 100, and 200 mg/kg/d, po, 1, 2, and 3 weeks	Ginsenosides Rg1, Re, Rb1 and Rd	CYP1A (↑) CYP2C (↑) CYP3A (↑)	NA	No PK studies mentioned	The expression of factors II, VII and protein Z elevated. Repeated GS could decrease the INR	[165]
	Warfarin 2 mg in first week and 5 mg in second week, po	Human ischemic stroke patients, open-label n = 12 & 13	*P. ginseng* aqueous extracts, 0.5 g, po, tid, 2 weeks	NA	NA	NA	No PK studies mentioned	No statistically difference in PT_{max}, $AUC_{PT,}$ $INR_{max,}$ and AUC_{INR}	[166]

	Warfarin 25 mg, po, single dose	Human healthy subjects, cross-over n = 12	Ginseng cap, 2's (each capsule containing GBE equivalent to 0.5 g *P. ginseng* root and 8.93 mg GS Rg1), po, tid, 1 week	Ginsenosides Rg1 and Rb1	CYP1A2 (↔) CYP3A4 (↔) CYP2C9 (↔)	NA	No significant changes	No significant change in INR and platelet aggregation.	[167]
	Warfarin 40.6 mg/week (in average), po, 17.1 years (in average)	Human cardiac valve replacement patients, cross-over n = 25	RGE, 1 g, po, 6 weeks	Ginsenosides Rg3, Rh2, and Rf	NA	NA	No PK studies mentioned	No significant differences in mean INR change but have a tendency	[168]
Ginkgo (*Ginkgo biloba*)	Atorvastatin 1 mg/kg, po, single dose	SD rats, n = 6 in each group	GLT, 80 mg/kg/d, po, 10 days	Ginkgolide A, ginkgolide B, bilobalide, quercetin, and kaempferol	CYP3A (↓)	NA	C_{max} (↑) 32.1% AUC_t (↑) 75.8% $t_{1/2}$ (↑) 26.7%	NA	[169]
	Atorvastatin 40 mg, po, single dose	Human healthy subjects, sequential n = 16	GBE 360 mg/d, po, 14 days	Ginkgolides A, B, C, J, bilobalide, quercetin, kaempferol, and isorhamnetin	CYP3A4 (↔) UGT1A1 (↔) UGT1A3 (↔)	OATP1B1 (↑)	C_{max} (↓) 28.9% AUC_t (↓) 14.3% CL/F (↑) 6.5%	No significant change in cholesterol-lowering efficacy	[125]
	Amlodipine 1 mg/kg, po, single dose	SD rats, n = 6 in each group	GLT 100 mg/kg/d, po, 10 days	Ginkgolides A, B, and C, bilobalide, quercetin, kaempferol, and isorhamnetin	CYP3A (↓)	NA	C_{max} (↑) 39.0% AUC (↑) 79.3% $t_{1/2}$ (↑) 67.6%	NA	[170]
	Cilostazol 100 mg, po	Human, healthy Korean subjects, n = 34	GBE, 80 mg, po, q12h, 7 days	NA	CYP3A4 (↔) CYP1A2 (↔) CYP2E1 (↔) CYP2D6 (↔)	NA	No significant changes	No significant changes in bleeding times and adverse drug reactions between the treatments	[171]
	Cilostazol 100 mg + Clopidogrel 75 mg, po	Human, healthy subjects, n = 10	*G. biloba*, 120 mg, single dose, po	NA	NA	NA	NA	Potentiated the bleeding time prolongation effect of cilostazol, but no significant change in anti-platelet activity, bleeding time, clotting time and platelet count	[172]

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Table 3. (continued)

