Review Article
Food Science and Technology

ISSN 0101-2061 (Print)
ISSN 1678-457X (Online)

DOI: https://doi.org/10.1590/fst.70722



# The role of OATP1A1 in cholestasis and drug-induced toxicity: a systematic review

Daopeng TAN[1#], Jinguo CUI[2#], Lin QIN[1], Li CHEN[1], Yuhe WANG[3], Qianru ZHANG[1*], Yuqi HE[1*]

**Abstract**

OATP1A1 is the first and founding member of the Organic anion transporting polypeptides (OATPs) family. OATP1A1 is usually considered to mediate the cellular uptake of endogenous and xenobiotics, such as bile acids, drugs and environmental toxins. However, some new research indicated that the decrease of Oatp1a1 expression can result in the cholestasis, which was confirmed by clinic case of drug-induced cholestatic liver injury and bile duct ligation surgery or Oatp1a1-null mice models. These results suggested that Oatp1a1 does not simply transport bile acids to hepatocytes, as is commonly believed. In this overview, we summarized the advances of OATP1A1 in drug induced toxicity, cholestasis and other pathological states as well as the differences of Oatp1a1 in different gender and age.

**Keywords:** organic anion transporting polypeptides; OATP1A1; cholestasis; drug-induced toxicity.

**Practical Application:** Important for precise clinical use of drugs.

## 1 Introduction

Membrane transporters play a crucial role in the absorption, distribution and elimination of endogenous and xenobiotics. Lack of transporter function can result in altered drug disposition, including loss of efficacy or toxicity (Teng & Piquette-Miller, 2008). Organic anion transporting polypeptides (OATPs) are membrane transporters belonging to the solute carrier (SLC) family that mediate the uptake of an extensive array of substrates, including bile acids, hormones, many drugs and imaging agents, in a manner independent of Na+ and ATP manner (Hagenbuch & Stieger, 2013). In the past decades, OATPs have been identified in some human organs such as liver, kidney, brain and intestine (Gong et al., 2011; Hagenbuch & Stieger, 2013). A clinically relevant aspect of OATPs is that their expression levels vary extensively in various disease states. On the other hand, OATPs proteins often act as critical transporters for unfavorable drug-drug interactions or adverse drug reactions (Kim, 2003; Shitara et al., 2003). In recent years, great progress has been made in identifying the endogenous substrates of OATPs, clarifying the role of OATPs in drug disposal and toxin transport, and describing genetic variants. Among the OATPs family members, OATP1A1 (Figure 1) is the first and founding member of the organic anion transporter SLCO superfamily and was isolated by expression cloning (Hagenbuch & Meier, 2004; Jacquemin et al., 1994). Functional characteristics of OATP1A1 in a heterologous expression system suggested that it can transport bile acids (e.g., CA) and bile acid conjugates (e.g., TCA) in a sodium-independent manner (Eckhardt et al., 1999; Hagenbuch & Stieger, 2013; Jacquemin et al., 1994). Therefore, bile acids can be considered as the first identified endogenous substrate of OATP1A1. However, in some cases of cholestasis, such as drug-induced cholestatic liver injury (Chen et al., 2016), bile duct ligation surgery model (Horiuchi et al., 2009) and Oatp1a1-null mice (Zhang et al., 2012a), Oatp1a1 expression is frequently reduced. These suggest that Oatp1a1 does not simply transport bile acids to hepatocytes, as is commonly believed.

In this review, we discussed the expression of Oatp1a1 in drug induced toxicity, cholestasis and other pathological states as well as the differences of Oatp1a1 in different gender and age. The aim is to draw more attention to the precise of drug dosing and drug-drug interactions of Oatp1a1-regulated medicines in the clinic.

## 2 Main text

### *2.1 OATP1A1 in physiological state*

Organic anion transport protein 1a1 (Oatp1a1) is the prototypical member of the Oatp family of highly homologous transport proteins that are highly expressed in the liver and kidney (Cheng et al., 2005; Imai et al., 2013). In the liver, Oatp1a1 is expressed in all hepatocytes, and uniformly distributed on the basolateral (sinusoidal) surface of hepatocytes (Wang et al., 2008). Oatp1a1 expression is influenced by gender. Oatp1a1 expression in rat liver is predominantly male (Hou et al., 2014). In contrast, Oatp1a1 in kidney is predominantly female (Cheng et al., 2006). However, it is also believed that the expression of Oatp1a1 is higher in kidney of males than that of females (Cheng et al., 2005). The expression of Oatp1a1 tends to be up-regulated and then down-regulated with increasing age. Oatp1a1 is barely detectable in the liver of fetal rats, and its expression is low at birth, and increase rapidly after weaning, reaching a peak at 60 days. It then remains stable from 60 to 180 days of age, and

*Received 29 May, 2022*
*Accepted 20 July, 2022*
[1] *Guizhou Engineering Research Center of Industrial Key-Technology for Dendrobium Nobile, School of Pharmacy, Zunyi Medical University, Zunyi, China*
[2] *Department of Pharmacy, Tianjin Baodi Hospital, Baodi Clinical College of Tianjin Medical University, Tianjin, China*
[3] *Department of Pharmacy, Affiliated Hospital of Zunyi Medical University, Zunyi, China*
*Corresponding author: yqhe.pharm@foxmail.com; 17134693@qq.com
[#]These authors contributed equally

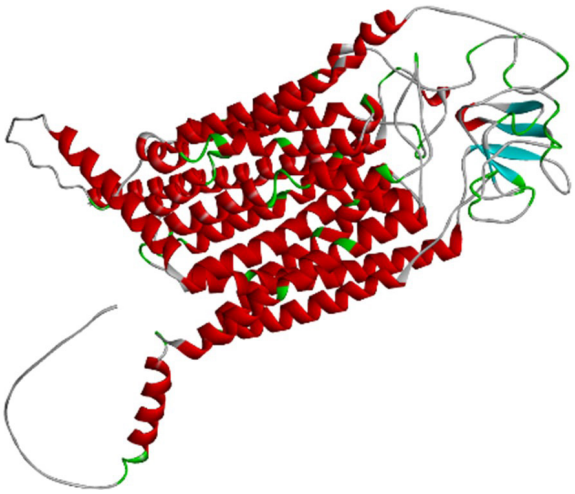

**Figure 1**. The theoretical 3D structures of OATP1A1 from AlphaFold v2.0 (Jumper et al., 2021), a protein structure database.

decreases at elder age (540 days) (Cheng et al., 2005; Fu et al., 2012; Hou et al., 2014; St-Pierre et al., 2004). In aged rat liver, Oatp1a1 expression has a consistent ontogenetic pattern at the mRNA and protein levels (Cheng et al., 2005). Further studies showed that androgens and growth hormone secretion patterns are responsible for Oatp1a1 expression in mice. Androgens increase Oatp1a1 mRNA in liver and kidney, whereas growth hormone increase Oatp1a1 mRNA in the liver only (Cheng et al., 2006).

Previous studies showed that the four amino acids at the C-terminal of Oatp1a1 in rat and mouse hepatocytes constitute a consensus binding site for PDZK1. PDZK1 mediates intracellular trafficking of Oatp1a1 by recruiting motor proteins to endocytic vesicles containing Oatp1a1 (Wang et al., 2005; Wang et al., 2019; Wang et al., 2014). Oatp1a1 appears to surface localize only when co-expressed with PDZK1(Wang et al., 2019). In the absence of PDZK1, Oatp1a1-containing vesicles fail to recruit kinesin-1 and instead bind dynein, which becomes the predominant end-directed motor (Wang et al., 2014). Oatp1a1 can be singly or doubly phosphorylated on serine or threonine residues in the C-terminal sequence SSATDHT (aa 634-640), and serine phosphorylation can inhibit the transport activity of Oatp1a1 without altering its cell surface content (Xiao et al., 2006). Although perturbations of in the cell surface expression of Oatps can lead to drug toxicity, little is known about mechanisms regulating their subcellular distribution. Many members of Oatps, including Oatp1a1, have a COOH-terminal PDZ consensus binding motif that interacts with PDZK1, while serines upstream of this site (S634 and S635) can be phosphorylated. Thus, PDZK1 binding is necessary for optimal Oatp1a1 expression at the cell surface, phosphorylation provides a mechanism to rapidly regulate the distribution of Oatp1a1 between the cell surface and intracellular vesicular pool (Choi et al., 2011).

