Medicine Insights

Review

Advances in Bile Acid Metabolites and Their Receptor-Targeted Interventions in Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) has traditionally been understood from a glomerular perspective: proteinuria and a decline in estimated glomerular filtration rate (eGFR) are regarded as core hallmarks of the disease, and current intervention options for CKD are limited. Recent studies have highlighted the critical role of the gut-kidney axis in the pathogenesis and management of CKD; metabolomics has shown that the accumulation of conjugated bile acids is associated with declining renal function and cardiovascular risk, whereas elevated levels of primary bile acids are associated with a lower risk of the disease. Research data, primarily from animal and cell culture models, indicate that bile acids (BAs) can influence CKD through the nuclear farnesoid X receptor (FXR) and the membrane G protein-coupled bile acid receptor (TGR5),This article provides a systematic review centered on the gut-kidney-vascular axis mediated by bile acid metabolites, elucidating the mechanisms of bile acid homeostasis remodeling and tissue damage in CKD, and highlighting that disease modification requires simultaneous targeting of specific bile acid subtypes and their receptors, rather than relying solely on existing therapies.

Keywords: bile acids; chronic kidney disease; gut-kidney axis; farnesoid X receptor (FXR); G protein-coupled bile acid receptor 1 (TGR5)

1. Introduction

Chronic kidney disease (CKD) is a persistent condition characterized by structural abnormalities or progressive renal dysfunction resulting from kidney damage lasting at least three months, accompanied by health consequences that ultimately lead to end-stage kidney disease (ESKD).According to the chronic kidney disease classification system currently used by the Kidney Disease Improvement Global Outcomes Organization (KDIGO), kidney disease is classified based on its etiology, glomerular filtration rate (GFR) (G1–G5), and albuminuria level (A1–A3). This classification system is abbreviated as CGA [1- 2]. According to the "Global Burden of Disease (GBD)" study, the global prevalence of CKD reached 674 million in 2021, accounting for 8.0% of the total global population [3]. Common underlying causes of CKD worldwide include chronic glomerular disease, type 2 diabetes, hypertension, obstructive nephropathy, cystic kidney disease, and rheumatic and immune system disorders such as systemic lupus erythematosus [3-4]. In recent years, attention has focused on the interorgan relationship between the kidneys and the gut, a relationship known as the gut-kidney axis. The gut-kidney axis is a new interorgan relationship centered on the kidneys and is increasingly recognized as a potential therapeutic target for chronic kidney disease [5]. More than one hundred trillion microorganisms, primarily bacteria, inhabit the human colon. They have coevolved with the host and perform diverse but predominantly beneficial functions. They consume excess calories by fermenting indigestible food, secrete vitamins, and ensure normal physiological development. Extensive research indicates that microorganisms can regulate the host's physiological homeostasis and are associated with diseases such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), chronic kidney disease, obesity, diabetes, anxiety, depression, Parkinson's disease, and schizophrenia [6-8]. One

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of the most important classes of metabolites in the gut microbiota is bile acids (BAs). BAs are amphiphilic cholesterol metabolites that dissolve dietary lipids by forming micelles in the small intestine, thereby facilitating their absorption or excretion. Furthermore, they act as hormones that regulate BA biosynthesis, lipid and glucose homeostasis, and immune signaling [9]. In this review, we will focus on bile acids, which are bioactive host molecules of hepatic origin that exhibit interdependence with the gut microbiota.

In recent years, comprehensive genomic sequencing has confirmed a close relationship between the gut microbiota and its byproducts and the onset and progression of CKD [10]. Therefore, research elucidating the relationship between the gut microbiota and CKD is expected to open new avenues for future kidney disease management and may pave the way for new therapeutic approaches involving BAs in the treatment of CKD. The relationship between the human body and the gut microbiota is primarily mediated by metabolites produced by the gut microbiota. Alterations in the gut microbiota exert a significant influence on the progression of kidney disease by modulating the production of these gut metabolites. Evidence supports an association between BAs and a range of kidney diseases, including CKD, ESRD, and diabetic nephropathy [11]. Although a link between BAs and kidney disease is widely recognized, a comprehensive understanding of the mechanisms by which BAs regulate disease onset and progression remains elusive. This article aims to delve into the role of BAs in the pathophysiology of CKD and to evaluate the potential for targeted therapeutic interventions, with a focus on reviewing the effects of dietary strategies, receptor-targeted interventions, and gut microbiota modulation on BA regulation. Thus, our goal is to elucidate the complex mechanisms underlying the role of BAs in CKD development and to propose innovative approaches for treating this disease.