TCM	Interacted CVD Drug	Study design	TCM administration (dose, route, duration)	Ingredient mentioned	Possible underlying mechanism		Significant effect on PK of concurrent drug[a]	Physiological impact	Ref
					Phase I & II	Transporter			
	Clopidogrel 7.5 mg/kg, po, single dose	SD rats, n = 7 in each group	GBE, 4, 20, and 100 mg/kg/d, po, 14 days pretreated	Ginkgolides and bilobalide	Low dose: CYP1A2 (↑) CYP2C19 (↑) CYP2D6 (↓) Medium dose: CYP2C19 (↑) CYP3A4 (↑) CYP2B6 (↑) CYP2C9 (↑) CYP2A1 (↑) High dose: CYP1A2 (↓) CYP2C19 (↓) CYP2D6 (↑)	High dose: P-gp (↓)	(1) Clopidogrel GBE 4 mg/kg/d: C_{max} (↓) 38.5% CL/F (↑) 64.1% GBE 20 mg/kg/d: C_{max} (↓) 56.3% AUC_{∞} (↓) 46.2% CL/F (↑) 96.1% GBE 100 mg/kg/d: C_{max} (↓) 87.5% AUC_{∞} (↓) 69.2% CL/F (↑) 264.1% (2) Clopidogrel active metabolite GBE 100 mg/kg/d: C_{max} (↑) 120.5% AUC_{∞} (↑) 140.1% CL/F (↓) 59.0%	NA	[173]
	Digoxin 0.1 mg/kg, po, single dose	SD rats, n = 6 in each group	GBE 160 mg/kg, po, single dose	Ginkgolides A, B, and C, bilobalide, quercetin, kaempferol, and isorhamnetin	NA	P-gp (↓)	C_{max} (↑) 25.4% AUC_t (↑) 27.8%	NA	[174]
	Losartan 10 mg/kg, po, single dose	SD rats, n = 6 in each group	GLT 80 mg/kg/d, po, 10 days pretreated	Ginkgolides A, B, bilobalide, quercetin and kaempferol	CYP3A (↓) CYP2C (↓)	NA	(1) Losartan: C_{max} (↑) 51.6% AUC_t (↑) 70.8% CL/F (↑) 42.7% (2) EXP3174: C_{max} (↓) 31.4% AUC_t (↑) 44.5% CL/F (↑) 72.0%	NA	[175]
	Pitavastatin 0.135 mg/kg, po, single dose	NAFLD rats, n = 6 in each group	GBE 3.6, 10.8, and 32.4 mg/kg/d, po 2 or 4 weeks pretreated	Ginkgolides A, B, C, bilobalide, quercetin, kaempferol, and isorhamnetin	NA	Oatp1b2 (↓)	(1) 2-weeks pre-treated GBE 10.8 mg/kg/d: C_{max} (↑) 155.9% GBE 32.4 mg/kg/d: C_{max} (↑) 210.8% AUC_t (↑) 129.6% (2) 4-weeks pre-treated GBE 3.6 mg/kg/d: CL/F (↓) 41.1% GBE 10.8 mg/kg/d: C_{max} (↑) 163.5% AUC_t (↑) 135.2% CL/F (↓) 57.2% GBE 32.4 mg/kg/d: C_{max} (↑) 219.0% AUC_t (↑) 199.3% CL/F (↓) 58.9%	NA	[126]

	Simvastatin 40 mg/d, po, 14 days	Human, healthy subjects, n = 14	GBE 120 mg, po, bid, 14 days	Quercetin, kaempferol, apigenin, ginkgolides A, B, C, J and M, and bilobalide	Effect on simvastatin: CYP3A (↑)	Effect on simvastatin: P-gp (↑) Effect on simvastatin acid: OATP1B1 (↓)	Simvastatin: C_{max} (↓) 32% AUC_{∞} (↓) 36% No significant differences in simvastatin acid PK	No significant PD change of simvastatin but trended towards lowering LDL-C efficacy ($p = 0.056$)	[124]
	Talinolol 100 mg, po, single dose	Human healthy Chinese subjects, sequential n = 10	GBE tab, 120 mg, po, tid, 14 days	NA	NA	P-gp (↓)	Single dose GBE: No effect on talinolol PK Repeated GBE: C_{max} (↑) 36.3% AUC_t (↑) 26.2%	NA	[176]
	Ticlopidine 250 mg, po, single dose	Human, healthy Korean subjects, cross-over n = 24	GBE 80 mg, po, single dose	Glycosidic flavonoids 24% and terpenoids 6% of GBE	NA	NA	No significant changes	No effects	[177]
	Warfarin 1.5 mg/kg/d for racemate (1:1), po, last 3 days of GBE administered	ICR mice, n = 4–6	GBE from 10 & 100 mg/kg/d, po, 5 days	Bilobalide	CYP1A1 (↑) CYP1A2 (↑) CYP2B (↑) CYP2C (↑) CYP3A (↑)	NA	GBE 100 mg/kg: (R)-Warfarin C_{max} (↓) 49.2%	No influence on blood coagulation but attenuates the anticoagulation action of warfarin	[178]
	Warfarin 25 mg, po	Human, n = 12	*G. biloba* tab, 2's (each tablet is equivalent to 2 g of *G. biloba* leaf, 9.6 mg of Ginkgo flavon glycosides, 2.4 mg of ginkgolides and bilobalide), po, tid, 7 days	Ginkgolides and bilobalide	CYP1A2 (↔) CYP3A4 (↔) CYP2C9 (↔)	NA	No significant changes in the PK parameters	No significant change in INR and platelet aggregation	[179]
Shenmai injection (SMI)	Diclofenac 0.8 mg/kg, iv	SD rat, n = 8	SMI, 5 mL/kg, ip, single or once daily, 7 days	NA	CYP2C (↓) *in vitro*	NA	AUC ↑ (15–31%) CL ↓ (14–27%)	NA	[131]
	Midazolam 1 and 4 mg/kg, iv, 0.5 h after the last herbal treatment	SD rat, n = 8	SMI, 5 mL/kg, ip, single or once daily, 7 days	Ophiopogonanone A Ginsenoside Rd	CYP3A (↓) *in vitro*	NA	AUC ↑ (22–33%) $t_{1/2}$ ↑ (22–76%) CL ↓ (19–29%)	NA	[131] [132]
	Theophylline 1 mg/kg, iv, 0.5 h after the last herbal treatment	SD rat, n = 8	SMI, 5 mL/kg, ip, single or once daily, 7 days	NA	NA	NA	AUC (↔) $t_{1/2}$ (↔) CL (↔)	NA	[131]
Shengmai-San (SMS) (Sheng-mai-Yin)	Nifedipine 3 mg/kg, po	SD rat, n = 6	SMS 0.95 g/kg, po, 1 h	Schisandrin B	CYP3A (↓)	NA	C_{max} ↑52%	NA	[133]
	Nifedipine 3 mg/kg, po	SD rat, n = 6	SMS 1.9 g/kg, po, 1 h	Schisandrin B	hepatic CYP3A activity (↓)	NA	CL/F (↓) 34% $t_{1/2}$ (↑) 142%	NA	[133]

