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## Organic anion transporter 1 and 3 contribute to traditional Chinese medicine-induced nephrotoxicity

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**[ABSTRACT]** With the internationally growing popularity of traditional Chinese medicine (TCM), TCM-induced nephropathy has attracted public attention. Minimizing this toxicity is an important issue for future research. Typical nephrotoxic TCM drugs such as Aristolochic acid, *Tripterygium wilfordii* Hook. f., *Rheum officinale* Baill, and cinnabar mainly damage renal proximal tubules or cause interstitial nephritis. Transporters in renal proximal tubule are believed to be critical in the disposition of xenobiotics. In this review, we provide information on the alteration of renal transporters by nephrotoxic TCMS, which may be helpful for understanding the nephrotoxic mechanism of TCMS and reducing adverse effects. Studies have proven that when administering nephrotoxic TCMS, the expression or function of renal transporters is altered, especially organic anion transporter 1 and 3. The alteration of these transporters may enhance the accumulation of toxic drugs or the dysfunction of endogenous toxins and subsequently sensitize the kidney to injury. Transporters-related drug combination and clinical biomarkers supervision to avoid the risk of future toxicity are proposed.

**[KEY WORDS]** Traditional Chinese medicine; Nephrotoxicity; Renal tubular epithelial cell; Organic anion transporter; Aristolochic acid; *Tripterygium wilfordii* Hook. f.; *Rheum officinale* Baill

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### Introduction

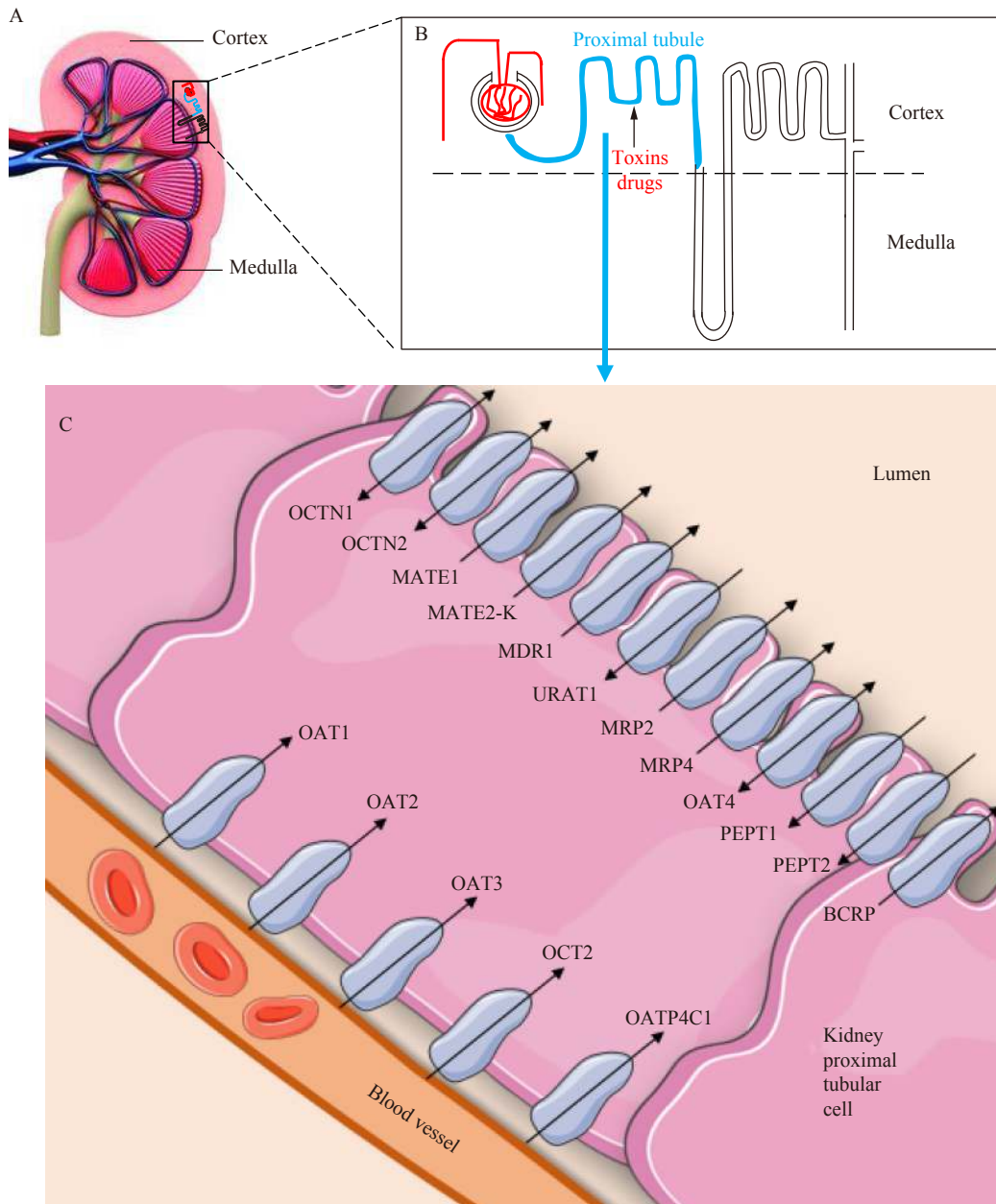
Traditional Chinese Medicine (TCM) has been used in China for over 2000 years and has become more widely accepted internationally, especially after Prof. TU You-You's discovery of artemisinin (also known as "Qing Hao Su", derived from the medicinal herb *Artemisia annua*), for which she received the Nobel Prize in 2015 [1]. Moreover, the 11th revision of the International Classification of Diseases, which is overseen by the World Health Organization (WHO), also contains a chapter on traditional medicine and its significance [2]. At present, more than 120 countries and regions in