2. Overview of Bile Acid Metabolism

Bile acids (BAs) are catabolic products of cholesterol; they are amphiphilic steroid acids synthesized from cholesterol in the liver and stored in the gallbladder, primarily existing in the human body as primary and secondary bile acids [12]. In the human body, the conversion of cholesterol to bile acids occurs primarily through two pathways: the classical (neutral) pathway, which takes place mainly in hepatocytes, and the alternative (acidic) pathway, which also occurs in the liver but involves additional enzymatic steps and may extend to extrahepatic tissues [13]. In the classical pathway, three cholesterol hydroxylases are involved: cholesterol 7α-hydroxylase (cytochrome P450 family A member 1, CYP7A1), sterol 12α-hydroxylase (cytochrome P450 family 8 subfamily B member 1, CYP8B1), and sterol 27-hydroxylase (cytochrome P450 family 27 subfamily A member 1, CYP27A1). These represent the core cytochrome P450 enzymes mediating the conversion of cholesterol into two primary bile acids: cholic acid (CA) and chenodeoxycholic acid (CDCA)[14]. In humans, primary bile acids (BAs) bind to glycine or taurine, whereas in mice they bind primarily to taurine; they are actively transported via the bile acid efflux pump (BSEP) to form bile salts stored in the gallbladder. During feeding, cholecystokinin released by the pancreas stimulates the secretion of bile acids (BAs) into the duodenum, where they are metabolized by the gut microbiota [15]. Approximately 95% of conjugated bile acids are actively reabsorbed by intestinal epithelial cells via the apical sodium-dependent bile acid transporter (ASBT) before reaching the ileocecal junction. After absorption, these conjugated bile acids bind to ileal bile acid-binding protein (ILBP) and cross the basolateral membrane via the organic solute transporter α/β (OSTα/OSTβ) complex, and are ultimately returned to the liver via the portal vein [14]. These recycled bile acids, together with newly synthesized bile acids from the liver, are secreted into bile and then released into the intestine during meals, thereby completing the enterohepatic circulation, which occurs six times daily [16]. Unconjugated primary BAs enter the colon and undergo chemical modifications by the gut microbiota, including dehydroxylation, dehydrogenation, and epimerization, to form secondary BAs, namely lithocholic acid (LCA) and deoxycholic acid (DCA)[17].

Bile acid metabolism is influenced by bacteria possessing BSH activity, a trait unique to gut bacteria that may have evolved through host-driven selection [15]. By de-conjugating BAs via bile salt hydrolases (BSHs), which hydrolyze and de-conjugate taurine or glycine from the BA sterol core, the active reabsorption of BAs via ASBT in the small intestine is inhibited, thereby increasing BA diversity in the enterohepatic circulation [18]. Genomic analysis indicates that functional BSH is present in all major bacterial phyla and archaeal species in the human gut, including members of Lactobacillus, Bifidobacterium, Clostridium, and Bacteroides [19]. The 7α-dehydroxylation reaction is the most important reaction carried out by gut bacteria; it is primarily performed by Clostridium cluster XIVa, leading to an increase in the hydrophobic index of bile acids (BA) and affecting intestinal permeability. The genes promoting 7α-dehydroxylation are encoded by the bile acid-inducible operon (bai), which is most prominent in highly active Clostridium strains such as C. hiranonis and C. scindens [20]. Furthermore, studies have shown that certain strains are capable not only of deconjugating bile acids via BSH but also of directly dehydrogenating conjugated bile acids via hydroxysteroid dehydrogenases (HSDs) to produce conjugated secondary bile acids; examples include the Actinobacteria, Bacillota, Bacteroidota, Fusobacteria, and Pseudomonadales [21]. Bile acids and the gut microbiota jointly regulate host metabolism through bidirectional interactions; bacterial enzymes chemically modify bile acids, while bile acids, in turn, alter the characteristics of gut bacteria. Bile acids can reshape the microbial community structure; free bile acids exert antibacterial activity by disrupting cell membranes. For example, DCA inhibits the growth of Clostridium difficile, and iso-lithocholic acid (iso-LCA) is effective against multidrug-resistant Gram-positive bacteria. The fewer hydroxyl groups present, the greater the permeability and the higher the antibacterial activity [22]. High concentrations of primary bile acids promote the enrichment of bacteria expressing bile acid metabolism genes in the small intestine. Bile acids can also induce DNA damage, protein misfolding, and oxidative stress, which reduce bacterial survival rates [23].