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Table 3. (continued)

TCM	Interacted CVD Drug	Study design	TCM administration (dose, route, duration)	Ingredient mentioned	Possible underlying mechanism		Significant effect on PK of concurrent drug[a]	Physiological impact	Ref
					Phase I & II	Transporter			
	Nifedipine 3 mg/kg, po	SD rat, n = 6	SMS 1.9 g/kg, po, 3 weeks	Schisandrin B Schisantherin A Methylophiopogonanone A	intestinal CYP3A activity (↓)	NA	C_{max} (↑) 101% AUC_t (↑) 73% CL/F (↓) 39%	Increased headache incidence and decreased all-cause mortality	[134] [135]
Shu-Jing-Hwo-Shiee-Tang (SJHST)	Warfarin 1.5 mg/kg, po	Rabbit, n = 6	1–2 mg/kg/day, po, 1–2 weeks	Coumarins	NA	NA	NA	Enhance warfarin-prolonged PT	[140]
	Warfarin 1 mg/kg, po	SD rat, n = 4	1 g/kg, po, 2 h after warfarin administration	Angelicin Hesperetin Naringenin Tetradrine	CYP2C (↓)	NA	C_{max} (↑) 135% AUC (↑) 208–215% CL/F (↓) 61%	Enhance warfarin-prolonged PT 24 h after warfarin administration	[141]
Wu-chu-yu (*Evodia rutaecarpa*)	Caffeine 5 mg/kg, iv	SD rat, n = 6	1 g/kg ethanolic extract, po, 3 days	Rutaecarpine	rat hepatic CYP1A (↑)	NA	AUC_u[c] (↓) 71% $t_{1/2}$ (↓) 63% CL_u[c] (↑) 244%	NA	[180]
	Theophylline 2 mg/kg, iv	SD rat, n = 6	1 and 2 g/kg ethanolic extract, po, 3 days	Rutaecarpine	rat hepatic CYP1A (↑)	NA	AUC_u (↓) 73% $t_{1/2}$ (↓) 79%–85% CL_u (↑) 269–259%	NA	[181] [182]
Wu-Chu-Yu-Tang (WCYT)	Caffeine 2 mg/kg, ip	C57BL/6Jmice, n = 6	5 g/kg decoction, po, 3 days	Rutaecarpine	mouse hepatic CYP1A (↑)	NA	AUC (↓) 44% $t_{1/2}$ (↓) 39% CL (↑) 78%	NA	[144] [183]
	Caffeine 5 mg/kg, iv	SD rat, n = 6	1 g/kg decoction, po, 3 days	Rutaecarpine	rat hepatic CYP1A (↑)	NA	AUC_u (↓) 44% $t_{1/2}$ (↓) 21% CL_u (↑) 93%	NA	[180]
	Theophylline 2 mg/kg, iv	SD rat, n = 6	1 and 5 g/kg decoction, po, 3 days	Rutaecarpine	rat hepatic CYP1A (↑)	NA	AUC_u (↓) 26–60% CL_u (↑) 35–146%	NA	[182]

The number of animals (n) shown in the study design was the number of animals in the treated group in the PK/PD study of herbal extracts or formula. AUC, area under curve; BA, bioavailability; CL: clearance; DEAE, Danshen ethyl acetate extract; DDP, Danshen dripping pills; EXP3174, active metabolite of losartan; GBE, *Ginkgo biloba* extract (from leaves, fruit, or both); GLT, Ginkgo leaf tablet; GMR, geometric mean ratio; INR, international normalized ratio; IPA, inhibition of platelet aggregation; NA, not available; NAFLD, non-alcoholic fatty liver disease; PD, pharmacodynamic; PT, prothrombin time; PK, pharmacokinetic; RG, red Ginseng; RGE, red Ginseng extract; SD rat, Sprague-Dawley rat; $t_{1/2}$, half-life; (↑), significantly increase; (↓), significantly decrease; (↔), no significant change.

