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Review

Emerging evidence of inter-organ interaction on drug transporters under liver injury

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ABSTRACT

Dysfunction of drug transporters significantly affects therapeutic outcomes and drug efficacy in patients with liver injury. Clinical and experimental evidence demonstrates that liver injury involves complex inter-organ interactions among the brain, eye, liver, intestine, and kidney. Recent advances in basic and clinical research have illuminated the physiologic and molecular mechanisms underlying transporter alterations in liver injury, particularly those associated with bilirubin, reactive oxygen species, ammonia, bile acid, and inflammatory factors. Notably, the influence of these transporter modifications on drug pharmacokinetics in liver injury patients remains inadequately understood. Additional research is necessary to fully comprehend these effects and their therapeutic implications. The documented alterations of transporters in distant organs across various liver diseases indicate that dosage modifications may be required when administering transporter-substrate drugs, including both traditional Chinese and Western medicines, to patients with liver dysfunction. This strategy helps maintain drug concentrations within therapeutic ranges while reducing adverse reactions. Furthermore, when utilizing transporter inducers or inhibitors clinically, consideration of their long-term effects on transporters and subsequent therapeutic impact is essential. Careful attention must be paid to avoid compromising the elimination of toxic metabolites and proteins when inhibiting these transporters. Similarly, prudent use of inducers or inducer-type therapeutic drugs is necessary to prevent enhanced drug resistance. This review examines recent clinical and experimental findings regarding the inter-organ interaction of drug transporters in liver injury conditions and their clinical relevance.

1. Introduction

Liver injury poses a substantial threat to human health, resulting in two million deaths annually and representing 4% of global mortality (1 in 25 deaths worldwide) [1]. This condition encompasses diverse etiological factors, including viruses, drugs, toxins, and alcohol [2-9]. In China, liver diseases affect approximately 300 million individuals, with viral hepatitis (predominantly hepatitis B virus, HBV), metabolism-associated steatosis liver disease (MAFLD), and alcoholic liver disease (ALD) representing the most prevalent forms [18]. The nation is experiencing an increasing incidence of various hepatic disorders, including viral hepatitis [10], ALD [11], MAFLD [12,13], autoimmune liver disease [14], drug-induced liver disease [15], cirrhosis [16], and hepatocellular carcinoma (HCC) [17].

Hepatitis A virus and hepatitis E virus cause acute, self-limiting infections with minimal chronic effects [19]. Chronic viral hepatitis infections, particularly HBV and hepatitis C virus (HCV), can progress to cirrhosis and mortality if left untreated. While current treatments effectively cure HCV with nearly 100% success rates, developing an effective cure for HBV remains challenging [20]. Traditional Chinese herbal medicines, historically used for liver diseases, represent potential treatments for HBV carriers but require a thorough evaluation of efficacy and safety profiles [10, 21]. Metabolic dysfunction-associated fatty liver disease (MAFLD) encompasses conditions ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, and cirrhosis, potentially progressing to HCC without evident cirrhosis. Natural compounds show promise as therapeutic agents for MAFLD and MASH [13, 22-24]. The pathophysiology of ALD primarily results from alcohol's direct toxic effects and its primary metabolite, acetaldehyde [25]. Treatment for alcoholic hepatitis primarily focuses on abstinence, nutritional support, and corticosteroid therapy [26]. Drug-induced liver injury (DILI) represents a substantial healthcare burden, manifesting from mild enzyme elevations to liver failure, necessitating transplantation, or resulting in death [27]. is broadly classified into two mechanistic categories: intrinsic (dose-dependent) hepatotoxicity and idiosyncratic (immune-mediated) liver injury. Intrinsic hepatotoxicity results from the direct action of a drug or its reactive metabolites, leading to cellular stress responses. This form of injury is exemplified by agents such as cadmium [28], isoniazid [29], and anti-

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psychotic drugs [30, 31] and antineoplastic drugs [32, 33]. Conversely, idiosyncratic DILI is mediated by dysregulated immune responses, often involving the activation of inflammatory signaling pathways [34]. Notable examples include triptolide [35-37] and acetaminophen [38, 39]. Multicenter prospective studies and online resources now provide enhanced DILI diagnostic approaches. Liver fibrosis, resulting from chronic hepatic damage, represents a dynamic process characterized by hepatocyte necrosis, inflammation, and excessive extracellular matrix accumulation. Despite significant advances in anti-fibrosis drug development and targeted delivery systems [42, 43], no therapeutic agent has received clinical approval for liver fibrosis treatment, primarily due to insufficient hepatic stellate cell targeting and collagen removal challenges [40, 41]. HCC ranks as the sixth most prevalent cancer and second leading cause of cancer mortality globally, with China accounting for approximately half of new cases. Various pharmaceutical approaches have been investigated for HCC treatment, including targeted tyrosine kinase inhibitors, immunotherapies, and combination chemotherapy regimens [44]. However, existing treatments face limitations, including chemoresistance due to liver cancer cell heterogeneity [44-46] and significant systemic adverse effects [47, 48].

The pathogenesis of liver injury involves complex cell-cell and organ-organ interactions, including cellular senescence [49], organelle damage [50], mitochondrial hydrogen peroxide generation [51], ionic imbalance [52], lipid peroxidation [53], and various physiological and biochemical activation processes [54-57]. Mounting evidence indicates that alterations in immunologic homeostasis and oxidative stress significantly contribute to liver injury-induced distant organ dysfunction [58-63]. Extensive organ crosstalk may occur, leading to dysfunction in multiple organs, including the eye, brain, intestine, liver, and kidney (Fig. 1). Consequently, implementing appropriate drug regimens for patients with liver injury to maximize efficacy and minimize adverse effects has become increasingly important.

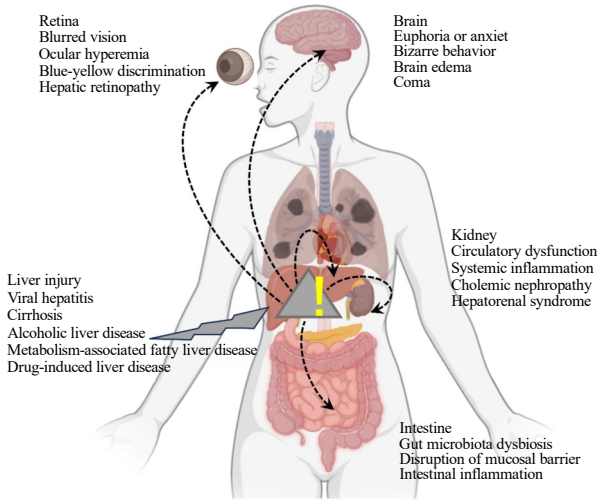


Fig. 1 The effect of liver injury on distant organs.