3. Bile Acid Receptors and Their Distribution in the Kidney

The kidneys are not only involved in bile acid metabolism and serve as an excretory pathway, but are also a key target organ for bile acid signaling pathways. Bile acid receptors are divided into two major categories: nuclear receptors, which include the farnesoic acid X receptor (FXR), the vitamin D receptor (VDR), the pregnane X receptor (PXR), and the constitutive androstane receptor (CAR);and membrane receptors, which primarily include the Takeda G protein-coupled bile acid receptor 5 (TGR5) and sphingosine-1-phosphate receptor 2 (S1PR2).It is worth noting that the nuclear receptor farnesoid X receptor (FXR)-specifically its subtypes FXRα3 and FXRα4-and Takeda G-protein-coupled bile acid receptor 5 (TGR5, also known as GPBAR1) are the most extensively studied bile acid receptors [24-25].

The farnesoid X receptor (FXR) is a member of the nuclear receptor superfamily that regulates the transcription of specific target genes and is significantly expressed in the liver, small intestine, kidneys, and adrenal glands [26]. FXR is widely expressed in all segments of the renal tubules, with relatively high expression in the proximal tubule and the thick ascending limb of the loop of Henle, followed by the distal tubule, the thin descending limb, and the collecting duct [27]. As endogenous ligands of FXR, bile acids activate FXR in order of binding affinity and potency: chenodeoxycholic acid (CDCA) > lithocholic acid (LCA) = deoxycholic acid (DCA) > cholic acid (CA)[28]. The function of FXR in the kidney involves multiple dimensions. Evidence suggests that FXR in the kidney regulates water metabolism; FXR-knockout mice exhibit increased urine output and decreased urine osmolality, which is associated with reduced AQP2 expression [27]. FXR triggers AQP2 gene transcription by binding to the farnesol X receptor response element (FXRE) in the AQP2 gene promoter [29]. Regarding lipid metabolism regulation, in mouse models of diabetes and diet-induced obesity, treatment with FXR agonists demonstrated renal protective effects by downregulating the expression of sterol regulatory element-binding protein 1c (SREBP-1c), thereby reducing renal fatty acid

synthesis and lipid accumulation [30]. Regarding anti-inflammatory and anti-fibrotic effects, in a sepsis-induced acute kidney injury (AKI) model, the FXR agonist obeticholic acid (OCA) suppressed the inflammatory response by inhibiting the NF-κB signaling pathway and reducing the NLRP3 inflammasome [31].

TGR5 belongs to the G protein-coupled receptor family and is expressed in the liver, gallbladder, intestines, kidneys, spleen, brain, skeletal muscle, and brown adipose tissue (BAT), among other tissues [32]. It is highly expressed in both renal tubular epithelial cells and glomerular cells [33]. As endogenous ligands of TGR5, bile acids activate TGR5 in the following order of binding affinity and potency: LCA > DCA > CDCA > CA [34]. After bile acids activate TGR5, they elevate intracellular adenylate cyclase/cyclic adenosine monophosphate (cAMP) levels through coupling with Gs proteins, thereby activating the protein kinase A (PKA) signaling pathway and rapidly mediating the phosphorylation of downstream target proteins [35]. TGR5 binds to the hydrophobic bile acids LCA or deoxycholic acid (DCA), activates intracellular cyclic adenosine monophosphate (cAMP) or protein kinase A (PKA), promotes the expression and intracellular transport of AQP2, facilitates the transport of AQP2 to the basolateral membrane of intracellular vesicles, and promotes water reabsorption [29]. Podocytes are critical for maintaining the integrity and function of the glomerular filtration barrier; podocyte damage can lead to glomerulosclerosis, proteinuria, and ultimately renal failure [36-37]. TGR5 is expressed near the cell membrane of podocytes. Inhibition of TGR5 signaling may reduce AMPKα activity, thereby affecting glucose uptake, lipid metabolism, and cytoskeletal stability in podocytes, ultimately leading to impaired podocyte function and increased albumin permeability of the filtration barrier [38]. In a mouse model of lithium-induced nephrogenic diabetes insipidus, INT-777 or INT-767 activated TGR5 and increased AQP2 expression via the cAMP/PKA signaling pathway [39]. It has been shown that TGR5 agonists upregulate the expression and membrane translocation of AQP2 and AQP3 in renal medullary collecting duct cells via the cAMP-PKA-CREB signaling pathway, thereby reducing urine volume, increasing urine osmolality, enhancing urine concentration capacity, and indirectly regulating blood pressure [40] (As shown in Table 1).