[a] The alterations of PK parameters were calculated by mean differences compared to the control group in the study.

[b] Conference abstract.

[c] The AUC or CL of unbound drug determined in the microdialysis experiment.

the complexity of the components in TCM, some of the active ingredients may show strong inhibitory effects on drug-metabolizing enzymes or transporters instantly after systemic exposure, but other pharmacologically active components may exert their transcriptionally or translationally inductive effects after long-term administration. For example, the hydrophobic Danshen ingredient tanshinone IIA inhibited CYP1A activity in HLMs (inhibitor concentration for causing 50% inhibition (IC_{50}) = 0.2–0.4 μM) [86] but induced CYP1A with aryl hydrocarbon receptor sensitivity after repeated treatments in mice [87]. On the other hand, tanshinone IIA had no effect on CYP2C activity in HLMs *in vitro* [86] and in mice after repeated treatments [87]. Consistently, repeated treatments with Fufan Danshen (Compound Danshen) dripping pill did not cause significant changes in warfarin PKs and warfarin-prolonged prothrombin time (PT) in rats [88] and possibly in patients with various SNPs [89]. Treatment time is not the only determining factor for the drug interactions with Danshen-containing prescription. The CYP selectivity of modulation, composition of Danshen extract, intake dose and achieved plasma levels of ingredients, and particularly the multiple metabolic pathways of victim drugs could be crucial in determining the dominant mechanism(s) involved in the interactions of CVD drugs with Danshen [90]. The controversial interaction between Danshen and prescribed drugs is not an isolated case and can be observed in many other TCMs that are concurrently administered, such as Schisandra, which is discussed in the following section of formula.

Danshen not only modulates CYPs to cause HDIs [79–87], but it also inhibits UGTs [90,91] and transporters [75,92]. Compared to the HDIs resulting from CYP modulation, there are relatively few reports regarding UGT/transporters-mediated interactions. A noteworthy clinical case associated with the induction of P-gp by Danshen has been published [72]. The systemic exposure (AUC) to the P-gp substrate, fexofenadine, significantly decreased by 37% after repeated treatments with Danshen ethanolic extract. To further confirm transporter/UGT-mediated HDIs with Danshen, more *in vivo* studies are warranted to evaluate the interactions between Danshen-containing formulas and CVD drugs.

3.2. Ginseng (*P. ginseng*)

P. ginseng, cultivated for its rhizomes (Ginseng Radix), is a medicinal plant belonging to the Araliaceae family. As a valued healthcare product, Ginseng has enjoyed a reputation for thousands of years and is now becoming increasingly popular worldwide [93,94]. The constituents of Ginseng [95], including ginsenosides, flavonoids, sterols, and polysaccharides (Table 2), have been shown to possess anti-fatigue, anti-hypertensive, immunomodulatory, anticancer, and antidiabetic properties, as well as to alleviate numerous other maladies. Thus, Ginseng is used as an adjuvant to a variety of compound TCMs, owing to its versatile disease treatments. Due to its low toxicity and safety for general consumption [96], patients could use Ginseng as a complementary medicine and even self-medicate without notifying their physicians. However, more than 40 ginsenosides belonging to a group of steroidal saponins are active components in Ginseng and may cause clinical HDIs [93,96,97].

According to Chinese medical practice, distinctly processed Ginseng should be used in patients with different symptoms of health status. Ginseng can be used in Chinese medical care for the treatment of myocardial infarction, angina pectoris, and congestive heart failure [98], making it highly suitable in combination with CVD drugs [94]. Reports of Ginseng-drug interactions are highly contradictory, and the causality remains uncertain due to variations in dosing regimens and experimental designs among studies [93]. However, a few reports have indicated that potential HDIs exist with the concurrent use of blood circulation aids or drugs primarily metabolized by CYP3A4 [99,100]. Most of the reports revealing significant Ginseng-drug interactions are based on *in vitro* findings, such as those involving hepatocytes, supersomes, and microsomes [93]. Direct exposure to the incubation matrix may exaggerate the modulatory strength of ginsenosides on metabolic enzymes or transporters owing to the lack of complete PK behavior and leading to inconsistent results in *in vivo* and *in vitro* studies. To our knowledge, only two clinical trials have shown significant Ginseng-drug interactions, which have the potential to be clinically relevant. However, these two studies revealed contradictory results regarding the changes in plasma levels of the CYP3A4 substrates, nifedipine and midazolam [101,102]. With the concurrent use of warfarin, several clinical observations have indicated that Ginseng products might increase the risk of bleeding [103,104]. A more recent case report demonstrated that Ginseng may indirectly result in liver injury and myositis in a patient consecutively treated with atorvastatin, potentially through Ginseng-mediated inhibition of CYP3A4 or OATP1B1 [105]. Although the reported interactions between Ginseng and co-administered Western

drugs are conflicting and most of them have been deemed clinically inconsequential, it is still recommended to closely monitor the plasma levels of CVD drugs with narrow therapeutic indices or heavy dependence on CYP3A4-mediated metabolism.