### *2.2 OATP1A1 in pathological state*

The liver plays important roles in the detoxification of xenobiotics. Hepatic Oatp1a1 contributes to the uptake and elimination processes of xenobiotics. Oatp1a1 expression can be regulated under many pathological conditions (Chiba et al., 2007). Inflammation is a host response to infection and injury, which is associated with altered expression of genes for metabolic enzymes, transporters, receptors and plasma proteins (Hanafy et al., 2012). In Long-Evans cinnamon (hepatitis model) rats, hepatic expression of Oatp1a1 was found to be decreased (Chiba et al., 2007). TNF-α and IL-1β are pro-inflammatory cytokines. TNF-α and IL-1β lead to down-regulation of Oatp1a1 and other hepatic organic anion transporters in cholestasis or high-fat diet induced hepatitis (Fisher et al., 2009; Geier et al., 2005).

Alcohol-related liver disease accounts for half of all cirrhosis-related deaths worldwide. The spectrum of disease varies from simple steatosis to fibrosis, cirrhosis and ultimately hepatocellular carcinoma. In chronic plus binge ethanol-fed mice, transcriptomic data indicated that Oatp1a1 was the most down-regulated mRNA, and it is negatively correlated with serum bile acid level (Jiang et al., 2020). Increased plasma bilirubin levels have been reported in rat models and patients with alcoholic liver disease (ALD). Chronic ethanol ingestion impairs the nuclear translocation of CAR, which is accompanied by increased serum bilirubin levels, and suppresses the expression of hepatic and renal Oatp1a1 and hepatic Mrp2 (Wang et al., 2017). In advanced fibrosis, changes in hepatocyte membrane transporters expression reduce the hepatic transport function of organic anions. In rats with advanced fibrosis, the Oatp1a1 expression is significantly decreased (Giraudeau et al., 2017). Furthermore, the level of Oatp1a1 decreased with increasing fibrosis (Sheng et al., 2017). In addition, in a rat model of partial liver congestion, the Oatp1a1 protein expression was also down-regulated in the congested liver (Shimizu et al., 2015).

In addition, other factors that can down-regulate Oatp1a1 expression include hyperthyroidism (Engels et al., 2015), high-cholesterol diet (Kawase et al., 2017), caloric restriction (Kulkarni et al., 2013), dysbiosis (Kuno et al., 2016), rheumatoid arthritis (Lin et al., 2017), intestinal ischemia-reperfusion (Maruyama et al., 2013), diabetes (Shuboni-Mulligan et al., 2019), hepatic metastatic tumors (Sun et al., 2006), oxidative stress (Tsujimoto et al., 2013) and polycystic kidney disease (Bezençon et al., 2019). From the available reports, almost all pathological changes down-regulate Oatp1a1 expression.

### *2.3 Correlation of OATP1A1 with other enzymes or proteins*

The effects of sterol carrier protein-2 (SCP-2) overexpression and cholesterol-rich diet is a down-regulation of proteins involved in cholesterol transport (L-FABP and SR-B1), cholesterol synthesis (associated with sterol regulatory element binding protein 2 and HMG-CoA reductase) and bile acid oxidation/transport (Oapt1a1, Oatp1a4, and SCP-x). Serum and liver bile acids levels were decreased in cholesterol-fed SCP-2 overexpression mice (Atshaves et al., 2009). In Chinese hamster ovaries (CHO cells), co-expression of rat Oatp1a1 and human ABCG2 enhanced the uptake and efflux of CGamF, bile acids, glycol bile acids, taurocholate bile acids, and taurolithocholic acid-3-sulfate, respectively (Blazquez et al., 2012). Na (+)-taurocholate co-transporting polypeptide (Ntcp) and Oatp1a1, Oatp1a4, and Oatp1b2 are the main transporters responsible for the uptake of

bile acids and other organic compounds into the liver. By using the various transcription factor-null mice, PPAR-α was shown to play a critical role in the down-regulation of Oatp1a1, Oatp1a4, Oatp1b2 and Ntcp by PFDA (Cheng & Klaassen, 2008). The bile salt export pump (BSEP) is expressed on the hepatocyte tubular membrane and regulates liver bile salt excretion, and impairment of BSEP function may lead to cholestasis in humans. in the SAGE Bsep knockout rat model, Mrp3 expression is increased and Oatp1a1 is decreased (Cheng et al., 2016). ATP11C is a homolog of ATP8B1, both of which catalyze the transport of phospholipids in biological membranes. Mice deficient in ATP11C are characterized by conjugated hyperbilirubinemia and unconjugated hyperbilirubinemia. Functional studies in ATP11C-deficient mice showed that hepatic uptake of unconjugated bile salts is severely affected, whereas uptake of conjugated bile salts is not affected, and the basal bile salt uptake transporters Oatp1a1, Oatp1a4, Oatp1b2 and Ntcp were virtually absent only in the central hepatocytes (Waart et al., 2016).

In WT mice fed the methionine and choline deficient diet, the mRNA expression of Oatp1a1 and Oatp1b2 in liver are decreased, whereas the Mrp4 expression is increased. However, in the H-RXRα-null mice, the methionine- and choline- deficient diet only decrease Oatp1a1, but induce both Oatp1a4 and Mrp4 mRNA expression (Gyamfi et al., 2009). Energy balance is maintained through controlling both energy intake and expenditure. Thyroid hormones play a critical role in regulating energy expenditure. The synergistic reduction of the half-life may be due to the synergistic induction of CAR and CAR target genes encoding enzymes and transporters involved in the hepatic elimination of T3, such as Oatp1a1, Oatp1a3, Ugt1a3 and Ugt1a10. The PPAR-α dependent induction of CAR and subsequent induction of T3 eliminating enzymes may have a role in fasting-induced energy expenditure by fatty acids as natural PPAR-α ligands (Wieneke et al., 2009). Fibrates are hypolipidemic drugs that function as activators of PPAR-α. In humans and rodents, females have been reported to be less responsive to fibrates than males. However, loss of PPAR-α in female mice increases mRNA expressions of bile acids synthetic enzymes (Cyp7a1, Cyp27a1, Cyp7b1 and Cyp781) and transporters (Oatp1a1, Oatp1b2, Ntcp, and Mrp3 (Zhang et al., 2018). In the liver of global 11β-Hydroxysteroid dehydrogenase-1-deficient mice, the mRNA expression of Oatp1a1 is decreased, whereas the mRNA expression of Ostb is increased (Penno et al., 2014). During 20 to 32 weeks of hepatocarcinogenesis in rat, mRNA of transporters (including Oatp1a1, Oatp1a4, Oatp1b2, Ntcp, Bsep and Mrp2) is progressively lost (Monte et al., 2005). Although the role of nuclear factor erythroid 2-related factor 2 (Nrf2) in bile acid homeostasis remains controversial. Oatp1a1, Oatp1b and Ntcp are down-regulated and result in a 39-fold increase of serum bile acids in Nrf2-null mice. And activation of Nrf2 in mice up-regulates Mrp2 and Mrp3 in the liver and down-regulates bile acids and cholesterol transporters in the intestine (Zhang et al., 2020b).

### *2.4 OATP1A1 and cholestasis*

Cholestasis is a clinical disorder defined as an impairment of bile flow, and that leads to toxic bile acids accumulation in hepatocytes. During cholestasis, the liver, kidney and intestine gene expression was altered to prevent bile acids accumulation, increase bile acids urinary excretion and decrease bile acids absorption, respectively.

In bile-duct ligation (BDL) surgery experiments, the hepatic Oatp1a1, Oatp1a5, Oatp1b2, CYP2C6, CYP3A2 and Ntcp mRNA expressions were found to be decreased, while the mRNA expressions of Oatp1a4, Bsep and Mrp1-5 were increased. In the kidney, Oatp1a1 and Mrp1-5 have the same expression changes as in the live. These results suggest that compensatory regulation of transporters in the liver, kidney and intestine cannot fully compensate for the loss of hepatic bile acids excretion (Geier et al., 2007; Horiuchi et al., 2009; Slitt et al., 2007). Oatp1a1 is expressed predominantly in liver of mice and is thought to transport bile acids from the blood to the liver. Since the expression of Oatp1a1 is normally markedly reduced in BDL mice. Oatp1a1-null mice would be protected from liver injury during BDL-induced cholestasis through reducing hepatic uptake of bile acids. Surprisingly, the total bile acids concentration in the liver of Oatp1a1-null mice is higher than that of WT mice, suggesting that Oatp1a1 deficiency does not prevent bile acids from accumulation in the liver. In addition, secondary bile acids dramatically increased in the serum of Oatp1a1-null BDL mice, but not WT BDL mice. These demonstrates that loss of Oatp1a1 function exacerbates liver cholestatic injury and suggests a unique role of Oatp1a1 in the liver adaptive responses to cholestasis (Zhang et al., 2012a). In obstructive cholestasis, the down-regulation of Bsep partitioning is associated with portal inflammation, mediated by TNF-α and IL-1β. Down-regulation of periportal Ntcp and induction of Oatp1a4 and Oatp1b2 may be adaptive mechanisms to reduce cholestatic injury in hepatocellular with profound downregulation of Bsep and Mrp2 (Donner et al., 2007).

