Drug Transporters in the Kidney: Perspectives on Species Differences, Disease Status, and Molecular Docking

Wei Zou1, Birui Shi2, Ting Zeng1, Yan Zhang2, Baolin Huang2, Bo Ouyang1, Zheng Cai2,3* and Menghua Liu2,3*

1Changsha Research and Development Center on Obstetric and Gynecologic Traditional Chinese Medicine Preparation, NHC Key Laboratory of Birth Defects Research, Prevention and Treatment, Hunan Provincial Maternal and Child Health Care Hospital, Changsha, China, 2Biopharmaceutics, NMMPA Key Laboratory for Research and Evaluation of Drug Metabolism, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou, China, 3TCM-Integrated Hospital, Southern Medical University, Guangzhou, China

The kidneys are a pair of important organs that excrete endogenous waste and exogenous biological agents from the body. Numerous transporters are involved in the excretion process. The levels of these transporters could affect the pharmacokinetics of many drugs, such as organic anion drugs, organic cationic drugs, and peptide drugs. Eleven drug transporters in the kidney (OAT1, OAT3, OATP4C1, OCT2, MDR1, BCRP, MATE1, MATE2-K, OAT4, MRP2, and MRP4) have become necessary research items in the development of innovative drugs. However, the levels of these transporters vary between different species, sex-genders, ages, and disease statuses, which may lead to different pharmacokinetics of drugs. Here, we review the differences of the important transports in the mentioned conditions, in order to help clinicians to improve clinical prescriptions for patients. To predict drug-drug interactions (DDIs) caused by renal drug transporters, the molecular docking method is used for rapid screening of substrates or inhibitors of the drug transporters. Here, we review a large number of natural products that represent potential substrates and/or inhibitors of transporters by the molecular docking method.

Keywords: renal drug transporters, species, sex-genders, ages, molecular docking, disease status

INTRODUCTION

The kidneys are the main excretory organs of the body, which play key roles in excretion of metabolites, acid-base balance, and homeostasis of the body system. The secretion and reabsorption effects of renal tubules are mainly mediated by transporters. It is not only an effective mechanism for the reabsorption of nutrients, such as glucose and amino acids, but also an effective way to remove endogenous waste and exogenous biological agents. Up to now, renal excretions of many drugs (including organic anion drugs, organic cationic drugs, and peptide drugs) are mediated by drug transporters concentrated on proximal renal tubules (Ivanyuk et al., 2017). On the one hand, uptake transporters, such as organic anion transporters (OATs) and organic cationic transporters (OCTs), on the basolateral membrane of renal tubular epithelial cells take up drugs from the blood side into cells. On the other hand, efflux transporters, such as
multidrug and toxin extrusion proteins (MATEs) and multidrug resistance proteins (MRPs), located on the brush edge of renal tubular epithelial cells discharge intracellular drugs into the lumen for secretion and excretion (Gozalpour and Fenner, 2018). The study on drug transporters has become one of the main trends in the field of pharmacokinetics. Impacts on 11 drug transporters in the kidneys, including OAT1, OAT3, organic anion transporter polypeptide 4C1 (OATP4C1), organic cation transporter (OCT2), multidrug resistance protein 1 [MDR1, namely p-glycoproteins (P-gp)], breast cancer resistance protein (BCRP), MATE1, MATE2-K, OAT4, multidrug resistance-associated protein 2 (MRP2), and MRP4, have become necessary research items in the development of innovative drugs (Food and Drug Administration, 2020). These drug transporters are mainly distributed on the basolateral membrane and apical membrane of renal proximal tubular cells, which are shown in Table 1 and Figure 1.

At present, pharmacokinetic data in drug instructions are primarily derived from healthy subjects, and most pharmacokinetic experiments are performed in healthy adult animals to evaluate drug safety and in vivo processes (absorption, distribution, metabolism, and excretion). However, two issues require attentions: 1) Which characteristics of the animal model (such as species, age, sex-gender, and disease status) can best reflect pharmacokinetic behaviour in humans? 2) Does the pharmacokinetic data from healthy subjects (human and/or animal) appropriately reflect the disease status? Extensive literature in recent decades has shown that the changes of drug transports in the disease status will lead to the changes of the drug pharmacokinetic behaviour, which directly affect the performance of drug efficacy or produce toxicities and side effects (Yang and Han, 2019). Therefore, it is very important to understand the changes of transporters in the disease status for optimizing clinical drug administration. In addition, patients often take multiple drugs simultaneously in clinic, and then drugs may cause drug-drug interactions (DDIs), which result in serious adverse reactions or an altered treatment outcome. A statistical study of hospitalized elderly patients has revealed that the prevalence of DDIs ranged from 8.34 to 100% (de Oliveira et al., 2021). Drug transporter variation is one of the mechanisms of DDIs, as the drugs may be substrates or mediators of the drug transporters. At present, computer-based drug design is widely used in drug development to simulate the chemical structural interactions between biomacromolecules and drugs, and hence, this technique has been used in transporter studies to quickly predict DDIs in clinic (Marques et al., 2019).

In this review, we mainly discuss the renal transporter expression differences on species, sex-gender, and age, as well as the changes of drug transporters under disease statuses. Furthermore, the molecular docking technology applied on renal drug transporters was reviewed, which could facilitate

### TABLE 1 | The main drug transporters on the proximal tubular cells.

| Protein | Full name | Location | Gene in human | UniProt ID |
|---------|-----------|----------|---------------|------------|
| OAT1    | Organic anion transporter 1 | Basolateral membrane | SLC22A6 | Q4U2R8 |
| OAT3    | Organic anion transporter 3 | Basolateral membrane | SLC22A8 | Q8TCC7 |
| OATP4C1 | Organic anion transporter polypeptide 4C1 | Basolateral membrane | SLC04C1 | Q6ZCN7 |
| OCT2    | Organic cation transporter | Basolateral membrane | SLC22A2 | O15244 |
| MDR1    | Multidrug resistance protein 1 | Apical membrane | ABCB1 | P08183 |
| BCRP    | Breast cancer resistance protein | Apical membrane | ABCG2 | Q8UNQ0 |
| MATE1   | Multidrug and toxin extrusion protein 1 | Apical membrane | SLC47A1 | Q96FL8 |
| MATE2-K | Multidrug and toxin extrusion protein 2-k | Apical membrane | SLC47A2 | Q86VL8 |
| OAT4    | Organic anion transporter 4 | Apical membrane | SLC22A11 | Q9NSA0 |
| MRP2    | Multidrug resistance protein 2 | Apical membrane | ABCC2 | Q92887 |
| MRP4    | Multidrug resistance protein 4 | Apical membrane | ABCC4 | O15439 |

UniProt: https://www.uniprot.org/

### FIGURE 1 | Distribution of the major transporters located in kidney.
| Species | Method | Units | OAT1 | OAT3 | OATP4C1 | OCT2 | MDR1 | BCRP | MATE1 | MATE2-K | OAT4 | MRP2 | MRP4 | Reference |
|---------|--------|-------|------|------|---------|------|------|------|-------|---------|------|------|------|------------|
| Human   | LC-MS/MS | pmol g⁻¹ | 107.7 ± 56.83 | 78.5 ± 164.2 | 0.3 ± 42.3 | 164.2 ± 18.16 | 39.8 ± 78.5 | 0.3 ± 3.89 | 100.6 ± 47.52 | 10.6 ± 0.10 | 164.2 ± 5.64 | 30.1 ± 0.15 | Basit et al. (2019) |
| Monkey  | LC-MS/MS | pmol g⁻¹ | 5.31 ± 242.5 | 9.68 ± 124.7 | 0.18 ± 52.4 | 9.68 ± 147.18 | 0.18 ± 52.4 | 3.05 ± 242.5 | 9.68 ± 147.18 | 0.18 ± 52.4 | Basit et al. (2019) |
| Dog     | LC-MS/MS | pmol g⁻¹ | 75.4 ± 308.8 | NC NC 32.1 ± 308.8 | NC NC 9.34 | NC NC 1.07 | NC NC 0.15 | NC NC 0.55 | NC NC 0.55 | Basit et al. (2019) |
| Rat     | LC-MS/MS | pmol g⁻¹ | 308.8 ± 308.8 | 79.24 ± 308.8 | NC NC 253.5 ± 79.24 | NC NC 11.76 | NC NC 1.09 | NC NC 0.27 | NC NC 0.27 | Basit et al. (2019) |
| Mouse   | LC-MS/MS | pmol g⁻¹ | 156.2 ± 156.2 | 92.06 ± 156.2 | NC NC 429.1 ± 92.06 | NC NC 134.67 | NC NC 5.99 | NC NC 0.88 | NC NC 0.88 | Basit et al. (2019) |

