Journal of Food and Drug Analysis

Volume 26 | Issue 2 Article 3

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Review Article

Organic solute carrier 22 (SLC22) family: Potential for interactions with food, herbal/dietary supplements, endogenous compounds, and drugs

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ARTICLE INFO

Article history:
Received 31 October 2017
Received in revised form
2 March 2018
Accepted 5 March 2018
Available online 24 March 2018

Keywords:
Hepatic transport
Nephrotoxicity
Organic anion transporter
Organic cation transporter
Renal transport

ABSTRACT

Many drugs, hormones, components of herbal medicines, environmental pesticides and toxins are Solute Carrier family 22 (SLC22) substrates. The last twenty years has seen great progress in determining SLC22 tissue expression profiles, membrane localization, energetics, substrate profiles and biopharmaceutical significance. However, much still remains to be answered in terms of SLC22 family member's roles in 'normal' physiology as compared to pathophysiological states, as well as in drug interactions that impact pharmacokinetics, efficacy and toxicity. This review begins with a brief synopsis of SLC22 family discovery, function and tissue expression. Subsequent sections provide examples establishing a role for SLC22 transporters in food-drug, herbal supplement-drug, endogenous substrate-drug and drug–drug interactions.

1. Introduction

Over the last few decades increasing numbers of people have turned to herbal/dietary supplements, often with a rich history in traditional Chinese medicine (TCM), to alleviate illness, treat pathological conditions, enhance cognitive ability, boost self-confidence, etc. With their branding of being "natural," the use of herbal and dietary supplements has gained popularity worldwide as complementary therapy to conventional medicines, giving rise to emerging concerns of herb–drug interactions (HDIs) [1]. Use of herbal products by populations of developed countries has been steadily increasing, ranging between 31 and 71% in a recent survey, with as much as 66% of the population of Norway reporting the combined use of herbal products with prescribed medications [2,3]. According to the 2012 National Health Interview Survey, nearly 20% of American adults were using herbal products [4]. A recent comprehensive study concluded that amongst herbal product users in the United States, 38% were also taking prescription medications and 42% were also using over-the-counter products [5]. Thus, there is increasing potential for unintended interactions between components of herbal products, active pharmaceutical ingredients and their metabolites, and

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https://doi.org/10.1016/j.jfda.2018.03.002

endogenous molecules that are competing for the same cellular transport pathways. Exacerbating this potential is the fact that, due to their perception as being innocuous, herbal medicines and dietary supplements are produced, marketed and consumed with little to no regard for quality or regulatory control [1,6].

Standardization is problematic on a number of levels. Unlike most approved medications which contain only one or two active ingredients, herbal supplements are often composed of a mixture of several different plant components that each contain multiple active compounds (regardless of whether or not they produce a therapeutic effect) leading to variations in the amounts and combinations of pharmacologically active ingredients in any given lot of product, for both a single manufacturer and between manufacturers [7,8]. A consequence of this is that the extremely limited data in the literature regarding plasma concentrations of components of herbal medicines/supplements after oral dosing do not accurately represent any marketed product(s). Indeed, often the studies do not actually use a marketed product at all, but rather custom prepared extracts that contain components believed to be the active ingredients in marketed products. Additional challenges associated with herbal medicines include scientific misidentification, product adulteration, active ingredient instability, as well as failure of patients to disclose their use to providers [9]. Given the dearth of randomized clinical trial data, efficacy and toxicity data for herbal remedies are difficult to obtain making the assessment of their claimed benefits challenging. Currently, adverse reactions associated with herbal supplement use, including HDIs, are likely to be underreported, and are likely to occur at increasing rates as long as these products continue to be sold to consumers [10–12]. As a culprit for synergizing, augmenting, antagonizing or neutralizing the effects of conventional medications, HDIs are responsible for a number of undesirable clinical outcomes as conveyed in several case reports [8,11–15]. Besides potentiating toxicity, pharmacokinetic drug interactions may also cause loss of pharmacotherapeutic efficacy of the victim drugs [16]. Consequently, it is paramount that increased effort be directed toward controlled studies characterizing the biological mechanisms that underlie HDIs.

Herbal components may affect the activity and function of endogenous metabolic enzymes and/or transporters and thus lead to changes in systemic levels and the extent of organ distribution of concomitant drugs. In conjunction with the well-established role of enzymes (*e.g.*, cytochrome P450s and uridine diphosphate-glucuronosyltransferases) in drug metabolism and clearance, increasing evidence has shown involvement of drug transporters in HDIs [8,17–24]. Drug transporters are known to be responsible for the translocation of both endogenous and exogenous compounds across cellular membranes affecting their absorption, distribution and elimination [25–29]. As a result, there is potential for both, disruption in the 'normal' distribution and elimination of endogenous compounds (*e.g.*, neurotransmitters, toxic waste products of metabolism) as well as HDIs involving pharmacologically active phytochemicals in herbal products interacting with drug transporters leading to clinically significant pharmacokinetic changes when taken concurrently with prescribed medicines, particularly medications with narrow therapeutic windows [30]. Therefore, the intent of this review is to explore recent evidence for potential contribution of members of the solute carrier 22 (SLC22) family to drug-food, -herbal supplement, -endogenous compound, and -drug, as well as possible herbal supplement/endogenous compound, interactions.

2. SLC22 transporter family

Almost a quarter century has passed since the cloning of the first member of what is now recognized as the SLC22 organic cation/anion/zwitterion transporter family. Currently, the Human Genome Organization Gene Nomenclature Committee recognizes some 50 SLC families (http://www.genenames.org/cgi-bin/genefamilies/set/752) with the SLC22 family containing 23 proposed members (Oat5 [Slc22a19] and Oat6 [Slc22a20] are currently rodent specific) [31]. Within this group, eight members are extensively understood in terms of transport function, substrate specificity and driving forces; OCT1 (SLC22A1), OCT2 (SLC22A2), OCT3 (SLC22A3), OAT1 (SLC22A6), OAT2 (SLC22A7), OAT3 (SLC22A8), OAT4 (SLC22A11) and URAT1 (SLC22A12). While SLC22 family members are expressed in virtually every barrier membrane within the human body (including the blood-testis barrier, blood-brain barrier, blood-cerebrospinal fluid barrier, and various CNS cell types) expression and function in kidney, liver and intestine has received the most attention (Fig. 1).