To date, the underlying mechanisms of Ginseng-related HDIs are primarily mediated by CYPs. Recent research on Ginseng-drug interactions has been extended to include transporters or UGTs [106–109]. Because some of deglycosylated ginsenosides are believed to be more active in interfering with the metabolism of co-therapeutic drugs [110,111], active metabolites produced by the gut microbiota are thought to be more likely to affect UGTs and transporters, especially in enterocytes [93]. In addition, it is worth noting that the inconsistencies in Ginseng-drug interactions between *in vitro* and *in vivo* results or between laboratory studies may be caused by many uncontrolled variables, such as dosing regimens, TCM cultivation conditions, and matrix differences. The dose-dependent biphasic effects of Ginseng may also be one of the reasons for the contradictory results [112].

3.3. Ginkgo (G. biloba)

The seeds of *G. biloba* (Ginkgo Semen) have been used as an herbal medicine in the Chinese Material Medica. The leaves of *G. biloba* (Ginkgo Folium) are now utilized globally, especially in Western countries. *G. biloba* is mainly used to improve cerebrovascular or peripheral vascular diseases and is frequently used to enhance cognition in the central nervous system [113,114]. *G. biloba* leaf extract (GBE) is a primary product (e.g., EGb 761) that is currently used in disease treatment or as a dietary supplement. Long-term use can promote peripheral blood circulation, improve the elasticity of blood vessels, lower blood lipids, and exhibit a myocardial protective effect [96,114]. The therapeutic effects of GBE on CVD are suggested to be mainly due to its two major types of active ingredients: flavonoids and terpene trilactones (Table 2). Published reports indicate that GBE mainly exerts antioxidant and anti-inflammatory effects through these two active ingredients, thereby protecting cardiovascular function [96].

Similar to Danshen, although there is more evidence regarding potential HDIs, the contraindications between Ginkgo and prescribed drugs remain highly uncertain [114]. Flavonoids have been shown to regulate the function of drug-metabolizing enzymes and transporters, and extensive research in this area has been reported [115,116]. Since one of the biological functions of Ginkgo itself is to improve blood circulation, it is common for patients to take GBE as a complementary medicine in the course of CVD treatment, especially concurrent with antithrombotic or antiplatelet drugs. Therefore, the most frequent case reports still involve drug interactions related to bleeding after the combined use of *G. biloba* [117–119]. Although a variety of *in vitro* results have indicated that GBE significantly decreased the oxidation activities toward CYP substrates [120,121], the results of clinical studies did not support the hypothesis that GBE can affect CYP activity in humans [121,122]. However, since there is a high possibility that GBE and anticoagulant or antiplatelet drugs could be co-administered, the risk of bleeding should be considered, particularly when they are concurrently used in long-term treatment [123].

In addition to drug substrates of CYPs, numerous studies have shown that *G. biloba* significantly alters the PK properties of statins by modulating transporter function [124–126]. The capability of GBE on the modulation of P-gp remains controversial (Table 3); however, more evidence suggested that OATP1B members could be the target transporters modulated by the active ingredients of *G. biloba* [124–127]. More detailed studies (such as PXR and gut microbiota) related to the underlying mechanism of transporter changes by *G. biloba* are currently in progress [126,128].

4. Potential HDIs between TCM formulas and prescribed CVD drugs

4.1. Shenmai injection (SMI) and Shengmai San (SMS) (Shenmai-Yin)

SMI is derived from the traditional Chinese herbal prescription Shendong yin, which consists of Ginseng and Ophiopogonis Radix (the tuber of *Ophiopogon japonicus*) [130]. In China, SMI has been widely used for the treatment of chronic heart failure. Both acute (0.5 h) and 7-day intraperitoneal treatment of rats with SMI (5 mL/kg) increased the AUC and decreased the clearance of midazolam (a CYP3A substrate), suggesting a potential PK interaction with CYP3A drug substrates [131,132]. Since midazolam was administered 0.5 h after SMI in both treatments, acute effects were included in the changes after repeated treatments. However, PKs of theophylline remained unchanged under the SMI treatment, suggesting the lack of influence on the metabolism of CYP1A2 drug substrates.

Different from the administration method and component herbs of SMI, SMS is administered

orally and contains an additional TCM, Schisandrae Fructus (the ripened fruit of *Schisandra chinensis*). In Taiwan's TCM prescriptions for patients with ischemic heart disease, 16% of prescriptions contained SMS, which was among the top three frequently used formulas [78]. A 1-h pretreatment of rats with SMS decreased nifedipine clearance, accompanied by decreased hepatic oxidation activity, which was primarily catalyzed by CYP3A [133]. However, 3-week repeated oral treatments with SMS suppressed rat intestinal, but not hepatic, nifedipine oxidation activity [134]. Accordingly, nifedipine clearance decreased and AUC_t increased. In patients taking nifedipine/felodipine, additional SMS treatment increased the incidence of headaches but decreased all-cause mortality [135].