NC: no conserved peptide; ↔: No significant difference; ND: sex difference was not determined; BLQ: below limit of quantification; /: not mentioned.
the prediction of DDIs for improving the safety and effectiveness of drugs in clinic.

**THE EXPRESSIONS OF DRUG TRANSPORTERS IN KIDNEY ACROSS SPECIES, SEX-GENDER, AND AGE**

**Species**

Preclinical trials are essential for evaluating drug safety, efficacy, toxicity, and pharmacokinetics. It is necessary to understand the difference between humans and animals at the levels of drug transporters. Along with quantitative real time-polymerase chain reaction (qPCR) and Western blot, the highly sensitive liquid chromatography tandem-mass spectrometry (LC-MS/MS) has become one of the most effective methods in the quantitative detection of drug transporters (Fallon et al., 2016; Nakamura et al., 2016; Basit et al., 2019). Table 2 has shown the species differences of renal drug transporters found in past decades. Basit et al. (2019) showed that the abundances of OAT1, OCT2, and MATE1 in human renal tissue were higher than the other eight drug transporters. The levels of OAT1, OAT3, OATP4C1, OCT2, MDR1, MATE1, OAT4, MRP2, and MRP4 in monkey were from 1.6-fold to 3.7-fold higher than that in human. OATP4C1, MATE1, MATE2-K, OAT4C1, and MRP2 in rat and mouse, as well as OATP4C1, OCT2, MATE1, MATE2-K, OAT4C1, MRP2, and MRP4 in dog, were not detected as no conserved peptide available (Basit et al., 2019). Fallon et al. (2016) have revealed three renal efflux transporters in human, monkey, dog, and rat. The concentrations of MDR1 and MRP2 were similar in human and monkey, but higher than that in rat. However, the BCRP level was the highest in rat (4.5 pmol mg$^{-1}$ protein), which is 50-fold than that in human (0.09 pmol mg$^{-1}$ protein). In another study, 11 transporters were detected in the pooled microsomal fraction of human kidney (Nakamura et al., 2016). All transporters, except for OATP4C1, have sensitive responses when detection. The content of BCRP (3.6–4.5 pmol mg$^{-1}$) was similar as the other reports (Fallon et al., 2016; Nakamura et al., 2016; Al-Majdoub et al., 2020). Many exogenous substances show species differences in excretion. Taking per- and polyfluoroalkyl substances (PFAS) as an example, a longer serum half-life in healthy men and women (Basit et al., 2019). Due to sex-gender differences in transporter expression, full consideration should be given to pharmacokinetic, safety, efficacy, and toxicity studies of drug to allow better interpretation of clinical data. For example, 2 h after oral administration of metformin at a dose of 500 mg/kg, the cumulative urinary excretion and renal tissue-to-plasma concentration ratio in female rats (26,689 ± 1,266 µg and 2.96 ± 0.47 ml/g, respectively) were markedly lower than that in male rats (32,949 ± 1,384 µg and 4.20 ± 0.31 ml/g, respectively), which are potentially explained by gender-related differences on renal OCT2 expression, as the metformin is the substrate of OCT2 (Ma et al., 2016). Pregnancy is an especial physiological status for women. Lu et al. have proved no significant differences among OAT1/3, OCT2, MRP2, and MATE1 mRNA expressions in the kidneys between pregnant and non-pregnant rats (Lu et al., 2020).

**Age**

Age affects the transcription and translation of drug transporters. Joseph et al. (2015) have determined 30 drug transporters in two groups of human kidneys (age <50 years and ≥50 years). Among them, the mRNA expression of the OCT2 in the <50 years group was greater than that in the ≥50 years group (Joseph et al., 2015). The nephrotoxicity of cisplatin exhibits an age dependence in human. Wen et al. (2015) had analyzed 182 cisplatin-treated patients to illuminate the influence of nongenetic factors on cisplatin-induced nephrotoxicity, and age (≥50 years) is closely associated with the decline of renal function with an odds ratio (OR) of 11.771. This might be due to the fact that the MATE1, which excretes cisplatin into urine, was significantly decreased with the increasing age (≥50 years), resulting in the specific accumulation of cisplatin in renal cells. Although it is difficult to investigate the changes of drug transporters in the human kidney throughout life, an age-related study on OAT1, OAT3, OATP4C1, OCT2, MDR1, BCRP, MATE1, MATE2-K, MRP2, and MRP4 mRNA expressions was performed in male rat kidneys with qPCR and Western blot methods (Xu et al., 2017). In this preclinical study, all the detected drug transporters showed different increasing trends. As shown in Figure 2, the mRNA expressions of OAT1, OATP4C1, OCT2, BCRP, MATE1, and MATE2-K reached the peaks at the 180th day and subsequently declined. Compared with the mRNA expressions at the -2nd day and/or the 1st day, the expressions at the peak were 35-fold, 35-fold, 18-fold, 18-fold, and 37-fold greater for six drug transporters, respectively. The mRNA expressions of OAT3 and MRP2 reached the peak at the 850th day. For OAT3, the mRNA
expression at the 180th day was 22-fold greater than that at the 1st day, while it was 3-fold greater at the 850th day than that at the -2nd day for MRP2. Interestingly, the mRNA expression of MRP2 was reduced almost 50% at the 14th and the 21st day compared with the -2nd day. The mRNA expression of MRP4 reached peak at the 28th day, and it was 6-fold higher in comparison with that at the -2nd day. Ren et al. (2015) used both young rats (aged 3 months) and old rats (aged 12 months) to illuminate age-related excretion of metformin. The values of t1/2, accumulation in urine, and total clearance (CLtot) (1.717 ± 0.30 h, 6,088.402 ± 931.55 μg, and 93.414 ± 11.47%, respectively) in young rats were significantly different from those indexes in old rats (2.002 ± 0.51 h, 4,287.087 ± 458.08 μg, and 57.161 ± 18.59%, respectively). A significant age-related decrease of OCT2 is probably responsible for renal excretion of metformin (Ren et al., 2015). Although the lives of experimental animals are much shorter than that of human, we still clarity that the drug transporter undergoes a dynamic change throughout the life. Thus, drug transporters should receive close attentions at fetal, neonatal, mature, and old ages during drug development and clinical use (Andreollo et al., 2012; Sengupta, 2013; Gleeson et al., 2021; Vinarov et al., 2021).