the world have established traditional Chinese medical institutions, and more than one-third of the global population are adopting Chinese medicinal therapy [3]. However, potential toxicity of several TCMS has drawn increasing attention. TCM-induced nephrotoxicity is a crucial adverse effect [4–5]. As of May 1, 2019, there were a total of 162 drugs in the Chinese Adverse Drug Reaction Information Bulletin, including 52 (32.1%) TCM drugs. Among the TCM drugs, 32 of them had nephrotoxicity risks, accounting for 61.5% of all adverse reactions [3]. It is believed that the kidney plays a pivotal role in the body's defence against toxic xenobiotics and metabolic wastes through elimination, and thus is vulnerable to toxicity. TCMS such as Aristolochic acid, *Tripterygium wilfordii* Hook. f., *Rheum officinale* Baill and cinnabar mainly damage proximal tubular epithelial cells (PTECs) in kidney cortex (Fig. 1A and B) or cause interstitial nephritis [6]. Notably, studies have shown that transporters in the proximal tubule are decisive in the disposition of xenobiotics [7]. Intensified toxicity in PTECs occurs possibly due to

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**Fig. 1** Sketch of kidney anatomy and major transporters distribution in PTECs. (A) Kidney profile. Cortex: the outer region of the kidney; extensions of the cortical tissue, contains about one million blood filtering nephrons. Medulla: inner region of the kidney contains 8–12 renal pyramids. (B) Nephron anatomy. The proximal tubule connects Bowman’s capsule with the proximal straight tubule, and it is essential for the reabsorption of drugs and toxins from filtrate within the nephron. (C) Major transporter distribution in PTECs. Several uptake proteins that are part of the SLC drug transporter family, including the OATs, the organic cation transporters (OCTs), the organic cation/carnitine transporters (OCTNs), and the organic anion transporting polypeptides (OATP). Renal efflux transporters include ATP-binding cassette (ABC) and SLC transporters. Multidrug resistance protein 1 (MDR1, ABCB1), multidrug resistance-associated protein 2, 4 (MRP2, 4, ABCC2, 4), and breast cancer resistance protein (BCRP, ABCG2) belong to the ABC transporter family. Multidrug and toxin extrusion 1 and 2-K (MATE1, 2-K, SLC47A1, 2) are efflux transporters in the SLC transporter family. The major drug transporters involved in organic anion transport in the human kidney are OAT1-3, OATP4C1, URAT1 and MRP2/4

the abnormal cellular transport of toxins and drugs by both apical and basolateral transporters (Fig. 1C). Anionic drug transporters include organic anion transporter 1-4 (OAT1-4), organic anion transporting polypeptide 4C1 (OATP4C1), urate transporter 1 (URAT1) and multidrug resistance-associated

protein 2 and 4 (MRP2/4). Cationic drug transporters consist of organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 and 2-K (MATE1/2-K), Organic zwitterions/cation transporter 1 and 2 (OCTN1/2), P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Peptide transporter 1 and 2 (PEPT1/2) uptake dietary di- and tripeptides as well as peptidomimetic substrates [81].

