

The Interactions of Herbal Compounds with Human Organic Anion/Cation Transporters

Xiaoxi Lu¹, Ting Chan¹, Chenghao Xu¹, Wee Vean Ng¹, Ling Zhu² and Fanfan Zhou^{2*}

¹Faculty of Pharmacy, The University of Sydney, NSW, Australia

²Retinal Therapeutics Research Group, Save Sight Institute, The University of Sydney, Sydney, NSW, Australia

Abstract

The Solute Carrier transporters (SLCs) are a superfamily of membrane proteins responsible for cellular influx of various molecules. The Organic anion transporting polypeptides (OATPs), Organic anion transporters (OATs) and Organic cation transporters (OCTs) are essential SLC subfamilies that largely impact on drug performance. These Organic anion/cation transporters are widely expressed in epithelium throughout the body, where they play essential roles in cellular uptake of many endogenous substances like hormones and a wide range of exogenous molecules including clinically important drugs such as statins, anti-cancer agents and antibiotics. Herbal medicines that derived from plants, fruits and vegetables have been long presumed to be safe by the general public. The growing use of herbal products together with other agents has raised many concerns due to unexpected adverse effects. Drug-drug/herb interactions through SLC transporters often result in unsatisfied therapeutic outcomes and/or unexpected toxicities. This review will give an update on the interactions of herbal compounds with human Organic anion/cation transporters in order to form the basis of better and safer drug therapies.

Keywords: Solute carrier transporters; Organic anion transporters; Organic cation transporters; Organic anion transporting peptides

Abbreviations

OATs: Organic Anion Transporters; OCTs: Organic Cation Transporters; OATPs: Organic Anion Transporting Peptides; SLCs: Solute Carrier Transporters

Introduction

The Solute carrier transporters (SLCs) are important membrane proteins responsible for cellular influx of a wide range of molecules. They have been widely studied by researchers especially in the renal and hepatic physiology field for a long period of time. The Organic anion transporting polypeptides (OATPs) encoded by *SLCO* gene family, Organic anion transporters (OATs) and Organic cation transporters (OCTs) falling into the *SLC21* gene family are the most important SLC subfamilies relevant to drug performance.

OATs, OCTs and OATPs widely distribute throughout the epithelium of human key organs including the kidney, liver and intestine, where they facilitate the access of many endogenous and exogenous substances to specific tissues (Table 1) [1-3]. Therefore, these transporters are broadly recognized to be clinically important in the absorption, distribution and elimination of drugs [4]. And pharmaceutical inventors are required by the regulatory authorities to evaluate the potentials of drug-drug interactions through the essential Organic anion/cation transporters in the pre-clinical phase of drug development.

Herbal medicines derived from plants, fruits and vegetables are widely adopted in the world especially in many Asian countries. They have been considered to be safe by the general public. However, there are reports of unexpected adverse events with the co-administration of herbal medicines and pharmaceutical agents. Arising knowledge in the recent decade indicated that many herbal compounds are modulators of OATs, OATPs and OCTs, which significantly impact on cellular uptake of other transporter substrates. With an increasing use of herbal medicines, it is plausible that therapeutic toxicities likely occur due to drug substrates competing for specific transporters with herbal

compounds. Therefore, knowledge about the interactions of natural compounds on the Organic anion/cation transporters is essential to prevent alterations of the performance of clinically important drugs [5]. In this review, tissue distribution, substrate specificity, clinical significance and interactions with herbal compounds are described for those well characterized OAT, OCT and OATP isomers.

Organic Anion Transporters

OATs are known to mediate uptake of water-soluble, negatively charged organic molecules with low molecular weight such as steroid hormones and their conjugates, biogenic amines, numerous drugs and toxins [6,7]. So far, there are nine human OAT isoforms identified with OAT1, OAT2, OAT3 and OAT4 better characterized [1,6].

Tissue distribution

OAT1 was first discovered as a para-aminohippurate (PAH) transporter in 1997 [7-9], which is abundantly expressed at the basolateral membrane of renal proximal tubular cells [10-15]. OAT2 was found to be predominantly expressed in the liver and also located at the blood-facing membrane of renal tubular cells [16,17]. OAT3 is widely expressed in the kidney, brain and liver [18]. OAT4 distributes at the apical membrane of renal proximal tubular cells and the basolateral membrane of syncytiotrophoblasts in the placenta [12,19-22]. OAT5 and OAT7 are found in human liver, while OAT10 distributes at the apical membrane of renal proximal tubules cells [23-25].