**EFFECT OF DISEASES ON TRANSPORTER EXPRESSION AND FUNCTION**

**Effect of Renal-Related Diseases on Drug Transporters in Kidney**

Kidney diseases, such as chronic kidney disease (CKD), acute kidney injury (AKI), and renal failure, can change the excretion rate of endogenous and/or exogenous substances, mainly due to a decrease in the glomerular filtration rate and the changes in drug transporters and metabolic enzyme activities. Levels of renal drug transporters are crucial for drug excretion, as drugs were mainly excreted through these transporters. As shown in Table 3, the mRNA and/or protein levels of drug transporters in renal-related disease models were summarized.
| Pathological state          | Specie | Model establishment | OAT1 | OAT3 | OATP4C1 | OCT2 | MDR1 | BCRP | MATE1 | MATE2-K | MRP2 | MRP4 | Reference |
|----------------------------|--------|---------------------|------|------|---------|------|------|------|-------|---------|------|------|-----------|
| Hyperuricemic nephropathy  | mice   | Mice were intraperitoneally injected with potassium oxonate (500 mg/kg) once daily for 7 days | protein ↓ | protein ↓ | — | — | — | protein ↓ | — | — | — | — | Zhao et al. (2021) |
| male SD rats              | Rats were oral administrated of adenine (0.1 g/kg) and potassium oxonate (1.5 g/kg) once daily for 3 weeks | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — | Wang et al. (2020a) |
| male ICR mice             | Mice were oral administrated with hyperuricemic (100 mg/kg) and ethanolic potassium (300 mg/kg) for 10 days | protein ↓ | — | — | — | — | — | — | — | — | — | Li et al. (2020) |
| male SD rats              | Rats were administrated with yeast pellets and adenine (60 mg/kg) for 5 weeks | mRNA ↓ | — | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Wang et al. (2019a) |
| male SD rats              | Rats were oral administrated with adenine (100 mg/kg) and ethanolic (250 mg/kg) daily for 5 weeks | protein ↓ | — | — | protein ↓ | — | protein ↓ | — | — | — | — | Wu et al. (2017) |
| male SD rats              | Rats were oral administrated with adenine (0.1 g/kg) and potassium oxonate (1.5 g/kg) once daily for 3 weeks | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — | Uus et al. (2015) |
| male SD rats              | Rats were administrated with adenine (50 mg/kg) and oteracil potassium (300 mg/kg) for 10 days | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Kim et al. (2017) |
| male SD rats              | Mice were intraperitoneally injected with potassium oxonate (250 mg/kg) once a day for 7 days | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Zhang et al. (2020) |
| Nephrotoxicity male C57/BL6J mice | Mice were injected intraperitoneally with cisplatin (20 mg/kg) at once | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | Freitas-Lima et al. (2020) |
| male ICR mice             | Mice were given a single dose of cisplatin (60 mg/kg) | protein ↓ | protein ↓ | — | — | — | — | — | — | — | — | Deng et al. (2006a) |
| male SD rats              | Rats were intraperitoneally injected of cisplatin (6 mg/kg) | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Jiang et al. (2019) |
| male Water SD rats        | Rats were received intraperitoneal injection of cisplatin (12 mg/kg) | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Wang et al. (2018b) |
| male Water SD rats        | Rats were given cisplatin (7 mg/kg) ip at once | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Soetikno et al. (2019) |
| male Water SD rats        | Mice received a single dose of cisplatin (18 mg/kg) | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | Aleksunes et al. (2006) |
| male C57/BL6J/6 J mice    | Rats were oral administrated with AA (10 and 30 mg/kg) for 7 days | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | Lou et al. (2011) |
| male Water SD rats        | Rats were given 0.28 M NH4Cl/2% sucrose for 2 or 7 days | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | Gottla Nivath et al. (2020) |
| male Water SD rats        | Rats were treated with doxorubicin (15 mg/kg) ip at once | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | Karimian Pour and Piquette-Miller (2003) |
| male Water SD rats        | Rats were intraperitoneally injected with methotrexate (7 mg/kg) for 3 days | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Uus et al. (2018) |
| male Water SD rats        | Rats were intraperitoneally injected with gentamicin (100 mg/kg) for 7 days | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | Mo et al. (2018) |
| male Water SD rats        | Rats were administrated intraperitoneally with ethanold (5 mg/kg) | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | mRNA ↓ | — | — | — | — | Karimian Pour and Piquette-Miller (2008) | (Continued on following page)
| Pathological state | Specie | Model establishment | OAT1 | OAT3 | OATP4C1 | OCT2 | MDR1 | BCRP | MATE1 | MATE2-K | MRP2 | MRP4 | Reference |
|-------------------|--------|---------------------|------|------|---------|------|------|------|-------|---------|------|------|-----------|
| male Wistar rats | Rats were injected with HgCl2 (4 mg/kg) at once | protein ↓ | protein ↓ | — | — | — | — | — | — | — | — | — | | |
| male Wistar rats | Rats were treated with a single injection (s.c.) of HgCl2 at a dose of 5 mg/kg | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| male Wistar strain rats | Rats were injected rats with CdCl2 (30 mg/kg), HgCl2 (30 mg/kg), HgS (30 mg/kg), CdS (30 mg/kg) and MeHgCl (3.1 mg/kg) for 7 days | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| KM mice | Rats were treated with a single injection of HgCl2 (34.6 mg/kg) and MeHgCl (3.2 mg/kg) for 7 days | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| Ischemia-Reperfusion in kidney | female SD rats | Rats model was induced by bilateral clamping of renal arteries for 45 min | mRNA 6 and 24 h ↓, 72 h ↓ | mRNA 6 and 24 h ↓, 72 h ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| male SD rats | Rats model was induced by vascular clamping over both pedicles for 30 min | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| male SD rats | Rats were induced by vascular clamps over both pedicles for 30 min | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| male Wistar rats | Rats were induced by occluding renal arteries | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| male FVB mice | Rats were induced by bilateral clamping of the renal artery and vein for 30 min | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| Chronic Renal Failure | Male SD rats | model rats were induced by two-stage 5/6 nephrectomy | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| Wistar rats | a 5/6 nephrectomy | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| Male SD rats | Rats were undergone subtotal nephrectomy operation (60% renal ablation) | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| Male Wistar abino rats | Rats were undergone 5/6 nephrectomy operation | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| Nephrotic Syndrome | male SD rats | rats were intravenously injected with adriamycin (6 mg/kg) for once | mRNA ↓ | mRNA ↓ | mRNA and protein, 6 and 12 weeks ↓ | mRNA and protein, 6 and 9 weeks ↓ | mRNA and protein, 6 weeks ↓ | mRNA and protein, 6 weeks ↓ | mRNA and protein, 6 and 9 weeks ↓ | mRNA and protein, 6 weeks ↓ | mRNA and protein, 6 weeks ↓ | mRNA and protein, 6 weeks ↓ | | |
| Obstructive nephropathy | male Wistar LEW rats | The ureteral obstruction was released after 24 h | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |
| Racial transplantation | male LBN and LEW rats | kidneys of LBN rats were transplanted into LEW rats | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | | |

SD rats: Sprague-Dawley rats; KM mice: kunming mice; FVB mice: Friend leukaemia virus B strain mice; LBN rats: lewis brown norway rats; LEW rats: lewis rats; ↓: decrease in expression; ↑: increase in expression; ↔: no significant difference; /: not mentioned.
### TABLE 4 | The changes of main drug transporters in liver and gallbladder related diseases on mRNA and/or protein levels.