The decreased CYP3A activity can be attributed, at least in part, to the Ophiopogonis Radix-mediated suppression of intestinal CYP3A activity. The results of the *in vitro* inhibition study indicated the presence of time-dependent CYP3A inhibitor(s) in SMS. Among the SMS ingredients, the Schisandra lignan, schisandrin B was reported to be a PXR activator [136] but also potently inhibited rat liver microsomal CYP3A activity [133]. Although drug interactions occur *in vivo*, reversible and irreversible inhibition, as well as induction, may work in a complex manner. At an equivalent dose to that from Schisandrae Fructus in SMS preparations, Schisandrae Fructus decoction (0.35 g/kg/day, 3 weeks) could not stimulate nifedipine oxidation activity [134]. These reports suggest a potential dose-dependent mixed type of CYP3A modulation by Schisandra ingredients. Thus, in addition to the impaired intestinal CYP3A function by Ophiopogonis Radix and its ingredients, the potent inhibition of nifedipine oxidation by schisandrin B/schisantherin A should be considered during repeated SMS treatments [134,135].

Methylophiopogonanone A, an active homoisoflavonoid of Ophiopogonis Radix, has been reported to strongly inhibit UGT1A1 ($IC_{50} = 1.23$ μM) and several other UGT isozymes ($IC_{50} < 8.30$ μM) in HLMs [137]. Six Schisandra lignans in *S. chinensis* have mild-to-moderate inhibitory effects on UGT1A1 and UGT1A3 activities ($IC_{50} > 15$ μM) in HLMs [138]. Deoxyschizandrin and schisantherin A inhibit UGT1A3 with IC_{50} values equal to 10.8 and 12.5 μM in a recombinant UGT system, respectively [139]. However, acute (1 h) and repeated (daily for 3 weeks) treatments with SMS powdered decoction did not cause significant changes in rat hepatic and intestinal UGT activities [133,134]. To reveal the impact of UGT inhibition by these ingredients of SMS component herbs, further studies on the PK changes in glucuronide metabolites are crucial.

4.2. Shu-Jing-Hwo-Shiee-Tang (SJHST)

SJHST is an herbal formula prepared using 17 herbs, namely Paeoniae Radix (*Paeonia lactiflora*), *Angelica sinensis* Radix (Danggui, *A. sinensis*), Rehmanniae Radix (*Rehmannia glutinosa*), Persicae Semen (*Prunus persica*), Cyathulae Radix (Chuan Niu Xi, *Cyathula officinalis*), Citri Reticulatae (*Citrus reticulate)*, Clematidis Radix (*Clematis chinensis*), Atractylodis Rhizoma *(Atractylodes lancea)*, Gentianae Radix et Rhizoma (*Gentiana scabra*), Poria (*Poria cocos*), Chuanxiong Rhizoma (*Ligusticum chuanxiong*), Stephaniae tetrandrae Radix (*Stephania tetrandra*), Notopterygii Rhizoma et Radix (*Notopterygium incisum*), Saposhnikoviae Radix et Rhizoma (*Saposhnikovia divariata*), Angelicae dahuricae Radix (Bai Zhi, *Angelica dahurica*), Zingiberis Rhizoma (Ginger, *Zingiber officinale*) and Glycyrrhizae Radix et Rhizoma (Gan cao, licorice, *Glycyrrhiza uralensis*) [140]. In patients with hypertension, the frequency of SJHST use in prescriptions was 4.5% in Taiwan [7]. SJHST has been frequently used in patients with thrombosis-associated pain and osteoarthritis, and prolonged PT has been observed in patients receiving both SJHST and warfarin treatments for 1–2 weeks [140]. A 2-week SJHST treatment did not affect coagulation parameters in rabbits. However, compared to rabbits treated with warfarin alone, the coagulation parameters PT and activated partial thromboplastin time (APTT) were significantly prolonged in the rabbit group concurrently and repeatedly treated with SJHST (1–2 mg/kg/day) and warfarin (1.5 mg/kg/day) for 2 weeks [140] (Table 3). In a rat study, co-treatment with SJHST (1 g/kg) and warfarin did not alter the PKs of warfarin [141]. However, SJHST administration to rats 2 h after warfarin treatment resulted in 2–3-fold increases in the C_{max} and AUC of warfarin. Consistent with the increased AUC, PT was prolonged 24 h after warfarin administration when SJHST was administered 2 h after warfarin. Alterations in the PK parameters of warfarin may be one of the factors leading to the increase in coagulation time by SJHST in the warfarin-treated group. In addition, there was no significant change in plasma warfarin level when SJHST-enhanced PT elongation was detected 24 h after warfarin treatment. At 8 h, with a maximal increase in plasma warfarin levels, PT remained unchanged. The lag time required for pharmacological changes in the victim drug should be considered in the HDI assessment. These animal studies suggest that an appropriate time interval

between the administration of SJHST and the drugs should be considered to prevent adverse effects in patients receiving both treatments.