These diverse forms of liver injury, pathological conditions, and inter-organ interactions require careful consideration in therapeutic approaches. Drug transport across plasma membranes, which determines absorption, distribution, and excretion, primarily occurs through specialized transporters. Solute carrier (SLC) transporters typically facilitate uptake, while ATP-binding cassette (ABC) transporters mediate efflux, collectively regulating drug disposition. Eleven ABC transporters have been identified in multidrug resistance, including P-glycoprotein (P-GP), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP). The SLC family encompasses organic anion-transporting polypeptides (OATPs), organic anion transporters (OATs), organic cation transporters (OCTs), organic cation and carnitine transporters (OCTNs), peptide transporters (PEPTs), and multidrug and toxin extrusions (MATEs). Current research emphasizes drug metabolism effects in liver injury, while drug transporter impacts receive less attention. Fig. 2 depicts common ABC and SLC transporters in the retina, brain, intestine, liver, and kidney. Most therapeutic agents interact with these transporters as substrates or inhibitors. In complex scenarios, significant drug-drug interactions may affect absorption, uptake, and secretion, potentially compromising therapeutic efficacy. Understanding liver disease effects on drug disposition, particularly regarding drug-clearing enzymes and transporters, along with their dysfunction mechanisms and clinical significance, may guide optimal dosing for narrow therapeutic window drugs, thereby enhancing pharmacotherapy outcomes in liver injury patients.

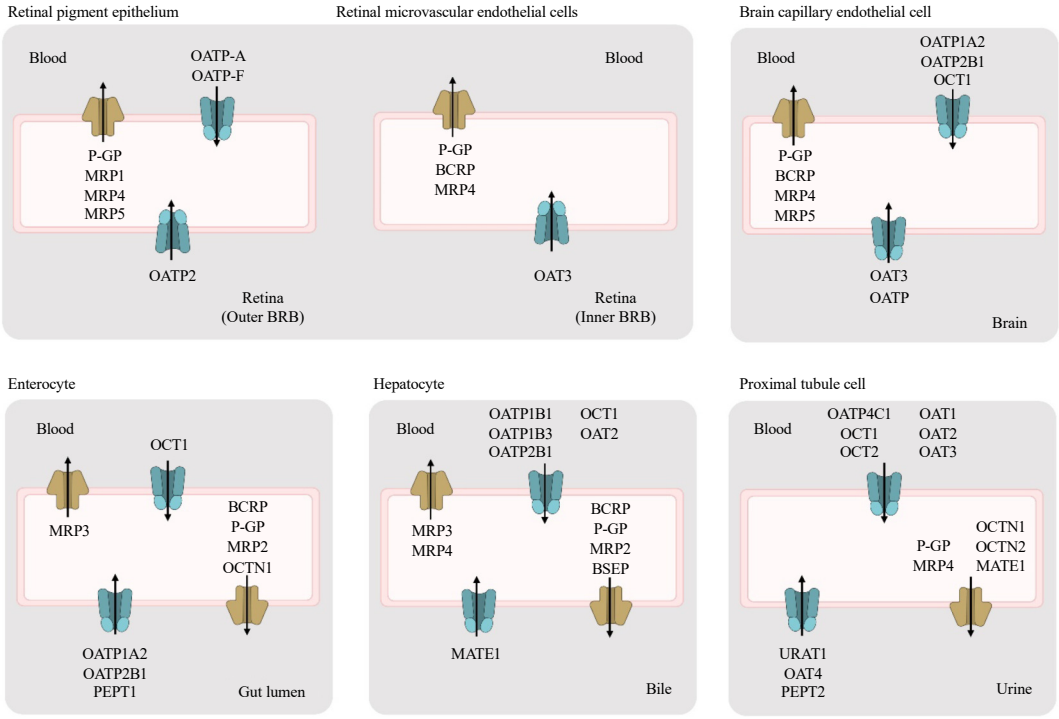
2. Liver-eye interactions

2.1. Clinical impact

The retina, a vital component of the central nervous system (CNS), exhibits structural and physiological characteristics similar to those of the brain [64]. Patients with hepatic insufficiency commonly present with ocular manifestations, including hyperemia, blurred vision, and impaired blue-yellow discrimination, typically associated with hepatic retinopathy [65-67]. Electroretinogram studies demonstrate a significant correlation between reduced amplitude values and increased latency values in oscillatory potential 2 with both hepatic retinopathy [67] and hepatic fibrosis [68]. Retinal dysfunction represents a key factor in hepatic retinopathy, potentially attributable to compromised blood-retinal barrier (BRB) function. The BRB consists of retinal microvascular endothelial cells (RMECs, inner BRB) and retinal pigment epithelium (RPE, outer BRB) [69, 70]. This barrier, incorporating tight junction proteins and uptake/efflux transporters, controls material exchange between the retina and blood, thus preventing toxic compounds or biological macromolecules from entering the neural retina and maintaining retinal homeostasis. In liver injury cases, elevated plasma levels of toxic components such as ammonia and bilirubin may compromise the internal retinal environment, leading to retinal pathologies. Studies indicate that bilirubin accumulation in the retina compromises its function, leading to bilirubin retinopathy [71]. For successful drug delivery to the retina, approaches should emphasize reducing efflux from the retina to blood while enhancing inflow from blood to the retina. The role of ABC transporters in restricting drug distribution within the retina warrants careful consideration.

2.2. Clinical evidence

Unlike the blood-brain barrier (BBB), research examining changes in efflux transporters on the BRB during disease states remains limited. Investigation of influx and efflux transporters at the BRB provides valuable insights for optimal drug design and ocular penetration prediction. P-GP, primarily expressed in the luminal membrane of RMECs, restricts the intraocular distribution of substrate drugs, including cyclosporine A and quinidine [72-74]. For organic anion drugs, consideration must be given to the combined effect of organic anion uptake by basolateral SLC transporters and excretion by luminal ABC transporters. As dual substrates of OCT3 and MRP4 at the inner BRB, β-lactam antibiotics and 6-mercaptopurine demonstrate rapid elimination from the vitreous, necessitating careful drug dosage consideration in liver disease and related complications [75, 76].



BRB, blood-retinal barrier; P-GP, P-glycoprotein, BCRP, breast cancer resistance protein; MRPs, multidrug resistance proteins; OATPs, organic anion-transporting polypeptides; OATs, organic anion transporters; OCTs, organic cation transporters; OCTNs, organic cation/carnitine transporters; PEPTs, peptide transporters; MATEs, multidrug and toxin extrusions.