| Pathological state | Species | Model establishment | OAT1 | OAT3 | OCT2 | MDR1 | BCRP | MRP2 | MRP4 | Reference |
|--------------------|---------|---------------------|------|------|------|------|------|------|------|------------|
| Nonalcoholic steatohepatitis | male C57BL/6J mice | Mice were fed with a methionine choline-deficient diet for 4 weeks | mRNA ↓ | mRNA ↓ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | Canet et al. (2015) |
| | male C57BL/6J mice | Mice were fed with a high-fat diet for 8 weeks | mRNA ↓ | mRNA ↓ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | Canet et al. (2015) |
| | ob/ob mice | Mice were fed with a methionine choline-deficient diet for 4 weeks | mRNA ↓ | mRNA ↓ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | Canet et al. (2015) |
| | db/db mice | Mice were fed with a methionine choline-deficient diet for 8 weeks | mRNA ↓ | mRNA ↓ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | Canet et al. (2015) |
| | male SD rats | Rats were fed with a methionine choline-deficient diet for 4 weeks | mRNA ↓ | mRNA ↓ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | Canet et al. (2015) |
| | female SD rats | Rats were fed with a high-fat diet for 8 weeks | mRNA ↓ | mRNA ↓ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | Canet et al. (2015) |
| Ischemia-reperfusion-induced in liver | male SD rats | Rats were undergone hepatic ischemia for 60 min | — | — | — | — | — | mRNA ↓ | mRNA ↓ | Canet et al. (2015) |
| Extrahepatic Cholestasis | male C57BL/6J mice | Mice were undergone a bile-duct operation for 1, 3, 7, and 14 days | — | — | — | — | — | mRNA ↓ | mRNA ↓ | Slitt et al. (2007) |
| | male Wistar rats | Rats were undergone a bile-duct operation for 21 h | protein in cortex homogenates ↑ | protein in cortex homogenates ↑ | protein in basolateral membranes ↑ | protein in basolateral membranes ↑ | — | — | — | Brandoni et al. (2006) |
| | Male Wistar rats | Rats were undergone a bile-duct operation for 24, 72 and 120 h | — | — | — | — | — | — | — | Tanaka et al. (2002) |
| | Male Wistar rats | Rats was injected (i.p.) with alpha-naphthylisothiocyanate (50 mg/kg) | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↑ | mRNA ↑ | mRNA ↑ | mRNA ↑ | Liu et al. (2012) |

SD rats: Sprague-Dawley rats; ob/ob mice: B6.Cg-Lep,ob/J mice; db/db mice: B6.BKS(D)-Lepr,db/J mice; fa/fa rats: Crl:ZUC-Lepr,fa. fatty rats; ↓: decrease in expression; ↑: increase in expression; ↔: no significant difference; /: not mentioned.
### Table 5: The changes of expression of main drug transporters in metabolic disease on mRNA and/or protein levels.

| Pathological state | Species | Model establishment | OAT1 | OAT3 | OCT2 | MDR1 | BCRP | MATE1 | MATE2-K | MRP2 | MRP4 | Reference |
|--------------------|---------|---------------------|------|------|------|------|------|-------|---------|-------|-------|-----------|
| hyperuricemia      | male SD rats | Rats were given drinking water with 10% fructose for 6 weeks | mRNA ↓ | mRNA ↓ | — | — | mRNA ↓ | — | — | — | — | Le et al. (2022) |
|                   | male SD rats | Rats were orally administered with lipodigemulsion (10 mL/kg) once daily for 8 weeks | — | — | — | — | — | — | — | — | — | — |
|                   | male SD rats | Rats were intraperitoneally injected with potassium oxonate (250 mg/kg) at once | mRNA ↓ | mRNA ↓ | — | — | mRNA ↓ | — | — | — | — | — |
|                   | male KM mice | Mice were continuously administrated with potassium oxonate and adenine for 21 days | protein from the 3rd to 21st day | ↓ | ↓ | mRNA ↓ | protein ↓ | — | — | — | — | — |
|                   | male Swiss | Mice were intraperitoneally administrated with potassium oxonate (250 mg/kg) once a day for 7 days | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | additional Mice | Mice were intraperitoneally injected with uric acid (100 mg/kg) at once | mRNA ↓ | mRNA ↓ | protein ↓ | — | mRNA ↓ | protein ↓ | — | — | — | — |
|                   | male Wistar | Rats were oral administrated of adenine (0.1 g/kg) and oxonic acid potassium salt (1.5 g/kg) suspended in 0.9% methylcellulose solution daily for 10 days | mRNA ↓ | mRNA ↓ | mRNA ↓ | mRNA ↓ | — | mRNA ↓ | mRNA ↓ | — | — | — |
|                   | male and female KM mice | Mice were administrated with potassium oxonate salt (500 mg/kg) for 7 days | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male SD rats | Mice were intraperitoneally administrated of hypoxanthine (200 mg/kg) followed by intraperitoneal injection of oxonic acid potassium salt (200 mg/kg) 1 h later | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | Male KM mice | Mice were administrated with lipid emulsion (25% lard, 10% cholest, 2% sodium deoxycholate, 1% propylthiouracil, 25% Tween-80, and 20% propylene glycol) daily for 10 days | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male SD rats | Rats were intraperitoneally injected with potassium oxonate (250 mg/kg) at once | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | Male KM mice | Mice were administrated with oxonic acid potassium salt (200 mg/kg) for 2 weeks | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male Wistar | Rats were administratively administrated with adenine (200 mg/kg) and ethylxylohydroxycine (200 mg/kg) once daily for 10 days | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male SD rats | Rats were administrated with streptozotocin (25% lard, 10% cholest, 2% sodium deoxycholate, 1% propylthiouracil, 25% Tween-80, and 20% propylene glycol) daily for 8 weeks | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | Male KM mice | Mice were administratively treated with potassium oxonate (250 mg/kg) for 7 days | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | Male ICR mice | Mice were fed with 30% fructose in drinking water for 6 weeks | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | Male KM mice | Mice were administrated with potassium oxonate (250 mg/kg) for 7 days | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male SD rats | Rats were treated with potassium oxonate at 650 mg/kg, ip | mRNA ↓ | mRNA ↓ | protein ↓ | — | mRNA ↓ | protein ↓ | — | — | — | — |
|                   | Male Wistar | Rats were orally administrated with 5% oxonic acid and uric acid at 2.5% for 10 days | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | SD rats | Rats were orally treated with choline potassium oxonate (100 mg/kg) | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male db/db mice | Mice could develop spontaneouly into Type 1 diabetes | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male Ins2Akita mice | Mice were treated with streptozotocin (300 mg/kg) | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male SD rats | Rats were treated with high-fat diet for 6 weeks, and injected with streptozotocin (50 mg/kg) | — | — | — | mRNA ↓ ↑ | mRNA ↓ ↑ | — | — | — | — | Wang et al. (2018a) |
|                   | male SD rats | Rats were intraperitoneally injected with streptozotocin (600 mg/kg) at once | mRNA ↓ | mRNA ↓ | protein ↓ | — | mRNA ↓ | protein ↓ | — | — | — | — |
|                   | male C57BL/6J mice | Mice were treated with a high-fat diet and streptozotocin (100 mg/kg) | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male SD rats | Rats were treated with 10% w/v fructose solution for drinking ad libitum | mRNA ↓ | mRNA ↓ | protein ↓ | — | mRNA ↓ | protein ↓ | — | — | — | — |
|                   | male Db/db mice | Mice were received LabDiet 5K20 food for 6 weeks | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male ob/ob mice | Mice could develop spontaneously into Type 1 diabetes | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | STZ/INS2AKITA mice | Mice were treated with streptozotocin (300 mg/kg) | mRNA ↓ | mRNA ↓ | — | — | — | — | — | — | — | — |
|                   | male SD rats | Rats were treated with high-fat pellet diet for 14 weeks | mRNA ↓ | mRNA ↓ | protein ↓ | — | mRNA ↓ | protein ↓ | — | — | — | — |
| Obese              | male SD rats | Rats were treated with high-fat pellet diet for 14 weeks | mRNA ↓ | mRNA ↓ | protein ↓ | — | mRNA ↓ | protein ↓ | — | — | — | — |