Positively and negatively charged hydrophilic organic molecules of low molecular weight enter cells through the organic cation and organic anion transport systems first identified well over a half-century ago [27]. Experiments with renal membrane vesicles, tissue slices and intact tubules demonstrated that the inside negative membrane potential of a cell drives the uptake (cellular entry) of organic cations [32]. That is, cellular entry of organic cations mediated by SLC22 family members is driven by facilitated diffusion, which is 'powered' by the membrane potential difference and chemical gradient (Fig. 2). The driving force for cellular exit mediated by this transport system was found to be a three-step process ending in organic cation/proton (H^+) exchange [32]. Initially, Na^+/K^+-ATPase directly hydrolyzes ATP and pumps Na^+ out of the cell to establish an inwardly directed Na^+ gradient, which is subsequently used by Na^+/H^+ exchanger 3 to establish an inwardly directed H^+ gradient, that ultimately serves to power cellular exit of organic cations via an organic cation/H^+ antiporter (Fig. 2).

For organic anions, cellular entry mediated by SLC22 family members requires energy input to drive their movement against the membrane potential (Fig. 2). Experiments utilizing the above-mentioned systems demonstrated that uptake was coupled to established ion gradients (*e.g.*, Na^+, α-ketoglutarate) and not to direct ATP hydrolysis [32]. That is, cellular entry of organic anions mediated by SLC22 family members is driven by a three step process (similar to exit of organic cations) in which Na^+/K^+-ATPase establishes the inwardly directed a Na^+ gradient, the Na^+/dicarboxylate symporter 3 utilizes the movement of Na^+ ions down their concentration gradient (into the cell) to power entry of α–ketoglutarate into the cell (maintaining an outwardly directed gradient) and,

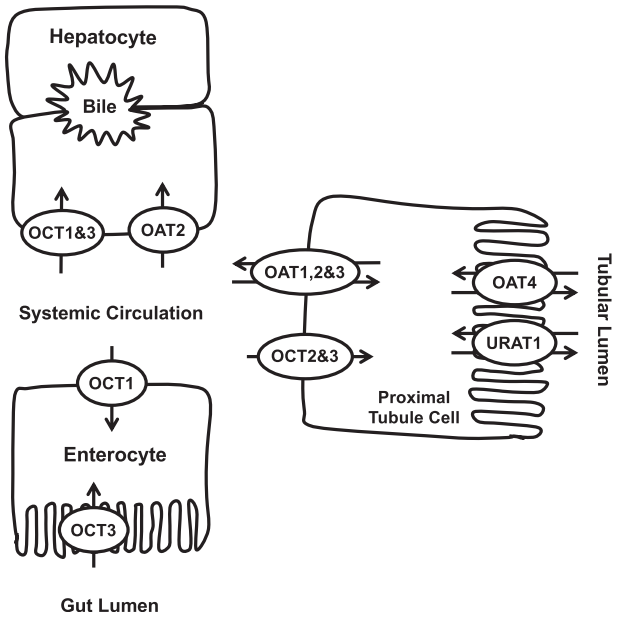

Fig. 1 – Prominent human SLC22 family members expressed in intestine, kidney and liver. Representative depictions of a human enterocyte, hepatocyte and renal proximal tubular cell indicating SLC22 transporters expressed in each tissue and their plasma membrane localization.

finally, an organic anion/dicarboxylate antiporter mediates organic anion uptake in exchange for α–ketoglutarate [32]. Evidence supports cellular exit via this transport system occurring either by facilitated diffusion (using the membrane potential as driving force) or anion exchange (antiport) [32].

OCT and OAT substrates cover a wide array of chemical structures and classes including pharmacological agents (*e.g.*, morphine, tamoxifen, metformin, cimetidine, penicillin G, furosemide, adefovir, cidofovir, indomethacin), neurotransmitters and their metabolites (*e.g.*, dopamine, serotonin 5-hydroxy-indoleacetic acid, homovanillic acid), hormones (*e.g.*, prostaglandins, epinephrine, estrone sulfate), environmental toxins/pollutants (*e.g.*, paraquat, 1-methyl-4-phenylpyridinium, ochratoxin A) and active components found in herbal preparations (*e.g.*, lithospermic acid, rosmarinic acid, rhein). A brief synopsis of the discovery of the well-characterized family members discussed in this review is presented below, for greater detail see Refs. [22,26–28].

2.1. Organic cation and anion transporters

OCT1 (SLC22A1). First isolated from rat kidney in 1994, orthologs have been identified in mouse and human (as well as other species) [33–35]. In humans, OCT1 expression has been conclusively reported in enterocytes and hepatocytes [33,36]. Rat OCT1 transport function correlated with changes in membrane potential, but not proton gradient manipulations, indicating OCT1 is driven by facilitated diffusion [35]. Protein expression in rats was subsequently confirmed by immunocytochemistry in renal proximal tubules and hepatocytes [37,38].

OCT2 (SLC22A2). Isolated in 1996 from rat kidney, orthologs have been identified in mouse and human (as well as other species) [33,39,40]. In humans, significant OCT2 expression has been reported in kidney, as well as in the CNS compartment [33,41–43]. Rat OCT2 transport function was ablated by membrane depolarization or a *trans*-applied proton gradient, indicating it is also driven by facilitated diffusion [44]. Renal expression and membrane targeting in intact rat proximal tubules was observed [25,45].

OCT3 (SLC22A3). Initially cloned from rat placenta [46], mouse and human orthologs (as well as other species) have been identified [47,48]. OCT3 appears to have the widest

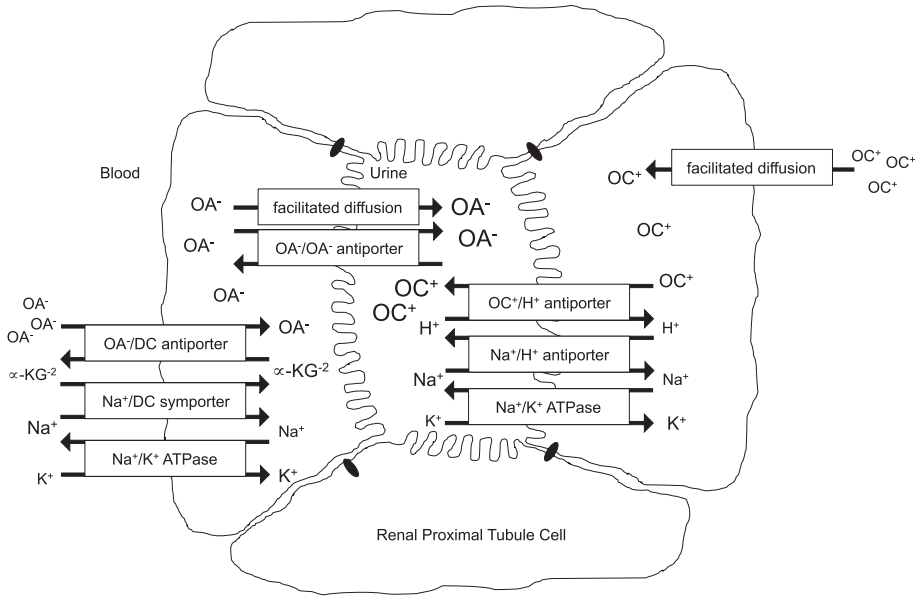

Fig. 2 – Model depicting driving forces for SLC22 family members. Mechanisms/driving forces utilized for cellular entry and exit on the 'classical' organic cation and organic anion transport systems, using renal proximal tubule cell as an example.

tissue distribution among the SLC22 family, including liver, kidney and intestine in humans [42,46,47]. Rat OCT3 function was demonstrated to be sensitive to changes in membrane potential indicating that it also is a facilitated diffusion carrier [46].