The extracts of some component herbs of SJHST showed potential antiplatelet aggregation and PK interactions with warfarin. Platelet aggregation decreased when ginger was administered at a high daily dose of 5 g, but not at 3.6 g, in healthy volunteers [142]. Indeed, SJHST (at a dose equivalent to the human daily dose of SJHST prepared from the decoction containing 3 g ginger) alone did not affect PT in rats. In rabbits, the aqueous extract of *A. sinensis* Radix (2 g/kg) has been reported to reduce PT without affecting the PKs of a single dose of warfarin (subcutaneous). In rats, the aqueous extract of Chuanxiong Rhizoma (10 g/kg) increased the AUC_t of warfarin (oral) [143], but Glycyrrhizae Radix et Rhizoma extract (0.9 g/kg) increased warfarin (intravenous) clearance [136]. The SJHST-mediated increase in the AUC of plasma warfarin can be associated with decreased 7-hydroxylation of warfarin, which is the primary metabolic pathway of pharmacologically active S-warfarin. This inhibition did not show the characteristics of a time-dependent CYP inhibitor [141]. Among the digested ingredients of component herbs, angelicin, hesperetin, naringenin and tetrandrine inhibit warfarin 7-hydroxylation [141]. These ingredients may contribute to the decreased elimination of warfarin after SJHST consumption.

4.3. Wu-Chu-Yu-Tang (WCYT) or Wu-Zhu-Yu-Tang

WCYT (Goshuyu-to in Japanese Kampo medicine) contains Evodiae Fructus (Wu-Chu-Yu or Wu-Zhu-Yu, *Evodia rutaecarpa*), Ginseng Radix (ginseng, *P. ginseng*), Zingiber Rhizoma (ginger, *Z. officinale*), and Zizyphi Fructus (Tai-Geui, *Ziziphus jujuba*). WCYT is used for the treatment of migraine and vomiting accompanied by a cold and heart failure [144,145]. WCYT has been reported to retain body temperature in chlorpromazine-treated rats and inhibit platelet aggregation in whole blood from guinea pigs [146,147]. Repeated treatment with WCYT decoction potently stimulates CYP1A activity and the expression of CYP1A2 in mice [144]. Among the component herbs of WCYT, Evodiae Fructus and its main alkaloids rutaecarpine contribute to CYP1A induction [144]. Consistent with CYP1A2 induction, oral administration of WCYT to mice or rats increased the clearance of CYP1A2 substrates caffeine and theophylline (Table 3). A 3-day oral treatment with the alkaloid rutaecarpine (25–80 mg/kg) resulted in 26–95% decreases in the AUCs of acetaminophen (intravenous), caffeine (oral), and theophylline (intravenous) [144,146,148]. Reports showing only the determination of mRNA levels and *in vitro* studies without corroborating *in vivo* effects are not discussed here. Further human studies are crucial to examine the therapeutic efficacy of CYP1A2 drug substrates in patients receiving TCMs containing Evodiae Fructus.

5. Summary and perspectives

This review collected updated evidence that multiple factors shown in Fig. 3 should be noted in the combined use of TCMs and drugs in CVD patients. Bi-functional modulations are common in studies on HDIs. Literature reports indicate that the extracts of Danshen, Ginseng and Ginkgo might have contradictory effects on drug exposure, potentially due to (1) different source/preparation of the herb remedies, (2) diverse mechanisms of drug metabolism modulation, and (3) enzyme-transporter interplay involved in drug absorption and elimination. Thus, the dosing regimen (dose and frequency), metabolism-mediated modulatory effects (reversible or irreversible), and PK/PD properties (absorption, distribution, metabolism, and elimination (ADME) and onset of efficacy) of herbs and drugs are the determining factors for the occurrence of HDIs (Fig. 3). Unlike the immediate effect exerted by reversible inhibition, the induction of CYP/UGT/transporters requires a period of time, and repeated treatments are generally required for HDIs. For time-dependent CYP inhibitors, such as SMS, the time-period is also essential for the formation and accumulation of inactivated CYP to cause HDIs. In clinics, the PK/PD properties of the herb/drug are important factors for HDI assessment. SJHST is a good example of that because the enhancement of warfarin-prolonged PT occurs in the late stage of elimination phase where no significant changes in plasma warfarin levels. However, it should be noted that, despite understanding the chemical composition of herbs, the involvement of herbal polysaccharides, proteins, and lipids in HDIs requires further evaluation. Finally, the three single herbs and four compound prescriptions discussed in this review are frequently prescribed as CVD treatments and therefore are very likely to be used in combination with CVD drugs. HDIs are a double-edged sword. The interactions between Chinese and Western medicines are not entirely unfavorable. If HDIs can be used wisely to improve the therapeutic effects of disease treatment (e.g., by reducing the drug dosage, prolonging the dosing interval, or

