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Bile Acids and Farnesoid X Receptor in Renal Pathophysiology

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Bile acid · Farnesoid X receptor · Kidney · Chronic kidney disease · Farnesoid X receptor agonist

Abstract
Background: Bile acids (BAs) act not only as lipids and lipid-soluble vitamin detergents but also function as signaling molecules, participating in diverse physiological processes. The identification of BA receptors in organs beyond the enterohepatic system, such as the farnesoid X receptor (FXR), has initiated inquiries into their organ-specific functions. Among these organs, the kidney prominently expresses FXR. ***Summary:*** This review provides a comprehensive overview of various BA species identified in kidneys and delves into the roles of renal apical and basolateral BA transporters. Furthermore, we explore changes in BAs and their potential implications for various renal diseases, particularly chronic kidney disease. Lastly, we center our discussion on FXR, a key BA receptor in the kidney and a potential therapeutic target for renal diseases, providing current insights into the protective mechanisms associated with FXR agonist treatments. ***Key Messages:*** Despite the relatively low concentrations of BAs in the kidney, their presence is noteworthy, with rodents and humans exhibiting distinct renal BA compositions. Renal BA transporters efficiently facilitate either reabsorption into systemic circulation or excretion into the urine. However, adaptive changes in BA transporters are evident during cholestasis. Various renal diseases are accompanied by alterations in BA concentrations and FXR expression. Consequently, the activation of FXR in the kidney could be a promising target for mitigating kidney damage.

Introduction

Bile acids (BAs) are a group of amphipathic steroid acids that are synthesized from cholesterol in the liver and stored in the gallbladder. The classical function of BAs is to act as detergents that facilitate the digestion and absorption of fat and fat-soluble vitamins in the intestine [1]. However, many studies have shown that BAs can function as signaling molecules that modulate a variety of biological processes [2, 3]. Different BA species play distinct roles in pathophysiological processes. For example, glycine-conjugated primary BAs are predominantly associated with the progression of hepatic fibrosis [4]. On the other hand, secondary BAs, such as isoallolithocholic acid, contribute to protection from enteropathogenic infection [5, 6]. Additionally, other secondary BA species, such as hyodeoxycholic acid (HDCA) in the ileum, may promote the progression of colorectal advanced adenoma [7]. The varied functions of BAs pose a significant challenge for researchers. However, this complexity can also be viewed as an opportunity to identify specific targets that may have therapeutic implications.

The endocrine functions of BAs mainly rely on BA sensors expressed in many organs and tissues. Among these receptors, the Farnesoid X Receptor (FXR;

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NR1H4) stands out as a crucial player. As a nuclear receptor, FXR activation by its ligand triggers the transcription of target genes involved in BA, lipid, glucose, and energy metabolism [1]. While the hepatic and intestinal roles of FXR have been extensively reviewed [8, 9], it is noteworthy that FXR, particularly its isoforms FXRα3 and 4, are highly expressed in the kidney [10]. A recent clinical trial showed that the FXR agonist Vonafexor not only reduced liver fat and fibrosis in non-alcoholic steatohepatitis (NASH) patients but also improved renal function [11]. This highlights FXR as a promising target for treating kidney diseases.

This review focused on recent insights into the roles of BAs and FXR in the kidney, covering their functions in physiological conditions and various renal diseases. We also discuss updated mechanisms related to the protective effects of FXR agonists and outline future research venues in this area.

BA Species in the Kidney

More than 60 different BA species have been identified in mammals [2]. They are classified into four groups based on their conjugation status and site of synthesis [12]. Unconjugated primary BAs, like cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized in the liver, where they can be conjugated with glycine or taurine, resulting in compounds such as TCA, GCA, TCDCA, and GCDCA. In contrast to humans, the murine liver specifically produces the hydrophilic primary BA muricholic acid (MCA), constituting approximately 40% of the murine BA pool [13]. In mice, conjugation to taurine is more efficient than with glycine, leading to the production of more water-soluble BAs [12]. Conjugated secondary BAs arise from the gut microbiota of the intestine, and deconjugation transforms them into unconjugated forms like deoxycholic acid (DCA) and lithocholic acid (LCA). BAs exhibit varying hydrophilicity: ursodeoxycholic acid (UDCA) >CA > CDCA > DCA > LCA; and taurine-conjugated BAs > glycine-conjugated BAs > free BAs [14]. The different BA compositions in mice and humans result in varying hydrophilicity, influencing the murine BA ability to activate the BA receptor FXR [13].

BAs are prominently present in the liver and intestine, with efficient enterohepatic circulation resulting in a minimal loss (~5% in the feces). Despite this, a fraction of BAs escapes hepatic extraction and enters the general circulation. BAs are mostly detected in the feces, intestine, and liver, which together account for about 50% of total BA levels, while only 0.78% are found in the kidney of rats [15] (Fig. 1a). Notably, the total relative BA level in the kidney is ~20.7 fold lower than that of the liver [16]. In terms of individual species, the major BAs detected in the rat kidney include TCA, T-β-MCA, CA, and THDCA (Fig. 1b). In mice, TCA, LCA, β-MCA, and CA are present at the highest levels compared to other species [16]. Similarly, other studies have also shown that free and tauro-conjugated BAs were the predominant species in the kidney, with TCA accounting for almost half of the BA pool in mice [17, 18] (Fig. 1c). In contrast to rodents, HDCA, CDCA, and DCA were detected in the kidneys of pigs [19].

BA Transporters in the Kidney

The accumulation of BAs in the kidney is regulated by several transporters located on both the apical and basolateral sides of tubular cells. A comprehensive overview of these transporters is depicted in Figure 2.