OAT1 (SLC22A6). Isolated in 1997 from rat kidney [49,50], orthologs have been identified in mouse and human (as well as additional species) [51–53]. OAT1 is expressed in kidney of all three species, but not in intestine or liver [43,50–52]. Renal expression and membrane targeting in isolated proximal tubules and human and rat kidney was observed [54–56]. Mechanistic examination of rat OAT1 transport function demonstrated it is an organic anion/dicarboxylate exchanger [50].

OAT2 (SLC22A7). OAT2 was initially cloned from rat liver [57] and human and murine orthologs have been isolated [58,59]. Expression of OAT2 in kidney and liver, but not intestine, has been detected in mouse, rat and human [43,58,60,61]. OAT2-mediated uptake was characterized as being insensitive to *trans*-stimulation by dicarboxylates leading to the interpretation it likely operates via facilitated diffusion [62]. However, mechanistically, this would be inconsistent with its postulated role as an uptake carrier.

OAT3 (SLC22A8). OAT3 was first isolated from rat [63] with mouse and human (as well as other species) orthologs identified [64,65]. OAT3 expression has been observed in human kidney, but not liver or intestine [64]. Hepatic expression was reported in rats, but not mice [61,65]. Immunohistochemistry yielded signal for OAT3 in rat and human renal proximal tubules [54,55]. Exploration of OAT3 transport energetics identified Na^+-dependent *trans*-stimulation by glutarate indicating that it is driven by organic anion/dicarboxylate exchange [66].

OAT4 (SLC22A11). OAT4 was discovered in human kidney and placenta [43,67]. No additional orthologs or tissues of expression have been identified. Immunodetection in proximal tubules has been observed [68]. However, OAT4's precise mechanism of action remains unclear as it has been reported to be a facilitated-diffusion carrier [67], an organic anion/dicarboxylate exchanger [69], and a urate/OH^- exchanger [70].

URAT1 (SLC22A12). Originally isolated from mouse kidney, with rat and human orthologs subsequently identified [71–73]. Expression of URAT1 appears to be kidney specific [72,73]. Characterization of URAT1-mediated transport indicated it functions as an organic anion/urate exchanger, however, tested dicarboxylates failed to inhibit [72,73].

Three key factors needed to most accurately define each individual SLC22 transporter's contribution to the transepithelial flux of substrate molecules in each tissue are (i) individual transporter affinities for each compound, *i.e.*, K_m, K_i, IC_{50} (Table 1), (ii) the concentration of each compound in the systemic circulation (Table 2), and (iii) absolute SLC22 protein expression levels in each tissue (Table 3), ideally in both normal and disease states. Robust affinity data are relatively easy to come by using *in vitro* expression systems of which a great deal already exists (Table 1). Limited clinical systemic concentration information is available in the literature (Table 2), however, interpretation of these data should be approached with caution at this time due to the use of non-standardized dosage forms and inconsistent amounts of individual compounds administered in each study. Thus, more formalized clinical studies that administer actual marketed products are required to obtain relevant, product-specific (unbound) C_{max} values for each compound. Within this framework, organ-specific SLC22 protein expression data will further enhance our ability to accurately predict their impact on the absorption/flux of drugs, herbal supplement components and endogenous compounds. Toward this end, advances in liquid chromatography/tandem mass spectrometry methodology have begun to yield preliminary data regarding 'normal' human transporter expression levels in native cell membranes (summarized for SLC22 transporters in Table 3).

Future studies quantifying transporter expression levels in patients suffering from acute and chronic renal disease appear essential, as recent studies using rat models of ischemia/reperfusion injury and chronic renal failure have demonstrated dramatic changes in SLC22 transporter expression levels. A common theme to all of these studies was a significant (~50–85%) downregulation of OAT1 and OAT3, and in one instance OCT2, protein expression in rat kidney as determined by immunoblotting [74–79]. When examined, this downregulation of SLC22 expression correlated with decreased renal clearance of prototypical OAT1 and OAT3 substrates [74,75,78]. For example, in the ischemia/reperfusion model, significant accumulation of endogenous indoxyl sulfate in the systemic circulation was observed beginning at 6 h post injury and the concentration of administered famotidine (20 mg/kg), a substrate for both OCTs and OATs, was significantly elevated compared to control rats [75,76]. Thus, quantifying transporter protein levels under conditions of renal dysfunction/insufficiency should substantially improve modeling and prediction of compound distribution in this patient population.

3. Compound interactions and SLC22 transporters

In contrast to marketed drugs approved by agencies such as the European Medicines Agency, the United States Food and Drug Administration, the Food and Drug Administration of Taiwan, and the Japanese Pharmaceuticals and Medical Devices Agency, little is known about the pharmacokinetic and pharmacological profiles of components of dietary/herbal supplements. Many of the purported active components of such products, and their metabolites (*e.g.*, sulfates and glucuronides), are often organic cations and anions. As such, members of the SLC22 transporter family may figure prominently in their pharmacokinetic and pharmacological profiles, potentially representing sites for adverse interactions when herbal products are used in combination therapy, particularly due to the polyspecific nature of these transporters and the broad structural array of their known substrates/inhibitors. Greater understanding of the roles transporters play in these interactions is essential in order to establish guidelines for the safe clinical use of drugs and herbal supplements. Recent examples highlighting the potential role of SLC22 family members in such interactions are summarized below.

Table 1 – Example compound interactions associated with SLC22 transporters.