In α-naphthylisothiocyanate (ANIT)-induced cholestasis, the mRNA expression of hepatic Oatp1a1, IL-6, IL-17A, IL-17F, TGF-β1, α-SMA, TGR5, NTCP and ileum ASBT were decreased, while the hepatic IL-10, FXR, CAR, VDR, BSEP, MRP2, MRP3, MRP4 was increased, but was restored to normal by Yinchenhaotang, a famous formulae for the treatment of liver disorders (Yan et al., 2017). Methotrexate is an important immunosuppressive and anticancer agent for the treatment of primary biliary cirrhosis. The serum biochemistry and expression of the major hepatic methotrexate transporters including Oatp1a1, Oatp1a4, Oatp1b2, Mrp2, Mrp3, Mrp4, and Bcrp elucidated the pathological cholestatic changes in the liver (Brcakova et al., 2009). All cholestatic drugs result in extensive alterations in most biliary transporters. Surprisingly, almost all steatotic drugs affect the expression of biliary transporters, too. The most common alterations triggered by both classes of drugs were the inhibition of OATP1A1, BSEP, and NTCP, and the induction of MRP2/3/4, MDR2 and ABCG5/8. Therefore, Oatp1a1 was proposed as a simple but useful screening biomarker for the prediction of cholestasis or steatosis (Donato et al., 2016).

Oatp1a1 is capable of transporting bile acids. While in Oatp1a1-null male mice, the concentrations of Deoxycholic acid (DCA) and taurodeoxycholic acid (TDCA) were increased in serum and liver. Further studies revealed that the loss of

Oatp1a1 significantly alters the intestinal bacteria composition in mice (Zhang et al., 2012b). In addition, intestinal permeability was enhanced in Oatp1a1-null mice. The present data indicated that Oatp1a1 does not mediate the hepatic uptake of DCA and/or TDCA, but loss of Oatp1a1 increases intestinal permeability, which enhances DCA absorption in mice (Zhang et al., 2011). Table 1 summaries the trends of some main bile acids transporters expression in cholestasis.

### *2.5 OATP1A1 and drug-induced toxicity*

*Alterations of OATP1A1 in modern medicine induced toxicity*

Drug transporters play a critical role in the uptake, disposition and elimination of various organic compounds through human biological membranes. Recent studies indicated that some drug transporters are related to drug-induced toxicity (Ohbayashi et al., 2013). Organic anion-transporting polypeptides (OATPs), as an important drug uptake transporters, mediate the uptake of many endogenous molecules and xenobiotic compounds, such as bile acids and drugs (Durmus et al., 2016), and their distribution to several pharmacokinetically relevant organs (Durmus et al., 2014) or their clearance (Iusuf et al., 2014). Among them, Oatp1a1 was confirmed to be an electroneutral anion exchanger (Martinez-Becerra et al., 2011). Acetaminophen (APAP), also known as N-acetyl-p-aminophenol or paracetamol (PARA) is one of the most popular analgesic and antipyretic agents. Acetaminophen can lead to liver injury under prolonged or overdose conditions. During acetaminophen hepatotoxicity, organic anion-transporting polypeptides Oatp1a1, Oatp1b2, bile salt export pump (Bsep), and sodium/taurocholate-co-transporting polypeptide (Ntcp) mRNA were reduced, in contrast, multidrug resistance-associated proteins Mrp1, Mrp2, Mrp3, and Mrp4, and multidrug resistance proteins Mdr1a and Mdr1b mRNA were increased in APAP-treated mice (Aleksunes et al., 2007; Aleksunes et al., 2005). Pyrazinamide is a first-line drug for the treatment of tuberculosis which can cause serious hepatotoxicity. Cholestasis plays an important role in pyrazinamide induced liver injury. During liver damage, the protein and mRNA expressions of bile acid synthesis and transporters were markedly altered, in which FXR, Cyp8b1, Oatp1a1, Oatp1b2, Bsep, Mrp2, Mdr2, and Ostα/β were decreased, while Mrp3, Ntcp, Oatp1a4, and Cyp7a1 were increased (Chen et al., 2016). Larotrectinib is an FDA-approved oral small-molecule inhibitor for treatment of neurotrophic tropomyosin receptor kinase fusion-positive cancer. In pharmacokinetic behaviour, ABCG2 and ABCB1 limit its oral availability and brain and testis penetration, while OATP1A/1B transporters restrict its systemic exposure by mediating hepatic uptake, thus allowing hepatobiliary excretion (Wang et al., 2020b). Empagliflozin is a next-generation oral SGLT-2 inhibitor for the treatment of diabetes. Following oral administration of empagliflozin for 2 years, renal tubular injury was identified in male mice. empagliflozin was found to be a substrate of Oatp1a1 in mouse and rat, through transfected Xenopus oocytes and HEK293 cells (Taub et al., 2015). Eprosartan is an angiotensin II receptor antagonist used for the treatment of hypertension and heart failure in clinical. Eprosartan is transported by Mrp2 and various Oatps such as Oatp1a1 and Oatp1a4 in rats and at least OATP1B1/MRP2 in humans (Sun et al., 2014). Doxorubicin is a highly potent and established anthracycline-based chemotherapeutic agent, which is commonly used in the treatment of various cancers. Although doxorubicin is known as a substrate of some efflux transporters including P-glycoprotein, MDR1 and ABCB1, recent study demonstrated that OATP1A/1B plays an important role in the uptake and disposition of doxorubicin (Lee et al., 2017). In isolated perfused rat liver, the disposition of rosuvastatin is mediated by Oatp1a1 and efflux is entirely by Mrp2 and Bcrp (Hobbs et al., 2012). Glyburide is a sulfonylurea hypoglycemic agent, which can completely inhibit rat hepatic Oatp1a1, Oatp1a4, and Oatp1b2 (Ishida et al., 2018). In indomethacin (IDM)-treated rats, the mRNA expression of hepatic transporters was decreased consistent with its intestinal injury. Ornoprostil can restore the mRNA expression of Oatp1a1, Oatp1b2 and Mrp2 (Fujiyama et al., 2013). Cisplatin is a first-line agent for the treatment of many solid tumors, whereas has significant

**Table 1**. The trends of main bile acids transporters expression in cholestasis.

| Transporters | Types | The trends of expression | Reference |
|---|---|---|---|
| Oatp1a1 | Uptake | Down-regulation | (Brcakova et al., 2009; Donner et al., 2007; Geier et al., 2007; Slitt et al., 2007; Yan et al., 2017; Zhang et al., 2012) |
| Oatp1a4 | Uptake | Up-regulation | (Gyamfi et al., 2009; Slitt et al., 2007) |
| Oatp1b2 | Uptake | Down-regulation | (Zhang et al., 2018) |
| Oatp1a5 | Uptake | Down-regulation | (Geier et al., 2007; Slitt et al., 2007) |
| Mrp1 | Efflux | Up-regulation | (Geier et al., 2007; Slitt et al., 2007) |
| Mrp2 | Efflux | Up-regulation | (Donner et al., 2007; Geier et al., 2007; Slitt et al., 2007) |
| Mrp3 | Efflux | Up-regulation | (Cheng et al., 2016; Zhang et al., 2018) |
| Mrp4 | Efflux | Up-regulation | (Gyamfi et al., 2009) |
| Ntcp | Uptake | Down-regulation | (Zhang et al., 2018) |
| Ostβ | Uptake | Up-regulation | (Penno et al., 2014) |
| Bsep | Efflux | Up-regulation | (Donner et al., 2007; Geier et al., 2007; Slitt et al., 2007) |
| ASBT | Uptake | Down-regulation | (Yan et al., 2017) |
| TGR5 | Uptake | Down-regulation | (Yan et al., 2017) |
| MDR2 | Efflux | Up-regulation | (Donato et al., 2016) |
| ABCG5 | Efflux | Up-regulation | (Donato et al., 2016) |
| ABCG8 | Efflux | Up-regulation | (Donato et al., 2016) |

nephrotoxicity. In cisplatin-induced mouse acute renal failure, gene and protein expression of various xenobiotic transporters were altered. Cisplatin-induced renal injury decreased gene expression of Oatp1a1, Oat1, Oat2 and Oct2, in contrast, increased gene and protein expression of the efflux transporters Mrp2, Mrp4, Mrp5, Mdr1a and Mdr1b. Reduced expression uptake transporters as well as enhanced transcription of efflux transporters may represents an adaptation to lower accumulation of toxic ingredients (Aleksunes et al., 2008).