Apical BA Transporter

The reabsorption of BAs in proximal tubules is mainly orchestrated by the apical sodium-dependent BA transporter (ASBT, also known as the ileal BA transporter [IBAT] and SLC10A2). ASBT, localized on the apical side of the brush border membrane in proximal convoluted tubular cells, is responsible for the uptake of BAs [21]. Repression of ASBT transcription is predominantly mediated by BAs, and one potential mechanism involves the induction of fibroblast growth factor-15/19 (FGF15/19) by FXR. *Fxr*$^{-/-}$ mice have elevated mRNA levels of *Asbt* in the kidneys, suggesting that the lack of FXR induces ASBT levels in kidneys [22]. Disruption of BA homeostasis also impacts ASBT levels in the kidneys. For instance, cholestatic disorders lead to a progressive increase of urinary BA excretion and an adaptive regulation of ASBT in kidneys. On the other hand, in response to cholesterol feeding, mice showed a significant reduction in ASBT protein levels in the kidney, aligning with increased urinary BA excretion [23]. One study has also shown a decreased uptake of TCA and a reduction of renal ASBT protein levels in rat kidneys 24 h after bile duct ligation (BDL), indicating enhanced renal clearance of BAs during the early phase of obstructive cholestasis [21]. In line with this result, another study confirmed a decreased expression of *Asbt* in renal

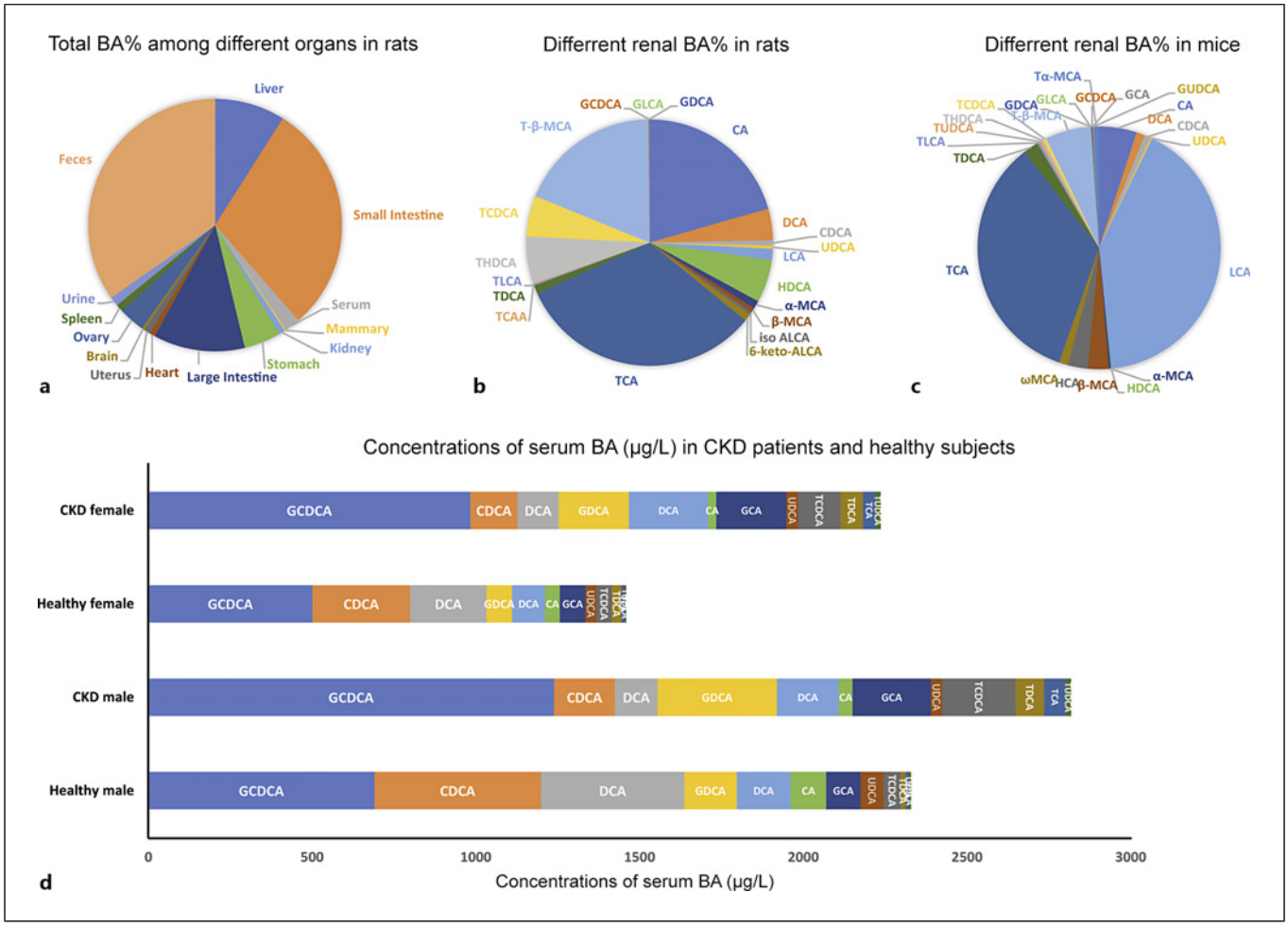

Fig. 1. Bile acid (BA) species detected in rodents and human. **a** Total BA% among different organs in rats, data acquired from the reference [15]. **b** Different BA species detected in kidneys from rats, data acquired from the reference [15]. **c** Different BA species detected in kidneys from mice, data acquired from the reference [17]. **d** Serum BA concentration in healthy subjects and patients with chronic kidney disease (CKD), data acquired from the reference [20]. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholate; UDCA, ursodeoxycholic acid; α/β/ω-MCA, α/β/ω-murocholic acid; LCA, lithocholic acid; HCA, hyocholic acid; HDCA, hyodeoxycholic acid; TCA, taurocholic acid; TCDCA, aurochenodeoxycholate; TDCA, taurodeoxycholate; TUDCA, tauroursodeoxycholate; TLCA, taurolithocholic acid; TCAA, taurocholanic acid; THDCA, taurohyodeoxycholic acid; T α/β/-MCA, tauro-α/β-muricholic acid; GCDCA, glycochenodeoxycholate; GDCA, glycodeoxycholate; GCA, glycocholic acid; GLCA, glyco-Lithocholic acid; GUDCA, glycolursodeoxycholic acid; isoALCA, isoalblithocholic acid; 6-keto-ALCA, 6-oxo-alblithocholic acid.