Perpetrator	Victim Substrate[b]	Transporter[c]	Cell Type[d]	Kinetics (μM)			Reference
				K_m	IC_{50}	K_i	
Aloe-emodin	6-CF	hOAT1	MDCK		2.29		[109]
	6-CF	hOAT3	HEK293		5.37		[109]
Chrysophanol	6-CF	hOAT1	MDCK		>10		[109]
	6-CF	hOAT3	HEK293		>10		[109]
Cisplatin		hOCT2	HEK293	11			[174]
CMPF[a]		hOAT1	HEK293	141			[135]
		hOAT3	HEK293	27			[135]
Diclofenac	Adefovir	hOAT1	CHO		4		[152]
Diflunisal	Adefovir	hOAT1	CHO		0.85		[152]
Emodin	6-CF	hOAT1	MDCK		0.61		[109]
	6-CF	hOAT3	HEK293		1.22		[109]
Ethambutol	MPP^+	hOCT1	HEK293		93		[159]
	MPP^+	hOCT2	HEK293		254		[159]
	MPP^+	hOCT3	HEK293		4100		[159]
Etodolac	Adefovir	hOAT1	CHO		50		[152]
Flurbiprofen	Adefovir	hOAT1	CHO		1.5		[152]
Gallic acid	PAH	hOAT1	CHO		1.2	1.1	[21]
	ES	hOAT3	HEK293		9	8.4	[21]
Ibuprofen	Adefovir	hOAT1	CHO		8		[152]
Indomethacin	Adefovir	hOAT1	CHO		3		[152]
Indoxyl sulfate		hOAT1	HEK293	21			[135]
		hOAT3	HEK293	263			[135]
Ketoprofen	Adefovir	hOAT1	CHO		1.3		[152]
Lithospermic acid	PAH	hOAT1	CHO			20.8	[24]
	ES	hOAT3	HEK293			0.59	[24]
	PAH	mOAT1	CHO			14.9	[24]
	ES	mOAT3	CHO			31.1	[24]
Nadolol		hOCT2	HEK293	122			[91]
Naproxen	Adefovir	hOAT1	CHO		5.8		[152]
p-cresyl sulfate		hOAT1	HEK293	128			[136]
		hOAT3	HEK293	>5000			[136]
Phenacetin	Adefovir	hOAT1	CHO		200		[152]
Physcion	6-CF	hOAT1	MDCK		>10		[109]
	6-CF	hOAT3	HEK293		>10		[109]
Piroxicam	Adefovir	hOAT1	CHO		20.5		[152]
Rhein	6-CF	hOAT1	MDCK		0.23		[109]
	6-CF	hOAT3	HEK293		0.08		[109]
	PAH	hOAT1	CHO		0.077	0.072	[107]
	ES	hOAT3	CHO		0.008	0.008	[107]
	ES	hOAT4	CHO		>100	>100	[107]
	PAH	mOAT1	CHO			0.198	[107]
	ES	mOAT3	CHO			0.216	[107]
Rosmarinic acid	PAH	hOAT1	CHO			0.35	[24]
	ES	hOAT3	HEK293			0.55	[24]
	PAH	mOAT1	CHO			5.5	[24]
	ES	mOAT3	CHO			4.3	[24]
Rosuvastatin	ES	hOAT3	*Xenopus* oocytes	7.4	25.7		[122]
Salvianolic acid A	PAH	hOAT1	CHO			5.6	[24]
	ES	hOAT3	HEK293			0.16	[24]
	PAH	mOAT1	CHO			4.9	[24]
	ES	mOAT3	CHO			21.3	[24]
Salvianolic acid B	PAH	hOAT1	CHO			22.2	[24]
	ES	hOAT3	HEK293			19.8	[24]
	PAH	mOAT1	CHO			236	[24]
	ES	mOAT3	CHO			845	[24]
Tanshinol	PAH	hOAT1	CHO			40.4	[24]
	ES	hOAT3	HEK293			8.6	[24]
	PAH	mOAT1	CHO			136	[24]
	ES	mOAT3	CHO			1940	[24]
Ursolic Acid	ES	hOAT3	HEK293		19		[119]

[a] CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid.
[b] 6-CF, 6-Carboxyfluorescein; MPP^+, 1-methyl-4-phenylpyridinium; PAH, *p*-aminohippurate; ES, estrone sulfate.
[c] h, human; m, murine.
[d] MDCK, Madin Darby canine kidney; HEK293, human embryonic kidney; CHO, Chinese hamster ovary.

Table 2 – Clinical concentrations of example compounds.

Compound	Mean C_{max} (μM)[a]	Route of Administration	Dose	Species	Reference
Aloe-emodin	0.29	PO	1.25 mg/kg[b]	Rat	[175]
Cisplatin	0.02–0.03	IV	80 mg/m^2	Human	[176]
Chrysophanol	4.7	PO	1.25 mg/kg[b]	Rat	[175]
CMPF[c]	24.8	–	–	Human	[177]
Diclofenac	6.6	PO	100 mg	Human	[178]
Diflunisal	247.8	PO	500 mg	Human	[179]
Emodin	0.14	PO	1.25 mg/kg[b]	Rat	[175]
Ethambutol	22, 4.8–26.9	PO	25 mg/kg, 400 mg	Human	[180,181]
Etodolac	26.1–57.1	PO	50 mg/kg	Rat	[182]
Flurbiprofen	172.3	PO	100 mg	Human	[183]
Gallic acid	0.55	PO	400 mg/kg (40 μg)[d]	Human	[184]
Ibuprofen	208.4–282.1	PO	800 mg	Human	[185]
Indomethicin	3.9–6.7	PO	40 mg, 50 mg	Human	[186]
Indoxyl Sulfate	2.5	–	–	Human	[132]
Ketoprofen	13.8–17.8	PO	100 mg	Human	[187]
Lithospermic Acid	55.7	IV	10 mL/kg (0.3 mg/kg)[e]	Rat	[188]
Nadolol	0.17	PO	30 mg	Human	[189]
Naproxen	187.1	PO	220 mg	Human	[190]
p-cresyl sulfate	425.1	–	–	Human	[132]
Phenacetin	12.5	PO	900 mg	Human	[191]
Physcion	1.7	PO	1.25 mg/kg[b]	Rat	[175]
Piroxicam	1.3	PO	20 mg	Human	[192]
Rhein	0.54, 2.6	PO	1.25 mg/kg[c], 6 g/kg[f]	Rat	[175,193]
Rosmarinic acid	317.2	PO	20 g/kg (0.391 mg/g)[g]	Rat	[194]
	516.2	IV	10 mL/kg (1.86 mg/kg)[e]	Rat	[188]
Rosuvastatin	0.012–0.076	PO	20 mg	Human	[195]
Salvianolic acid A	0.28	PO	15 g/kg (37.9 mg/kg)[h]	Rat	[196]
	66.7	IV	10 mL/kg (0.33 mg/kg)[e]	Rat	[188]
Salvianolic acid B	0.14	PO	15 g/kg (15 mg/kg)[h]	Rat	[196]
	237.9	IV	10 mL/kg (1.714 mg/kg)[e]	Rat	[188]
Tanshinol	781.7	PO	20 g/kg (0.743 mg/g)[g]	Rat	[194]
Ursolic acid	2	PO	0.1 g/kg[i]	Rat	[197]

[a] Converted to μM from original study.
[b] Semen Cassiae extract.
[c] CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid.
[d] Mang-Guo-Zhi-Ke tablet, value in parenthesis represents amount of compound quantified in dosage form.
[e] Danshen injection, value in parenthesis represents amount of compound quantified in dosage form.
[f] Rhubarb extract.
[g] Denshen-Chuanxiong-Honghua extract; value in parenthesis represents amount of compound quantified in dosage form.
[h] Jitai tablet; value in parenthesis represents amount of compound quantified in dosage form.
[i] Folium Eriobotryae effective fraction.