Fig. 2 The location of drug transporters in the eye, brain, intestine, liver, and kidney.

2.3. Laboratory evidence

Cholestasis represents a common clinical manifestation of liver diseases. If left untreated, cholestasis can advance to liver fibrosis, cirrhosis, and ultimately liver failure requiring transplantation [77]. Our laboratory has extensively employed bile duct ligation (BDL) as a cholestasis model. MRP1, which is highly expressed in rat RPE, effectively prevents toxins, including unconjugated bilirubin (UCB) from penetrating the neural retina. Research findings indicate that the BRB remains intact in BDL rats, and the elevated distribution of MRP1 substrates in the retina may stem from compromised MRP1 function, coupled with decreased MRP1 protein levels. MRP1 function assessment using retina-to-plasma ratios (Kr/p) of two characteristic substrates, fluorescein and 2,4-dinitrophenyl-*S*-glutathione, revealed significantly increased Kr/p of both substrates, alongside elevated retinal UCB (an endogenous MRP1 substrate) levels. Notable alterations in mitogen-activated protein kinase (MAPK) signaling were detected in the retina of BDL rats, including markedly increased phosphorylation of extracellular regulated kinase 1/2 (ERK1/2), p38 MAPK, and MAPK-activated protein kinase 2, as well as decreased phosphorylation of c-Jun *N*-terminal kinase. *In vitro* studies established UCB's role in compromising MRP1 expression and function, with elevated UCB impairing MRP1 *via* p38 MAPK pathway activation. HB rats, modeling UCB accumulation in liver injury, also showed reduced MRP1 function and expression and retinal ganglion cell loss [78]. Recent studies confirmed that BDL and hyperbilirubinemia impaired light sensitivity in rats. Moreover, BCRP, situated on the luminal membrane of mouse RMECs, can efflux light-sensitive phototoxins, including pheophorbide a and protoporphyrin IX [79]. The retina, being highly photosensitive, is vulnerable to light-induced damage caused by various phototoxic compounds [80]. Similarly, protoporphyrin IX reduced the cell count of porcine RPE [81]. BCRP1$^{-/-}$ mice demonstrated a novel form of protoporphyria and increased erythrocyte protoporphyrin IX levels, indicating that humans or animals with low or absent BCRP activity might face a heightened risk of protoporphyria and diet-dependent phototoxicity [82]. Research revealed that BDL-induced BCRP downregulation in rat BRB involved multiple pathways. Ammonia decreased BCRP protein expression in RMECs, while UCB reduced it in RPE. Additionally, BCRP expression is notably higher in the inner BRB compared to the outer BRB. These findings were validated in hyperbilirubinemia and hyperammonemia rats (unpublished data). This indicates that BCRP protein expression and function in the retina are essential for maintaining stable endogenous substances and drug efficacy in liver injury.

3. Liver-brain interactions

3.1. Clinical impact

Liver injury frequently leads to various complications, with hepatic encephalopathy (HE) representing one of the most significant. HE is defined as a syndrome of CNS dysfunction arising from metabolic disorders [83]. Although the precise pathogenesis of HE remains unclear, evidence suggests that BBB dysfunction, resulting in neurotoxin accumulation in the brain, serves as a primary mechanism [84,85]. The BBB consists of brain microvascular endothelial cells, connected by adherens and tight junctions that form a junctional complex [86]. Beyond preventing unrestricted substance passage between blood and the brain, these cells abundantly express transporters, particularly ABC and SLC transporters, which regulate solute movement to maintain brain homeostasis [87,88]. ABC transporters function primarily as efflux transporters, facilitating the movement of drugs and metabolites against concentration gradients through ATP hydrolysis, while SLC transporters operate as influx transporters, facilitating substrate uptake into cells, typically utilizing ion concentration gradients across the cell membrane as a driving force [89-91]. Disease progression in liver injury, target site modifications, and al-

terations in other protein expressions affect brain drug transporter function. Research demonstrates that ABC and SLC transporters possess broad substrate spectra, including CNS therapeutic drugs. Thus, changes in their function and expression substantially influence drug disposition, bioavailability, efficacy, and pharmacokinetic behavior, potentially resulting in excessive brain exposure to their substrates when both are affected. While clinical reports on drug transport and metabolism in the brains of liver damage patients remain limited, existing research demonstrates that carnitine and acetylcarnitine supplementation can prevent ammonia toxicity and enhance ammonia elimination in hyperammonemia syndrome patients [92]. This treatment approach extends to patients with liver cirrhosis and HE caused by hepatitis C and/or hepatitis B, alcohol abuse, and other factors [93, 94]. The increased carnitine concentration in the cerebrospinal fluid (CSF) of these patients may stem from competitive inhibition of transporters by drugs or bile acids or from compensatory increases related to impaired tricarboxylic acid cycle function [95]. Additionally, recent research by Weiss and colleagues analyzing the CSF of patients with liver cirrhosis and HE revealed brain accumulation of drugs, such as quinolones or fluconazole, which are ABC transporter substrates. Despite insufficient post-metabolized drug concentrations to enter the CSF, the findings indicate that transporter alterations may enhance BBB transport or reduce brain drug clearance [96]. Clinical cases examining liver damage effects on brain drug delivery remain relatively scarce, necessitating additional research to expand current understanding.