brush border membrane vesicles in rats after BDL [24]. The adaptive response of ASBT in kidneys may help to reduce systemic effects resulting from the accumulation of toxic BAs during cholestatic liver injury. Pharmaceutical inhibition of ASBT in the kidneys using the ASBT inhibitor A3907 significantly increased the excretion of urinary BAs, particularly hydrophilic TMCAs and TCA, compared with vehicle controls in BDL mice. This suggests that inhibiting ASBT in the kidneys enhances renal BA clearance, thereby reducing BA load and liver toxicity [25]. Similar findings were observed in a recently published study where blocking renal ASBT with the specific ASBT inhibitor AS0369 prevented BDL-induced cholemic nephropathy (CN), a severe complication of cholestatic liver diseases [26]. Interestingly, AS0369 enhanced urinary excretion of more toxic hydrophobic BAs in *Cyp2c70*$^{-/-}$ mice, which harbor a humanized BA composition, indicating potential human relevance [26].

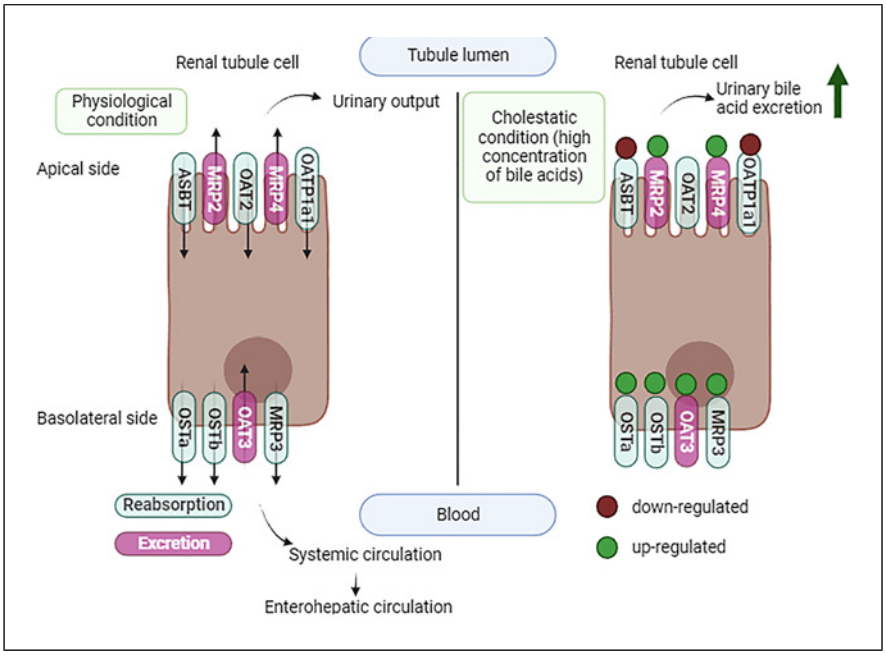

Fig. 2. Apical and basolateral bile acid (BA) transporters under (patho)physiological conditions. Under physiological condition (left panel), apical BA transporters ASBT, OAT2, and OATP1a1 as well as basolateral BA transporters OSTα/β and MRP3 are responsible for the reabsorption of BAs that escape from the enterohepatic cycle. Most of reabsorbed BAs go back to systemic circulation and enter enterohepatic circulation again. While there are still a small number of BAs excreted into the urine, apical BA transporters MRP2 and MRP4, and basolateral BA transporter OAT3 are responsible for this excretion process. Under cholestatic condition (right panel), when there is a high concentration of BA, the expression of ASBT and OATP1a1 decreased, while the expression of MRP2, MRP4, OSTα/β, OAT3, and MRP3 increased. These adaptive changes in the expression of transporters limit the reabsorption of renal BA and favor urinary BA excretion, leading to a reduction in the accumulation of toxic BA during cholestatic injury. ASBT, apical sodium-dependent bile acid transporter; MRP2/3/4, multidrug resistance-associated protein 2/3/4; OAT2/3, mouse organic anion transporter 2/3; OATP1a1, organic anion-transporting protein 1a1; OSTα/β, organic solute transporter α/β.

Other Apical BA Transporters (MRP2, MRP4, OAT2, OATP1A1)

Multidrug resistance-associated protein 2 (MRP2, ABCC2), expressed on the apical membrane of the proximal tubule, is responsible for excreting bile salt-divalent conjugates, including bile salt glucuronides and sulfates. Increased renal expression of *Mrp2* was observed in rats upon CA feeding, suggesting adaptive changes in response to endogenously accumulating BAs [27]. Obstructive cholestasis also induces the accumulation of BAs, leading to a significant rise of the urinary BA excretion, particularly those conjugated with sulfates, known substrates for MRP2. Renal MRP2 protein levels are concurrently upregulated during common BDL [24]. Similar to MRP2, MRP4 also belongs to the ATP-binding cassette superfamily, and it is localized to the apical membrane of proximal tubules in kidneys. It facilitates the ATP-dependent efflux of organic anions and also acts as an efflux pump for BAs such as GCDCA and TCDCA [28]. Adaptive changes in response to common BDL induce a significant increase in renal MRP4 expression, suggesting an alternative excretory pathway for toxic BA clearance via renal MRP4 [29, 30].