Table 3 – Absolute native tissue protein expression levels for human SLC22 transporters.

Transporter	Kidney[a]	Liver[a]	Intestine[a]	Reference
OAT1	5.33 ± 1.88	NE[b]	NE[b]	[43]
OAT2	0.93 ± 0.32	1.91 ± 0.58	NE[b]	[43,198]
OAT3	3.50 ± 1.55	NE[b]	NE[b]	[43]
OAT4	0.52 ± 0.23	NE[b]	NE[b]	[43]
OCT1	NE[b]	7.35 ± 3.26, 4.45 ± 1.89	0.50[c]	[198–200]
OCT2	7.42 ± 2.84	NE[b]	NE[b]	[43]
OCT3	NR[d]	NR[d]	0.10[c]	[200]

[a] Data are presented as pmol/mg protein ± SD.
[b] NE = not expressed in this tissue in humans.
[c] Values estimated from Figure 4 in Ref. [200], expressed in ileum only.
[d] NR = not reported.

3.1. Food, herbal/dietary supplements

3.1.1. Green tea

Green tea (*Camellia sinensis*), having thousands of years of historical use in TCM, is one of the most commonly ingested beverages or herbal supplements world-wide [80]. Green tea (GT) consumption has garnered much attention due to its perceived benefits for weight loss [81], as well as for reducing the risk of cancer [20,82] and cardiovascular disease [83]. Despite these apparent benefits and the generalized view of GT as a safe natural product, there are increasing case reports of patients presenting with acute toxicities attributed to the consumption of GT and GT extracts as supplements [11,84–86]. The major purported active ingredients in GT are the polyphenolic catechins, epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG), which comprise 30–40% of GT's dry weight [87,88].

In a recent clinical study investigating potential drug interactions with GT, subjects were administered a single oral dose (30 mg) of the β-blocker nadolol (used to control high blood pressure and chest pain) following daily consumption of green tea (700 mL) for 14 days [89]. Both the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) of nadolol were significantly decreased by ~85%, and total urinary excretion was reduced by 82%, accounting for an acute effect of GT consumption on nadolol pharmacokinetics potentially involving active transporters. Subsequently, when examined *in vitro*, EGCG (100 μM) inhibited metformin (10 μM) transport by human OCT1 and OCT2 by 60% and 37%, respectively, and EC (50 μM) inhibited human OAT3 activity by 32%, but was without effect on human OAT1 and OAT4 activity [23,90]. A key piece of information that is still lacking is determining the plasma concentrations of these compounds after taking a high dose GT herbal supplement vs drinking green tea. However, given nadolol's low predicted unbound plasma concentration (~0.2 μM after a single 30 mg oral dose) and K_m on human OCT2 of ~120 μM, clinically significant alteration of nadolol pharmacokinetics via inhibition of human OCT1 and/or OCT2 by EGCG seems unlikely [91]. Nonetheless, predicting the overall *in vivo* inhibitory effects of consuming GT or GT based herbal supplements on SLC22 transporter function via examination of single active components is likely insufficient, as GT contains multiple compounds with the potential to interact with a variety of transporters and the overall inhibitory effect *in vivo* may reflect additive effects of all the components [8]. In addition, EC and EGC each have multiple sulfate and glucuronide metabolites that also exhibit inhibitory potential on transporters [92].

Indeed, prior studies have demonstrated that the glucuronide and sulfate metabolites of EC and ECG are the most predominant moieties found in plasma [93,94]. After administration of GT extract (40 mg/mL) to rats, the plasma concentrations of combined glucuronide/sulfate metabolites of EC and ECG were found to be 32 and 33 μM, respectively [92]. The anionic nature of these glucuronide and sulfate metabolites at physiological pH suggested they might interact with OATs as substrates and/or inhibitors. In support of this contention, when examined *in vitro*, equivalent GT metabolite mixtures to those seen in rat plasma *in vivo* produced ~60% inhibition of human OAT1 and ~30% inhibition of human OAT3 [92]. Clearly, further investigation of the *in vivo* effects of EC, ECG, EGC, EGCG and their glucuronide and sulfate metabolites is required to fully understand the potential for clinically relevant GT-drug interactions involving SLC22 family members, as well as members of other transporter families, *e.g.*, SLC0 (OATP) and SLC47 (MATE).

3.1.2. Rhubarb

Rhubarb (*Rheum* sp.) is another well-known TCM/herbal supplement, with the stalk of the plant commonly utilized as the main ingredient in desserts and other sweet dishes in western culinary cooking [95]. In TCM, rhubarb is utilized to treat patients suffering from chronic renal disease and diabetic nephropathy [96,97] and is thought to possess laxative [98], vasodilatory [99], anti-oxidant [100], anti-inflammatory [101], anti-microbial [96,102] and anti-cancer activities [103]. The pharmacological benefits of rhubarb are largely attributed to the actions of the anthraquinones, rhein, emodin, aloe-emodin, chrysophanol and physcion, although it also contains gallic acid and catechins [101,104].

Rhein, in addition to dietary sources, is the major metabolite of the prodrug, diacerin, which is prescribed in the treatment of arthritis [105]. Clinically, diacerein is often co-administered with NSAIDs or methotrexate in the treatment of osteo- and rheumatoid arthritis, increasing the potential for significant herbal supplement/food/drug–drug interactions involving SLC22 transporters [106]. Indeed, rhein (at clinically relevant concentrations) was recently identified as one of the most potent OAT inhibitors known to date (Table 1), with K_i values in the nanomolar range for human OAT1 (~72 nM) and OAT3 (~8 nM), on par with the affinities of some hormones for OATs, raising the possibility of significant drug-endogenous molecule interactions, as well [107]. While some inhibition of human OAT4 activity was observed, the K_i was predicted to exceed 100 μM [107]. The drug–drug interaction index (DDI index = unbound C_{max}/K_i or IC_{50}) [108] for rhein on human OAT1 (DDI index = 5; ~83% inhibition) and OAT3 (DDI index = 46; ~98% inhibition) indicated a strong potential for OAT-mediated drug interactions [107]. Additionally, emodin and aloe-emodin were shown to strongly inhibit human OAT1 (IC_{50} = 610 nM and 2.29 μM, respectively) and OAT3 (IC_{50} = 1.22 μM and 5.37 μM, respectively) [109]. Despite significant inhibition of human OAT1 and OAT3 by chrysophanol and physcion *in vitro*, IC_{50} values were predicted to be greater than 10 μM (Table 1) [109]. Again, however, overall *in vivo* inhibition of OATs might occur via the combined effects of these compounds.