(Continued on following page)
### Table 5 (Continued)

| Pathological Model | Species | Reference |
|--------------------|---------|-----------|
| MRP2               | C57BL/6J mice | Abdussalam et al. (2017) |
| MRP4               | C57BL/6J mice | Lu et al. (2019) |
| Reference          | C57BL/6J mice | Abdussalam et al. (2017) |

| Pathological Model | Species | Reference |
|--------------------|---------|-----------|
| MDR1               | C57BL/6J mice | Gai et al. (2016) |
| MDR2               | C57BL/6J mice | Gai et al. (2016) |
| MDR3               | C57BL/6J mice | Gai et al. (2016) |
| MDR4               | C57BL/6J mice | Gai et al. (2016) |

| Pathological Model | Species | Reference |
|--------------------|---------|-----------|
| OCT2               | Sprague-Dawley rats | Wu et al. (2017) |
| OCT3               | Sprague-Dawley rats | Wu et al. (2017) |
| OCT4               | Sprague-Dawley rats | Wu et al. (2017) |

Uric acid nephropathy, mainly caused by hyperuricemia, is a common kidney disease associated with hypertension, proteinuria, oedema, etc. (Perry et al., 1976). In animal experiments, adenine and potassium oxonate are often employed to construct uric acid nephropathy models for drug screening, development, and drug interaction research (Liu et al., 2017; Wu et al., 2017; Wang et al., 2020b). To date, OAT1 and OAT3 are the two most studied drug transporters in uric acid nephropathy, as these proteins are responsible effects for uric acid excretion. Reduced OAT1/3 mRNA and protein levels are consistently noted in uric acid nephropathy (Liu et al., 2015; Liu et al., 2017; Wang et al., 2020b; Zhang et al., 2020). The same trend was observed in the uptake transporter OCT2 and efflux transporter BCRP (Wu et al., 2017; Wang et al., 2019a). Nephrotoxic substances, such as cisplatin, gentamicin, and heavy metals, are causative agents of AKI in clinic. In the cisplatin-induced nephrotoxicity model, the mRNA and protein levels of renal OAT1/3 were decreased in both rats and mice, which could prevent the absorption of cisplatin from blood into renal tubular epithelial cell (Wang et al., 2018a; Deng et al., 2020b). MATE1 is an efflux transporter that mediates the excretion of cisplatin from renal tubules into urine. Previous study has proved that the survival time of Mate1−/− mice was significantly shorter than that of the control group. After cisplatin administration, the blood concentration and accumulation in the kidney of Mate1−/− mice were higher than that in the control mice. Using combination of cisplatin and the MATEs inhibitor pyrimethamine was found to be more nephrotoxic than using cisplatin alone. These results suggest that MATE1 mediates the renal excretion of cisplatin and participates in its nephrotoxicity (Kusuhara et al., 2011; Song et al., 2016). However, OCT2 mRNA and protein levels exhibited the species differences, which were decreased in mice but were increased in rats (Aleksun et al., 2008; Soetikno et al., 2019). It is worth noting that mRNA and protein levels may also show different trends during the course of disease. For instance, oral administration of NH4Cl caused downregulation of OAT1 mRNA and protein levels on the 2nd day, but the levels returned to its original levels on the 7th day (Gottier Nwafor et al., 2020). In the model of heavy metal-induced nephrotoxicity, the uptake transporters OAT1/3, OATP4C1, and OCT2 showed decreasing trends, whereas the efflux transporters MDR1, MATE2-K, and MRP2/4 showed increasing trends (Liu et al., 2016; Ljubojević et al., 2016; Zhang et al., 2017a), which decreased absorption, enhanced urinary clearance of heavy metals, and prevented accumulation in the kidney. Ischemia-reperfusion injury (IRI) in the kidney is another most common clinical cause of AKI, which often occurs during the clinical course of shock, acute renal artery occlusion, or renal transplantation. At present, the nonclinical IRI model is usually constructed by sealing the bilateral renal pedicle with a mini-artery clip (Shiva et al., 2020). Interestingly, the drug transporters OAT1/3, OCT2, MDR1, MATE1, and MRP2/4 in this model showed reducing trends. Schneider et al. (2007) reported that the OAT1/3 levels are associated with recovery time after IRI in kidney. Compared with the sham group, OAT1/3 mRNA and protein levels were completely restored to the preoperative level after 7 days posts ischemic reperfusion. Given that renal OAT1/3 play significant roles in the excretion of many anionic drugs, IRI induced AKI changes the pharmacokinetics of these drugs,
including increases in plasma levels and t1/2. An animal model with 5/6 nephrectomy is often used to simulate chronic renal failure in humans. Previous studies have reported the downregulation of uptake transporters OAT1/3 and OCT2, as well as the downregulation of efflux transporters MDR1, BCRP, and MRP2 in animal kidneys during the disease statuses (Laouari et al., 2001; Nagura et al., 2016; Kong et al., 2017). Nephrotic syndrome (NS) is a group of clinical symptoms characterized by increased glomerular basement membrane permeability, high proteinuria, hypoproteinemia, high oedema, and hyperlipidemia (Hull and Goldsmith, 2008). During the 12-week experiment, OAT1 mRNA and protein levels consistently exhibited trends of reduction. OCT2 protein level showed a downward trend within 9 weeks, but increased in the 12th week. The same trends were observed in MRP2 and MRP4 (Dong et al., 2020). The unilateral ureteral obstruction (UUO) animal model is often used to simulate clinical obstructive nephropathy. A study reported reduced OAT1/3 protein levels in the UUO model, indicating reduced renal excretion rates and pharmacokinetic changes of some drugs (Brandoni and Torres, 2015). Downregulation of OCT2 protein level was observed in the kidney transplanted rats. Atenolol, pindolol, and ofloxacin are the substrates of OCT2, and their appropriate doses are difficult to achieve in kidney transplanted patients (Carimboli et al., 2013).

In summary, in renal-related diseases, the expressions of OAT1/3 transporters are invariably reduced. The OAT1/3 are responsible for the uptake of endogenous and/or exogenous substances from the blood into renal tubular epithelial cells. The reduction in the renal-related diseases is like a double-edged sword. On the one hand, it prevents some toxic substances (e.g., indole sulfate) from entering renal tissue during the kidney injury, subsequently reduces renal damage, and thus plays a role in protecting the kidney. On the other hand, it also reduced drug excretion, resulting in increased drug concentration in plasma, which leads to toxic side effects. Clinical pharmacokinetics of morinidazole has proved that sulfate conjugate of morinidazole M7 was a substrate of OAT1 and OAT3, while the glucuronide conjugates of M8-1 and M8-2 were substrates of OAT3. After intravenous infusion of 500 mg morinidazole, the area under the curve (AUC) values for M7, M8-1, and M8-2 were 15.1-, 20.4-, and 17.4-fold, respectively, higher in patients with severe renal impairment than those in healthy subjects (Zhong et al., 2014; Kong et al., 2017). The expressions of efflux transporters are different in different renal diseases. It is noteworthy that the increased MRP2/4 in nephrotoxic pathology will transfer the toxic substances from renal tubular epithelial cells into the urine to exert the detoxification effect. However, the increased MRP2/4 also promote the transfer of some therapeutic drugs. Therefore, both changes should be carefully considered in the treatment of the renal-related diseases.

