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Transporter modulation by Chinese herbal medicines and its mediated pharmacokinetic herb–drug interactions

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ABSTRACT

The increasing use of Chinese herbal medicines (CHMs) as complementary therapy and dietary supplement has been greatly raising the concerns about potential herb–drug interactions (HDIs). HDIs may cause the augmented or antagonized effects of prescription drugs, resulting in unexpected clinical outcomes. Therefore, it is of significance to identify or predict potential HDIs, and to delineate the underlying mechanisms. Drug transporters play key roles in transmembrane passage of a large number of drugs, affecting their absorption, distribution and elimination. Modulation of drug transporters has been recognized as one of the main causes of HDIs. In the last decade, a growing number of Chinese medicinal herbs and their derived phytochemicals have been identified to have modulatory effect toward transporter proteins, leading to pharmacokinetic HDIs when concomitantly used with conventional drugs. Some of these transporter-mediated interactions have already shown clinical significance. This review article focuses on two major transporter superfamilies, the solute carrier (SLC) and the ATP-binding cassette (ABC) transporters, to provide the recent advanced knowledge on CHMs and their inherent phytochemicals that interact with these transporters, and their induced pharmacokinetic HDIs from both preclinical and clinical aspects. In addition, the challenges and strategy for studying HDIs are also discussed.

1. Introduction

Chinese herbal medicines (CHMs) have been used to prevent or treat diseases for thousands of years in China, and are gaining increasing acceptance worldwide. As complementary medicine, the use of CHMs is often integrated into Western medicines. It has been demonstrated that many CHMs in combination therapies with Western medicines exert synergistic and/or additive effects, and in some cases alleviate side effects or toxicity of the concomitantly used drugs [1–6]. However, in the recent years, detrimental herb–drug interactions (HDIs) have been constantly reported. For instance, the risk of bleeding was enhanced when warfarin was concurrently administered with herbal medicines containing Yinxingye (*Ginkgo* Folium), Danggui (*Angelicae sinensis* Radix), or Danshen (*Salviae miltiorrhizae* Radix et Rhizoma) [7–9]. Xiao-chaihu-tang, a compound herbal formulation, could significantly decrease blood concentrations of prednisolone [10], and thus reduce its efficacy. More importantly, it has been pointed out that the risk of adverse drug reactions (ADRs) induced by HDIs is usually underestimated [11], which is primarily because of the limited knowledge on HDIs. Therefore, it is crucial to identify potential HDIs and evaluate the underlying mechanisms for guiding the rational use of such combinational therapies.

HDIs are commonly associated with the alteration of the victim drug's pharmacokinetics and/or pharmacodynamics. To date, most reported HDIs are of pharmacokinetic origin. Herbal medicines may increase or decrease the activity of drug metab-

Abbreviations: ADR, adverse drug reaction; ABC, ATP-binding cassette; AUC, area under plasma concentration *versus* time curve; BCRP, breast cancer resistance protein; CAR, constitutive androstane receptor; CE, capillary electrophoresis; CHM, Chinese herbal medicine; CL, clearance; C_{max}, the maximum plasma concentration; GC–MS, gas chromatography coupled to mass spectrometry; HDI, herb–drug interaction; LC–MS, liquid chromatography coupled to mass spectrometry; MRP, multi-drug resistance associated protein; NMR, nuclear magnetic resonance; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; PBPK, physiologically based pharmacokinetic; P-gp, P-glycoprotein; PXR, pregnane X-receptor; SAR, structure-activity relationship; SLC, solute carrier; CFDA, The China Food and Drug Administration; TCM, traditional Chinese medicine; $t_{1/2}$, half life.

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olizing enzymes and/or transporter proteins, and subsequently affect the metabolism and disposition of concomitant drugs, thus leading to changes in drug levels in plasma and specific tissues. HDIs are expected to occur during intestinal absorption, distribution, renal excretion and/or hepatic elimination of drugs. Besides the well-recognized drug metabolizing enzymes [*e.g.,* the cytochrome P450 isozymes (CYPs) and uridine diphosphate (UDP)-glucuronosyltransferases] that are important for drug metabolism and clearance, drug transporters have been greatly acknowledged to play an essential role in HDIs [12–14]. Transporters are widely expressed in the epithelial cells of the intestine and kidney, hepatocytes, and also in sanctuary sites, such as the brain, testes, and placenta, that is, at level of barriers crucial for drug intestinal absorption, tissue distribution, and elimination [15]. Indeed, alteration of transporter expression and/or functions caused by herbal medicines often lead to untoward consequences regarding altered efficacy and safety of co-administered substrate drugs, especially for those drugs with narrow therapeutic windows. In the past few years, a large number of CHMs and their derived phytochemicals were found to exhibit modulatory effect toward different transporters, and transporter-mediated HDIs have been extensively reported. Some of these transporter-mediated interactions have been already known to show clinical significance.

Therefore, this review aims to highlight up to date knowledge on CHMs and their derived phytochemicals that interact with two major transporter families [solute carrier (SLC) and ATP-binding cassette (ABC) transporters], and their induced pharmacokinetic HDIs from both preclinical and clinical reports. Challenges and strategies for studying HDIs are also discussed.