After an extensive search of renal transporters related reports of 15 nephrotoxic TCMs, we found that OAT1 and OAT3 (OAT1/3) play important roles in nephrotoxicity. Organic anion transporters (OATs) belong to the SLC22A family and consist of more than 10 transporters. Human OATs transport low-molecular-weight organic anions, uncharged molecules, and even some organic cations. Typical substrates of OATs are exogenous substances such as drugs ( $\beta$ -lactam antibiotics, antivirals, diuretics, nonsteroidal anti-inflammatory drugs), environmental toxins (mercury, ochratoxin A), and nutrients (vitamins, flavonoids), as well as endogenous substances such as uremic toxins, dicarboxylates, cyclic nucleotides, and prostaglandins [9]. OATs are highly conserved among humans and rodents [10], providing the rationale for using rats and mice as research alternatives. Human OAT1/3 (SLC22A6/8) proteins are mostly found on the basolateral membrane of PTECs while OAT2 (SLC22A7), OAT4 (SLC22A11) and OAT5 (SLC22A10) localize to the apical side [11]. Human OAT1 protein, which is almost exclusively expressed in the kidney, is found along the whole proximal tubule while rat Oat1 protein is expressed mostly in the S2 segment, and mouse Oat1 is located at higher levels in segments S1 and S2 than in segment S3, respectively. A typical OAT1 substrate is a molecule that is negatively charged or partially negatively charged and contains one hydrophobic domain. Computer-aided substrate structure mining has shown that for optimal transport, a distance of 6–7 Å should exist between the two carboxylate moieties [12]. Unlike OAT1, OAT3 is also more generally expressed, with expression in the choroid plexus, the brain capillary endothelium, and retina in addition to the kidney [10]. OAT1/3 share specificity for some substrates due to their similar protein structures, e.g., p-aminohippurate (PAH), with higher affinity to OAT1 than OAT3 [13]. Therefore, PAH accumulation in renal cortical slices reflects the transport function of OAT1/3 [14]. Recent reports have indicated leading roles of OAT1/3 in the nephrotoxicity or detoxification of some drugs, such as OAT1/3 expression resulted in reduced cisplatin sensitivity in PTECs [15] and up-regulation renal Oat1/3 by puerarin improved methotrexate-induced renal toxicity [16]. In this review, we focus on TCMs with notably reported clinical nephrotoxicity, and assess the contribution of kidney transporters OAT1/3 to nephrotoxicity.

### Organic anion transporters mediate TCMs-induced nephrotoxicity

The interaction of kidney transporters with four typical nephrotoxic TCMs and functional and expression change of transporters after administration with these TCMs are discussed in detail. Table 1 provides a list of interaction of these TCMs with various OATs and reported kinetic parameters. Other cases are listed in Table 2.

### *Aristolochic acid*

Aristolochic acid (AA), which is abundant in the Chinese herbs Fang Chi and Mu Tong, is a mixture of structurally related nitrophenanthrene carboxylic acids, e.g. Aristolochic acid I (AAI) (Fig. 2) and II (AAII). AAI is the major cause of Aristolochic acid Nephropathy (AAN), characterized by severe renal fibrosis and upper urothelial cancer. Despite warnings from the Food and Drug Administration (FDA), AAN cases remain frequently reported around the world [49, 51]. Forty days after single oral dose of AAI in rats, the kidneys had the highest level of AAI compared with other organs [52]. The selective toxicity for PTECs in AAN suggests that the involvement of specific molecular mechanism(s) could be responsible for the cell accumulation of the toxins [53]. Since AA exhibit anionic properties, OATs have been considered key players in AA-mediated toxicity. AAI is a high-affinity substrate for human and mouse OAT1 and OAT3 but a weaker substrate for the human OAT4 [46]. When OAT1 and OAT3 were inhibited, the renal accumulation and renal toxicity of AAI were reduced both *in vitro* and *in vivo* [47, 48, 54]. OATs, therefore, play a crucial role in the tubular accumulation of AAI and induction of AAN. Zhang proved that OAT1 mediated the transport of AA while leading to apoptosis of HEK293 cells in a concentration-dependent manner and inferred that an epidermal growth factor downregulated the expression of OAT1 after an analysis of renal biopsy samples of AAN patients [55]. Down-regulation of renal Oat1/3, Oct1/2 and Octn1/2 expressions and disorder of fatty acid metabolism were observed after 10 mg/kg AA once daily for 7 days in rats [56]. These results indicate that alterations of organic ion transportation are part of AAN, contribute to the altered urinary metabolic profile and may lead to further proximal tubule injury. As for the apical side, AAI may possibly undergo efflux via BCRP, rather than P-gp or MRP2 [57–58]. In addition, MDCK-OAT1/CYP1A2 cells showed a much greater decrease in viability than did MDCK-CYP1A2 and MDCK-OAT1 cells, suggesting that OAT1 and CYP1A2 might play a synergistic role in AAI-induced toxicity [59].