Table 1. Identified Bile Acid Receptors

Receptor	Ligand	Expression	Key Features	References
FXR (Farnesoid X receptor, NR1H4)	CDCA > DCA = LCA > CA	Liver, heart, kidneys, intestines	Regulates bile acid synthesis, transport, and the enterohepatic circulation; Regulates lipid, glucose, and energy homeostasis; Maintains intestinal barrier integrity and antimicrobial defense; Inhibits inflammation in the liver and intestines	[26-30]
TGR5 (Takeda G-protein-coupled bile acid	LCA > DCA > CDCA > CA	Intestine, stomach, liver, spleen, kidneys, gallbladder,	Stimulates GLP-1 secretion by enteroendocrine L cells; Promotes energy expenditure and thermogenesis in brown adipose tissue; Regulates glucose and bile acid homeostasis;	[32-38]

receptor 5, GPBAR 1)		adipose tissue	Exerts anti-inflammatory effects in macrophages; Regulates intestinal motility and the release of gastrointestinal hormones	
VDR (Vitamin D Receptor)	LCA, DCA	Ileum, kidneys, liver, bones, skin, endocrine tissues	Regulates calcium/ phosphorus absorption and bone mineralization homeostasis; Induces antimicrobial peptides involved in innate immunity; Regulates T-cell diff-erentiation and Treg function; Maintain the intestinal epithelial barrier and mucosal immunity; Shapes the composition of the gut microbiota; Associated with IBD and colorectal cancer	[41-42]
PXR (Pregnan X receptor, NR1I2)	3-keto-LCA, LCA, DCA	Liver,intestines	Detects exogenous substances and secondary bile acids, inducing the CYP3A/UGT/MDR1 detoxification system; Protects the liver and intestines from damage caused by toxic bile acids and gut microbiota metabolites; Antagonizes NF-κB signaling and inhibits inflammation; Regulates lipid/cholesterol and energy metabolism	[43]
S1PR2 (Sphingosine-1-phosphate receptor 2)	TCA, TDCA, GCA	Liver, brain, heart, lungs, spleen, kidneys (most tissues)	Upon activation of S1PR2 by conjugated bile acids, the ERK1/2 and AKT signaling cascades are initiated; in the renal tubules, this receptor regulates sodium-potassium ATPase activity via the Rho kinase–PI3K–NO pathway; It contributes to high-glucose-induced mitochondrial damage in glomerular endothelial cells and participates in the regulation of lipid metabolism. Regulates lymphocyte efflux and immune cell migration; Regulates endothelial barrier integrity and angiogenesis;	[44-45]

CAR (constitutive androstane receptor, NR1I3)	LCA	Liver, small intestine, kidneys	Regulates vascular tone and cardiovascular homeostasis; Coordinates drug -metabolizing enzymes and transporters; Acts as a cellular defense sensor against cholestasis; Regulates gluconeogenesis, lipid, and energy metabolism; Regulates hepatocyte proliferation and tumor promotion; Supports the intestinal barrier and mucosal defense	[46]