2. Role of transporters in HDIs

Drug metabolizing enzymes and transporters are two major factors involved in pharmacokinetic HDIs. Although, comparing with drug metabolizing enzymes, the current knowledge on the impact of transporters on drug efficacy and safety is still limited, it has been globally recognized that transporters governing the drug movement across the biological membranes are highly related with drug absorption, distribution and elimination [16].

There are two major transporter superfamilies, namely SLC and ABC transporters, involved in transporter-mediated HDIs. In general, the ABC transporters, including P-glycoprotein (P-gp or MDR1), multi-drug resistance associated proteins (MRPs) and breast cancer resistance protein (BCRP or ABCG2), mainly mediate efflux of drug substrates, whereas the SLC transporters, including organic cation transporters (OCTs), organic anion transporters (OATs) and organic anion-transporting polypeptides (OATPs), are considered to be responsible for uptake of substrates into cells. These efflux and uptake transporters are extensively expressed in the apical and luminal membrane of epithelia of many organs (*e.g.,* intestines, kidney, liver, brain, testis and placenta) that relate to drug disposition. Therefore, the modulation of these transporters by CHMs may occur in various organs, leading to the alteration of pharmacokinetic fates of concomitantly used drugs that are substrates of transporters.

To predict potential HDIs, or delineate the underlying mechanisms, it is critical to understand the tissue distribution of transporters and to identify their substrates, inhibitors and inducers. Fig. 1 illustrates the major SLC and ABC transporters expressed in the major human organs and the major CHMs and/or their derived constituents that are involved in the modulation of drug transporters.

2.1. Transporters and drug absorption

Efflux transporters like P-gp, MRP2, and ABCG2 are highly expressed in the apical membrane of enterocytes, serving as first-line barrier of many orally administered substrate drugs entry into the systemic circulation. CHMs that inhibit or induce efflux transporters may significantly alter the intestinal absorption of co-administered drugs. Specifically, inhibition of efflux transporter function results in increased bioavailability of substrate drugs, whereas the induction of efflux transporter expression may lead to restricted drug absorption. A large number of herbal extracts and specific constituents have been demonstrated to modulate efflux transporters in the intestines. For instance, herbal extracts, such as Yinxingye extract and Nanwuweizi (Schisandrae aphenontherae Fructus) extract, were reported to inhibit human intestinal P-gp, improving the absorption of some substrate drugs like talinolol and tacrolimus [17,18]. In contrast, long-term oral administration of Danshen (*S. miltiorrhizae* Radix et Rhizoma) extract can induce intestinal P-gp and consequently decrease systemic exposure of fexofenadine in healthy subjects [19].

Major uptake transporters expressed in the membrane of enterocytes include OATP1A2 and OATP2B1. They also play a role in the absorption of substrate drugs like fexofenadine, ouabain, statins, the opioid receptor agonists DPDPE and deltorphin II, and the thrombin inhibitor CRC-220. Thus the oral bioavailability of these substrate drugs is readily affected when foods or medicinal herbs with modulatory effect toward OATPs are co-administered. It was reported that fruit juices, such as grapefruit, orange and apple juices, decreased the oral bioavailability of fexofenadine in humans by inhibition of OATP1A2 [20,21]. Modulation of OATP1A2 and OATP2B1 by several flavonoids such as kaempferol, quercetin and apigenin derived from Yinxingye can also result in clinically relevant HDIs [22,23].

HDIs frequently occur during the absorption process of orally administrated substrate drugs through transporter modulation. The risk is of particular high because most herbal medicines are taken orally and the concentrations of their effective constituents can be high in the gastrointestinal tract.

2.2. Transporters and drug distribution and excretion

Transporters are widely expressed in organs that are involved in drug distribution and excretion, such as liver, kidney, brain, testes and placenta (Fig. 1).

In the liver and kidney, efflux pumps (*e.g.*, P-gp, ABCG2, MRPs) are mainly found in the canalicular of the hepatocytes, and the luminal membrane of kidney proximal tubules, while uptake transporters (*e.g.*, OATs, OCTs, OATPs) are mostly expressed in the basolateral membrane of hepatocytes and proximal tubule epithelia [15,24]. These efflux and uptake transporters are important for distribution of substrate drugs into liver and kidney, and excretion from these organs. Inhibition of efflux transporters by CHMs and constituents thereof have been well recognized, usually leading to reduced excretion of transporter substrates. Quercetin, a flavonoid from Yinxingye caused increased systemic exposure of the anticancer drug irinotecan by reducing P-gp-mediated excretion from liver [25]. On the other hand, inhibition of uptake transporters has also been frequently reported. Metformin is an oral antidiabetic drug that has been identified as an OCT substrate. Concurrent use of metformin with berberine resulted in significantly decreased metformin elimination from kidney due to OCT2 inhibition by berberine [26]. In addition, extract of Dahuang (Rhei Radix et Rhizoma) and its major constituent rhein can inhibit OAT1/3 and cause HDIs [27]. OATPs are also expressed in the liver, and their known inhibitors from natural products include ursolic acid [28], saikosaponin A [29], icariin [30] and quercetin [22].