3.2. Laboratory evidence

Research demonstrates that modifications in brain drug transporters affect drug exposure in the brain, potentially leading to adverse effects [97]. Our laboratory has demonstrated that liver damage from various factors in liver injury models significantly alters the expression and function of drug transporters across different brain regions. These regulatory mechanisms demonstrate transporter-specific characteristics. For example, in thioacetamide (TAA)-induced acute hepatic failure (AHF) rats, the effects on expressions and functions of P-GP, BCRP, and MRP2 at the BBB show distinct patterns. AHF enhanced the brain distribution of a P-GP-specific substrate, rhodamine 123, and BCRP substrates, prazosin and methotrexate, indicating diminished P-GP and BCRP functions and expressions [98, 99]. In contrast, the brain distribution of bromosulfophthalein, an MRP2-specific substrate, decreased significantly, indicating upregulated MRP2 function. This pattern was also observed in TAA-induced AHF mice [99, 100]. Our research has shown that hyperammonemia in TAA-induced AHF rats may trigger oxidative stress, resulting in ERK1/2-mediated downregulation of BCRP at the BBB. Studies in primary rat brain microvessel endothelial cells confirmed that reduced expression and function of BCRP at BBB partially resulted from hyperammonemia. Ammonia decreased BCRP expression and function partially through activating reactive oxygen species-mediated ERK1/2 phosphorylation. P-GP alterations, however, may be linked to elevated deoxycholic acid levels. Previous findings indicated that increased oxidative stress and inflammatory factors in BDL rats activated the NF-κB pathway, subsequently enhancing P-GP function and expression at the BBB. Additionally, BCRP function and expression in the rat cortex and hippocampus decreased primarily due to elevated UCB levels [101]. Consequently, zidovudine, a typical BCRP substrate, showed altered brain permeability and levels when BCRP function and expression decreased in BDL rats' brains [102]. Research revealed that BDL significantly reduced membrane BCRP expression and increased membrane P-GP expression in the rat cortex and hippocampus, attributed to increased membrane Ezrin and decreased membrane Radixin protein expression caused by hyperammonemia and hyperbilirubinemia [103]. Similarly, phenobarbital exhibited increased brain concentration and brain-to-plasma ratio in TAA-induced AHF due to significantly reduced BBB P-GP function and expression [100]. Furthermore, research indicates that hepatic ischemia-reperfusion causes substantial arginase release from the injured liver, subsequently depleting systemic arginine. This arginine deficiency impairs BBB by inhibiting brain microvascular endothelial cell proliferation through cell cycle arrest [104].

Studies have shown that partial hepatectomy increases cyclosporine A permeability at the BBB in mice through P-GP inhibition, intensifying cyclosporine A-induced neurotoxicity. This indicates heightened neurotoxicity risk in early liver transplantation [105]. Liver damage is commonly associated with complications including hyperbilirubinemia and hyperammonemia [106, 107]. For instance, hyperbilirubinemic rats showed increased P-GP activity but decreased MRP1 expression [108]. Furthermore, in rats with hyperammonemia, both the function and expression of P-GP and MRP2 at the BBB are enhanced [106]. These observations suggest a significant relationship between liver damage-induced alterations in endogenous substances and encephalopathy development. Charlotte's team observed that rats developed HE six weeks after BDL, accompanied by decreased MRP5 messenger ribonucleic acid (mRNA) expression in brain microvessels [109]. Moreover, 24 hours after hepatic ischemia-reperfusion injury (HIRI), rats exhibited a 24% overexpression of P-GP at the BBB and a 30% reduction in the apparent brain uptake clearance rate of rhodamine 123 [110]. Clinical treatments require careful monitoring of altered transporter effects on substrates and drugs in the brain to prevent central adverse events.

4. Liver-intestine interactions

4.1. Clinical impact/evidence

While extensive research has focused on drug transporters in the liver and kidney, the role of uptake and efflux transporters in the intestine remains less thoroughly investigated. Intestinal transporters significantly influence the extent of oral drug absorption into the systemic circulation, suggesting that alterations in their function may affect oral drug pharmacokinetics. Understanding the changes in ABC transporters and SLC carriers in the gastrointestinal tract during liver failure is essential, particularly regarding the role of uptake and efflux transporters located in the apical and basolateral membranes of enterocytes in relation to substrates and exogenous xenobiotics [111]. Clinical trials examining liver disease have demonstrated significant effects of hepatic dysfunction on the pharmacokinetics of zidovudine, a rapidly absorbed anti-HIV medication [112]. Patients with hepatic injury showed an increased area under the curve (AUC) and earlier maximum plasma concentration (C_{max}) of zidovudine in single-dose pharmacokinetic studies [113]. A study of 14 HIV-negative subjects revealed that those with cirrhosis exhibited decreased oral clearance and increased C_{max} and half-life ($t_{1/2}$) [114]. HIV-infected individuals with mild liver disease demonstrated a relatively smaller reduction in zidovudine oral clearance compared to healthy subjects [115]. Research indicates that zidovudine serves as a substrate for ABC drug transporters, including P-GP and BCRP [116-118], which are predominantly located on the apical membranes of intestinal epithelial cells. Clinical data on BCRP levels in the duodenum of patients with liver injury due to obstructive cholestasis [119] showed downregulation in mRNA and protein expression. However, Dietrich *et al.* [120] observed unchanged duodenum BCRP protein levels. This discrepancy may be explained by the correlation between reduction and cholestasis duration, which proved reversible after bile flow restoration through com-

mon bile duct stenting.

4.2. Laboratory evidence

Intestinal P-GP functions as a primary absorption barrier by limiting influx and as a secretory detoxification mechanism by facilitating the efflux of P-GP substrates from blood to the intestinal lumen. Research investigating intestinal P-GP modification in TAA-induced AHF revealed enhanced intestinal absorption of zidovudine and downregulated intestinal P-GP expression, with minimal effect on intestinal BCRP. This confirmed impaired intestinal P-GP function, resulting in increased oral plasma exposure to zidovudine in rats [121]. These findings aligned with observations in carbon tetrachloride (CCl_4)-induced AHF rats, where *in vivo* intestinal P-GP function showed a significant reduction, as measured by absorption and exsorption of P-GP substrates [122]. An *in vitro* study demonstrated that plasma from AHF rats significantly inhibited P-GP function in Caco-2 cells, while normal rat plasma showed no such effects [123]. Additionally, approximately twofold higher plasma levels of corticosterone, an endogenous P-GP substrate/inhibitor, were observed in glycerol-induced ARF and CCl_4-induced AHF rats [124]. These findings demonstrate the substantial impact of intestinal P-GP on substrate drug bioavailability and targeted delivery in liver disease. The cholestatic model induced by BDL showed no effect on P-GP levels in rat ileum but significantly increased BCRP protein expression. Studies of CCl_4-induced AHF with hyperbilirubinemia in rats showed decreased jejunal MRP2 protein levels. Similar findings regarding intestinal MRP2 levels were reported in BDL rats [120, 125], showing 2.5-fold higher oral bioavailability of the MRP2 substrate [2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP)] compared to sham-operated rats.

The small intestine expresses OCT1, OCT2, and OCT3, which regulate intestinal absorption and participate in various disease processes [126, 127]. Research has shown that OCT3 deletion intensifies liver fibrosis induced by TAA and BDL [128]. Current evidence indicates that OCT2 protein is primarily expressed on enterocytes' apical membrane, while OCT3 protein appears predominantly on the basolateral membrane. Studies demonstrate that BDL significantly reduces intestinal metformin absorption, an OCT substrate. Furthermore, BDL decreases intestinal OCT2 protein expression without affecting OCT3, partially explaining reduced plasma exposure to oral metformin in BDL rats. Evidence suggests that decreased intestinal bile salts, particularly chenodeoxycholic acid, primarily account for intestinal OCT2 downregulation in BDL rats [129].