*Alterations of OATP1A1 in traditional herbal medicine induced toxicity*

Hepatotoxicity of herbal medicines is of increasing concern. *Polygonum multiflorum* is considered as a common tonic traditional Chinese medicine in China. However, in recent years *Polygonum multiflorum* and its stems, another traditional Chinese medicine named Ploygoni Multiflori Caulis have been found to be hepatotoxic. The expression of Oatp1a1, Oatp1b2 and MRP2 mRNA in mice was significantly decreased by Ploygoni Multiflori Caulis and its extractive, which is an important cause of hepatotoxicity (Li et al., 2017). Oleanolic acid is a triterpenoid with many beneficial effects including hepatoprotection. However, long-term and high doses use can produce adverse effects, such as dose-dependent pathological damage to the liver, including hepatocyte apoptosis, inflammation, necrosis, and cholestasis. RT-PCR showed that Oleanolic acid produced a dose-dependent increase in acute phase proteins (MT-1, Nrf2, Ho-1 and Nqo1), a decrease in hepatic bile acid transporters (Oatp1a1, Oatp1b2, Ntcp, Bsep and Ostβ) and bile acid synthesis genes (Cyp7a1 and Cyp8b1) (Lu et al., 2013). Rutaecarpine is an alkaloid of Evodia rutaecarpa that has been used as traditional Chinese medicine to treat human diseases. Rutaecarpine has been found to induce Cyp1a2, Cyp2b10, Cyp2e1, Cyp3a11 and Cyp4a10. For phase-2 enzyme genes, rutaecarpine increased glucuronyltransferases (Ugt1a6 and Ugt1a1), and hepatic organic anion transporting peptides (Oatp1a1, Oatp1b2, Oayp1a4, and Oatp2b1) and induced multidrug resistance-associated proteins (Mrp1, Mrp2, Mrp3, and Mrp4) (Zhu et al., 2013). The accumulation of berberine in hepatocytes is highly dependent on active uptake. Oatp1a1, Oatp1a4 and Oatp1b2 contribute to berberine accumulation in the liver. Oatps play an important role in the hepatic disposition of berberine and potential clinically relevant drug-drug interactions (Chen et al., 2015). Yuanhuzhitong preparation consists of Corydalis yanhusuo (CYH) and Angelica dahurica (AD), which can relieve pain by suppressing the central system. This effect is achieved by inhibiting the uptake of tetrahydropalmatine (TDE, the major component of CYH) in the liver and kidneys by stimulatory components of AD to enhance TDE exposure in the blood and brain (Zhang et al., 2020a). Alpha-naphthylisothiocyanate (ANIT) is a toxic substance that is widely used in rodents to mimic human intrahepatic cholestasis. Dioscin is an herbal ingredient with antihepatitis activity. The hepatic uptake of dioscin is involved in Oatps such as Oatp1a1, Oatp1a4, Oatp1b2 (Zhu et al., 2013). Dioscin ameliorated cholestasis, as evidenced by a reduction in biochemical parameters and improvement in liver pathology. Dioscin prevented ANIT-induced adaptive downregulation of Oatp1a1, 1b2 and contributed to upregulation of Oatp1a4, Mrp2 and Bsep, suggesting that dioscin may prevent impairment of liver function by restoring the expression of hepatic transporters (Zhang et al., 2016).

*Alterations of OATP1A1 in environmental chemicals induced toxicity*

It is well documented that environmental chemicals cause endocrine disruption in humans and wildlife and result in local or regional changes (Vos et al., 2000). Perfluoroalkyl sulfonates (PFSAs) have a wide range of applications in domestic consumption and industrial production. PFSAs was discovered to be widely distributed in biomonitoring samples of the humans and wildlife (Chou & Lin, 2019). Previous studies indicated that rat OATPS such as OATP1A1, OATP1A5, OATP1B2, and OATP2B1 transport PFSAs and promote their enterohepatic circulation and prolong their elimination half-life of human serum (Zhao et al., 2017). The renal clearance of perfluorocarboxylates depends on chain length, species, and in some cases on sex within the species. It was shown that Oat1 and Oat3 are involved in the renal secretion of perfluorooctanoate and perfluorononanoate, while Oatp1a1 promotes the reabsorption of perfluorooctanoate to perfluorodecanoate with the highest affinity for perfluorooctanoate and perfluorodecanoate. These results strongly supported the tubular reabsorption role of Oatp1a1 in the elimination of perfluorocarboxylates from the rat kidney (Weaver et al., 2010; Yang et al., 2009). Ochratoxin A (OTA) is a dietary mycotoxin that can cause hepatotoxicity, nephrotoxicity, neurotoxicity and carcinogenicity. In mice, OTA is transported by ABCB1 and/or ABCG2, OATP1A/1B. When administered orally, absence of OATP1A/1B resulted in a substantial decrease in hepatic and small intestinal exposure (Wang et al., 2020a). Epyrifenacil is a novel herbicide, which acts as an inhibitor of protoporphyrinogen oxidase (PPO) and produces hepatotoxicity by inhibiting PPO. Previous study showed that the hepatotoxicity of epyrifenacil is mainly caused by its metabolite S-3100-CA. Oatp1a1 is a major transporter in male mice, which is the main contributor to the hepatic uptake of S-3100-CA and consequently results in sex differences (Sakurai et al., 2021).

## 3 Conclusion

Oatp1a1 is generally considered to transport many endogenous molecules and xenobiotic compounds, such as bile acids and drugs to the liver (Durmus et al., 2016). Recent studies have found that Oatp1a1 is associated with drug toxicity (Ohbayashi et al., 2013), and indeed Oatp1a1 expression is reduced during many drug toxicity reactions and pathological state. It is commonly believed that this is an adaptive protective response to drug toxicity, aiming to reduce the continued transport of drugs to the liver and mitigate toxic effects. Surprisingly, in some cases of cholestasis caused either by drugs or by bile duct ligation surgery model, Oatp1a1 expression also appears to be decreased (Geier et al., 2007; Horiuchi et al., 2009; Slitt et al., 2007). Given the ability of Oatp1a1 to transport bile acids to the liver, why is exacerbated cholestatic liver injury, especially DCA accumulation in the liver, when the function of Oatp1a1 is absence (Zhang et al., 2012a). Recent studies indicated that lack of Oatp1a1 significantly alters the intestinal bacteria composition to generate more secondary

bile acid (DCA) (Zhang et al., 2012b), and increase intestinal epidermal permeability to facilitate DCA absorption (Zhang et al., 2011), which may partially explain this phenomenon. Therefore, Oatp1a1 was proposed as a simple and useful screening biomarker for the prediction of cholestasis or steatosis (Donato et al., 2016). However, the mechanism of Oatp1a1 reduction is not cleared and needs to be further investigated. In addition, the expression level of Oatp1a1 varies markedly by gender and age, thus the precision of clinical dosing in different is particularly important.

## Conflict of interest

All authors have no conflicts of interest to declare.

## Ethical approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Acknowledgements

This work was supported by the Department of Science and Technology of Guizhou Province (Nos. QKHZC [2021] normal 476, QKHPTRC [2019]5657, QKHZC [2019]2829, QKHZDZXZ [2019]3001, QKHZC [2019]2953, QKHZC [2020]4Y072, QKHPTRC [2018]5772-001), Department of Education of Guizhou Province (QJHKY[2021]049) and Guizhou Engineering Research Center of Industrial Key-technology for Dendrobium Nobile (QJJ[2022]048 and QJJ[2022]006).

## References

Aleksunes, L. M., Augustine, L. M., Cherrington, N. J., & Manautou, J. E. (2007). Influence of acetaminophen vehicle on regulation of transporter gene expression during hepatotoxicity. *Journal of Toxicology and Environmental Health. Part A.*, 70(21), 1870-1872. http://dx.doi.org/10.1080/15287390701457662. PMid:17934960.

Aleksunes, L. M., Augustine, L. M., Scheffer, G. L., Cherrington, N. J., & Manautou, J. E. (2008). Renal xenobiotic transporters are differentially expressed in mice following cisplatin treatment. *Toxicology*, 250(2-3), 82-88. http://dx.doi.org/10.1016/j.tox.2008.06.009. PMid:18640236.

Aleksunes, L. M., Slitt, A. M., Cherrington, N. J., Thibodeau, M. S., Klaassen, C. D., & Manautou, J. E. (2005). Differential expression of mouse hepatic transporter genes in response to acetaminophen and carbon tetrachloride. *Toxicological Sciences*, 83(1), 44-52. http://dx.doi.org/10.1093/toxsci/kfi013. PMid:15496496.