### *Tripterygium wilfordii* Hook. f

Tripterygium glycosides (TG), extracted from the Chinese herb *Tripterygium wilfordii* Hook. f (TWHF), is a widely used anti-inflammatory and immunosuppressive agent [60]. However, according to a case report from the National Adverse Drug Reaction Monitoring Centre, there were 839 cases involving TWHF from Jan 2004 to Sep 2011, 73 of which were serious [3]. The incidence of adverse reactions to TWHF is about 26.7% to 58.1% [61–62], of which 5.81% is nephrotoxicity [63]. Increased blood urine nitrogen (BUN) and serum creatinine (Scr), as well as oliguria, were observed 20 days after treatment with a TWHF preparation in humans [64]. Biopsy samples from injured human kidneys showed tubular epithelial cell necrosis and interstitial inflammatory cell infiltration [65], suggesting that the proximal tubule is one of the sensitive targets. DAN *et al.* found that 16 days of TG at a

**Table 1** Interaction of main compounds from four TCMs with OATs.

Compound	Transporter <sup>a</sup>	Interaction <sup>b</sup>	System <sup>c</sup>	Kinetics( $\mu\text{M}$ )			Reference
				$K_m$	$K_i$	$\text{IC}_{50}^d$	
aristolochic acid I	hOAT1	S	<i>X. laevis</i>	/	/	/	46
	hOAT1	I	HEK293		$0.63 \pm 0.15$ (10PAH)		46
	hOAT1	I	HEK293		$1.35 \pm 0.31$ (40 CF)		47
	hOAT1	I	HEK293		$34.74 \pm 10.69$ (1000 CRB)		47
	mOat1	S	CHO	$0.79 \pm 0.01$			48
	mOat2	S	CHO	$0.36 \pm 0.05$			48
	hOAT3	S	<i>X. laevis</i>	/			46
	hOAT3	I	HEK293		$0.50 \pm 0.10$ (0.05 ES)		46
	hOAT3	I	HEK293		$0.71 \pm 0.39$ (40 CF)		47
	hOAT3	I	HEK293		$2.76 \pm 0.87$ (1000 CRB)		47
	mOAT3	S	CHO	$0.51 \pm 0.06$			48
	hOAT4	S	<i>X. laevis</i>	/			46
	hOAT4	I	HEK293		$20.63 \pm 1.70$ (0.05 ES)		46
	emodin	hOAT1	I	MDCK			$0.61 \pm 0.09$ (4 CF)
hOAT3		I	HEK293			$1.22 \pm 0.22$ (5 Fluo)	49
rhein	hOAT1	I	MDCK			$0.23 \pm 0.03$ (4CF)	49
	hOAT1	I	CHO		$0.07 \pm 0.01$ (1 PAH)	$0.08 \pm 0.01$ (1 PAH)	50
	mOat1	I	CHO		$0.20 \pm 0.03$ (1 PAH)	$0.22 \pm 0.03$ (1 PAH)	50
	hOAT3	I	HEK293			$0.08 \pm 0.01$ (5 Fluo)	49
	hOAT3	I	CHO		$0.08 \pm 0.00$ (1 PAH)	$0.08 \pm 0.00$ (1 PAH)	50
	mOat3	I	CHO		$0.22 \pm 0.07$ (1 ES)	$0.24 \pm 0.07$ (1 ES)	50
	hOAT4	I	CHO			>100 (1 ES)	50
chrysophanol	hOAT1	I	MDCK			>10 (4CF)	49
	hOAT3	I	MDCK			>10 (5 Fluo)	49
aloe-emodin	hOAT1	I	MDCK			$2.29 \pm 0.18$ (4 CF)	49
	hOAT3	I	HEK293			$5.37 \pm 1.28$ (5 Fluo)	49
physcion	hOAT1	I	MDCK			>10 (4 CF)	49
	hOAT3	I	HEK293			>10 (5 Fluo)	49

a Transporter species: h human, m mouse; b Interaction: I inhibitor, S substrate; c Expression system: CHO Chinese hamster ovary cells, HEK293 human embryonic kidney cell line, MDCK Madin-Darby canine kidney cell line, S2 cell line derived from second segment of proximal tubule, *X. laevis* *Xenopus laevis* oocytes; d  $\text{IC}_{50}$ : concentration of inhibited substrate is shown in parentheses (in micromolars), substrate abbreviations: CF carboxyfluorescein, ES estrone sulfate, PAH paraaminohippurate, PRB probenecid, Fluo Fluorescein;