5. Liver-liver interactions

5.1. Clinical impact

Liver injury is commonly associated with substantial changes in hepatic transporters and drug pharmacokinetics in patients. These transporter modifications demonstrate specificity potentially linked to pathogenic factors, patient ethnicity, and specific measured parameters. For instance, in patients with MASH, the hepatic CL_{uptake} of ^{99m}Tc-mebrofenin, a substrate of OATP1B1/1B3 and MRP2, showed a significant decrease. This reduction correlated with a marked decrease in biliary clearance (from 0.035 ± 0.008 to 0.017 ± 0.002 L·min^{-1}) and a reduced central volume of distribution (from 11.1 ± 0.57 to 6.32 ± 1.02 L). Consequently, systemic $AUC_{0\text{-}300,\ blood}$ increased from 1780 ± 242 to 2440 ± 775 μCi·min·L^{-1}, while hepatic $AUC_{0\text{-}180,\ liver}$ increased from 277 ± 36.9 to 433 ± 40.3 kcounts min/sec. These results indicate that OATPs and MRP2 in the livers of MASH patients adapt to the pathological environment, leading to increased exposure of ^{99m}Tc-mebrofenin in both systemic circulation and liver (from 11.1 ± 0.57 to 6.32 ± 1.02 L), the systemic [130]. Repaglinide, a novel insulin secretagogue metabolized primarily in the liver and a substrate for OATP1B1, has demonstrated modified pharmacokinetics in clinical trials. Single-dose studies of 4 mg repaglinide revealed that patients with chronic liver injury display increased AUC and C_{max} values compared to controls. While T_{max} remained constant between groups, the $t_{1/2}$ was notably prolonged in patients with chronic liver disease compared to healthy subjects [131]. Research by Schrieber's team demonstrated that the pharmacokinetics of silymarin flavonolignans, substrates for BCRP and MRP2 [132, 133] are modified in patients with HCV and MAFLD, with the highest exposure of major flavonolignans observed in cirrhotic patients. In non-cirrhotic patients with chronic hepatitis C receiving oral doses of silymarin ranging from 0.42 to 2.1 grams per day for seven days, silymarin A and silymarin B exhibited nonlinear pharmacokinetics and demonstrated good tolerability [134]. Sofosbuvir, a substrate of P-GP and BCRP, has also shown altered pharmacokinetics in patients with liver impairment. According to Lawitz *et al*., compared to non-cirrhotic controls, the AUC values of sofosbuvir increased by 80% and 130% in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, accompanied by an increase in C_{max} [135]. Therefore, in liver injury patients, the dosage of transporter substrates like sofosbuvir requires reduction to prevent altered pharmacological effects due to increased AUC or C_{max}. Pitavastatin, utilized for stroke prevention and treatment, is a substrate of organic anion transporting polypeptide 1B1/3, BCRP, and MRP2. Clinical trial results showed that, compared to healthy controls, the $AUC_{0\text{-}inf}$ and C_{max} of pitavastatin in patients with liver cirrhosis (Child-Pugh B score) increased by 3.6-fold and 2.5-fold, respectively, while those for pitavastatin lactone decreased by 0.7-fold and 0.5-fold, respectively [136]. Suzanne *et al.* analyzed prospective randomized controlled trials examining statin therapy efficacy in cirrhosis and identified several challenges in trial design, including appropriate patient selection criteria and determination of statin formulation, dosage, and treatment duration. Although statins demonstrate an acceptable safety profile in cirrhosis, they recommended caution in use for those with Child-Pugh C cirrhosis due to adverse effects and lack of robust data and emphasized caution in use for advanced cirrhosis (Child-Pugh ≥ 9) as well as avoidance of high-dose simvastatin (40 mg daily) until additional prospective evidence becomes available [137].

5.2. Clinical evidence

Liver dysfunction significantly influences the expression and function of hepatic transporters and transporters in distant organs [138, 139]. For instance, HCC is characterized by decreased expression of OATP1B1 and OATP1B3 [140]. Patients with severe cirrhosis exhibit impaired hepatic OATP1B3 function [141]. In patients with alcohol-related liver disease and hepatitis C, hepatic OCT1 expression decreases significantly, while MATE1 and MRP3 expressions increase markedly. Additionally, OATP1B1 and OATP1B3 expressions are substantially reduced. P-GP expression is elevated in alcoholic liver cirrhosis, while BCRP and OATP2B1 expressions increase specifically in hepatitis C-related cirrhosis [142]. However, some studies present conflicting results. Research has shown that in hepatitis C cirrhotic livers, mRNA expressions of OCT1, OATP1B1/1B3/2B1, MRP2/3, MATE1, and BCRP were significantly reduced compared to controls [143]. In contrast, liver biopsies from MASH patients demonstrated significantly elevated expression of efflux transporters (MRP2/3/4) and markedly reduced expression of uptake transporters (OATPs) [144]. Further studies have highlighted the significance of OATP1B1, OATP1B3, P-GP, MRP2, and MRP4 in bilirubin and bile salt trans-

port [145, 146]. Changes in these transporter levels during liver failure correlate with alterations in the concentrations of these endogenous substances [147].

The enhanced expression of multiple efflux transporter proteins and reduced expression of uptake transporters in compromised livers may constitute an adaptive mechanism to reduce the accumulation of exogenous substances and toxic intermediates, serving as a protective response under pathological conditions. Research indicates that during MASH, alterations in drug transporters can affect subsequent drug disposition and response. For example, pediatric MASH patients exhibit upregulated hepatic MRP3 and altered MRP2 localization in tubules. After administration of a 1000 mg dose of acetaminophen (APAP), serum and urine levels of APAP-glucuronide metabolite increased, while serum APAP-sulfate levels decreased. These changes are directly linked to the alterations in hepatic MRP2/3 [148].