*Corresponding author: Fanfan Zhou, Faculty of Pharmacy, The University of Sydney, Sydney, NSW, 2006, Australia, Tel: 61-2-9351-7461; Fax: 61-2-9351-4391; E-mail: fanfan.zhou@sydney.edu.au

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	Liver	Intestine	Kidney	Blood Brain Barrier	Placenta
Apical membrane		OATP1A2 OATP2B1 OCT1 OCTN1 OCTN2	OATP1A2 OAT4 OCTN1 OCTN2	OATP1A2 OATP2B1	OATP4A1
Basolateral membrane	OATP1B1 OATP1B3 OATP2B1 OAT2 OCT1 OCT3		OATP4C1 OAT1 OAT2 OAT3 OCT2 OCT3		OATP2B1 OAT4

Table 1: Localization of the major SLC transporters in human epithelium [1-3].

Substrate specificity

OATs are responsible for the transport of lower molecular mass molecules compared to OATPs. Their endogenous substrates include α -ketoglutarate, prostaglandins and cyclic guanosine monophosphates [9,26,27]. Additionally, they are capable of mediating the uptake of therapeutic drugs such as NSAIDs, antivirals and anti-cancer agents. For example, OAT3 is responsible for the uptake of cimetidine, a histamine H2-receptor antagonist widely used in treating heartburn and peptic ulcers, as well as that of methotrexate, an anti-metabolite and anti-folate drug frequently used to manage cancers and autoimmune diseases [28].

Clinically significance

In vitro and *in vivo* studies have shown that OAT1 and OAT3 are primarily responsible for uptake of common drug substrates from blood to renal proximal tubular cells [29]. Due to their broad substrate specificities, OAT1 and OAT3 play essential roles in renal excretion of many drugs and toxins. For instance, the drug-drug interaction between probenecid and methotrexate was discovered in 1970s [30,31], which was later identified as probenecid-induced down-regulation of methotrexate transport via OAT1 and OAT3 [32].

The interactions of herbal compounds with OATs

Several previous studies of others and us have demonstrated that various natural compounds are potent inhibitors or substrates of OATs (Table 2). OAT1 and OAT3 are the two well-known OAT isoforms mainly distributed at the blood-facing basolateral membrane of the renal proximal tubular cells, where they facilitate the renal excretion of a wide range of substances; while OAT4 is one of the key players of renal re-absorption present at the luminal-facing apical membrane of the proximal tubule. The transport activities of these three OAT isoforms are of the most interests to researchers with many studies extensively evaluated their roles in drug performance.

Our laboratory conducted a series of studies to explore the interactions of clinically important natural compounds with thirteen essential SLC transporters that are best characterized so far. These transporters broadly cover the ranges of OATs, OATPs and OCTs/OCTNs and greatly influence the pharmacokinetic performance of many pharmaceutical agents. In our studies, we identified that ursolic acid, the active component of *Punica granatum* Linnaeus (pomegranate), was found to inhibit OAT3 transport activity [19]. Due to the anti-oxidant property and anti-diabetic potentials of pomegranate, products derived from this fruit are very popular worldwide, the increasing use of which might significantly impact on therapies involved with drugs that are substrate of OAT3. In addition, wogonin and baicalin, the two major active ingredients of *Scutellaria baicalensis* were shown to markedly inhibit OAT1-, OAT3- and OAT4-mediated substrate uptake [33]. Since these compounds commonly

used in treating inflammation, hypertension and many infections [34], such finding is also clinically significant.

Wang et al. revealed that Lithospermic acid (LSA), salvianolic acid A (SAA) and rosmarinic acid (RMA) that are enriched in commercial Danshen preparations, are potent inhibitors of OATs. In details, RMA was shown to significantly down-regulate the transport activity of OAT1 and OAT3; while LSA and SAA was found to potently interact with OAT3 [35]. Since Danshen has been long used in cardiovascular treatment, there might be herb-drug interactions in situations of co-administration of Danshen with clinical agents known to be substrates of these OATs. In another study of this group, the authors demonstrated that rhein, the main component of Rheum sp. in treating osteoarthritis and diabetic nephropathy, selectively inhibit the uptake of OAT1 and OAT3; while it has much less impairment on OAT4-mediated substrate influx [36]. Gallic acid, a major component of many herbal products has also been demonstrated to be a potent inhibitor of hOAT1 and hOAT3, the plasma concentration of which is sufficient to cause drug-herb interactions [37].