dose of  $600 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  by gavage to rats decreased PAH accumulation in renal cortical slices and the renal mRNA expression of Oat1 and Oat3<sup>[14]</sup>. Triptolide (Fig. 2) is thought to be the major nephrotoxic compound of TG<sup>[66]</sup>. Our previous study suggested that the proximal tubule is the target of triptolide-induced injury<sup>[67]</sup> and that this toxicity is related to the disruption of cell-cell junctions and alterations in the paracellular permeability of the proximal tubule<sup>[68]</sup>. LI *et al.* assessed the rat urine metabolome after continued administra-

tion of  $0.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  triptolide for 7 days. They observed increases in acetate on the first day, betaine on the third day and acetone on the seventh day, which suggested that injury began with the S1 segment of the kidney cortex, gradually moved to the renal papillae, and ultimately reached the S3 segment<sup>[69]</sup>. Since Oat1 is strongly expressed in the proximal tubule S2 segment and weakly in the S3 segments and Oat3 is localized in the S1, S2, and S3 segments<sup>[70]</sup>, the inhibition of the expression and function of Oats observed by DAN *et al.*

**Table 2 Nephrotoxic TCM drugs' renal accumulation and alterations of transporters.**

Nephrotoxic TCM drugs (Toxic compounds)	Toxic drug accumulation	Alteration of transporters at toxic dose	Function
		Expression	
Realgar (As <sub>2</sub> O <sub>3</sub> , As, Cu) [17]	70% accumulated in human kidney, <i>t</i> <sub>1/2</sub> = 65 ~ 70 days [19]. Three months after clinical dose arsenic accumulated 6.8 times more than single dose in rat kidney [19]	rOat1 <sup>a</sup> , rOat3 mRNA↓ [20]	PAH <i>t</i> <sub>1/2β</sub> ↑, AUC↑, V <sub>d</sub> ↓, CL↓, kidney and serum PAH ratio ↓, PAH uptake in rat kidney slice↓ [20]
<i>Strychnos nux-vomica</i> L. (brucine, strychnine) [21-22]	Distribution of strychnine and brucine was mostly in kidney [23,24]. No accumulation in human blood after administration for 8 weeks [25]	/	OAT1/3 inhibited [26]
<i>Radix Aconiti</i> (aconitine, meseconitine, hypaconitine) [27]	No accumulation of aconitine in the body since it is excreted via the kidney within 24 h [28]	/	OAT1/3 inhibited [26]; PAH accumulation in mice kidney↑ [29,30]
<i>Cinnamomum cassia</i> Presl (cinanamidehyde, cinnamic acid)	Distributed mostly in spleen, liver and kidney and no long-term accumulation of cinnamaldehyde in rats [31]	mOat2, mOat3 mRNA↑ [29]	PAH accumulation in kidney ↑ [29,30]
<i>Leonurus artemisia</i> (leonurine) [32,33]	No accumulation in rats after oral administration of leonurine for 28 days [34]	mOat1, mOat2 mRNA↑, mOat3 mRNA↓ [29]	PAH accumulation in kidney ↑ [29]
<i>Radix Sophorae Flavescens</i> (matrine, oxymatrine)	No accumulation after single dose of Ganku oral liquid; Almost 85.3% (iv <sup>a</sup> ), 80.1% (ig) of oxymatrine excreted into urine after oxymatrine administration for 24 h [35]	mOat3 mRNA↓ [29]	PAH accumulation in kidney ↑ [29]
<i>Scelopendra</i> (histamine, haemolysin) [36]	/	mOat1, mOat3 mRNA↓ [29]	PAH accumulation in kidney ↑ [29]
<i>Rhizoma corydalis</i> (corydalis B) [37,38]	MRT and <i>t</i> <sub>1/2</sub> are less than 8 h for all the alkaloids so they are not easy to accumulate in mice [39]	/	PAH accumulation in kidney↑, PAH uptake in kidney slice↓ [30]
<i>Heracleum hemsleyanum</i> Diels (xanthotoxin) [40]	/	/	PAH accumulation in kidney ↑ [30]
<i>Euphorbia kansui</i> T. N. Liou ex S. B. Ho (kansuine A, kansuine B) [41,42]	/	/	PAH accumulation in kidney↑; PAH uptake in kidney slice↓ [30]
<i>Isatis tinctoria</i> L. (indigo, indirubin) [43]	Indican increased indoxyl sulfate (IS, major metabolite of indican) in blood, especially for patients with chronic kidney disease, who had accumulated IS [44]	mOat1, mOat2, mOat3 mRNA↓ [45]	PAH accumulation in kidney↑; PAH uptake in kidney slice↓ [45]

a Transporter species: r rat, m mouse; b Administration route: iv intravenous, ig intragastric; c Change: ↑ increase, ↓ decrease.