Atshaves, B. P., McIntosh, A. L., Martin, G. G., Landrock, D., Payne, H. R., Bhuvanendran, S., Landrock, K. K., Lyuksyutova, O. I., Johnson, J. D., Macfarlane, R. D., Kier, A. B., & Schroeder, F. (2009). Overexpression of sterol carrier protein-2 differentially alters hepatic cholesterol accumulation in cholesterol-fed mice. *Journal of Lipid Research*, 50(7), 1429-1447. http://dx.doi.org/10.1194/jlr.M900020-JLR200. PMid:19289417.

Bezençon, J., Beaudoin, J. J., Ito, K., Fu, D., Roth, S. E., Brock, W. J., & Brouwer, K. L. R. (2019). Altered expression and function of hepatic transporters in a rodent model of polycystic kidney disease. *Drug Metabolism and Disposition: the Biological Fate of Chemicals*, 47(8), 899-906. http://dx.doi.org/10.1124/dmd.119.086785. PMid:31160314.

Blazquez, A. G., Briz, O., Romero, M. R., Rosales, R., Monte, M. J., Vaquero, J., Macias, R. I., Cassio, D., & Marin, J. J. (2012). Characterization of the role of ABCG2 as a bile acid transporter in liver and placenta. *Molecular Pharmacology*, 81(2), 273-283. http://dx.doi.org/10.1124/mol.111.075143. PMid:22096226.

Brcakova, E., Fuksa, L., Cermanova, J., Kolouchova, G., Hroch, M., Hirsova, P., Martinkova, J., Staud, F., & Micuda, S. (2009). Alteration of methotrexate biliary and renal elimination during extrahepatic and intrahepatic cholestasis in rats. *Biological & Pharmaceutical Bulletin*, 32(12), 1978-1985. http://dx.doi.org/10.1248/bpb.32.1978. PMid:19952415.

Chen, C., Wu, Z. T., Ma, L. L., Ni, X., Lin, Y. F., Wang, L., Chen, K. P., Huang, C. G., & Pan, G. (2015). Organic anion-transporting polypeptides contribute to the hepatic uptake of berberine. *Xenobiotica*, 45(12), 1138-1146. http://dx.doi.org/10.3109/00498254.2015.1042537. PMid:26068524.

Chen, Y., Chen, X., Xiang, T., Sun, B. G., Luo, H. X., Liu, M. T., Chen, Z. X., Zhang, S. J., & Wang, C. J. (2016). Total saponins from dioscorea septemloba thunb reduce serum uric acid levels in rats with hyperuricemia through OATP1A1 up-regulation. *Journal of Huazhong University of Science and Technology*, 36(2), 237-242. http://dx.doi.org/10.1007/s11596-016-1573-z. PMid:27072969.

Cheng, X., & Klaassen, C. D. (2008). Critical role of PPAR-alpha in perfluorooctanoic acid- and perfluorodecanoic acid-induced downregulation of Oatp uptake transporters in mouse livers. *Toxicological Sciences*, 106(1), 37-45. http://dx.doi.org/10.1093/toxsci/kfn161. PMid:18703564.

Cheng, X., Maher, J., Chen, C., & Klaassen, C. D. (2005). Tissue distribution and ontogeny of mouse organic anion transporting polypeptides (Oatps). *Drug Metabolism and Disposition: the Biological Fate of Chemicals*, 33(7), 1062-1073. http://dx.doi.org/10.1124/dmd.105.003640. PMid:15843488.

Cheng, X., Maher, J., Lu, H., & Klaassen, C. D. (2006). Endocrine regulation of gender-divergent mouse organic anion-transporting polypeptide (Oatp) expression. *Molecular Pharmacology*, 70(4), 1291-1297. http://dx.doi.org/10.1124/mol.106.025122. PMid:16807376.

Cheng, Y., Freeden, C., Zhang, Y., Abraham, P., Shen, H., Wescott, D., Humphreys, W. G., Gan, J., & Lai, Y. (2016). Biliary excretion of pravastatin and taurocholate in rats with bile salt export pump (Bsep) impairment. *Biopharmaceutics & Drug Disposition*, 37(5), 276-286. http://dx.doi.org/10.1002/bdd.2011. PMid:27059119.

Chiba, M., Itagaki, S., Kobayashi, M., Hirano, T., & Iseki, K. (2007). Characterization of hepatobiliary organic anion transporters in Long-Evans Cinnamon rats. *Drug Metabolism and Pharmacokinetics*, 22(5), 387-390. http://dx.doi.org/10.2133/dmpk.22.387. PMid:17965523.

Choi, J. H., Murray, J. W., & Wolkoff, A. W. (2011). PDZK1 binding and serine phosphorylation regulate subcellular trafficking of organic anion transport protein 1a1. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 300(3), G384-G393. http://dx.doi.org/10.1152/ajpgi.00500.2010. PMid:21183661.

Chou, W. C., & Lin, Z. (2019). Bayesian evaluation of a physiologically based pharmacokinetic (PBPK) model for perfluorooctane sulfonate (PFOS) to characterize the interspecies uncertainty between mice, rats, monkeys, and humans: development and performance verification. *Environment International*, 129, 408-422. http://dx.doi.org/10.1016/j.envint.2019.03.058. PMid:31152982.

Donato, M. T., Lopez-Riera, M., Castell, J. V., Gomez-Lechon, M. J., & Jover, R. (2016). Both cholestatic and steatotic drugs trigger extensive alterations in the mRNA level of biliary transporters in rat hepatocytes: application to develop new predictive biomarkers for early drug development. *Toxicology Letters*, 263, 58-67. http://dx.doi.org/10.1016/j.toxlet.2016.10.008. PMid:27765674.

Donner, M. G., Schumacher, S., Warskulat, U., Heinemann, J., & Haussinger, D. (2007). Obstructive cholestasis induces TNF-alpha- and IL-1 -mediated periportal downregulation of Bsep and zonal regulation of Ntcp, Oatp1a4, and Oatp1b2. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 293(6), G1134-G1146. http://dx.doi.org/10.1152/ajpgi.00079.2007. PMid:17916651.

Durmus, S., Naik, J., Buil, L., Wagenaar, E., van Tellingen, O., & Schinkel, A. H. (2014). In vivo disposition of doxorubicin is affected by mouse Oatp1a/1b and human OATP1A/1B transporters. *International Journal of Cancer*, 135(7), 1700-1710. http://dx.doi.org/10.1002/ijc.28797. PMid:24554572.

Durmus, S., van Hoppe, S., & Schinkel, A. H. (2016). The impact of Organic Anion-Transporting Polypeptides (OATPs) on disposition and toxicity of antitumor drugs: insights from knockout and humanized mice. *Drug Resistance Updates*, 27, 72-88. http://dx.doi.org/10.1016/j.drup.2016.06.005. PMid:27449599.

Eckhardt, U., Schroeder, A., Stieger, B., Höchli, M., Landmann, L., Tynes, R., Meier, P. J., & Hagenbuch, B. (1999). Polyspecific substrate uptake by the hepatic organic anion transporter Oatp1 in stably transfected CHO cells. *The American Journal of Physiology*, 276(4), G1037-G1042. PMid:10198348.

Engels, K., Rakov, H., Zwanziger, D., Moeller, L. C., Homuth, G., Kohrle, J., Brix, K., & Fuhrer, D. (2015). Differences in mouse hepatic thyroid hormone transporter expression with age and hyperthyroidism. *European Thyroid Journal*, 4(Suppl. 1), 81-86. http://dx.doi.org/10.1159/000381020. PMid:26601077.

Fisher, C. D., Lickteig, A. J., Augustine, L. M., Elferink, R. P. O., Besselsen, D. G., Erickson, R. P., & Cherrington, N. J. (2009). Experimental non-alcoholic fatty liver disease results in decreased hepatic uptake transporter expression and function in rats. *European Journal of Pharmacology*, 613(1-3), 119-127. http://dx.doi.org/10.1016/j.ejphar.2009.04.002. PMid:19358839.

Fu, Z. D., Csanaky, I. L., & Klaassen, C. D. (2012). Effects of aging on mRNA profiles for drug-metabolizing enzymes and transporters in livers of male and female mice. *Drug Metabolism and Disposition: the Biological Fate of Chemicals*, 40(6), 1216-1225. http://dx.doi.org/10.1124/dmd.111.044461. PMid:22446518.