Mouse organic anion transporter 2 (OAT2; SLC22A7) is predominantly found in kidneys, specifically, on the apical side of proximal tubular epithelial cells in rodents, while the human OAT2 protein is basolateral [31]. OAT2 transports various organic anion substrates including endobiotic cGMP. However, one study indicates that BA species such as TCDCA and GCDCA can strongly inhibit uptake activity in human renal cell lines [32].

Organic anion-transporting protein 1a1 (OATP1A1) is located on the apical side of epithelial cells in proximal tubules [33]. *Fxr*$^{-/-}$ mice had lower mRNA levels of *Oat3*, *Oatp1*, *Oatp2*, *Oct2*, and *Octn1* transporters in the kidney [22]. BDL decreases renal *Oatp1a1* expression while increasing *Mrp* mRNA expression in mouse kidneys, suggesting that altered protein levels of BA transporters contribute to decreased cellular BA concentrations in the kidney during obstructive cholestasis [34].

Basolateral BA Transporters – OSTa and OSTβ

The organic solute transporters α and β (OSTα and OSTβ) are expressed in the basolateral membrane of renal proximal tubular cells, serving as key BA transporters. They play a crucial role in mediating the facilitated diffusion of BAs and sterols out of the cell [35]. A deficiency of OSTα in mice leads to a significant reduction of BA pool size and altered expression of other BA transporters in the kidney, with upregulated *Mrp3* and *Ostβ* [36]. *OSTα*$^{-/-}$ mice show higher renal clearance of BAs compared to control mice upon CA feeding [37]. In *Ostα*$^{-/-}$ mice after BDL, expression of the apical BA uptake transporter *Asbt* is further reduced, whereas the apical export transporters *Mrp2* and *Mrp4* are increased, leading to a significant increase in urinary BA excretion [38]. During cholestasis, associated with hepatic and systemic BAs accumulation, renal expression of *Ostα* and *Ostβ* is increased in response to BDL [39].

The expression of *Ostα*/*Ostβ* is induced by BAs in an FXR-dependent manner. Unlike the liver, where *Cyp7a1* is a specific FXR target gene [40], *Ostα* and *Ostβ* have been identified as target genes for FXR in the kidney. They facilitate the uptake of conjugated BAs into renal cells, activate FXR, and induce endogenous FXR target genes [41]. Ostα and Ostβ are responsible for the reabsorption of steroid-derived molecules such as glycine or taurine-conjugated BA species [35]. Both natural and synthetic FXR agonists (CDCA and GW4064) can induce the expression of *Ostα* and *Ostβ* in primary cultured proximal tubule cells isolated from rat kidney [42]. The lack of FXR does not alter the expression of *Ostα* and *Ostβ,* but it prevents the induction of *Ostα* expression upon CA feeding in mice [43].

Other Basolateral BA Transporters (MRP3, OAT3, OATP4C1)

The multidrug resistance-associated protein 3 (MRP3, ABCC3) protein localizes to the basolateral membrane of distal convoluted tubule cells. In addition to transporting glucuronide conjugates and chemotherapeutic drugs, MRP3 also transports BAs such as CA, HCA, α-MCA, TCA, TDCA, and GDCA, taurochenodeoxycholate-3-sulfate, taurolithocholate-3-sulfate [17, 44]. Increased expression of *Mrp3* has been observed in mice after BDL, suggesting adaptive changes to limit uptake of BAs from the tubular lumen [34, 38]. MRP3 plays a key role in exporting BAs when other basolateral BA transporters are not available. For example, the loss of OSTα results in an increase in MRP3 protein, and MRP3 is responsible for limiting the reabsorption of renal BAs [36]. The expression of *Mrp3* is positively correlated with the severity of chronic kidney disease (CKD), and its induction decreases urinary excretion of toxic BAs, whose concentration are elevated in CKD mouse models [45].

Organic anion transporter 3 (OAT3) is localized to the basolateral membrane of proximal tubule cells, and it is responsible for the secretion of a wide range of anionic compounds, including BAs such as CA, GCA, and TCA [46]. In cholestatic rat models, OAT3 protein levels are increased, stimulating the renal secretion of BAs [46]. Other cholestatic models, such as BDL, also lead to an increase in the abundance of OAT3 in homogenates from the renal cortex [47].

The renal drug transporter organic anion-transporting polypeptide 4C1 (OATP4C1) is a primary anion transporter responsible for the influx of anions in renal secretion and is localized on the basolateral surface of renal proximal tubular cells. BAs such as CDCA, LCA, GLCA, and TLCA are also substrates of OATP4C1 [48, 49]. Inhibition of OATP4C1 may lead to the accumulation of uremic toxins and BAs [49].

BAs in Renal Disease

Most renal diseases are accompanied by perturbed BA concentrations in the plasma and kidney, along with abnormal urinary excretion of BAs (as outlined in Table 1). These changes contribute to the oxidative damage of tubular cell membranes, leading to reduced glomerular filtration rates and renal function. Consequently, kidney diseases impact BA metabolism, while changes in the synthesis and secretion of BAs can exacerbate kidney diseases.

In a study where BAs were quantified in different biospecimens, kidney and serum compositions and concentrations of BAs exhibited a strong correlation, suggesting the potential identification of specific BAs as biomarkers for kidney diseases [15]. For instance, renal parameters such as urinary albumin excretion and kidney injury molecule 1 levels were positively associated with serum Tβ-MCA in mice with diabetic nephropathy [50]. BAs like DCA and GCDCA hold promise as biomarkers for hepatotoxicity in polycystic kidney diseases, given their significantly elevated levels in the hepatic tissue, serum, and urine of polycystic kidney rats [56]. HDCA and GHDCA, two metabolites from the gut, were recognized as biomarkers for calcium oxalate nephrolithiasis [51]. Additionally, serum CDCA and CA were identified as biomarkers for the progression of tubulo-interstitial nephropathy, which were validated in various experimental models and CKD patients [53].