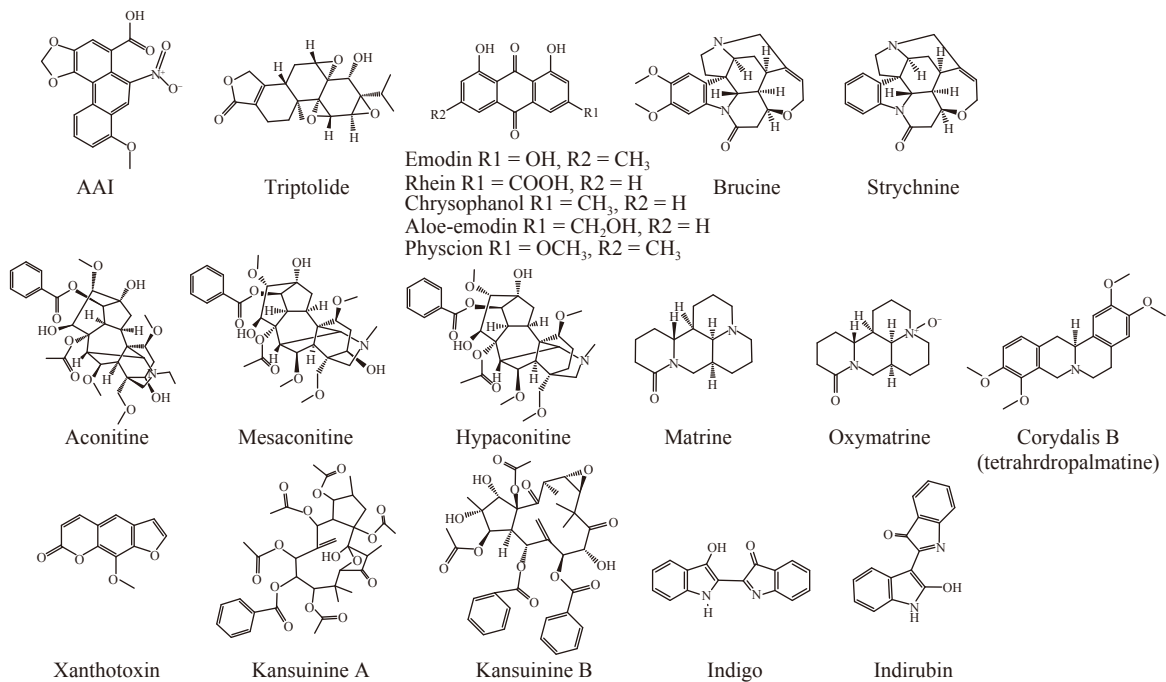


Fig. 2 Chemical structures of major toxic components from TCMs mentioned in this paper

could be explained by injury to proximal tubule cells. As for the apical side, TP is proved to be the substrate of P-gp rather than BCRP, MRP2, OATP1B1, or OATP1B3 by cellular uptake assay, nor does it inhibit the transport activity of MRP2 or P-gp by vesicular transport assay [71-72], whereas intraperitoneally injection of TP at 1.0 mg·kg<sup>-1</sup> in mice decreased both the mRNA and protein levels of MRP2. In mice livers, TP led to the disorder of bile acid profiles, it was confirmed that these hepatic transporters mainly contributed to the accumulation of bile acids but not TP [72]. Therefore, TP exposure may also cause OATs-related injury of proximal tubules, and the inhibition of the expression and function of OATs and MRP2 probably affect imbalance of renal endogenous substances, e.g., uremic toxins and subsequently aggravate the renal injury.