Grapefruit juice has long been implicated in drug-herb interactions of therapies. The main constituents of grapefruit juice are flavonoids, five of which including morin, silybin, naringin, naringenin and quercetin have been explored for their interactions with OAT1 and OAT3 [38]. Morin and silybin are potent inhibitors of OAT1; while all the five flavonoids tested in this study has less pronounced interactions with OAT3.

Nephrotoxicity related incidents have been reported following consumptions of common herbal products made from Aristolochiaceae [39-41]. Aristolochic acids (mainly AA-I and AA-II) contained in these herbal medicines were later found to be associated with these adverse effects. Both AA-I and AA-II potently inhibit the substrate uptake mediated through OAT1 and OAT3 as well as moderately impact on that of OAT4 [42].

Interestingly, the major metabolites and/or derivatives of various natural compounds were also reported to be inhibitors or substrates of OATs. For instance, 3-monoglucuronyl-glycyrrhetic acid (3MGA), one of the major metabolites of glycyrrhizin (GL), has been demonstrated to be a substrate of OAT1 and OAT3 [43]. And GL is the main component of the root of *glycyrrhiz* widely used in treating chronic hepatitis C and gastric ulcers in Japan and Europe [44,45]. It is noteworthy that steviol (the aglycone metabolite of the noncaloric natural sweetener Stevioside) but not its parental compound, markedly inhibits the transport activity of OAT1 and OAT3 [46].

Organic Anion transporting peptides (OATPs)

OATPs govern cellular uptake of amphipathic molecules with molecular weights of more than 350Da [6]. They are widely distributed in many tissues, including the blood-brain-barrier, choroid plexus,

Transporter	Herbal compound	Substrate/ Inhibitor	IC ₅₀ (μ M)	Ki (μ M)	Km (μ M)	Reference
OAT1	Baicalein	Inhibitor	11.8 \pm 6.2	ND	ND	[33]
	Wogonin	Inhibitor	5.4 \pm 2.8	ND	ND	[33]
	Rosmarinic acid	Inhibitor	ND	0.35 \pm 0.06	ND	[36]
	Aristolochic acids (AA-I)	Inhibitor	0.44 \pm 0.08	0.08 \pm 0.15	ND	[42]
	Aristolochic acids (AA-II)	Inhibitor	1.06 \pm 0.09	ND	ND	[42]
	Rhein	Inhibitor	0.0771 \pm 0.0055	0.0715 \pm 0.0052	ND	[36]
	Gallic acid	Inhibitor	1.24 \pm 0.36	1.08 \pm 0.26	ND	[37]
	3-monoglucuronyl-glycyrrhethinic acid	Substrate	ND	ND	50.9	[43]
	OAT3	Ursolic acid	Inhibitor	18.9 \pm 8.20	ND	ND
Baicalin		Inhibitor	13.0 \pm 5.1	ND	ND	[33]
Baicalein		Inhibitor	2.4 \pm 1.3	ND	ND	[33]
Wogonin		Inhibitor	1.3 \pm 0.3	ND	ND	[33]
Rosmarinic acid		Inhibitor	ND	0.55 \pm 0.25	ND	[36]
Lithospermic acid		Inhibitor	ND	0.59 \pm 0.26	ND	[36]
Salvianolic acid A		Inhibitor	ND	0.16 \pm 0.03	ND	[36]
Aristolochic acids (AA-I)		Inhibitor	0.65 \pm 0.08	0.84 \pm 0.10	ND	[42]
Aristolochic acids (AA-II)		Inhibitor	1.28 \pm 0.18	ND	ND	[42]
Rhein		Inhibitor	0.0084 \pm 0.0025	0.0077 \pm 0.0074	ND	[36]
Gallic acid		Inhibitor	9.02 \pm 3.24	8.44 \pm 3.03	ND	[37]
3-monoglucuronyl-glycyrrhethinic acid		Substrate	ND	ND	21.3	[43]
OAT4		Baicalin	Inhibitor	15.6 \pm 5.50	ND	ND

ND: Not determined.

Table 2: The interactions of herbal compounds with human OATs.

intestine, kidney, placenta and testes [47]. Until now, 11 human OATP isoforms have been identified, which are divided into six subcategories (OATP1-6).