Fujiyama, N., Shitara, Y., & Horie, T. (2013). The mechanism of the down-regulation of hepatic transporters in rats with indomethacin-induced intestinal injury. *Digestive Diseases and Sciences*, 58(7), 1891-1898. http://dx.doi.org/10.1007/s10620-013-2587-z. PMid:23443493.

Geier, A., Dietrich, C. G., Trauner, M., & Gartung, C. (2007). Extrahepatic cholestasis downregulates Oatp1 by TNF-α signalling without affecting Oatp2 and Oatp4 expression and sodium-independent bile salt uptake in rat liver. *Liver International*, 27(8), 1056-1065. http://dx.doi.org/10.1111/j.1478-3231.2007.01523.x. PMid:17845533.

Geier, A., Dietrich, C. G., Voigt, S., Ananthanarayanan, M., Lammert, F., Schmitz, A., Trauner, M., Wasmuth, H. E., Boraschi, D., Balasubramaniyan, N., Suchy, F. J., Matern, S., & Gartung, C. (2005). Cytokine-dependent regulation of hepatic organic anion transporter gene transactivators in mouse liver. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 289(5), G831-G841. http://dx.doi.org/10.1152/ajpgi.00307.2004. PMid:15860642.

Giraudeau, C., Leporq, B., Doblas, S., Lagadec, M., Pastor, C. M., Daire, J. L., & Van Beers, B. E. (2017). Gadoxetate-enhanced MR imaging and compartmental modelling to assess hepatocyte bidirectional transport function in rats with advanced liver fibrosis. *European Radiology*, 27(5), 1804-1811. http://dx.doi.org/10.1007/s00330-016-4536-7. PMid:27553933.

Gong, L., Aranibar, N., Han, Y. H., Zhang, Y., Lecureux, L., Bhaskaran, V., Khandelwal, P., Klaassen, C. D., & Lehman-McKeeman, L. D. (2011). Characterization of organic anion-transporting polypeptide (Oatp) 1a1 and 1a4 null mice reveals altered transport function and urinary metabolomic profiles. *Toxicological Sciences*, 122(2), 587-597. http://dx.doi.org/10.1093/toxsci/kfr114. PMid:21561886.

Gyamfi, M. A., Tanaka, Y., He, L., Klaassen, C. D., & Wan, Y. J. (2009). Hepatic effects of a methionine-choline-deficient diet in hepatocyte RXRalpha-null mice. *Toxicology and Applied Pharmacology*, 234(2), 166-178. http://dx.doi.org/10.1016/j.taap.2008.09.022. PMid:18952117.

Hagenbuch, B., & Meier, P. J. (2004). Organic anion transporting polypeptides of the OATP/ SLC21 family: phylogenetic classification as OATP/ SLCO superfamily, new nomenclature and molecular/ functional properties. *Pflügers Archiv*, 447(5), 653-665. http://dx.doi.org/10.1007/s00424-003-1168-y. PMid:14579113.

Hagenbuch, B., & Stieger, B. (2013). The SLCO (former SLC21) superfamily of transporters. *Molecular Aspects of Medicine*, 34(2-3), 396-412. http://dx.doi.org/10.1016/j.mam.2012.10.009. PMid:23506880.

Hanafy, S., El-Kadi, A. O., & Jamali, F. (2012). Effect of inflammation on molecular targets and drug transporters. *Journal of Pharmacy & Pharmaceutical Sciences*, 15(3), 361-375. http://dx.doi.org/10.18433/J30300. PMid:22974786.

Hobbs, M., Parker, C., Birch, H., & Kenworthy, K. (2012). Understanding the interplay of drug transporters involved in the disposition of rosuvastatin in the isolated perfused rat liver using a physiologically-based pharmacokinetic model. *Xenobiotica*, 42(4), 327-338. http://dx.doi.org/10.3109/00498254.2011.625452. PMid:22035568.

Horiuchi, I., Mori, Y. I., Taguchi, M., Ichida, F., Miyawaki, T., & Hashimoto, Y. (2009). Mechanisms responsible for the altered pharmacokinetics of bosentan: analysis utilizing rats with bile duct ligation-induced liver dysfunction. *Biopharmaceutics & Drug Disposition*, 30(6), 326-333. http://dx.doi.org/10.1002/bdd.671. PMid:19639656.

Hou, W. Y., Xu, S. F., Zhu, Q. N., Lu, Y. F., Cheng, X. G., & Liu, J. (2014). Age- and sex-related differences of organic anion-transporting polypeptide gene expression in livers of rats. *Toxicology and Applied Pharmacology*, 280(2), 370-377. http://dx.doi.org/10.1016/j.taap.2014.08.020. PMid:25168429.

Imai, S., Kikuchi, R., Kusuhara, H., & Sugiyama, Y. (2013). DNA methylation and histone modification profiles of mouse organic anion transporting polypeptides. *Drug Metabolism and Disposition: the Biological Fate of Chemicals*, 41(1), 72-78. http://dx.doi.org/10.1124/dmd.112.047969. PMid:23033256.

Ishida, K., Ullah, M., Tóth, B., Juhasz, V., & Unadkat, J. D. (2018). Transport kinetics, selective inhibition, and successful prediction of in vivo inhibition of rat hepatic organic anion transporting polypeptides. *Drug Metabolism and Disposition: the Biological Fate of Chemicals*, 46(9), 1251-1258. http://dx.doi.org/10.1124/dmd.118.080770. PMid:29891589.

Iusuf, D., Ludwig, M., Elbatsh, A., van Esch, A., van de Steeg, E., Wagenaar, E., van der Valk, M., Lin, F., van Tellingen, O., & Schinkel, A. H. (2014). OATP1A/1B transporters affect irinotecan and SN-38 pharmacokinetics and carboxylesterase expression in knockout and humanized transgenic mice. *Molecular Cancer Therapeutics*, 13(2), 492-503. http://dx.doi.org/10.1158/1535-7163.MCT-13-0541. PMid:24194565.

Jacquemin, E., Hagenbuch, B., Stieger, B., Wolkoff, A. W., & Meier, P. J. (1994). Expression cloning of a rat liver Na(+)-independent organic anion transporter. *Proceedings of the National Academy of Sciences of the United States of America*, 91(1), 133-137. http://dx.doi.org/10.1073/pnas.91.1.133. PMid:8278353.

Jiang, L., Chu, H., Gao, B., Lang, S., Wang, Y., Duan, Y., & Schnabl, B. (2020). Transcriptomic profiling identifies novel hepatic and intestinal genes following chronic plus binge ethanol feeding in

mice. *Digestive Diseases and Sciences*, 65(12), 3592-3604. http://dx.doi.org/10.1007/s10620-020-06461-6. PMid:32671585.

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., Back, T., Petersen, S., Reiman, D., Clancy, E., Zielinski, M., Steinegger, M., Pacholska, M., Berghammer, T., Bodenstein, S., Silver, D., Vinyals, O., Senior, A. W., Kavukcuoglu, K., Kohli, P., & Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, 596(7873), 583-589.

Kawase, A., Handa, A., & Iwaki, M. (2017). Effects of high-cholesterol diet on pravastatin disposition in the perfused rat liver. *European Journal of Drug Metabolism and Pharmacokinetics*, 42(3), 519-526. http://dx.doi.org/10.1007/s13318-016-0367-9. PMid:27511381.

Kim, R. B. (2003). Organic anion-transporting polypeptide (OATP) transporter family and drug disposition. *European Journal of Clinical Investigation*, 33(Suppl. 2), 1-5. http://dx.doi.org/10.1046/j.1365-2362.33.s2.5.x. PMid:14641549.

Kulkarni, S. R., Xu, J., Donepudi, A. C., Wei, W., & Slitt, A. L. (2013). Effect of caloric restriction and AMPK activation on hepatic nuclear receptor, biotransformation enzyme, and transporter expression in lean and obese mice. *Pharmaceutical Research*, 30(9), 2232-2247. http://dx.doi.org/10.1007/s11095-013-1140-2. PMid:23949303.

Kuno, T., Hirayama-Kurogi, M., Ito, S., & Ohtsuki, S. (2016). Effect of intestinal flora on protein expression of drug-metabolizing enzymes and transporters in the liver and kidney of germ-free and antibiotics-treated mice. *Molecular Pharmaceutics*, 13(8), 2691-2701. http://dx.doi.org/10.1021/acs.molpharmaceut.6b00259. PMid:27376980.

Lee, H. H., Leake, B. F., Kim, R. B., & Ho, R. H. (2017). Contribution of organic anion-transporting polypeptides 1A/1B to doxorubicin uptake and clearance. *Molecular Pharmacology*, 91(1), 14-24. http://dx.doi.org/10.1124/mol.116.105544. PMid:27777271.