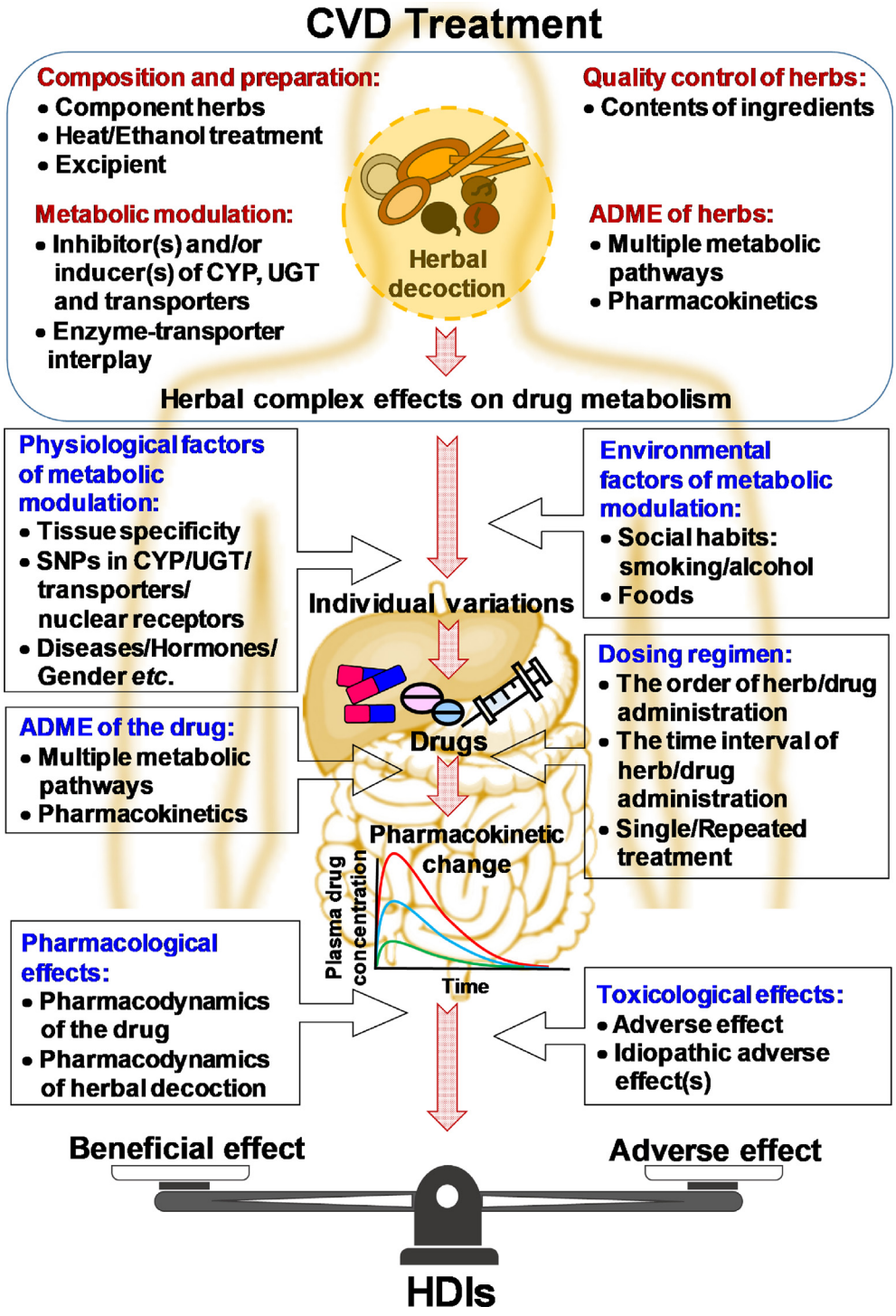

Fig. 3. Determinants of the adverse or beneficial effect in patients receiving both the herbal decoction and drug treatments. The composition and preparation, the CYP/UGT/transporter modulatory effects and ADME (absorption, distribution, metabolism and elimination) of the herbal decoction determine its complex effects on drug metabolism. When patients receive both herbal and drug treatments, in addition to the herb-induced complex effects, the herb-induced PK interaction with the drug can be affected by the physiological/environmental factors of metabolic modulation, dosing regimen of herb/drug, and ADME of the drug. Finally, the pharmacodynamics and toxicities of herb/drug should be considered to assess the beneficial and adverse effects in patients. ADME: absorption, distribution, metabolism and elimination; SNP: single nucleotide polymorphism.

diminishing the side effects), clinicians will have one more option in their choice of treatments. However, in the application of TCMs in patients with CVD, particularly those who require long-term drug treatment, both the metabolic alterations and PK/PD properties of herbs and drugs should

be considered to weigh the advantages and disadvantages of their combination therapy.

Declaration of competing interest

The authors declare no conflict of interest.

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