Tissue distributions: OATP1A2 is the first classic OATP membrane isolated in human with tissue localization in multiple organs [48,49]. OATP1A2 is expressed in cholangiocytes and is involved in the reabsorption of xenobiotics excreted into the bile [50]. It is also expressed at the apical membrane of the distal nephron [50], where it is responsible for the reabsorption from or the secretion of xenobiotics into the urine. OATP1B1 and OATP1B3 are liver specific OATP isoforms [51-53]. OATP2A1 is ubiquitously located throughout the body as a prostaglandin transporter [54,55]. OATP2B1 is another isoform with wide tissue distribution [56]. OATP4C1 is a renal specific isoform with high-affinities to digoxin and thyroid hormones [57]. Among all the OATPs, OATP1A2, OATP1B1, OATP1B3 and OATP2B1 are well characterized with regards to drug performance [58].

Substrate specificity: OATPs have a wide spectrum of substrates, the majority of which are large hydrophobic anions. The prototypical endogenous substrates of OATPs include bile acids, thyroid hormones, prostaglandins, eicosanoids, steroids and their conjugates [59]. For instance, OATPs mediate the hepatic uptake of microcystin, the toxin in blue-green algae that is a major water-borne pollutant in the world [60]. The classic exogenous drugs that transported through OATPs are imatinib, fexofenadine, methotrexate, HIV protease inhibitors and statins [6,61].

Clinical significance: OATPs expression has been found to be altered in disease states. Previous studies have shown that mRNA expressions of OATP1A2, OATP1B1 and OATP1B3 were decreased in the liver under conditions of cholestasis [62-64]. OATP1B1 expression is reduced in patients with severe versus mild viral hepatitis [65].

Defective genes that encode variant OATPs may impair the clearance

of albumin-bound bilirubin leading to severe neonatal jaundice and unconjugated hyperbilirubinemia (Gilbert's Syndrome, affecting 2-5% of the population) [66,67]. Moreover, it has been suggested that OATP dysfunction is a significant pathological component of fibrosis [68], inflammatory bowel disease [69] and cholestasis [70].

Several genetic variants coded by OATP polymorphisms possess decreased or abolished transport function. Naturally occurring variants of OATP1A2 have been implied to influence the disposition of methotrexate, imatinib and central nervous drug entry [50,61,71]. Several single nucleotide polymorphisms of OATP1B1 have been indicated to be associated with altered pharmacokinetic performance of drugs such as pravastatin and nateglinide [72-76]. Research also demonstrated that natural mutations in OATP2B1 gene might be important in pharmacokinetics of fexofenadine [77].

The interactions of herbal compounds with OATPs: OATP1B1, OATP1B3, OATP2B1 are in charge of the uptake of molecules into the hepatocytes to initiate the subsequent biliary excretion and/or drug metabolism; while OATP1A2 assists in the reabsorption of clinically important and frequently prescribed drugs from the bile duct in liver. OATP1A2 is also involved in the reabsorption from or the secretion of xenobiotics into urine in the kidney and OATP2B1 facilitates the intestinal absorption of many drugs at the apical membrane of enterocytes. Therefore, these OATP isomembers are essential to drug absorption, distribution and elimination. Up to date, a wide range of herbal compounds has been shown to possess inhibitory effects on OATP-mediated uptake (Table 3). The findings have profound significance in clinical settings as to prevent drug-drug/herb interactions through these transporters in therapies.

Our group recently reported that Baicalein and baicalin isolated from *Scutellaria baicalensis* have potent inhibitory effect on OATP1B3 uptake; while baicalin can also impair the substrate uptake mediated through OATP2B1 [33]. And the active components of pomegranate,