5.3. Laboratory evidence

Laboratory studies have consistently demonstrated that liver disease can substantially alter the pharmacokinetics of commonly prescribed drugs. In MASH rats, increased hepatic MRP3 expression led to enhanced systemic exposure to the morphine metabolite morphine-3-glucuronide, suggesting potential increased exposure to morphine-6-glucuronide in MASH patients. However, the altered localization and subsequent functional decline of hepatic MRP2 in MASH rats affected morphine-3-glucuronide metabolism, resulting in decreased biliary excretion [149]. Studies of pravastatin, a substrate for hepatic OATP, OATP1B1, OATP1B3, and OATP2B1, in MASH mice induced by a methionine- and choline-deficient (MCD) diet revealed that the compensatory decrease in OATs, combined with OATP1b2 gene loss in Slco1b2 knockout mice, produced a synergistic increase in plasma AUC and tissue concentration in kidney and muscle [150]. Research has established that alterations in drug transporters correlate with changes in other transporters. Studies using BDL rats demonstrated that obstructive cholestasis caused hepatic MRP2 downregulation, particularly in liver lobules' periportal regions. In rats with 72-h cholestasis, MRP3 expression increased in periportal hepatocytes, substantially overlapping with MRP2 substrate specificity. This compensatory MRP3 upregulation was most prominent in MRP2-deficient mutant rats, indicating that MRP3 upregulation in cholestatic livers may represent an adaptive response to impaired MRP2 function [151, 152]. Additional research revealed that BCRP and MRP2 inhibition by baicalein significantly enhanced silybin absorption and bio-efficacy, a natural component treating hepatic disorders, suggesting a novel combination therapeutic approach for chronic liver diseases [153]. Epimedii Folium (EF), a traditional Chinese medicine, reduced expressions of sodium taurocholate co-transporting polypeptide, MRP4) and lumen transporter (MDR1), MRP2, and MRP3, inducing cholestasis in mice by interfering with bile acid transport [154]. Therefore, additional research should examine whether liver injury causes hepatic transporter changes, or whether altered liver transporter function and expression contribute to liver damage.

6. Liver-kidney interactions

6.1. Clinical impact

Liver diseases associated with renal complications can be categorized into two main types based on their etiology: hepatitis virus-associated nephropathy [155, 156] and hepatorenal syndrome (HRS) [157]. Substantial evidence demonstrates that renal transporters and metabolic enzymes are essential in regulating systemic and local concentrations of drugs and their metabolites [158]. During hepatic dysfunction, physiological changes in the kidneys can alter drug disposition, primarily through modifications in the expression and function of renal transporters induced by liver injury [159], ultimately affecting drug distribution, activity, and toxicity in the body. The modifications and interactions of renal transporters during liver injury significantly influence the clinical efficacy and adverse reactions of drugs and their metabolites. Consequently, the expression patterns of these transporters can function as indicators for disease prognosis and the physiological status of endogenous substrates. In managing liver injury clinically, practitioners should consider alterations in drug metabolism due to the modified expression and function of renal transporters and thoroughly assess medication risks.

6.2. Clinical evidence

Transport interactions commonly occur in the kidney due to substrate overlap between different transporters. OAT1/OAT3, located on the basolateral membrane of proximal tubular cells, function synergistically to mediate the active transport of drugs and their metabolites from blood into proximal tubular cells for subsequent urinary excretion [158, 160]. Different types and severities of liver injury distinctly affect the regulation of OAT expression. Research demonstrates that patients with MASH, ALD, HCV infection, and combined ALD/HCV show significantly decreased expression of renal OAT3 compared to control groups. However, reduced OAT4 expression has been verified only in MASH patients. Therefore, when determining appropriate drug dosages for patients with liver diseases, consideration must be given to both pharmacokinetic changes and the specific liver condition etiology [161]. Clinical observations indicate that ALD may modify the function and expression of renal OATs. In chronic ALD patients, furosemide transport to the renal tubules is hindered, leading to elevated plasma drug levels and increased furosemide resistance. Since furosemide efficacy correlates with its urinary concentration, it suggests that altered expression and function of renal OAT1/3 in liver dysfunction patients result in decreased furosemide transport to its action site and reduced therapeutic effectiveness [162]. The impaired liver function also affects the expression of renal transporters such as BCRP and MRPs [163]. Clinical studies reveal that in subjects with moderate hepatic impairment, a single oral dose of 1000 milligrams of imeglimin, a substrate of OCT1/2 in the liver and kidneys, resulted in increases of 1.3-fold and 1.5-fold for C_{max} and AUC, respectively, compared to those in subjects with normal liver function [164, 165]. Similarly, downregulation of these transporters has been observed in liver disease, resulting in decreased hepatic uptake, reduced biliary elimination, and increased drug bioavailability for OATP substrates sartans [166]. A physiologically based pharmacokinetic (PBPK) model for oral rosuvastatin under MAFLD status demonstrated significant reduction in hepatic uptake transporter expression. Despite this reduction, rosuvastatin's pharmacokinetic properties remained largely unchanged, potentially due to complex interactions with renal OAT3 and BCRP across different organs [167]. Clinical studies show that in subjects with moderate hepatic impairment, a single oral dose of 1000 milligrams of imeglimin, a substrate of OCT1/2 in the liver and kidneys, resulted in increases of 1.3-fold and 1.5-fold for C_{max} and AUC, respectively, compared to those in subjects with normal liver function. However, clinical pharmacokinetic data for imeglimin in patients with severe hepatic impairment remain insufficient and require additional investigation [168]. Currently, direct clinical data regarding renal transporter expression and function in liver dysfunction patients are limited, necessitating further comprehensive research in this field.

6.3. Laboratory evidence

Consistent with clinical studies, extensive animal experiments have yielded comparable findings. These investigations demonstrate that during impaired hepatobiliary function, renal transporters adapt to the pathological conditions and modify *in vivo* disposition. For instance, BDL rats exhibited decreased hepatic MRP2 protein levels, leading to diminished biliary excretion efficiency of bile salts. However, renal MRP2 levels showed compensatory upregulation to offset hepatic MRP2 deficiency, potentially explaining enhanced urinary excretion of bile salts [169, 170]. Additionally, rats with CCl_4-induced parenchymal liver injury demonstrated increased renal MRP2 mRNA levels [171]. In a related study, MRP2-deficient rats showed significant upregulation of renal MRP3 and MRP4 expression and protein abundance [172]. In MASH rats, adefovir, an HBV treatment primarily secreted by MRP4 in the tubular system, showed extended elimination half-life, decreased volume of distribution, and reduced hepatic levels due to upregulated renal MRP4 expression [173]. Furthermore, a HIRI rat model study revealed that protein levels of OCT2 and MATE1 in renal tubules' basolateral and apical membranes decreased by 67% and 61%, respectively. These rats exhibited reduced systemic and renal tubular secretion clearance rates of cimetidine by 78% and 55%, respectively, primarily attributed to decreased renal OCT2 levels [174].