Confirming the potential for *in vivo* drug interactions on OATs, when rhein was administered (5 g/kg/day) as single or multiple (7 days) dose to rats, the AUC of co-administered furosemide (OAT substrate, 10 mg/kg) was increased by 32% and 52%, respectively [109]. These findings are consistent with decreased renal elimination of furosemide due to OAT inhibition, which has already been demonstrated to lead to decreased diuretic efficacy [110]. Importantly, marked species differences exist in terms of rhein's inhibitory potency on human vs murine OATs, with human OAT1 and OAT3

exhibiting ~3 and ~30 fold higher affinity for rhein as compared to their murine orthologs, murine K_i = 198 nM and 216 nM, respectively [107]. Thus, animal studies may severely underestimate the human impact.

More recently, rhein acyl glucuronide, the major metabolite of rhein, was found to significantly inhibit methotrexate uptake (*in vitro*) mediated by human OAT1 (67% inhibition) and OAT3 (89% inhibition) [111]. When examined in rats *in vivo*, the AUC for methotrexate (2 mg/kg) was increased by 60%, and its half-life was increased by 40%, when co-administered with rhein acyl glucuronide (5 mg/kg), consistent with decreased renal elimination via OATs [111]. Previously, studies in OAT3 knockout mice revealed a significant reduction in methotrexate elimination as compared to wildtype, indicating OAT3 might contribute to methotrexate elimination in the intact organism [112]. Considering that rhein and methotrexate combination therapy is used for the treatment of arthritis, these data strongly suggest monitoring for potential HDIs in the clinic, when herbal supplements containing *Rhubarb* sp. are being used.

3.1.3. *Pomegranate*

Preparations containing pomegranate (*Punica granatum*) fruit have been consumed for centuries and pharmacologically exploited by many cultures for their purported antioxidant and anti-inflammatory health benefits [113], as well as for treating acidosis, hemorrhage, diarrhea, infections, and even diabetes mellitus [114,115]. The active components of pomegranate believed to most significantly contribute to its perceived health benefits are the triterpenoids ursolic acid (UA) and oleonic acid (OA), as well as the polyphenol gallic acid (GA, also found in *Rhubarb* sp.) [116–118]. Therefore, due to their acidic nature, OATs might play a role in the pharmacological disposition of pomegranate's bioactive compounds. In support of this contention, *in vitro* kinetic studies demonstrated that UA and GA are potent inhibitors (Table 1) of human OAT3 (IC_{50} = 19 and 9 μM, respectively), with GA also strongly inhibiting human OAT1 (IC_{50} = 1.2 μM), indicating these transporters might be involved in their active tubular secretion [21,119]. The DDI index for GA for human OAT1 and OAT3 indicated ~50% inhibition suggesting high potential for drug interactions on OAT1 and OAT3 *in vivo* [21].

When examined in rats, co-administration of GA (10 mg/kg) and rosuvastatin (1 mg/kg intravenously or 5 mg/kg orally), increased rosuvastatin's AUC by 62% when given intravenously and by 134% when given orally [120]. Additionally, in the orally dosed group, systemic clearance decreased by 37% [120]. When UA (80 mg/kg) was orally co-administered to rats with rosuvastatin (100 mg/kg), rosuvastatin's AUC increased by 2.7-fold and overall elimination decreased by ~60% [121]. Finally, in an *in vitro* study, rosuvastatin was demonstrated to be a potent substrate of human OAT3 with a K_m = 7.4 μM (no interaction was detected with human OAT1) [122]. In the same study, rosuvastatin (10 μM) uptake was completely abolished in rat kidney slices when co-incubated with the OAT3 substrate benzyl-penicillin (50 μM), suggesting OAT3 may play a role in rosuvastatin transport across the basolateral membrane in kidney [122]. Taken together, these data clearly indicate high potential for an HDI between GA or UA and rosuvastatin on OATs *in vivo*. However, other transporter families, *e.g.*, SLC0 (OATPs), which also interact strongly with statins, are also likely involved. Based on the evidence, patients and clinicians should be wary of the consumption of pomegranate, or herbal supplements that contain pomegranate extracts, when concomitantly taking statins.

3.1.4. *Danshen*

Danshen, derived from the dried root of the plant *Salvia miltiorrhiza*, has been used in TCM primarily for the treatment of various cardiovascular disease conditions including angina, cardiac ischemia, atherosclerosis, hyperlipidemia, and acute ischemic stroke [123–125]. Like other herbal supplements, Danshen contains a wide array of phytochemical ingredients, including phenolic acids such as lithospermic acid (LSA), rosmarinic acid (RMA), salvionolic acid A (SAA), salvionolic acid B (SAB), and tanshinol (TSL), all suggested to be major components and therapeutically active [126–129]. When examined *in vitro*, LSA, RMA, SAA, SAB and TSL were all found to be potent competitive inhibitors for both human OAT1 (K_i = 20.8, 0.35, 5.6, 22.2 and 40.4 μM, respectively) and OAT3 (K_i = 0.59, 0.55, 0.16, 19.8 and 8.6 μM, respectively) [24]. Similar to what was observed for rhein, marked species differences exist between human and murine OAT1 and OAT3, with the human transporters exhibiting 2–16 fold higher affinity for these compounds (Table 1), again indicating that animal studies may severely underestimate the human impact [24].

Using pharmacokinetic modeling, the cumulative inhibitory effect of LSA, RMA and TSL on human OAT1 and OAT3 mediated substrate transport was investigated [8]. The predicted cumulative DDI index of the overall Danshen preparation was found to be significantly higher than that of the DDI indices of each individual component. This suggested that the true DDI potential of Danshen products (and, thus, any multicomponent herbal product) is likely underestimated when examining the DDI index of single active components of the complex mixture [8]. Finally, when TSL and rosuvastatin were co-administered to rats, the *in vivo* pharmacokinetics of rosuvastatin were significantly altered; AUC was increased 3-fold and elimination was decreased by ~60% [121]. Considering the K_m value of rosuvastatin (~7 μM) and the K_i value of TSL (~9 μM) on human OAT3, combined use of statins and Danshen should be approached cautiously [24,122].