Table 1. Bile acids (BAs) changes in different renal diseases

Renal diseases	Species	BA changes	References
Diabetic nephropathy	Mouse	Increased serum total BA, conjugated BAs and primary BAs, especially TCA and Tβ-MCA.	[50]
Calcium oxalate nephrolithiasis	Rat	Increased gut HDCA and GHDCA	[51]
Chronic renal failure/CKD	Human	Elevated serum BAs (especially GCDCA, GDCA, and GCA) while decreased BAs in urine	[20, 52]
	Rat	Elevated serum CA and CDCA	[53]
End-stage renal disease	Human	Increased serum BAs (especially TCA, TCDCA, THCA, Tα-MCA)	[54]
Cholemic nephropathy	Mouse	Increased serum BAs (especially CA, β-MCA, TDCA, TCA, Tα-MCA, Tβ-MCA, and Tω-MCA) and hepatic BAs (especially β-MCA, TCA, Tβ-MCA, and Tω-MCA)	[55]

Several studies have shown increased serum BA levels and decreased urine BA in patients with CKD [52, 57]. CKD patients have higher concentrations of conjugated BAs compared to healthy subjects with GCDCA, GDCA, GCA contributing significantly to the increase [20] (Fig. 1d). In CKD patients with normal liver function, eGFR and serum BA levels are correlated, suggesting that decreased BA filtration results in elevated serum BAs [52]. Moreover, certain hydrophobic BAs, like sulfolitho-CA and CDCA, are significantly elevated in CKD rats and are strongly correlated with serum creatinine levels [58], indicating potential cytotoxicity to kidney glomeruli and proximal tubules [59]. Finally, increased plasma BA levels have also been found in rats after a 5/6 subtotal nephrectomy, due to an increased efflux of BAs across the basolateral hepatocyte membrane [42]. CKD progression to end-stage renal disease (ESRD) is associated with a dramatic increase in total serum BAs, specifically TCA, TCDCA, THCA, and Tα-MCA in the death group [54].

BAs also have a direct role in causing acute kidney injury (AKI) [60]. CN is one of the causes of AKI. CN initiates kidney injury with leaky collecting ducts, leading to tubule cell damage, cast formation, progressive tubular dilatation, and interstitial fibrosis [61]. Excessive BA excretion in the proximal convoluted tubules contributes to tubular cell membrane damage in CN patients. In mice, common BDL leads to CN with severe tubular epithelial injury, primarily triggered by the accumulation of alternative urinary-excreted toxic BAs [62]. Furthermore, bile casts are formed due to high BAs amounts, alternating the pH in tubules during CN [63]. One study has shown that feeding mice hydrophilic norursodeoxycholic acid (norUDCA) results in less severe CN [55]. Altered BA composition in kidneys has also been found in norUDCA-fed mice, suggesting that more hydrophilic metabolites from norUDCA are enriched in the kidney and excreted via the urine [55, 62]. Notably, *Fxr*$^{-/-}$ mice, with a more hydrophilic BA pool, are protected against CN in common BDL mice, underscoring the pivotal role of BAs as key determinants of CN [62].

Mechanisms of the Protective Effect of FXR Activation in Kidneys

FXR is ubiquitously distributed in renal tubules, and it is recognized for its roles in regulating urine volume and urine osmolality by modulating the expression of *Aq2* in medullary collecting duct cells [64, 65]. Notably, *Fxr* expression is reduced in many renal diseases, including gentamicin-induced nephrotoxicity [66], folic acid-induced renal fibrosis [67], lupus nephritis [68], cisplatin-induced AKI [69], and I/R renal injury [70]. However, an opposite trend has been reported in patients with diabetic nephropathy, where upregulated *Fxr* expression has been detected compared to healthy controls [71]. The protective effect of FXR in proximal tubular cells in diabetic kidneys suggests that the increase in *Fxr* expression might be an adaptive change. The dynamic expression changes of *Fxr* in various renal diseases suggest that targeting renal FXR might have the potential to reduce renal injuries. A recent clinical trial involving the FXR agonist Vonafexor has demonstrated promising outcomes in patients with NASH. Indeed, a 12-week Vonafexor treatment not only reduced lipid content but also improved eGFR in patients, indicating improved renal function in these patients [11]. Over the last 2 decades, numerous preclinical studies have explored

Table 2. Potential mechanisms of renal protective effects of FXR natural or synthetic agonists