Laboratory findings demonstrated that BDL increases renal and hepatic OCT2 protein expression, resulting in significantly lower plasma metformin exposure following both oral and intravenous administration, thus reducing its anti-diabetic effect. Studies using Caco2, HepG2, HK2 cells, and primary rat hepatocytes revealed that chenodeoxycholic acid, bilirubin, and farnesoid X receptor (FXR) agonist GW4064 enhance OCT2 while reducing OCT1 protein expressions. FXR inhibitor glycine β muricholic acid and FXR silencing notably attenuated these effects [129]. These findings indicate that thiamine deficiency in liver injury partially results from both intestinal OCT2 downregulation and renal OCT2 upregulation, which regulates carnitine homeostasis through carnitine and derivative transport. The induction of renal OCT2 and intestinal OCT2 downregulation in liver injury may explain clinical observations where patients with abnormal liver tests show reduced plasma carnitine levels and increased urinary excretion of free and acylcarnitine [175-177]. In TAA-induced AHF rat experiments, liver injury showed no significant effect on intestinal absorption of OCT substrate metformin, aligning with unchanged intestinal OCT2 expression. Despite consistent intestinal absorption, metformin AUC increased significantly, and clearance decreased markedly in liver-injured rats. These results suggest that TAA-induced AHF may elevate metformin plasma levels through impaired renal excretion. Further studies revealed that abnormally elevated serum Tumor necrosis factor alpha (TNFα) and estrogen levels in AHF rats reduced renal MATE1 expression, likely causing decreased renal metformin excretion in liver injury [178].

7. Conteraction of drug transporters in distant organs against liver injury

Emerging research indicates that acute kidney injury has substantial effects on hepatic inflammatory responses, drug metabolism, and nutrient processing [179]. Disruptions in transporter expression can compromise intestinal barrier function, intensifying systemic inflammation and subsequently exacerbating liver damage through the gut-liver axis [180]. A randomized controlled study revealed that acute kidney injury in patients with acute liver injury increases mortality from 28% to 58% [181]. These observations suggest that during liver injury, transporters in distant organs actively participate in regulating or aggravating liver damage through multiple mechanisms rather than merely responding to hepatic pathology. This intricate relationship is demonstrated by how kidney and intestinal injuries affect hepatic metabolic load and toxin exposure. For instance, kidney injury triggers the release of inflammatory cytokines, including interleukin-6, from activated immune cells, leading to the downregulation of drug-metabolizing enzymes and transporters in hepatocytes, thereby altering drug and toxin metabolism [182]. Moreover, research using a mouse model of gut microbiota dysbiosis demonstrated a marked reduction in hepatic OAPT1A1, BCRP1, and OCT1 levels, indicating that gut microbiota alterations significantly influence transporter protein expression in the liver and kidneys [183]. These modifications may facilitate the transport of gut-derived endotoxins into the portal vein, consequently intensifying hepatic inflammation and fibrosis. Additionally, altered transporter function or expression in distant organs can modify the systemic distribution of drugs and metabolites, potentially affecting liver injury progression. However, these changes may also provide protective effects by reducing the liver's metabolic burden. For example, in mice lacking nucleotide oligomerization domain 2, the upregulation of MRP2 and MRP4 in renal tubular epithelial cells following three weeks of BDL enhances urinary excretion of bile acids, including sulfated bile acids, thus protecting against cholestatic liver injury and fibrosis. This response helps decrease bile acid concentrations in hepatocytes [184]. Similarly, Laouari *et al.* demonstrated that in rats with chronic kidney injury following 5/6 nephrectomy, hepatic glutathione-S-transferase activity and glutathione levels decreased, while renal MRP2 expression increased by 70%–200% three weeks post-surgery, with comparable hepatic MRP2 upregulation observed at six weeks. This suggests that MRP2 overexpression in both kidneys and liver may represent an adaptive response facilitating the elimination of accumulated drugs and uremic toxins [185]. In conclusion, transporters in distant organs significantly influence liver pathology, providing new therapeutic perspectives. However, additional research is needed to fully understand their role in liver injury.

8. Hepatoxicity and therapeutic effects of natural medicines

China leads globally in the prevalence of liver diseases. Many Chinese patients with liver injuries, particularly those unresponsive to Western medical treatments, frequently seek traditional Chinese medicine as a complementary or alternative therapy. However, appropriate medication dosage and potential side effects require careful consideration regardless of the treatment approach. Natural products have demonstrated significant therapeutic effects in various diseases, yet their hepatotoxicity is closely linked to alterations in transporter function. Extended use of EF may directly influence transporter expression, potentially resulting in cholestatic liver injury [186]. In ICR mice, oral administration of aqueous EF extract for 14 weeks reduced MDR1, MRP2, MRP3 protein levels and MDR1 mRNA levels, indicating compromised bile acid metabolism and liver dysfunction [154, 187]. Similarly, isopsoralen's hepatotoxicity has been extensively documented to correlate with expressions of drug transporters, including MDR1, MRP1, and MRP2 [188-191]. Herbal medicines can interact with pharmaceutical drugs, potentially causing liver injury. Docetaxel, known for causing hepatotoxicity [32, 192, 193], interacts with compounds such as curcumin [194] and myricetin [195, 196]. Magnesium isoglycyrrhizinate has shown hepatoprotective effects [28, 197-199]. QU *et al.* discovered that combining magnesium isoglycyrrhizinate with docetaxel substantially reduced hepatotoxicity and downregulated P-GP protein levels compared to docetaxel alone, indicating potential interaction with P-GP substrate drugs [32]. Glycyrrhizin, an MRP2 inhibitor [200, 201], prevents MASH in mice and rapidly attenuates acetaminophen-induced liver injury by inhibiting TNFα-induced hepatocyte apoptosis [202, 203]. Another study revealed that co-administration of *N*-acetylcysteine and glycyrrhizin decreased the biliary excretion of acet-

aminophen and its glucuronide, causing acetaminophen accumulation in the liver and systemic circulation, whereas co-administration of *N*-acetylcysteine and spironolactone produced the opposite effect [201]. Triptolide, a P-GP substrate [204], has restricted clinical application due to its significant hepatotoxicity [37, 205], as demonstrated in sandwich-cultured rat hepatocytes [206, 207]. The P-GP-mediated detoxification of triptolide indicates potential interaction risks with P-GP inhibitors or substrates [204].