### Effect of Liver and Gallbladder—Related Diseases on Drug Transporters in Kidney

The Inner Canon of Huangdi, an ancient Chinese medical scripture that is the basis for traditional Chinese medicine, states that “the liver and kidney are homologous.” This means that, although the structure and function of the liver and kidney are different, they exhibit a close relationship based on physiological and pathological features. For example, renal injury is often also associated with liver-related diseases, such as hepatorenal syndrome (Raj et al., 2020; Simonetto et al., 2020). In Table 4, we have summarized the characteristics of nonalcoholic fatty liver disease (NAFLD), ischemia reperfusion (IR), and bile duct obstruction pathology on renal drug transporters, providing information for optimizing the drug prescriptions. NAFLD is a global disease (with an approximately 25% of global incidence rate) induced by many factors except alcohol and other specific factors, characterized by excessive deposition of fat in hepatocytes (Younossi et al., 2016). Nonclinical NAFLD models have shown that OAT1 mRNA expression was decreased in mice, but no significant difference was found in rats. Elevated OAT3, MDR1, and MPR2/4 mRNA expression levels were observed in both mouse and rat models, but BCRP protein level was decreased (Canet et al., 2015). Clinical treatments for NAFLD typically include metformin, vitamin E, and statins to exert anti-IR, antioxidiant, and lipid-lowering effects. Clarke et al. (2015) revealed that metformin exposure is increased in nonalcoholic steatohepatitis mice model (60% of metformin dose excreted in urine) than that in control group (82% of metformin dose excreted in urine), which might be caused by the decreases of OCT2 and MATE1 in the kidneys of disease mice. In patients, 25% of NASH may lead to an impaired kidney function that highlights a need to adjust drug dosage (Targher et al., 2010). A recent research showed that the novel targeting therapeutic agents mainly target peroxisome proliferator-activated receptors (PPARs), farnesoid X receptor (FXR), and glucagon-like-1 (GLP-1) (Zhou et al., 2020b). As one of the subtypes of PPARs, PPARα is widely expressed in the liver, adipose tissue, heart, skeletal muscle, and kidney. Given that PPARα has a regulatory effect on the drug transporters MATE1 and OCT2 (Freitas-Lima et al., 2020), attention should be given to drug disposition in vivo during the clinical use of this novel drug simultaneously with other drugs. IRI of the liver is an inevitable complication during liver resection and liver transplantation. The animal model confirmed that hepatic IRI could increase the kidney MRP2/4 levels (Tanaka et al., 2008). Interestingly, the increases of proteins showed obvious delays, compared to those of mRNAs. The increased renal MRP2 accompanied with decreased hepatic MRP2 may protect against oxidative stress and inflammation after hepatic IRI. Extrahepatic cholestasis is a pathophysiological process caused by the obstruction of bile secretion and excretion. This disease status could induce the expressions of the efflux transporter MRP2/4 in the kidney which will promote the excretion of bile acids and some therapeutic drugs (Slitt et al., 2007). OAT1/3 levels are different in various animal models, which may be related to the way and/or time of modeling (Brandoni et al., 2006; Liu et al., 2012). In general, with liver and bile duct-related diseases, the expressions of MRP2/4 are increased, which accelerates the excretion of endogenous/exogenous toxic substances in the kidney to play a protective role in the body.

### Effect of Metabolic Disease on Drug Transporters in Kidney

As shown in Table 5, metabolic diseases can also cause changes in drug transporters in the kidney. Hyperuricemia is a chronic metabolic disease caused by purine metabolism disorder, and
the condition is primarily caused by excessive production and reduced excretion of uric acid. A cross-sectional study in China reported that, with the improvement of people’s quality of life, the prevalence of hyperuricemia has increased from approximately 26.1% in 2010 to approximately 34.4% in 2019 among men in Wuhan city (Wan et al., 2021). High uric acid level is associated with hypertension, CKD, obesity, metabolic syndrome, etc. Therefore, a combined medication is a common treatment for hyperuricemia. Thus, the levels of renal transporters should attract clinician attentions. In animal models, the OAT1/3, OCT2, and BCRP expressions are decreased under the pathological condition, whereas MDR1 and MRP2/4 expressions are not affected by hyperuricemia (Nishizawa et al., 2019; Le et al., 2020). A growing number of studies have reported that OAT1/3, OCT2, and BCRP are involved in urate efflux from epithelial cells to urine (Taniguchi et al., 2021), and
TABLE 6 | Summary of published molecular docking models for assessing the substrates and inhibitors of drug transporters.

| Transporters | Type of compounds | No. of compounds for test | Descriptors | Reference |
|--------------|-------------------|---------------------------|-------------|-----------|
| OAT1         | inhibitors        | 22 natural compounds     | A eukaryotic phosphate transporter from *Piriformospora indica* (Protein Data Bank ID: 4J05) was used as OAT1 | Wang et al. (2018c) |
|              | substrates        | 2 aristolochic acid analogues | The homology modeling of OAT1 was conducted using SWISS-MODEL. Docking was performed using LeDock software | Ji et al. (2020) |
| OAT3         | inhibitors        | 22 natural compounds     | The structure of *Escherichia coli* multidrug resistance transporter MdfA (Protein Data Bank ID: 4ZP2) were used as OAT3 | Wang et al. (2018c) |
|              | substrates        | 3 dicaffeoylquinic acids | *Escherichia coli* multidrug resistance transporter MdfA (PDB ID: 4ZP2) was used as OAT3 for homology modeling | Wang et al. (2019b) |
| OCT2         | substrates        | 14 compounds             | The ribOCT2 sequence was used as a “probe” to search homologous sequences (PSI-BLAST, NCBI database) and sequence-based structural relatives (3D-PSSM) | Zhang et al. (2005) |
| MDR1         | substrates        | 5 chemotherapeutic drugs | The three-dimensional crystal structure of *Mus musculus* MDR1 (PDB ID: 4KSB) was used for modeling | Subhani et al. (2015) |
|              | inhibitors        | 10 acetylated androstano-arylpyrimidines | Homology model of the human MDR1 was obtained from the SWISS-MODEL. Molecular dockings were performed with AutoDock | Gopisetty et al. (2021) |
|              | substrates        | 3 compounds              | The Mdr1p 3D model based on the 3D model of MDR1–6 (Exasy Q9URI1) | Redhu et al. (2016) |
|              | inhibitors        | neochamaejasmin B        | The co-crystal of MDR1 (PDB entry: 3G5U) was obtained from the RCSB Protein Data Bank | Eliaa et al. (2020) |
|              | inhibitors        | 12 oxadiazolothiazin-3-one compounds | The crystal structures of the MDR1 from mouse. three-dimensional model was built | Rosano et al. (2013) |
|              | ligands or inhibitors | 21 compounds             | P-glycoprotein were created using sequence homologies between Sav186618 and the protein sequence of Pgp (Uniprot entry P08183) | Wise (2012) |
| inhibitor    | glibridin         |                            | The initial structure of P-gp was obtained from the RCSB protein data bank with ID of 4Q9I | Qian et al. (2019) |
| substrates   | 31 drugs          |                            | MDR1 (PDB ID: 4Q9H-L) docking model was built with fifty side-chain variants | Mukhametov and Rauvovsky (2017) |
| inhibitors   | 22 1,2,3,4-Tetrahydroisoquinoline/2H-chromen-2-one conjugates | MDR1 homology model was optimized with AUTODOCK 4.2.6 | | Rullo et al. (2019) |
| inhibitors   | 21 candidate drugs | The structure of MDR1 was obtained from Protein Data Bank (PDB 6GEX) | | Beiklen et al. (2020) |
| inhibitors   | 87 natural flavonoids | The three-dimensional structures of all the ligands were prepared in Avogadro, the mouse MDR1 (PDB IDs: 3G60 and 4M1M) and three available cryo-EM structures of the human MDR1 (PDB IDs: 6C0V, 6GEE, and 6GEX) were used | | Marques et al. (2021) |
| substrates   | 2 flavonoids from *Pistacia integerrima* | The 3-D structure of mice MDR1 was used from protein data bank with ID of 4Q9I | | Rauf et al. (2016) |
| inhibitors   | 50 major herbal constituents | The crystal structure of mouse MDR1 (PDB: 3G60) was selected for molecular analysis | | Li et al. (2014) |
| substrates   | 51 chemicals      | A human MDR1 homology model was established based on the mouse (Mus musculus) MDR1 protein (PDB ID: 3G6U) | | Li et al. (2021) |
| inhibitors   | 75 flavonoids     | The crystal structure of mouse MDR1 (PDB: 3G60) was used for docking | | Bai et al. (2019) |
| inhibitors   | 15 curcumin derivatives | The X-ray crystal structure of murine MDR1 (PDB ID: 4M11) and in complex with inhibitors QZ59Se-RRR (PDB ID: 4M2S), QZ59Se-SSS (PDB ID: 4M2T) were prepared for experiment | | Sagnou et al. (2020) |
| inhibitors   | 6 cardiotonic steroids | Molecular docking was carried out on the crystal structure of mouse P-glycoprotein (PDB code: 3G60) | | Zeino et al. (2015) |
| inhibitors   | 3 natural products and 9 3,4-dihydroisocoumarins | The cryo-EM structure of MDR1 (PDB ID: 6FN1) was prepared for molecular docking | | Sachs et al. (2019) |