Li, H. P., Zhu, H. Y., Gao, X., Ma, P. K., Chen, J. H., Bi, X. N., Wang, Q., & Zhang, Y. J. (2017). Study on mechanism of hepatotoxicity of Ploygoni Multiflori Caulis based on function inhibition of bilirubin-associated transporters in idiosyncratic rat. *Zhongguo Zhongyao Zazhi*, 42(18), 3591-3595. PMid:29218947.

Lin, C. H., Hsu, K. W., Chen, C. H., Uang, Y. S., & Lin, C. J. (2017). Differential changes in the pharmacokinetics of statins in collagen-induced arthritis rats. *Biochemical Pharmacology*, 142, 216-228. http://dx.doi.org/10.1016/j.bcp.2017.06.118. PMid:28636885.

Lu, Y. F., Wan, X. L., Xu, Y., & Liu, J. (2013). Repeated oral administration of oleanolic acid produces cholestatic liver injury in mice. *Molecules*, 18(3), 3060-3071. http://dx.doi.org/10.3390/molecules18033060. PMid:23470335.

Martinez-Becerra, P., Briz, O., Romero, M. R., Macias, R. I., Perez, M. J., Sancho-Mateo, C., Lostao, M. P., Fernandez-Abalos, J. M., & Marin, J. J. (2011). Further characterization of the electrogenicity and pH sensitivity of the human organic anion-transporting polypeptides OATP1B1 and OATP1B3. *Molecular Pharmacology*, 79(3), 596-607. http://dx.doi.org/10.1124/mol.110.069971. PMid:21173039.

Maruyama, H., Ogura, J., Fujikawa, A., Terada, Y., Tsujimoto, T., Koizumi, T., Kuwayama, K., Kobayashi, M., Yamaguchi, H., & Iseki, K. (2013). Intestinal ischemia-reperfusion suppresses biliary excretion of hepatic organic anion transporting polypeptides substrate. *Journal of Pharmacy & Pharmaceutical Sciences*, 16(5), 722-731. http://dx.doi.org/10.18433/J3NC8P. PMid:24393554.

Monte, M. J., Fernandez-Tagarro, M., Macias, R. I., Jimenez, F., Martin, F. G.-S., & Marin, J. J. G. (2005). Changes in the expression of genes related to bile acid synthesis and transport by the rat liver during hepatocarcinogenesis. *Clinical Science*, 109(2), 199-207. http://dx.doi.org/10.1042/CS20050035. PMid:15853769.

Ohbayashi, M., Yamamoto, C., Shiozawa, A., Kohyama, N., Kobayashi, Y., & Yamamoto, T. (2013). Differential mRNA expression and the uptake of methotrexate in primary MAEC and MLF cells: involvement of the Abc and Slco/Oatp transporters in alveolar epithelial cell toxicity. *The Journal of Toxicological Sciences*, 38(1), 103-114. http://dx.doi.org/10.2131/jts.38.103. PMid:23358144.

Penno, C. A., Morgan, S. A., Rose, A. J., Herzig, S., Lavery, G. G., & Odermatt, A. (2014). 11β-Hydroxysteroid dehydrogenase-1 is involved in bile acid homeostasis by modulating fatty acid transport protein-5 in the liver of mice. *Molecular Metabolism*, 3(5), 554-564. http://dx.doi.org/10.1016/j.molmet.2014.04.008. PMid:25061560.

Sakurai, K., Kuroda, T., Abe, J., Toda, H., & Kitamoto, S. (2021). Identification of the organic anion transporting polypeptides responsible for the hepatic uptake of the major metabolite of epyrifenacil, S-3100-CA, in mice. *Pharmacology Research & Perspectives*, 9(5), e00877. http://dx.doi.org/10.1002/prp2.877. PMid:34619012.

Sheng, R. F., Wang, H. Q., Yang, L., Jin, K. P., Xie, Y. H., Fu, C. X., & Zeng, M. S. (2017). Assessment of liver fibrosis using T1 mapping on Gd-EOB-DTPA-enhanced magnetic resonance. *Digestive and Liver Disease*, 49(7), 789-795. http://dx.doi.org/10.1016/j.dld.2017.02.006. PMid:28237298.

Shimizu, A., Kobayashi, A., Motoyama, H., Sakai, H., Yamada, A., Yoshizawa, A., Momose, M., Kadoya, M., & Miyagawa, S. (2015). Features of acute liver congestion on gadoxetate disodium-enhanced MRI in a rat model: role of organic anion-transporting polypeptide 1A1. *Journal of Magnetic Resonance Imaging*, 42(3), 828-836. http://dx.doi.org/10.1002/jmri.24839. PMid:25581836.

Shitara, Y., Itoh, T., Sato, H., Li, A. P., & Sugiyama, Y. (2003). Inhibition of transporter-mediated hepatic uptake as a mechanism for drug-drug interaction between cerivastatin and cyclosporin A. *The Journal of Pharmacology and Experimental Therapeutics*, 304(2), 610-616. http://dx.doi.org/10.1124/jpet.102.041921. PMid:12538813.

Shuboni-Mulligan, D. D., Parys, M., Blanco-Fernandez, B., Mallett, C. L., Schnegelberger, R., Takada, M., Chakravarty, S., Hagenbuch, B., & Shapiro, E. M. (2019). Dynamic contrast-enhanced MRI of OATP dysfunction in diabetes. *Diabetes*, 68(2), 271-280. http://dx.doi.org/10.2337/db18-0525. PMid:30487262.

Slitt, A. L., Allen, K., Morrone, J., Aleksunes, L. M., Chen, C., Maher, J. M., Manautou, J. E., Cherrington, N. J., & Klaassen, C. D. (2007). Regulation of transporter expression in mouse liver, kidney, and intestine during extrahepatic cholestasis. *Biochimica et Biophysica Acta - Biomembranes*, 1768(3), 637-647. http://dx.doi.org/10.1016/j.bbamem.2006.10.008. PMid:17141734.

St-Pierre, M. V., Stallmach, T., Grundschober, A. F., Dufour, J.-F., Serrano, M. A., Marin, J. J. G., Sugiyama, Y., & Meier, P. J. (2004). Temporal expression profiles of organic anion transport proteins in placenta and fetal liver of the rat. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 287(6), R1505-R1516. http://dx.doi.org/10.1152/ajpregu.00279.2003. PMid:15345472.

Sun, H., Liu, L., & Pang, K. S. (2006). Increased estrogen sulfation of estradiol 17beta-D-glucuronide in metastatic tumor rat livers. *The Journal of Pharmacology and Experimental Therapeutics*, 319(2), 818-831. http://dx.doi.org/10.1124/jpet.106.108860. PMid:16895976.

Sun, P., Wang, C., Liu, Q., Meng, Q., Zhang, A., Huo, X., Sun, H., & Liu, K. (2014). OATP and MRP2-mediated hepatic uptake and biliary excretion of eprosartan in rat and human. *Pharmacological Reports*, 66(2), 311-319. http://dx.doi.org/10.1016/j.pharep.2014.02.013. PMid:24911086.

Taub, M. E., Ludwig-Schwellinger, E., Ishiguro, N., Kishimoto, W., Yu, H., Wagner, K., & Tweedie, D. (2015). Sex-, species-, and tissue-specific metabolism of empagliflozin in male mouse kidney forms an unstable hemiacetal metabolite (M466/2) that degrades to 4-hydroxycrotonaldehyde, a reactive and cytotoxic species. *Chemical Research in Toxicology*, 28(1), 103-115. http://dx.doi.org/10.1021/tx500380t. PMid:25489797.

Teng, S., & Piquette-Miller, M. (2008). Regulation of transporters by nuclear hormone receptors: implications during inflammation. *Molecular Pharmaceutics*, 5(1), 67-76. http://dx.doi.org/10.1021/mp700102q. PMid:18072749.

Tsujimoto, T., Ogura, J., Kuwayama, K., Koizumi, T., Sasaki, S., Terada, Y., Kobayashi, M., Yamaguchi, H., & Iseki, K. (2013). Effect of oxidative stress on expression and function of human and rat organic anion transporting polypeptides in the liver. *International Journal of Pharmaceutics*, 458(2), 262-271. http://dx.doi.org/10.1016/j.ijpharm.2013.10.013. PMid:24409515.

Vos, J. G., Dybing, E., Greim, H. A., Ladefoged, O., Lambré, C., Tarazona, J. V., Brandt, I., & Vethaak, A. D. (2000). Health effects of endocrine-disrupting chemicals on wildlife, with special reference to the European situation. *Critical Reviews in Toxicology*, 30(1), 71-133. http://dx.doi.org/10.1080/10408440091159176. PMid:10680769.