3.2. *Endogenous compounds*

3.2.1. *Uremic toxins*

Patients suffering from chronic kidney disease (CKD) often exhibit 'uremia' or 'uremic syndrome,' wherein a broad array of endogenous organic metabolic waste products that are normally efficiently removed from the systemic circulation by active tubular secretion, accumulate to toxic levels. This, in turn, negatively impacts the function of additional organ systems, *e.g.*, liver and CNS. Thus, the accumulation of these uremic retention solutes, or uremic toxins, not only contributes to the progression of CKD, but also cardiovascular disease, uremic encephalopathy and all-cause mortality [92]. Uremic toxins include more than 150 compounds known to increase in CKD patients (http://www.uremic-toxins.org/DataBase.html) [130–132], many of which are small organic cations and anions, *e.g.*, guanidine, methylguanidine, indoxyl

sulfate and *p*-cresyl sulfate. As such, there is strong *in vitro* evidence that at least 21 of these compounds act as inhibitors or substrates of OAT1-4, URAT1 and OCT1-3 [133,134].

Indoxyl sulfate (IS) and *p*-cresyl sulfate (PCS) are both known substrates (Table 1) of human OAT1 (K_m = 21 μM and 128 μM, respectively) and OAT3 (K_m = 263 μM and >5000 μM, respectively) [135,136]. A recent *in vivo* study utilizing a chronic renal failure rat model demonstrated elevation of IS and PCS in serum [92]. Oral administration of GT to these animals over several consecutive days resulted in reduced IS and PCS elimination, likely through inhibition of renally expressed OAT1 and OAT3, and exacerbated the level of renal impairment [92]. Thus, it was concluded that consumption of GT is contraindicated in CKD patients as GT-uremic toxin interactions might accelerate the disease pathology through increased exposure to uremic toxins. Similarly, the NSAIDs diclofenac and ketoprofen have been shown to inhibit human OAT1 and OAT3 transport activity [137]. When examined in rats *in vivo*, diclofenac or ketoprofen administration (10 mg/kg intravenous bolus) decreased the systemic clearance of co-administered IS (10 mg/kg intravenous) by 71% and 82%, respectively [137]. While further investigation of this drug interaction is needed, the data suggest a cautious clinical approach to NSAID selection and use, and by extension consumption of rhubarb, pomegranate or danshen, is warranted in CKD patients.

Recently, uremic solute toxicity was implicated in the progression of gestational diabetes/β-cell dysfunction through 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) [138]. Metabolomic profiling of serum from patients that developed gestational diabetes revealed CMPF was significantly elevated. Induction of serum CMPF levels in mice equivalent to that observed in these patients lead to defective insulin secretion. A similar effect was observed *in vitro* when isolated human islets were exposed to CMPF. Subsequently, OAT1 and OAT3 expression in human pancreatic β-cells was confirmed [138]. CMPF is a known human OAT1 (K_m = 141 μM) and OAT3 (K_m = 27 μM) substrate [135]. As such, in both experimental systems, the deleterious effects of CMPF were prevented by probenecid (inhibitor of OAT1 and OAT3) and benzyl-penicillin (OAT3 inhibitor), but not *p*-aminohippurate (OAT1 inhibitor) [138]. Thus, elevated CMPF might represent at least one cause of gestational diabetes through OAT3-mediated accumulation in pancreatic β-cells, and inhibition of OAT3 function via drug interaction, *e.g.*, co-administration of NSAIDs or certain herbal supplements, might represent a preventative clinical strategy.

3.2.2. *Guanidine derivatives*

Guanidine, an endogenous molecule generated as a by-product of cellular metabolism, weakly inhibits human OCT3 (IC_{50} = 2200–6200 μM) [139]. However, a number of marketed drugs that are guanidine derivatives, *e.g.*, famotidine, imatinib, rosuvastatin and metformin, more potently interact with OCTs, implicating these transporters as potential sites for drug interactions involving such medications. In addition, increasing evidence has shown that OCT2 and OCT3 expressed in the CNS (including man), particularly in glial cells and astrocytes, contribute to the low affinity, high capacity 'uptake-2' system and, thus, serve as a possible alternative and/or complementary route to the high affinity, low capacity 'uptake-1' system for synaptic clearance of aminergic neurotransmitters (*e.g.*, serotonin, dopamine, norepinephrine) [26,140–142]. Therefore, human OCT2 and OCT3 might serve as novel targets for the treatment of mood disorders associated with an imbalance of CNS monoamine concentrations. As such, a recent study examined a series of phenylguanidine analogs, based upon lead compounds with *in vivo* antidepressant-like activity in mice [143], for their inhibitory potential on human OCTs [144]. Compared to guanidine, the phenylguanidine derivatives had up to a 1000-fold increase in inhibition potency for OCTs, with higher potency being proportional to increased lipophilicity and size of substituent on the phenyl ring, particularly for human OCT3 (IC_{50} = 1.5–~450 μM) [144]. Thus, one possible explanation for any anti-depressant-like activity of these compounds *in vivo* might be inhibition of OCT2 and OCT3 mediated 'uptake 2' clearance of monoamine neurotransmitters. What, if any, connection exists between OCTs as a component of the uptake 2 pathway and purported CNS effects of various herbal supplements remains unknown.

3.3. *Drugs*

Many patients today are not prescribed just one, but many concomitant medications as a consequence of having multiple underlying co-morbid disease states, especially amongst the elderly population. The type of interactions, whether they are pharmacokinetically favorable, unfavorable, or benign, vary depending on the medications taken. Unfortunately, DDIs are responsible for an increasing number of negative clinical outcomes that have caused emergency room visits or hospitalizations to become more frequent, contributing to rising healthcare costs for both patients and the healthcare system [145,146]. It was reported in 2005, that 4.3 million hospital visits in the United States were attributed specifically to drug interactions, driving an estimated 30% increase in healthcare cost [147]. Achieving an improved mechanistic understanding of DDIs should help drug developers and clinicians eschew unfavorable and sometimes deadly ADRs, as well as aid in exploiting certain drug interactions that can be applied to improve patient outcomes.