(Continued on following page)
these transporters have been extensively studied in the hyperuricemia. Cephalexin is a substrate of OAT1 and is excreted via MATE1. Compared with that in control group, the AUC_{inf} of cephalexin was 2.66-fold and the CLR was 0.36-fold in hyperuricemic rats, which were responsible for variations of drug transporters (Nishizawa et al., 2019). Clinically, it is suggested that, in the treatment of the hyperuricemia, it is necessary to pay special attentions to the dosage of the drugs.

TABLE 6 | (Continued) Summary of published molecular docking models for assessing the substrates and inhibitors of drug transporters.

| Transporters | Type of compounds | No. of compounds for test | Descriptors | Reference |
|--------------|-------------------|---------------------------|-------------|-----------|
| BCRP inhibitor | 11 flavonoids | The cryo-EM structures of human BCRP (PDB ID: 6FFC) was selected for experiment | Fan et al. (2019) |
| substrates and inhibitors | 51 chemicals | Three-dimensional crystal structure of BCRP (PDB ID: 5NJ3) was used for docking | Li et al. (2021) |
| inhibitors | 10 compounds from Heterotheca inuloides | The dimensional structures of BCRP (PDB ID: 5NJ3) was used | Rodríguez-Chávez et al. (2019) |
| substrates | 5 bisbenzylisoquinoline alkaloids | BCRP model is based on the X-ray structure of mouse P-glycoprotein (Protein Data Bank code 3G5U) | Tian et al. (2013) |
| inhibitors | 11 molecules | The experiment was performed using the Glide docking engine and the OPLS2005 force field | Garg et al. (2015) |
| inhibitors | 13 chromone-based molecules | The two-fold symmetry axis of ABCG2 (PDB ID: 6FFC) was used as a putative multidrug-binding site | Roussel et al. (2019) |
| inhibitors | 13 compounds | The human ABCG2-MZ29eFab (PDB ID: 6HIJ) was taken for experiment | Roussel et al. (2020) |
| substrates and inhibitors | 22 compounds | The human BCRP homology model developed in-house were used as templates for molecular docking | Ferreira et al. (2018) |
| inhibitors | 14 Homo- and hetero-dimerization of indeno [1,2-bj]indoles | The cryo-electron microscopy structure of ABCG2 (PDB ID 5NJ3) was used to docking | Guragossian et al. (2021) |
| inhibitors | 16 differently 6-substituted 4-anilino-2-phenylpyrimidines | MZ29 (PDB ID: 6FFC) was from Protein Data Bank (PDB) was used for BCRP docking analysis | Silbermann et al. (2021) |
| MATE1 inhibitors | 881 compounds from the literature | The FASTA sequence of human MATE1 was retrieved from NCBI protein sequence database (Accession: Q96FL8) and develop by four steps | Xu et al. (2015a) |
| inhibitor | 3 compounds | The three-dimensional structure of hMATE1 was predicted using Modeller, based on the NorM-VC (Protein Data Bank ID: 3MKT) X-ray crystal structure data | Goda et al. (2021) |
| hMATE2K inhibitor | 3 compounds | The three-dimensional structure of hMATE2K was predicted using Modeller, based on the NorM-VC (Protein Data Bank ID: 3MKT) X-ray crystal structure data | Goda et al. (2021) |
| MRP2 substrates | 11 polyphenolic compounds | The Homology modeling of MRP2 were the structure of Caenorhabditis elegans P-gp (PDB code: 4F4C) and the human MRP1 (PDB code: 2CBZ) | Fang et al. (2019b) |
| substrates | 44 compounds | MRP2 was modeled on the template of bovine MRP1 bound to leukotriene C4 (PDB ID: 5UJA) | Deng et al. (2020a) |
| MRP4 substrates and inhibitors | 10 endogenous substrates, 12 drug substrates, and 16 drug inhibitors | The structure of MRP4 was performed using its primary sequence (code: O15439) from UniProt database | Becerra et al. (2021) |
| MRP4 substrates and inhibitors | 11 polyphenolic compounds | The structure of MRP4 was performed using its primary sequence (code: O15439) from UniProt database | Becerra et al. (2021) |
| substrates | 4 model substrates | The homology model of MRP4 was built based on the X-ray structure of P-glycoprotein (P-gp) from Mus musculus (PDB ID: 3G5U) | Wittgen et al. (2012) |
| substrates | two mycophenolic acid-based compounds | A 3D model of the human MRP4 protein in an inward facing conformation was used for analysis | Berthier et al. (2021) |
| substrate | ginsenoside compound K | Homology modeling of MRP4 was built by PSI-BLAST, Clustal Omega and SAVES software | Zhou et al. (2019) |
that are primarily excreted by OAT1/3. Streptozotocin is the most commonly used agent to construct animal models of diabetes, due to its selective destruction of islet β cells in animals (Goyal et al., 2016). In the diabetes model, the decreased OAT1/3 and OCT2 expressions and increased BCRP and MRP2/4 expressions were observed in the kidney (Xu et al., 2015a; Zhang et al., 2017b; Wang et al., 2018b). The excretion of antidiabetic drugs could be affected by these changed transporters. For example, metformin is excreted through OCT2, and sitagliptin is transported by OAT3 (Chu et al., 2007; Koepsell, 2013). Therefore, the clinical uses of these drugs during different disease statuses should take their pharmacokinetic changes into consideration. In general, most renal drug transporters are not affected by a long-term administration of a high-fat diet, but decreased expressions of the uptake protein OAT1/3 was observed in the kidney (Lu et al., 2019), which can lead to an accumulation of endogenous toxic substances that may contribute to obesity-related diseases, such as hyperlipidemia, NAFLD, CKD, and diabetes.

Effect of Other Diseases on Drug Transporters in Kidney

Rheumatoid arthritis (RA) is an autoimmune disease mainly characterized by synovitis and with a prevalence of 0.24% in the world. This disease could decrease the protein level of OAT1, which may lead to an increased t1/2 for some drugs (Wang et al., 2020a). In the high-altitude condition, the efflux drug transporters of MDR1 and MRP2 were increased, and clinicians should take it into consideration when drug prescription (Luo et al., 2017). It is noteworthy that different viral infections bring different changes of the renal transporter levels. The poly I:C infected pregnant rat showed lowered levels of OAT1/3, OATP4C1, BCRP, and MRP2 (Karimian Pour and Piquette-Miller, 2020), but the HIV-1 transgenic rat showed reduced OCT2 and MATE1 levels (Karimian Pour and Piquette-Miller, 2018). A hepatitis B virus infection could also damage kidneys, and it could downregulate some kidney transporters (Zuo et al., 2020). This difference should call attentions to pharmacokinetic performance shift of the used drug when different virus-infection in clinic. In an acute lymphoblastic leukemia mice model, the MRP 2/4 levels and the clearance of MRP-mediated drugs were significantly reduced, but the MDR1, OAT3, and OCT2 levels were increased, corresponding to the increased clearances of MDR1-mediated digoxin, OAT3-mediated furosemide, and OCT2-mediated metformin (Zhou et al., 2020a). A study reported that female obese Zucker spontaneously hypertensive fatty rats showed a strongly decreased expression of OAT2 in the kidneys, and OAT2-mediated furosemide renal excretion could be impaired in these rats (Babelova et al., 2015). There may be other diseases affecting the levels of renal transporters and needing further explorations.