#### *Rheum officinale* Baill

*Rheum officinale* Baill, also called rhubarb, is one of the most frequently used TCMs. There are more than 800 kinds of compounds in the proprietary Chinese medicines that contain rhubarb. However, hyaline droplets and pigment deposition were observed in renal tubules of rats after oral administration of rhubarb total extract. The toxicity increased gradually over time but was reversible after cessation [73-74]. Anthraquinones such as emodin, rhein, chrysophanol, aloe-emodin, and physcion (Fig. 2) are rhubarb's essential active components. Our previous research indicated that thirteen-month exposure to total rhubarb anthraquinones in both rats and dogs resulted in swelled and denatured PTECs [75-77]. Anthraquinones are a new class of OAT inhibitors rather than substrates [50], and the more acidic the substituent, the more potent the inhibition. Rhein, which bears a carboxylic group, was the most potent inhibitor of OAT1/3. Comparison of the

estimated IC<sub>50</sub> values with clinical unbound plasma concentrations (67–387 nmol·L<sup>-1</sup>) of rhein indicated its potential clinically relevant drug-drug interactions (DDIs) on OAT1/3 in the kidney, leading to unintended changes in pharmacokinetics, pharmacodynamics, toxicity or therapeutic effects. In addition, there was a marked species difference in inhibitory potency; OAT1/3 exhibit 3- and 28-fold higher affinity for rhein than their murine orthologs, respectively [50]. Furthermore, the rat urine metabolome after continued administration of 1500 mg·kg<sup>-1</sup> emodin for 16 days showed significant decreases in citrate and ketoglutarate [78]. Since OATs exchange extracellular organic anions for intracellular α-ketoglutarate or glutarate, it was likely that OATs were downregulated by emodin, but results from a recent study indicated the opposite. When rhubarb extract was administered to rats for 30 days, the expression of renal Oat1/3 mRNA in rats receiving the efficacy dose were 24% and 26% higher than those in normal rats, while administration of the toxic dose increased expression by 10% and 15%, respectively [79]. The change in expression might be a compensatory protective effect that is weaker at toxic doses. Other transporters Oatp1b3, Oatp2b1, and Oat2 mediated hepatic rhein uptake, while Bcrp rather than P-gp, Mrp2 and Mrp3 mediated its hepatic efflux [80]. Therefore, Bcrp would possibly be responsible for its renal efflux.

#### *Cinnabar*

Cinnabar is the active constituent of approximately 50 kinds of TCM recipes as a sedative. However, increases in BUN, Scr, and alanine transaminase (ALT), as well as oliguria, were observed two-month oral doses in humans [80,81]. Additionally, eight-week administration of cinnabar caused renal inflammatory cell infiltration, vacuoles and albumen

ducts in rats [82]. Cinnabar mostly consists of  $\alpha$ -HgS (> 98.0%), with a small amount of mercury, and soluble mercury salts such as HgCl<sub>2</sub> and MeHg. The chemical form of mercury is a major determinant of mercury disposition and toxicity, and  $\alpha$ -HgS is less nephrotoxic than HgCl<sub>2</sub> and MeHg [83–84]. The kidney is the main target of mercury toxicity and mercuric ions (Hg<sup>2+</sup>) accumulate preferentially in PTECs [82]. Hg<sup>2+</sup> gets access to proximal tubule cells primarily by Oat1/3 and the removal into the lumen is mediated by the Mrp2 [85–86]. And the knock-out of *Oat1* abolished most of the HgCl<sub>2</sub> nephrotoxicity [87]. YU *et al.* found that PAH uptake in mouse renal slices and the mRNA expression of Oat1/3, were significantly reduced after six-day oral treatment with 30 mg·kg<sup>-1</sup> cinnabar in mouse kidneys [88]. The expression of Oat1, Oat3, and Oatp4c1, was also decreased in other reports, while the expression of the renal efflux transporters Mrp2 was increased following HgCl<sub>2</sub> and MeHg administration in rats, but unaffected by HgS [89–91]. Giusto *et al.* found that Oat1 protein expression increased in renal homogenates and decreased in renal basolateral membranes in HgCl<sub>2</sub> rats, while Oat3 protein decreased both in kidney homogenates and basolateral membranes [92]. Overall, the alteration on the expression and/or the function of Oat1/3 might be an effective therapeutic strategy for reducing the nephrotoxicity of mercury.