Moreover, herbal medicine-drug interactions may enhance therapeutic outcomes. Silymarin demonstrates efficacy in liver diseases [208-211]. Baicalein, a BCRP and MRP2 inhibitor, significantly elevated the AUC and C_{max} of silymarin, augmenting its hepatoprotective effect in rats with CCl_4-induced liver injury [153]. Similarly, naringenin, an inhibitor of BCRP, MRP2, and P-GP, increased the AUC and C_{max} of silymarin in the same model [132]. These findings indicate that efflux transporters adversely affect the low bioavailability of silymarin. Atorvastatin, a P-GP substrate, demonstrated increased AUC, C_{max}, and T_{max} when co-administered with the P-GP inhibitor berberine, accompanied by improved liver pathology and enhanced hypolipidemic effect [212-215]. In another investigation, gentian polysaccharides treatment for five days ameliorated symptoms and reversed downregulated MRP4 and MDR1 mRNA levels in α-naphthylisothiocyanate-induced cholestatic liver injury mice [216]. In BDL rats, oleanolic acid administration induced MRP3, MRP4, MDR1, and MDR2 expression while reducing inflammation and cholestasis [217]. Similarly, swertianlarin treatment significantly increased basolateral transporters (MRP3 and MDR1 expressions, respectively [218]. In conclusion, the hepatotoxicity and therapeutic effects of natural medicines are intricately linked to transporter expressions and functions, necessitating more careful consideration of these interactions in clinical applications.

9. Conclusion

Multiple mechanisms frequently operate concurrently, resulting in diverse forms of organ damage and organ-organ interactions. A comprehensive analysis of the occurrence and development of various multiple-organ dysfunctions is essential. Supplementary Table 1 summarizes the remote organ damage in drug transporters and their effects on drug disposition induced by liver injury. Additionally, many drugs, including antivirals (lamivudine, zidovudine, and abacavir), antibiotics (levofloxacin), antiepileptics (lamotrigine), and immunomodulators (mycophenolate mofetil, sirolimus, tacrolimus, and cyclosporine A) are substrates of BCRP or P-GP [78-80], some of which are also MRP2 substrates. These drugs may be administered to liver failure patients or liver transplant patients [91]. Understanding and utilizing the complex interaction between the liver and remote organs facilitates the development of new drug treatments for patients with various liver diseases. Liver injury commonly causes systemic hemodynamic changes [219, 220], electrolyte disturbance [221, 222], oxidative stress [223-225], and immune imbalance [77, 226]. Researchers can further investigate the pathophysiology and mechanism of dysfunctional organs in liver injury, including the direct and indirect effects on ABC and SLC transporters by the accumulation of abnormal factors and newly discovered components under liver damage, such as UCB [227], reactive oxygen species [225], ammonia [228], bile acids [229], lactate [230], and inflammatory cytokines [231]. These mechanistic studies will support the development of treatment strategies for remote organ dysfunction. For instance, oral administration of Fxr antagonist stigmasterol attenuates the increased expressions of intestinal OCT2 protein and plasma exposure of metformin following oral dose by CDCA administration, suggesting that targeting Fxr might improve dysfunction of OCTs in liver disease [129]. Current research indicates that selectively targeting soluble TNFα and preferentially preventing TNFR1 activation and synaptic instability may serve as potential therapeutic targets to prevent many inflammatory diseases. As observed, infliximab, a monoclonal antibody designed to intercept and neutralize TNFα, significantly reversed downregulated OAT3 in the brain of rats with kidney injury, which attenuated the transport of brain uremic toxins and substrate drugs and subsequently improved CNS behaviors [232]. The altered plasma exposure of substrate drugs in animals can be explained using PBPK models based on changes in the function and expression of drug uptake transporters, drug efflux transporters, and CYP450 enzymes in disease states, thus enabling quantitative prediction of pharmacokinetics from animals to humans. A semi-PBPK characterizing alterations in protein expressions of intestinal, hepatic, and renal OCTs has been successfully developed to simulate the pharmacokinetics of metformin in BDL rats, which was also proven suitable for humans, demonstrating that plasma and hepatic concentrations of metformin in patients with liver failure are remarkably lower than those in healthy subjects [129]. Similar simulations from PBPK based on OATP, P-GP, and BCRP in diabetic rats have been developed to explain atorvastatin pharmacokinetics [215]. Additionally, sensitivity analysis from PBPK facilitates the investigation of how alterations in drug transporter activity contribute to variability in systemic drug exposure. Therefore, the establishment of PBPK models enables the elucidation of the pathophysiological significance of changed drug transporters and quantitative prediction of pharmacokinetics for the clinical rational use of drugs in liver injury.

Animal models, while instrumental for investigating fundamental mechanisms, cannot completely capture the clinical intricacies of human liver injury due to interspecies variations. The disparities between drug disposition in clinical studies and animal data underscore species-specific differences in transporter expression and function. For example, pharmacokinetic studies have demonstrated significantly reduced renal clearance in cirrhosis patients [233], whereas BDL rats show significantly induced renal OCT2 expression, resulting in enhanced clearance of its substrate, cimetidine [234]. Additionally, the restricted genetic diversity of inbred animal strains inadequately represents the polymorphic genetic background present in humans. Therefore, researchers must approach the extrapolation of pharmacokinetic behaviors from animals to humans with appropriate caution. Future investigations should focus on understanding not only the mechanisms of organ-to-organ interactions but also the complex interplay within broader organ networks.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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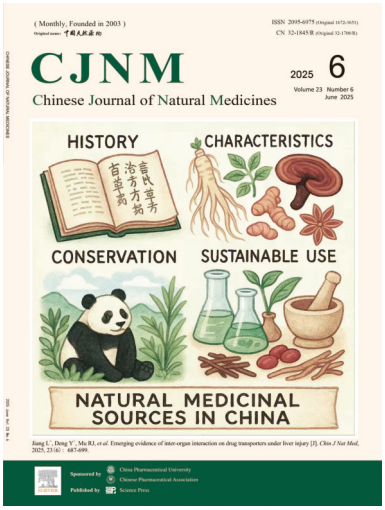

This cover design visually encapsulates the interplay between natural medicine and drug transporter biology in treating liver injury. It highlights key herbs like *Panax ginseng*, *Ganoderma lucidum*, and *Curcuma longa*, symbolizing their bioactive compounds' therapeutic potential and bidirectional interaction with dysfunctional drug transporters. Such transporter alterations disrupt pharmacokinetics (absorption, distribution, metabolism, excretion), impacting drug efficacy and safety. The design integrates ecological conservation (panda, foliage) and scientific tools (lab glassware, mortar/pestle), bridging traditional herbal knowledge with modern research. This synergy underscores the need to preserve natural medicinal resources while advancing transporter-focused therapies to optimize dosing and reduce adverse effects in liver disease. By merging natural imagery with scientific symbolism, the cover advocates for integrating traditional medicine and biomedical innovation to develop safer, efficacious liver treatments rooted in transporter biology and sustainable practices.