Transporter	Herbal compound	Substrate/ Inhibitor	IC ₅₀ (μ M)	Ki (μ M)	Km (μ M)	Reference
OATP2B1	Ursolic acid	Inhibitor	11.0 \pm 5.0	ND	ND	[19]
	Baicalin	Inhibitor	5.6 \pm 3.2	ND	ND	[33]
	Baicalein	Inhibitor	ND	ND	ND	[33]
	Wogonin	Inhibitor	ND	ND	ND	[33]
	Icariin	Inhibitor	6.4 \pm 1.9	ND	ND	[78]
	Silybin A	Inhibitor	4.5	ND	ND	[80]
	Silybin B	Inhibitor	0.8	ND	ND	[80]
	Silychristin	Inhibitor	3.6	ND	ND	[80]
OATP1B3	Gallic acid	Inhibitor	1.6 \pm 0.6	ND	ND	[19]
	Baicalin	Inhibitor	13.7 \pm 3.6	ND	ND	[33]
	Baicalein	Inhibitor	7.7 \pm 2.4	ND	ND	[33]
	Wogonin	Inhibitor	7.7 \pm 3.1	ND	ND	[33]
	Icariin	Inhibitor	3.0 \pm 1.3	ND	ND	[78]
	Silybin A	Inhibitor	2.7	ND	ND	[80]
	Silybin B	Inhibitor	5.0	ND	ND	[80]
	Silychristin	Inhibitor	36.4	ND	ND	[80]
	Epicatechin-gallate	Substrate	ND	ND	34.1	[81]
	Epigallocatechin gallate	Substrate	ND	ND	13.2	[81]
OATP1B1	Dioscin	Substrate	ND	ND	2.08 \pm 0.27	[84]
	Baicalin	Inhibitor	121.0 \pm 9.3	ND	ND	[33]
	Baicalein	Inhibitor	172.6 \pm 6.3	ND	ND	[33]
	Wogonin	Inhibitor	>200	ND	ND	[33]
	Icariin	Inhibitor	21.9 \pm 2.0	ND	ND	[23]
	Silybin A	Inhibitor	9.7	ND	ND	[80]
	Silybin B	Inhibitor	8.5	ND	ND	[80]
	Silychristin	Inhibitor	9.0	ND	ND	[80]
	Periplocin	Inhibitor	ND	ND	ND	[85]
	Epigallocatechin gallate	Inhibitor	7.8	ND	ND	[81]
	OATP1A2	Epicatechin gallate	Substrate	10.2	ND	10.4
Epigallocatechin gallate		Substrate	54.8	ND	18.8	[81]
Quercetin		Substrate	ND	ND	2.3 \pm 1.5	[83]
OATP4C1	3-monoglucuronyl-glycyrrhetic acid	Substrate	ND	ND	33.1	[43]

ND: not determined

Table 3: The interactions of herbal compounds with human OATPs.

ursolic acid and gallic acid significantly inhibit OATP2B1 and OATP1B3 activities [19]. We also showed Icariin, a natural prenylated flavonol glycoside popularly used to treat sexual dysfunction in males and osteoporosis remarkably impairs the substrate uptake via OATP1B1, OATP1B3 and OATP2B1, which observation is consistent with the early study [78,79].

The modulated functions of OATPs have also been widely reported in a number of early studies. The flavonolignans silybin A, silybin B and silychristin isolated from hepatoprotective *Silybum marianum* (milk thistle) are all capable of down-regulating the activities of OATP1B1, OATP1B3 and OATP2B1 [80]. Uptake of OATP1A2, OATP1B1 and OATP2B1 could be impaired by two of the flavonols enriched in Green Tea (*Camellia Simensis*), epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) [81]. Both flavonols were also confirmed to be substrates of OATP1A2 and OATP1B3 but not of OATP1B1 or OATP2B1 [81]. Because of the large consumption of green tea world-widely as to its reputed health benefits, such findings have profound clinically significance widely influencing pharmaceutical regimens. The wide screening of flavonoids present in Ginkgo biloba and grapefruit showed that these compounds have competitive inhibitions on substrate uptake mediated by OATP1B1 and OATP1B3 with quercetin, apigenin and naringenin being the most potent [82]. In the recent study of Glaeser et

al., quercetin showed a significantly increased uptake into OATP1A2-, OATP2A1- and OATP2B1-expressing cells; while Kaempferol was not likely a substrate of all these transporter isoforms [83].

Literatures also revealed several other natural compounds impair the activities of OATP isoforms. Dioscin is a natural spirostane saponin, which can be obtained from many oriental vegetables and traditional medicinal plants with anti-hepatitis, anti-tumor and anti-fungal effects. Literature revealed that dioscin is a potent substrate of OATP1B3 with high binding affinity [84]. Periplocin is the root of *Periploca sepium Bge* used in ancient china for alleviating rheumatic conditions. Its tumor suppressive and anti-chronic heart failure has recently been recognized. Liang et al. implied that OATPs (OATP1A2/1B1/1B3/2B1) might be involved with the intestinal absorption and biliary excretion of such compound [85], but further studies will be required to explore the interactions of periplocin with these OATP isoforms.

Similar to the cases of OATs, metabolite and/or derivatives of natural compounds have also been indicated to interact with OATPs, such as the liquorice metabolite 3MGA being a substrate of OATP4C1 [43].