Waart, D. R., Naik, J., Utsunomiya, K. S., Duijst, S., Ho-Mok, K., Bolier, A. R., Hiralall, J., Bull, L. N., Bosma, P. J., Elferink, R. P. O., & Paulusma, C. C. (2016). ATP11C targets basolateral bile salt transporter proteins in mouse central hepatocytes. *Hepatology*, 64(1), 161-174. http://dx.doi.org/10.1002/hep.28522. PMid:26926206.

Wang, J., Gan, C., Qi, X., Lebre, M. C., & Schinkel, A. H. (2020a). Human organic anion transporting polypeptide (OATP) 1B3 and mouse OATP1A/1B affect liver accumulation of Ochratoxin A in mice. *Toxicology and Applied Pharmacology*, 401, 115072. http://dx.doi.org/10.1016/j.taap.2020.115072. PMid:32470353.

Wang, P., Hata, S., Xiao, Y., Murray, J. W., & Wolkoff, A. W. (2008). Topological assessment of oatp1a1: a 12-transmembrane domain integral membrane protein with three N-linked carbohydrate chains. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 294(4), G1052-G1059. http://dx.doi.org/10.1152/ajpgi.00584.2007. PMid:18308854.

Wang, P., Wang, J. J., Xiao, Y., Murray, J. W., Novikoff, P. M., Angeletti, R. H., Orr, G. A., Lan, D., Silver, D. L., & Wolkoff, A. W. (2005). Interaction with PDZK1 is required for expression of organic anion transporting protein 1A1 on the hepatocyte surface. *The Journal of Biological Chemistry*, 280(34), 30143-30149. http://dx.doi.org/10.1074/jbc.M503969200. PMid:15994332.

Wang, P., Wang, W. J., Choi-Nurvitadhi, J., Lescaille, Y., Murray, J. W., & Wolkoff, A. W. (2019). Rat organic anion transport protein 1A1 interacts directly with organic anion transport protein 1A4 facilitating its maturation and trafficking to the hepatocyte plasma membrane. *Hepatology*, 70(6), 2156-2170. http://dx.doi.org/10.1002/hep.30772. PMid:31102415.

Wang, W. J., Murray, J. W., & Wolkoff, A. W. (2014). Oatp1a1 requires PDZK1 to traffic to the plasma membrane by selective recruitment of microtubule-based motor proteins. *Drug Metabolism and Disposition: the Biological Fate of Chemicals*, 42(1), 62-69. http://dx.doi.org/10.1124/dmd.113.054536. PMid:24115750.

Wang, X., Zheng, L., Wu, J., Tang, B., Zhang, M., Zhu, D., & Lin, X. (2017). Constitutive androstane receptor activation promotes bilirubin clearance in a murine model of alcoholic liver disease. *Molecular Medicine Reports*, 15(6), 3459-3466. http://dx.doi.org/10.3892/mmr.2017.6435. PMid:28393244.

Wang, Y., Sparidans, R. W., Li, W., Lebre, M. C., Beijnen, J. H., & Schinkel, A. H. (2020b). OATP1A/1B, CYP3A, ABCB1, and ABCG2 limit oral availability of the NTRK inhibitor larotrectinib, while ABCB1 and ABCG2 also restrict its brain accumulation. *British Journal of Pharmacology*, 177(13), 3060-3074. http://dx.doi.org/10.1111/bph.15034. PMid:32087611.

Weaver, Y. M., Ehresman, D. J., Butenhoff, J. L., & Hagenbuch, B. (2010). Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths. *Toxicological Sciences*, 113(2), 305-314. http://dx.doi.org/10.1093/toxsci/kfp275. PMid:19915082.

Wieneke, N., Neuschäfer-Rube, F., Bode, L. M., Kuna, M., Andres, J., Carnevali, L. C. Jr., Hirsch-Ernst, K. I., & Püschel, G. P. (2009). Synergistic acceleration of thyroid hormone degradation by phenobarbital and the PPAR alpha agonist WY14643 in rat hepatocytes. *Toxicology and Applied Pharmacology*, 240(1), 99-107. http://dx.doi.org/10.1016/j.taap.2009.07.014. PMid:19631232.

Xiao, Y., Nieves, E., Angeletti, R. H., Orr, G. A., & Wolkoff, A. W. (2006). Rat organic anion transporting protein 1A1 (Oatp1a1): purification and phosphopeptide assignment. *Biochemistry*, 45(10), 3357-3369. http://dx.doi.org/10.1021/bi052437v. PMid:16519530.

Yan, J., Xie, G., Liang, C., Hu, Y., Zhao, A., Huang, F., Hu, P., Liu, P., Jia, W., & Wang, X. (2017). Herbal medicine Yinchenhaotang protects against α-naphthylisothiocyanate-induced cholestasis in rats. *Scientific Reports*, 7(1), 4211. http://dx.doi.org/10.1038/s41598-017-04536-5. PMid:28646179.

Yang, C. H., Glover, K. P., & Han, X. (2009). Organic anion transporting polypeptide (Oatp) 1a1-mediated perfluorooctanoate transport and evidence for a renal reabsorption mechanism of Oatp1a1 in renal elimination of perfluorocarboxylates in rats. *Toxicology Letters*, 190(2), 163-171. http://dx.doi.org/10.1016/j.toxlet.2009.07.011. PMid:19616083.

Zhang, A., Jia, Y., Xu, Q., Wang, C., Liu, Q., Meng, Q., Peng, J., Sun, H., Sun, P., Huo, X., & Liu, K. (2016). Dioscin protects against ANIT-induced cholestasis via regulating Oatps, Mrp2 and Bsep expression in rats. *Toxicology and Applied Pharmacology*, 305, 127-135. http://dx.doi.org/10.1016/j.taap.2016.06.019. PMid:27317372.

Zhang, X., Zhang, K., Wang, Y., & Ma, R. (2020a). Effects of myricitrin and relevant molecular mechanisms. *Current Stem Cell Research & Therapy*, 15(1), 11-17. http://dx.doi.org/10.2174/1574888X14666181126103338. PMid:30474534.

Zhang, Y., Csanaky, I. L., Cheng, X., Lehman-McKeeman, L. D., & Klaassen, C. D. (2012a). Organic anion transporting polypeptide 1a1 null mice are sensitive to cholestatic liver injury. *Toxicological Sciences*, 127(2), 451-462. http://dx.doi.org/10.1093/toxsci/kfs123. PMid:22461449.

Zhang, Y., Csanaky, I. L., Lehman-McKeeman, L. D., & Klaassen, C. D. (2011). Loss of organic anion transporting polypeptide 1a1 increases deoxycholic acid absorption in mice by increasing intestinal permeability. *Toxicological Sciences*, 124(2), 251-260. http://dx.doi.org/10.1093/toxsci/kfr236. PMid:21914718.

Zhang, Y., Lickteig, A. J., Csanaky, I. L., & Klaassen, C. D. (2018). Activation of PPARα decreases bile acids in livers of female mice while maintaining bile flow and biliary bile acid excretion. *Toxicology and Applied Pharmacology*, 338, 112-123. http://dx.doi.org/10.1016/j.taap.2017.11.014. PMid:29175453.

Zhang, Y., Lickteig, A. J., Liu, J., Csanaky, I. L., & Klaassen, C. D. (2020b). Effects of ablation and activation of Nrf2 on bile acid homeostasis in male mice. *Toxicology and Applied Pharmacology*, 403, 115170. http://dx.doi.org/10.1016/j.taap.2020.115170. PMid:32738332.

Zhang, Y., Limaye, P. B., Lehman-McKeeman, L. D., & Klaassen, C. D. (2012b). Dysfunction of organic anion transporting polypeptide 1a1 alters intestinal bacteria and bile acid metabolism in mice. *PLoS One*, 7(4), e34522. http://dx.doi.org/10.1371/journal.pone.0034522. PMid:22496825.

Zhao, W., Zitzow, J. D., Weaver, Y., Ehresman, D. J., Chang, S. C., Butenhoff, J. L., & Hagenbuch, B. (2017). Organic anion transporting polypeptides contribute to the disposition of perfluoroalkyl acids in humans and rats. *Toxicological Sciences*, 156(1), 84-95. PMid:28013215.

Zhu, Q. N., Zhang, D., Jin, T., Wu, Q., Liu, J., & Lu, Y. F. (2013). Rutaecarpine effects on expression of hepatic phase-1, phase-2 metabolism and transporter genes as a basis of herb-drug interactions. *Journal of Ethnopharmacology*, 147(1), 215-219. http://dx.doi.org/10.1016/j.jep.2013.03.005. PMid:23510861.