FXR agonists	Dose	In vitro or in vivo models	Renal diseases	Potential mechanisms	References
OCA(INT-747)	Diet: 20 mg/kg/day for 2 weeks	db/db mice	Diabetic nephropathy	Renal lipogenesis pathway	[18]
–	–	$FXR^{-/-}$ mice/FXR siRNA	Folic acid-induced renal fibrosis	Pro-inflammatory NF-κB activation	[67]
GW4064	I.P.: 30 mg/kg/day 3 days before I/R	$FXR^{-/-}$ Proximal tubule specific $FXR^{-/-}$ other tubules specific $FXR^{-/-}$	Acute kidney injury (cisplatin-induced)	Fatty acid oxidation (FXR-PPARg pathway)	[69]
GW4064	I.P.: 30 mg/kg/day for 3 months	db/db mice	Diabetic nephropathy	Lipid metabolism, peroxidation, and oxidative stress	[72]
GW4064	I.P.: 30 mg/kg twice daily for 1 week	db/db mice/mice with HFD	Diabetic nephropathy	Renal lipid metabolism, fibrosis	[73]
GW4064	I.P.: 30 mg/kg	C57BL/6 mice	Acute kidney injury (I/R- and cisplatin-induced)	Lipid metabolism (renal G9a/FXR-Ces1 axis)	[74]
OCA	I.P.: 5 mg/kg for 3 times	ICR mice	Acute kidney injury (lipopolysaccharide-induced)	Renal inflammation and oxidative stress	[75]
6-ECDCA	I.P.: 5 mg/kg for once	C57/BJ mice	Acute kidney injury (I/R-induced)	Antioxidant pathways and glutathione metabolism	[76]
Dioscin	Gavage: 10, 20 or 40 mg/kg/day for 14 days	Wistar rats/FXR siRNA	Nephrotoxicity (doxorubicin-induced kidney injury)	Oxidative stress and inflammation	[77]
OCA	Azert osmotic pump: 10 mg/kg/day for 2 weeks	Sprague-Dawley rats	Hepatorenal syndrome (Common bile duct ligation)	Apoptosis, oxidative stress (NOX-2-ROS, COX-TXA2 pathways)	[78]
OCA	Diet: 25 mg/kg for 8 weeks	C57/BJ mice	Renal injury (HFD and uninephrectomy- induced)	Oxidative stress/ER stress/glutathione metabolism	[79]
Alisol B 23-acetate	I.P.: 60 mg/kg/day for 4 day	$FXR^{-/-}$ mice	Acute kidney injury (I/R-induced)	Apoptosis, inflammation, oxidative stress	[80]
GW4064	Gavage: 30 mg/kg/day for 4 days	$FXR^{-/-}$ mice	Acute kidney injury (cisplatin-induced)	Ferroptosis/glutathione metabolism	[81]
–	–	$FXR^{-/-}$ mice/FXR siRNA	Acute kidney injury (I/R-induced)	Renal autophagy, apoptosis, ROS production	[82]
CDCA	I.P.: 50 mg/kg/day for 6 days	C57BL/6 J mice	CKD (unilateral ureteral obstruction)	TGF-β-SMAD3 pathway	[83]
GW4064	Gavage: 30 mg/kg/day for 5 days	$FXR^{-/-}$ mice/FXR siRNA	CKD (unilateral ureteral obstruction)	Renal fibrosis (Src-YAP/hippo pathway)	[84]
EDP-305	Gavage: 10 or 30 mg/kg/day for 8 days	C57BL/6 mice	CKD (unilateral ureteral obstruction)	Inflammation, peritubular capillary loss, renal fibrosis (nuclear localization of YAP)	[85]

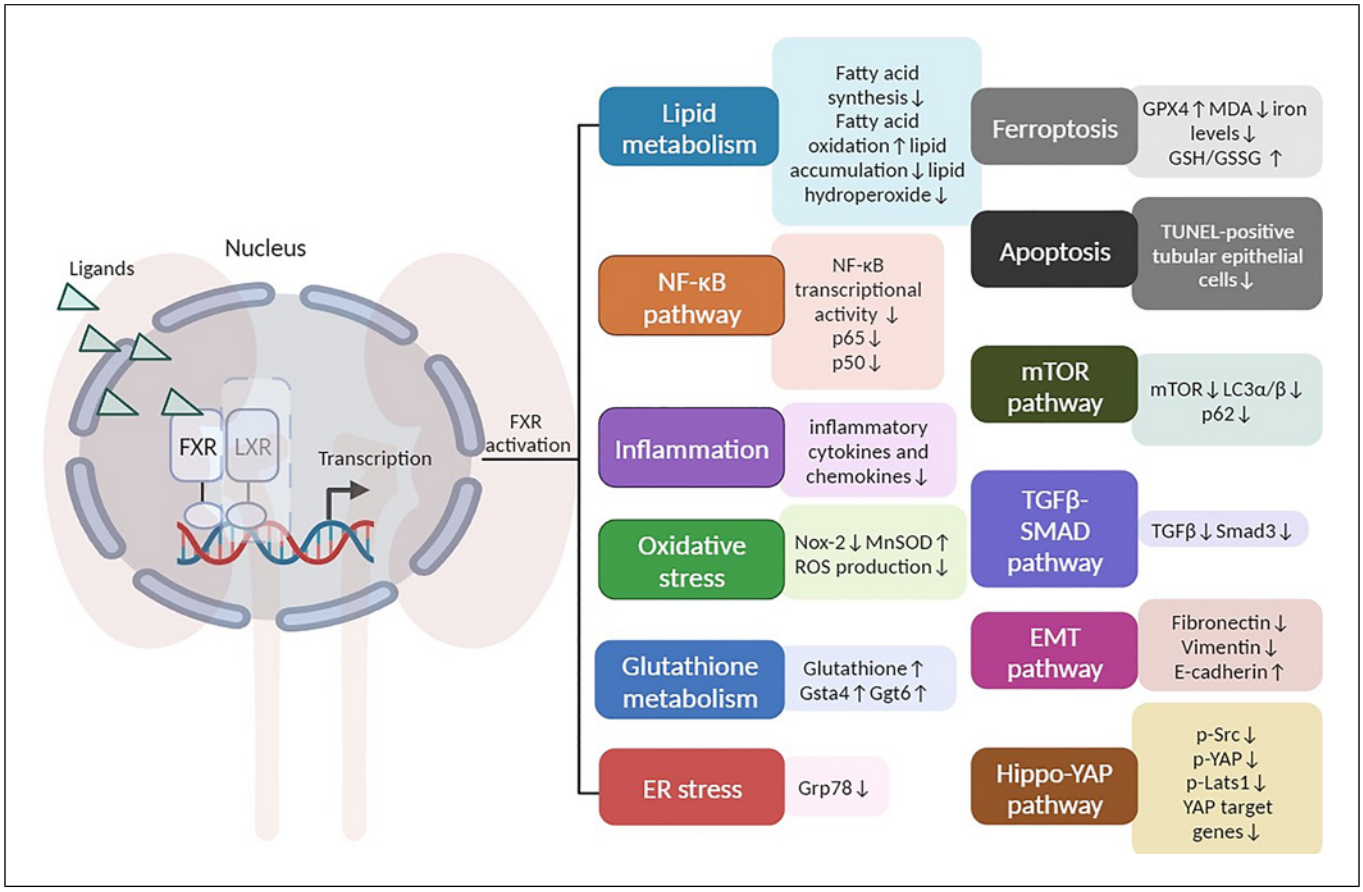

Fig. 3. Potential mechanisms for protecting the effect of FXR activation in different renal diseases. FXR is a nuclear receptor, and it can bind to the DNA as monomer or to LXR forming heterodimer. FXR in the kidney can be bound by different FXR agonists, leading to transcriptional activation of FXR target genes. These genes are involved in different pathways and regulation of these pathways protecting kidney from injury in different renal diseases.