One classic example of a clinically exploited DDI is prolonging the half-life of the once scarce and expensive β-lactam antibiotic, penicillin, by utilizing probenecid as adjunct therapy to inhibit organic anion transporter mediated renal tubular secretion [148]. Subsequently, probenecid was used as adjunct therapy for other β-lactams with short half-lives, *e.g.*, cefazolin, cephaloridine, successfully reducing their frequency of administration and increasing patient compliance in their use [149]. We now know that this clinical benefit is the result of a drug–drug interaction between probenecid and β-lactams on human OAT3 expressed in renal proximal tubule cells [150]. Thus, combination of rhubarb, pomegranate and/or danshen consumption with β-lactam use might similarly impact drug pharmacokinetics and, if the therapeutic target is the urinary space to treat a urinary tract infection, efficacy might be negatively impacted as well.

HIV patients represent a highly vulnerable patient population susceptible to numerous opportunistic infections and

co-morbid conditions, necessitating the use of multiple medications. Prolonged treatment with antivirals such as the HIV therapeutics adefovir and cidofovir can lead to nephrotoxicity [151]. Both adefovir and cidofovir (Table 1) are substrates of human OAT1 (K_m = 30 μM and 46 μM, respectively) and mitigation of their cytotoxicity via co-administration of NSAIDs has been demonstrated *in vitro*, suggesting inhibition of OAT1 mediated antiviral transport may effectively prevent renal cell accumulation and the subsequent nephrotoxicity observed in the clinic [51,152]. Indeed, when healthy volunteers were given probenecid with the antiviral prodrug adefovir dipivoxil, renal clearance of adefovir was decreased by 45% [153].

It was recently disclosed in a 2012 report by the World Health Organization that amongst the 9 million newly diagnosed tuberculosis (TB) patients in 2011, 13% were co-infected with HIV [154]. It was further reported that 10% of all TB sufferers also have diabetes. The treatment complexity for these various patient co-morbidities can be challenging, especially when considering the high probability for drug interactions. A number of pre-clinical and clinical studies on metformin, a first-line monotherapy for the initial onset of type 2 diabetes, have implicated human OCT1-3 as playing a role in its renal transport [155–158]. Ethambutol, a first line therapeutic in the treatment of TB, was recently shown to inhibit human OCT1 and OCT2 transport activity (IC_{50} = 93 μM and 254 μM, respectively) [159]. The DDI index, calculated using clinically relevant unbound plasma concentrations of ethambutol, was 0.6 (~38% inhibition) for human OCT1 expressed in the GI tract or liver (well above the 0.1 threshold), suggesting that in TB-diabetes patients there is a marked chance for ethambutol–metformin interactions involving at least OCT1 [159]. Similarly, the DDI index for ethambutol on human OCT3 expressed in enterocytes was 83 times higher than threshold (8.3 vs 0.1), indicating the potential for ethambutol to interfere (89% inhibition) with metformin absorption in the GI tract [159]. Given that many antiviral medications are also substrates for human OCTs, analogous outcomes might be experienced in TB-HIV patients. While currently much less is known about herbal supplement components that interact with human OCTs, these DDI data suggest their use should be approached cautiously in this patient population.

SLC22 transporters have also been linked to mediating the membrane transport, pharmacologic action and toxicity of platinum containing antineoplastics (*e.g.*, cisplatin, oxaliplatin) [160–163]. Cisplatin, although highly effective in treating malignant tumors, is plagued clinically by its dose limiting irreversible nephrotoxicity and ototoxicity [164–167]. Cisplatin is a relatively high affinity substrate for human OCT2 (K_m = 11 μM) and several *in vitro* and *in vivo* studies have implicated OCT2 as playing a major role in the cellular accumulation and off-target toxicity of cisplatin in nephrons and the outer hair cells of the cochlea [43,162,163,168,169]. Urinary levels of cisplatin were significantly reduced in OCT1 or OCT2 knockout mice and OCT1/OCT2 double knockout mice were protected from severe tubular damage [168]. Ototoxicity was absent in cisplatin treated OCT1/OCT2 double knockout mice, and co-administration of cimetidine in wildtype mice reduced nephrotoxicity and completely protected against developing ototoxicity [169]. Co-administration of imatinib also reduced cisplatin accumulation and cytotoxicity in human OCT2 expressing cells and resulted in an increased AUC for cisplatin in rats [170]. Similarly, in tumor bearing rats, treatment with cisplatin plus cimetidine was reported to maintain antitumor efficacy without producing any associated nephrotoxicity [171]. Moreover, patients carrying the OCT2 variant 808G > T exhibited reduced nephrotoxicity following treatment with cisplatin [168]. Thus, there is strong evidence implicating OCT2 in mediating cisplatin associated nephrotoxicity and ototoxicity *in vivo* and that inhibition of OCT2 transport activity through drug interaction is protective.

In addition, there is recent evidence suggesting a role for human and murine OAT1 and OAT3 in the residual cisplatin induced nephrotoxicity observed in the above studies. Both OAT1 and OAT3 knockout mice exhibited a reduced nephrotoxic response to cisplatin administration [160]. Transport of N-acetylcysteine S-conjugates by human and rat OAT1 and OAT3 has been known for some time [172,173] and it appears that OAT mediated renal accumulation of the mercapturic acid cisplatin metabolite, NAC-1, is responsible for non-OCT2 mediated cisplatin associated renal toxicity in man [160]. Furthermore, without compromising the positive therapeutic effects of cisplatin, co-administration of the tyrosine kinase inhibitor, nilotinib, blocked all cisplatin induced nephrotoxicity [160]. Thus, in the context of cisplatin therapy, concomitant use of certain herbal supplements might provide beneficial clinical outcomes. Clearly, a more detailed understanding of SLC22 transporter function and affinity can aid the development of treatment strategies that lead to increased clinical safety, particularly for patients suffering co-morbid disease states like TB, HIV, diabetes and cancer.

4. Conclusion

SLC22 family members are known to interact with hundreds of endogenous, therapeutic and xenobiotic compounds, including many active components of herbal products. SLC22 substrates exhibit a broad array of chemical structures and it is due to this 'polyspecific' nature that SLC22 transporters are prime sites for drug-food, drug-botanical and drug–drug interactions. Unlike medications that require the approval of governmental agencies before being marketed to patients, components of TCMs and herbal supplements are poorly understood in terms of their content, let alone their pharmacokinetic and pharmacological characteristics. As highlighted in this review, there are increasing numbers of examples where herbal products are implicated in drug interactions, often resulting in adverse outcomes. In addition to more complete understanding of the components found in natural products and improved regulatory oversight in their manufacture, greater understanding of SLC22 mediated drug-natural product interactions is needed if guidelines for their safe and effective clinical use are to be established, particularly for patients suffering from co-morbid disease states. By further extending drug transporter research to improve our present understanding of substrate–transporter interactions, current standard treatment guidelines will inevitably be modified to improve patient lives through the reduction of preventable adverse reactions.

Conflicts of interest

The authors have no conflicts of interest to report.

Support statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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