Organic Cation Transporters (OCTs)

Besides OATs, the *SLC22A* gene family also encodes the Organic

Transporter	Herbal compound	Substrate/Inhibitor	IC ₅₀ (μ M)	K _i (μ M)	K _m (μ M)	Reference
OCT1	Quercetin	Substrate	ND	ND	2.2 \pm 0.2	[83]
OCT3	Wogonin	Inhibitor	3.7 \pm 1.3	ND	ND	[33]

ND: not determined

Table 4: The interactions of herbal compounds with human OCTs.

cation transporters (OCT1, OCT2 and OCT3) as well as the organic cation/carnitine transporters (OCTN1 and OCTN2). Like other SLC transporters, OCTs and OCTNs are also responsible for the uptake of numerous endogenous and exogenous substrates [6].

Tissue distribution: In common, OCT1, OCT2 and OCT3 are expressed in a variety of tissues such as the intestines, placenta and lung. OCT1 is mainly expressed at the basolateral membrane of hepatocytes [86]; while OCT2 protein is localized to the apical membrane of the distal convoluted tubules [87]. OCT3 is abundantly distributed in brain tissues. OCTN1 and OCTN2 have their tissue localization to the heart, placenta, skeletal muscle, kidney and pancreas [6].

Substrate specificity: OCTs facilitate the movement of small cationic molecules including catecholamines, monoamine neurotransmitters, 1-methyl-4-phenylpyridinium (MPP⁺) and about half of the therapeutic agents used in human like tetraethylammonium (TEA) [6]. OCTN1 and OCTN2 have extensive physiological roles in mediating bidirectional movements of important endogenous substrates, eg. both OCTN1 and OCTN2 are involved in the transport of carnitine and OCTN1 also facilitates the uptake of acetylcholine [88-90]. TEA is the common drug substrate of both OCTN1 and OCTN2; while the mushroom metabolite L-ergothioneine is a specific substrate of OCTN1 [91-93].

Clinical significance: OCT1 have been extensively studied for their associations with the pharmacokinetics of anti-diabetic drug metformin as well as the pharmacological responses of front-line anti-cancer agent imatinib [94-107]. OCT2 has also been implicated in pharmacokinetics of various drugs [108-111].

Deficiency of the diet component L-carnitine leads to immunosuppression and intestinal inflammation. Since L-carnitine is a shared substrate of OCTN1 and OCTN2, genetic polymorphisms of OCTN1 and OCTN2 have been intensively explored for their associations with many common gastrointestinal disorders such as inflammatory bowel disease, colorectal cancer and Crohn's disease [112-115]. Additionally they have also been implicated in other prevalent diseases like rheumatoid arthritis [116-119].

The interactions of herbal compounds with OCTs and OCTNs: Limited information is available with the influence of natural compounds on the transport activity of OCTs and OCTNs. OCT3 activity can be down-regulated in the presences of wogonin [33]. And quercetin is a substrate of OCT1; while its structurally similar flavonoid kaempferol is not a substrate of OCT1 [83] (Table 4). As mentioned above, the essential dietary component L-carnitine can be transported by both OCTN1 and OCTN2 [89,90]; while L-ergothioneine enriched in mushrooms selectively interact with OCTN1 [91-93].

Perspectives

Consumption of herbal products continuously increases in the world due to their reputed health benefits. They are often considered as supplementary and/or alternative to conventional therapies. In recent years, co-administration of drugs with herbal remedies widely raises concerns due to numerous cases of drug-herb interactions. Therefore

it is essential to review potential drug-drug/herb interactions as well as the underneath molecular mechanisms so as to prevent serious adverse effects in therapies.

SLC transporters especially OATs, OATPs and OCTs are widely expressed throughout the body and responsible for the cellular influx of many endogenous and exogenous substrates including numerous clinically important drugs and natural compounds. Drug-drug/herb interactions often occur when drugs competing specific transporter proteins with other drugs or herbal compounds. Limited knowledge about these transporter-mediated substrate interactions largely impedes the therapeutic optimization to avoid unfavorable adverse events. Studies to elucidate the influence of herbal preparations (as mixtures) on drug performance are not sufficient to reveal the problematic components leading to side effects, which then restrict the clinical applications of many herbal medicines. Therefore, exploring the interactions of individual herbal compounds with specific transporters should be warranted in order to serve better in developing safer and more efficient treatment strategies. Considering herbal products often have multiple constituents, the potential cumulative influence of herbal compounds on drug performance mediated through transporters could then be developed so as to better predict therapeutic outcomes in patients.

Disclosure statement

The authors claim no conflict of interests.

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