various FXR agonists in animal models of kidney diseases. This section focuses on potential mechanisms illustrated in these studies, summarizing the most representative findings from the literature in Table 2 and Figure 3.

Lipid Metabolism

FXR is a key regulator of cholesterol and lipid metabolism in the liver. When systemic FXR agonists are administered to animals with kidney disease, they exert dual effects. First, they impact systemic lipid homeostasis, and second, FXR activation demonstrates a direct improvement in lipid metabolism within the kidneys. Notably, FXR in the proximal tubule plays a protective role against AKI by mitigating lipid accumulation through the regulation of fatty acid oxidation [69]. The FXR agonist GW4064 has been shown to reduce lipid hydroperoxide in the kidney and improve renal lipid metabolism in obese mice [72]. GW4064 also inhibits lipogenic genes, including SREBP-1c, suggesting a direct role of FXR in modulating renal lipid metabolism in diabetic nephropathy [73]. The natural FXR agonist CDCA has been demonstrated to prevent triglyceride accumulation in the kidneys of rats fed with high fructose [86]. In a recent report, the histone methyltransferase G9a, encoded by Ehmt2, was found to regulate the expression of the renal lipolytic enzyme carboxylesterase 1 (Ces1). Interestingly, G9a competes with FXR for binding sites on the *Ces1* promoter. FXR activation, in turn, activates Ces1, leading to reduced I/R-induced renal lesions and lipid accumulation in the kidneys [74]. Collectively, the modulation of renal lipid accumulation and lipotoxicity plays a crucial role in preventing renal damage and dysfunction. Renal FXR contributes significantly by regulating key processes such as lipogenesis, fatty acid oxidation, and triglyceride clearance.

NF-κB Pathway/Inflammation

Analysis of the kidney transcriptome in lupus nephritis patients from the GEO database and transcriptome-sequencing studies reveals a downregulation of *Fxr* expression and an increase in nuclear factor kappa B (NF-κB) transcriptional activity [68]. NF-κB is known to be activated in various kidney diseases, including I/R-induced AKI and IgA nephropathy [87]. Interestingly, FXR activation inhibited NF-κB activity and blocked nuclear translocation of NF-κB p65 and p50 subunits in tubular epithelial cells of the renal cortex in mice with AKI as well as in diabetic mice [75, 88]. NF-κB is one of the most important transcription factors in inflammation, regulating immune cell activation and recruitment. FXR activation has been shown to reduce LPS-induced chemokine expression in NRK52E kidney tubule epithelial cells, suggesting a protective role of FXR in modulating inflammatory responses [67].

Oxidative Stress/Glutathione Metabolism/ER Stress

Renal tubule cells are particularly susceptible to oxidative stress, and the development of renal diseases often triggers the production of free radicals, exacerbating kidney lesions. Numerous studies have shown the beneficial effect of FXR activation in mitigating oxidative stress during the development of AKI. FXR activation reduces reactive oxidative species (ROS) production in hypoxia-treated HK2 cells and in mice with AKI [70, 76]. Additionally, pre-treatment with the FXR agonist OCA inhibits the upregulation of renal NADPH oxidase during LPS-induced AKI [75]. FXR, through its regulation of renal NADPH oxidases, effectively reduces oxidative stress, a mechanism demonstrated by both the natural ligand CDCA and synthetic ligand OCA [86, 88, 89]. *Fxr* gene overexpression has similar effects, reducing hypertension and renal fibrosis by increasing renal nitric oxide (NO) levels [90]. In other renal diseases, FXR activation reduces oxidative stress by reducing levels of p-AMPKα, NRF2, HO-1, and GST [77]. Chronic OCA treatment significantly reduces oxidative stress in renal vessels of BDL rats, contributing to the overall amelioration of hepatorenal syndrome in ascitic cirrhotic rats [78]. These studies collectively indicate that FXR has antioxidant effects, emphasizing how renal FXR activation alleviates oxidative stress.

Glutathione, a crucial antioxidative molecule, plays a pivotal role in mitigating oxidative stress. Disruptions in glutathione metabolism can induce oxidative stress, and the FXR agonist GW4064 has been found to significantly affect glutathione metabolism in proximal tubular cells [91]. Co-treatment of FFA and an FXR agonist induced the mRNA expression of glutathione-metabolizing genes, including *Gclm*, *Gpx1*, and *Gsr* [79]. Moreover, the activity of renal glutathione S-transferase, another key player in glutathione metabolism, has been shown to be reduced by FXR agonist treatment in I/R injury [80]. Upregulation of genes related to glutathione metabolic processes, such as *Gsta4* and *Ggt6*, in the kidneys of mice treated with GW4064 has also been reported [81], suggesting that FXR activation favors the scavenging of ROS by activating glutathione metabolism.

Oxidative stress and endoplasmic reticulum (ER) stress often coexist in pathological states. While oxidative stress contributes to ER stress-induced cell death, FXR activation leads to lower levels of ER stress and reduced apoptosis in kidneys in obese uninephrectomy mice [79, 92]. Consistently, TUDCA, an FXR agonist, protects the tubular compartment in *db/db* mice by ameliorating ER stress in tubular cells [93]. Interestingly, combined intervention with TUDCA and the angiotensin-converting enzyme inhibitor enalapril more efficiently reduced albuminuria in *db/db* mice than enalapril alone [93].