## Conclusion and discussion

Drug transporters on the cell membrane of the proximal tubule protect against systemic toxicity by eliminating drugs and toxins. This review indicates that OAT1/3 play critical roles in the renal transport of a variety of TCMs with well-known nephrotoxic potential. The transport function of OAT1/3 was inhibited *in vitro* by most nephrotoxic TCMs (Table 1). The expression and/or function of OAT1/3 were down-regulated in most cases *in vivo* after administration of nephrotoxic TCMs (Table 2), yet no definitive conclusions have been reached about efflux transporters. A few reports indicated that the toxic components of some TCMs (*e.g.*, AAI and rhein) were substrates of BCRP or MRP2, but reports on the expression and function changes of these transporters under toxicological conditions are rare. Although the molecular mechanisms by which OAT1/3 regulate the toxicity of these TCMs remain unclear, here we describe two possible mechanisms (graphical abstract). On the one hand, since some TCMs or their metabolites are substrates of OAT1/3, long-term use or overdose may cause renal accumulation of these toxins, thus lead to toxicity. As mentioned above, a carboxyl group is crucial for high-affinity interaction with OATs. The carboxyl group in the structure of AAI may allow it to act as a substrate of OATs thus gain entry to PTECs. Its cytotoxic effect can subsequently sensitize the kidney to damage. On the other hand, most TCM-s or their metabolites, such as triptolide and rhein, are inhibitors of OATs rather than their substrates. In these cases, toxic substances are probably the endogenous substrates of OATs, such as fatty acids in the ex-

amples of AA and bile acids in the case of triptolide. Since OAT1/3 handle over 35 uremic toxins and solutes (*e.g.*, indoxyl sulfate, urate, and creatinine), including those derived from the gut microbiome (*e.g.*, phenylsulfate and indole-3-acetic acid) [70], it is likely that TCMs or their metabolites (most of them are acidic, judging from their structures) compete with these endogenous substances for the binding sites of OATs, attenuate their excretion or affect their balance in the body, and lead to kidney injury. For example, administration of either ketoprofen or diclofenac (nonsteroidal anti-inflammatory drugs, OAT1/3 inhibitors) significantly decreased the renal clearance of indoxyl sulfate thereby increasing systemic exposure of this uremic toxin, which led to the pathogenesis of analgesic nephropathy [93–94]. Similarly, in cisplatin-induced rat nephrotoxicity, the gene and protein expression of Oat1/3 were decreased, while the concentration of serum indoxyl sulfate was markedly increased [95]. It is also worth considering that why renal expression of OAT1/3 were down-regulated after long-term administration of TCMs. Since hepatocyte nuclear factor HNF-1 $\alpha$ /HNF-1 $\beta$ , liver X receptors (LXR), transcription factor B cell CLL/lymphoma 6 (BCL6) [96] and protein kinase PKC/Akt and PKC $\alpha$ /NF- $\kappa$ B [97] regulate the expression of OAT1/3, it is likely that long-term administration of TCMs change these upstream factors [98]. Taken together, partial blockade of OAT1/3-mediated transport of uremic toxins by TCMs may alter their excretion and cause toxicity.

## Future perspective

Compared with Western medicine, TCM drugs are sometimes more effective for chronic health issues (*e.g.* nonerosive reflux disease) [99] and have less side effects [100]. In China, traditional herbal medicinal preparations constituted 30% to 50% of the total consumption of medicines [101]. Faced with increasing universal health coverage for an ageing population, the WHO also welcomes the modernization of TCMs, particularly, to give traditional medicine an evidence-based place within the healthcare system, where mainstream modern medicine dominates [2]. If we could explain how TCMs lead to toxicity from the perspective of transporters, then corresponding detoxification strategies might be developed. For example, since probenecid inhibits OAT1, it is used in clinical practice to prevent the nephrotoxicity induced by cidofovir (an antiviral agent, accumulates in tubular cells via OAT1) [102]. This application motivates us to determine the actual mechanism responsible for this combination: the combined use of rhubarb with Aristolochic acid reduces the distribution of AAI in the kidney, which mitigates the nephrotoxicity of Aristolochic acid [103]. These effects might be due to the inhibition of OAT1/3 by rhubarb. Since TCM formulas are often composed of multiple herbs, compatibility plays a significant role in the TCM theory. Perhaps we could elucidate the principals of compatibility based on DDIs mediated by transporters and thus identify the mechanisms underlying the reduction in toxicity, additive effects, and synergism of

different components. In addition to combining TCMs with OATs inhibitors, we could also take precautions by monitoring clinical biomarkers of OATs in case of OATs mediated nephrotoxicity or DDI. In the case of TG, there were no significant changes in serum urea and creatinine when PAH accumulation significantly decreased. In other words, these traditional biochemical tests are not sensitive enough. For OAT1/3, endogenous biomarkers such as taurine, hippurate, and 6 $\beta$ -hydroxycortisol, and GCDCA-S are recommended<sup>[104]</sup>. Although current studies highlight OAT1/3-mediated transport than apical efflux for their uptake as the first step of toxic compounds gain entry and many researchers believe that OATs have diverse functions in substrate transport and metabolic regulation as well as in remote sensing and signaling<sup>[105–106]</sup>, future research should explore apical transport to describe the whole picture.

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