MOLECULAR DOCKING METHOD OF DRUG-DRUG INTERACTIONS

Currently, polypharmacy has become a common treatment in clinic. If two or more drugs are secreted simultaneously through the same drug transporters in the renal tubules, adverse drug events may increase due to DDIs. It has been reported that the incidence of DDIs can be as high as 8.34–100% of hospital admissions, which has attracted worldwide attention (de Oliveira et al., 2021). For instance, tenofovir, a representative substrate of OAT1, is a widely used antiviral drug. A clinical investigation showed that, when it was used with para-aminosalicylic acid (PAS, a long-standing antibiotic), the values of Cmax and AUC0-τ of tenofovir were increased to approximately 3-fold in the co-administration group than that in the alone group. In contrast, the cumulative amount of tenofovir in urine (Ae) was 20.87 ± 5.60 mg when alone use, and that is 7.45 ± 2.56 mg when it was co-administered with PAS (Parvez et al., 2021). Therefore, fast and accurate prediction of DDIs will effectively reduce unexpected clinical adverse events. Over the past decades, the FDA has issued a series of technical guidelines for DDI research, and the Center for Drug Evaluation of China has listed the common drugs as substrates and inhibitors (Sudsakorn et al., 2020; Center for Drug Evaluation and NMPA, 2021). Of note, in addition to in vivo and in vitro methods, an in silico approach has been officially promoted in the latest guidelines (Sudsakorn et al., 2020). Since it is not feasible to test all drugs for DDIs in vivo and/or in vitro, in silico modeling has become a useful tool to predict DDIs and help prescribing drugs.

Molecular docking is an in silico method based on the “lock-and-key principle” that is used to find the best match between small molecule (ligand) and biological macromolecule (receptor) via electrostatic interaction, hydrophobic interaction, van der Waals force interaction, etc. (Pinzi and Rastelli, 2019). It consists of three interrelated parts: binding site recognition, conformational search algorithm, and scoring function. Binding site recognition refers to the identification of the active site in the target protein molecule that interacts with the ligand. Conformational search algorithm is to search the position, orientation, and conformation of ligand with some optimization algorithm only considering that ligand molecules are flexible. The scoring function is the evaluation of the combined conformation in the search (Kitchen et al., 2004). To date, molecular docking has been proven to be extremely useful in identifying substrate and/or inhibitor of drug transporters in a large group of compounds (Ai et al., 2015). A three-dimensional structure is a prerequisite for molecular docking. As shown in Figure 3, the homology models of OAT1, OAT3, OCT2, MDR1, BCRP, MATE1, MATE2-K, OAT4, MRP2, and MRP4 have been established (https://swissmodel.expasy.org/). Taking the MDR1 protein and its substrates and inhibitors as an example (Figure 4), the process of molecular docking is as follows: defining the binding site of the receptor protein, placing the small molecule at the binding site, and then searching for the optimal conformation of the interaction between the small molecule and the macromolecule by continuously optimizing the relative position, conformation, the side chain, and amino acid residues of the receptor. Ultimately, the scoring function is used to identify the ideal binding conformation with the highest score, in which the binding free energy of the receptor and ligand is the lowest and the affinity activity is the highest. Molecular docking provides a rapid method for a priori identification of
potential transporter-mediated DDIs and/or drug-induced organ injury.

A large number of clinical events have demonstrated that the modulation of drug transporter activity could easily increase the potential risks of DDIs. Based on this notion, the FDA has explicitly stated that, when a drug under development is a transporter substrate and/or inhibitor, its interaction with a transporter should be evaluated (Sudsakorn et al., 2020). As shown in Table 6, a large number of compounds, especially natural products, have been assessed as drug transporter substrates and/or inhibitors using molecular docking models. For instance, flavonoids are widely found in foods, such as fruits and vegetables. Bai et al. (2019) determined the inhibitory effects of 75 flavonoids on MDR1 protein, and confirmed that at least five flavonoids had significant inhibitory effect on MDR1, which was manifested in the increase of AUC and Cmax of digoxin when co-administration of digoxin and five flavonoids. Fan et al. (2019) have revealed the inhibitory effects of 99 flavonoids on BCRP, and found that 11 flavonoids had significant inhibitory effect on BCRP, which was manifested in the increase of AUC0–t of mitoxantrone when co-administration of mitoxantrone and these flavonoids. Chemical structure is the determining factor in binding the compound to the target protein, but it must be pointed out that many other factors, such as dose, genetics, and disease status, also play a role in the final biological effect of the compounds. In addition, the molecular docking was simulated independently by computer, and the potential involvement of other proteins from related pathways has not been considered. Therefore, although molecular docking provides a rapid screening method for the study of DDIs, it is essential for in vitro and in vivo experimental verification.

**CONCLUSION**

The systemic exposure of drug is influenced by complex systems, not just age, sex-gender, disease, and drug interactions, and renal drug transporter is one of the important factors determining the systemic exposure. The determinant roles of renal drug transporters have been identified in the renal excretion and disease progression. Their expressions in different species have direct impacts on drug disposal, which subsequently has the potential to influence the clinical efficacy of drugs from animals to the clinic in drug development. The expressions of transporters can vary up to 5-fold among species (e.g., BCRP). Interestingly, transporter expression significantly differs in different species and sexes. For instance, different MDR1 expression patterns were noted in rats and mice of different sexes. Therefore, it is very necessary to assess males and females in preclinical studies. Even in the same individual, the expressions of drug transporters could be decreased or increased under different pathological states. As mentioned, renal diseases, liver diseases, and systemic metabolic diseases could alter OAT1, OAT3, OCT2, MDR1, BCRP, MATE1, MATE2-K, MRP2, and MRP4 mRNA and/or protein levels. Therefore, we hypothesize that the expression levels of transporters can be used as an evaluation index for drug treatment effects. Unfortunately, changes in OATP4C1 and OAT4 in disease statuses have not been reported. Changes in transporter expression or the inhibition of transporter function will affect the pharmacokinetics of drugs in vivo, and reduce the therapeutic effect of drugs or increase the adverse reactions with the drug accumulation. Especially for drugs with strong toxicity or narrow therapeutic window, their side effects may even threaten the human life. Thus, the clinical dose of the transporter substrate may need to be adjusted when the level of the transporter changes. When the level of the transporter that promotes drug excretion is lowered, consideration should be given to reducing the dose or extending the duration of administration to avoid adverse reactions. Nevertheless, the adjustment of drug dose also depends on metabolic enzyme activity and other factors that affect the pharmacokinetic processes of drugs. With the wide application of drug combination, how to predict and avoid DDIs caused by drug transporters early has become an important challenge in drug administration. Traditional evaluation methods are mainly used in vivo animal models and in vitro renal cell line models. The in silico method provides an effective approach for rapidly screening of drug transporter substrates or inhibitors. In this paper, a large number of natural products were identified as substrates and/or inhibitors of transporters by molecular docking method. However, crystal structures of some drug transporters are still lacking, and the homology simulation method has inevitable disadvantages. Therefore, considerable work must be performed in the future to understand the structure-activity relationship of the interaction between transporters and drugs.

**AUTHOR CONTRIBUTIONS**

Conceptualization, ZC and ML; writing—original draft preparation, WZ and BS; writing—review and editing, WZ, TZ, ML, and ZC; tables, BS and YZ; figures, BH and BO; supervision, ZC. All authors have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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