Cell Death-Related Mechanisms (Ferroptosis/ Autophagy/Apoptosis)

Reports on the impact of FXR activation on renal autophagy and apoptosis present divergent findings. One study indicated that FXR activation inhibits renal autophagy and apoptosis [70]. Conversely, another study showed that FXR deficiency improves renal function and reduces apoptosis after I/R [82]. Notably, the conflicting results may stem from the temporal dynamics of FXR expression post-I/R. The first study reveals a decrease in FXR expression 48 h after I/R, while the second study demonstrates an increasing trend in FXR expression within the 0–24-h time frame post-I/R. The timing after reperfusion appears crucial for assessing renal lesions in $Fxr^{-/-}$ mice. Different from apoptosis, ferroptosis represents another type of cell death due to an iron-dependent accumulation of lipid hydroperoxide [81]. FXR deficiency exhibits heightened ferroptotic responses, while FXR activation reduces cisplatin-induced AKI by downregulating ferroptosis-related genes [81], suggesting that FXR may play a role in regulating both apoptotic and ferroptotic pathways in the context of renal diseases.

Other Pathways (mTOR Pathway, TGF-β-Smad Signaling, EMT Pathway, Hippo-YAP Pathway)

There are other pathways that have been studied to explain the essential role of FXR in renal diseases. A recent study demonstrated the involvement of the histone methyltransferase DOT1L in regulating autophagy and

mitochondrial fission by mediating *Fxr* expression. DOT1L was found to transactivate the FXR promoter in renal cancer cell lines via the mTOR pathway [94], a pathway known for its impacts on renal cell homeostasis since it plays key roles in cell growth, proliferation, survival, and metabolism [95]. FXR activation has been shown to inhibit mTOR signaling in the liver [96] and renal cancer cell lines [94], suggesting a potential tumor-suppressive role for FXR in renal cancers similar to its established role in liver cancer [97, 98].

The TGF-β/Smad signaling pathway, crucial in renal fibrosis, has been implicated in FXR-related effects. The natural FXR ligand CDCA reduces renal fibrosis and suppresses *Smad3* expression in UUO mice [83]. FXR activation by 6-ECDCA also ameliorates TGF-B1 and Smad-4 protein levels in cisplatin-induced CKD [99]. Given the role of TGF-β in promoting epithelial-mesenchymal transition (EMT), which is implicated in renal cancers and fibrosis, FXR activation has been shown to reduce EMT in vitro in HK2 cells treated with advanced glycation end products (AGEs), suggesting a potential benefit in diabetic kidney disease [71].

The Hippo-YAP pathway, critical for regulating cell growth, differentiation, and survival in kidneys, has also been associated with various renal pathological states in which it modulates both podocyte and interstitial homeostasis [100]. FXR activation was found to modulate the phosphorylation and localization of YAP in human tubular epithelial cells [84]. In vivo, UUO-injured mice exhibited increased nuclear expression of YAP within the interstitium, and treatment with the FXR agonist EDP-305 reduced YAP activation and the expression of YAP transcriptional targets [85]. By inducing YAP phosphorylation and suppressing nuclear YAP localization, FXR activation might exert, at least in part, its antifibrotic effects on kidney.

Conclusions and Future Perspectives

BAs are now regarded as signaling molecules influencing various organ functions, including the kidney, where BA receptors are expressed. Elevated serum BA concentrations are observed in patients with CKD. Remarkably, recent studies underscore FXR, a pivotal BA sensor, as a novel player in kidney diseases. In fact, its activation by several agonists has been shown to protect kidneys from the development of renal lesions after an initial injury. In these pathological settings, FXR seems able to modulate several signaling pathways, such as NF-κB, mTOR, TGF-β, and Hippo, but also oxidative stress or ferroptosis. While clinical data are still needed to validate the relevance of these experimental findings to humans, a promising study in NASH patients is encouraging [11].

Despite a number of studies that have been published on the role of BAs and FXR (as reviewed in this manuscript), several aspects need to be clarified. First, we need to define the BA species and their specific functions, as well as the role of BA transporters, to better understand BA metabolism in the kidney. Second, it is known that FXR isoforms exert different metabolic functions in the liver. In contrast to the liver, where FXRα1/2 are the major isoforms, FXRα3/4 are the most dominant isoforms in the kidneys. However, very little is currently known about the functions of these isoforms in the kidney. Third, there is increasing evidence showing gender disparities in the incidence, development, and progression of CKD. Furthermore, sex-specific differences in BA levels have also been confirmed. For example, murine male kidneys have higher FXR expression levels than females. However, we do not know whether these gender differences have an impact on the protective role of FXR activation in renal diseases. Fourth, besides FXR, other BA receptors such as TGR5 are also expressed in kidneys. Intriguingly, crosstalk between FXR and TGR5 was discovered in enteroendocrine L cells. However, it is not known whether the crosstalk between FXR and TGR5 results in antagonistic or cooperative effects in the kidney. Studies exploring the role of different BA receptors are required. Finally, as mentioned above, despite many preclinical studies showing the promising effects of FXR agonists on kidneys, only one clinical trial demonstrating the benefit of FXR activation on eGFR in NASH patients has been performed. Hence, more clinical trials are required to test the potential beneficial impacts of FXR agonists on CKD. If this is indeed the case, FXR agonists could expand the limited arsenal of therapeutic strategies currently deployed to treat the progression of CKD, a prevalent and significant health challenge.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jiufang Yang: conceptualization and writing-original draft preparation. Marco Pontoglio: reviewing. Fabiola Terzi: conceptualization, writing-reviewing and editing, and funding acquisition.

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