4. Bile Acid Metabolites and Chronic Kidney Disease

4.1. Bile Acids and CKD

CKD has become an increasingly serious global public health issue, with its incidence and mortality rates rising year by year [47]. The prevalence of type 2 diabetes, hypertension, obesity, and an aging population in China is increasing year by year, which will exacerbate the burden of CKD in the country. CKD is often complicated by cardiovascular disease, mineral and bone disorders, disturbances in water, electrolyte, and acid-base balance, and anemia; among these, cardiovascular disease is one of the leading causes of death among CKD patients.Metabolomic studies of serum samples from CKD patients have revealed significantly elevated levels of conjugated bile acids, such as glycocholate, and their concentrations are negatively correlated with estimated glomerular filtration rate (eGFR)[48]. In a mouse model of adenine-induced CKD, levels of taurine-conjugated bile acids-such as taurine-deoxycholate and taurine-β-muracholate-were elevated, while levels of deoxycholic acid (DCA) and lithocholic acid were reduced [49]. Furthermore, in a study of cats with CKD, concentrations of the renoprotective secondary bile acid ursodeoxycholic acid (UDCA) in feces were significantly reduced and correlated with the degree of gut dysbiosis [50]. A prospective study showed that in patients with newly diagnosed type 2 diabetes, higher levels of circulating primary bile acids (such as chenodeoxycholic acid and glycocholic acid) were actually associated with a lower risk of CKD [51]. UDCA levels are reduced in patients with CKD; supplementation with UDCA can alleviate kidney damage and slow the progression of CKD through its antioxidant and anti-inflammatory effects [49].

4.2. Mechanisms of Bile Acid Action in the Progression of CKD

The physiological roles of bile acids in slowing the progression of CKD are gradually being elucidated, including the suppression of inflammatory responses, the inhibition of oxidative stress, anti-fibrotic effects, and improvements in energy metabolism and immune pathways. Gut microbiota dysbiosis in chronic kidney disease (CKD) alters bile acid metabolism; primary bile acids that escape reabsorption in the ileum are converted into secondary bile acids by gut bacteria. CKD-related dysbiosis is characterized by a reduction in beneficial bacteria-such as those of the genus Lactobacillus-that possess bile salt hydrolase (BSH) activity, resulting in reduced deconjugation and subsequent 7α-dehydroxylation of primary bile acids. This leads to insufficient production of UDCA and LCA and a relative accumulation of conjugated bile acids [52]. These bile acids act as signaling molecules transmitted through the host receptors FXR and TGR5.These pathways regulate glucose and lipid metabolism, epithelial barrier integrity, and immune homeostasis [53,25]. Chronic kidney disease (CKD) is a persistent, aseptic state of low-

grade inflammation [54]. Bile acids activate FXR, which reduces renal injury by inhibiting NF-κB nuclear translocation and decreasing the production of pro-inflammatory factors such as TNF-α and IL-6[55]. Studies have shown that in two mouse models of hereditary CKD-Alport syndrome and APRT deficiency-renal FXR activity is significantly reduced; following treatment with the FXR agonist obeticholic acid (OCA), renal S1P signaling is suppressed, leading to a reduction in neutrophil extracellular traps (NETosis) and an alleviation of disease severity [56]. In db/db diabetic mice, Roux-en-Y gastric bypass surgery activates the TLCA-TGR5 pathway by elevating serum taurocholic acid (TLCA) levels, thereby inhibiting NF-κB phosphorylation, alleviating renal inflammation and podocyte damage, and improving renal function [57]. In DN mice, the selective TGR5 synthetic agonist INT-777 induces renal mitochondrial biosynthesis, reduces oxidative stress, and induces fatty acid β-oxidation [58]. In kidney organoids derived from human induced pluripotent stem cells, the dual bile acid receptor agonist INT-767 reversed TGF-β1-induced fibrosis by activating FXR and downregulating p-SMAD3 and TAZ [59]. Furthermore, abnormalities in bile acid metabolism are closely associated with renal lipid metabolism disorders in patients with CKD. FXR activation suppresses SREBP-1c and its downstream targets, fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), thereby reducing de novo fatty acid synthesis in the kidney and alleviating lipotoxicity [60-61].

4.3. Interaction between the Gut-Kidney Axis and Uremic Toxins

Bile acids and uremic toxins in CKD are not two independent systems. Microbiota dysbiosis in CKD involves the depletion of short-chain fatty acid-producing bacteria and proteolysis, as well as the proliferation of uremic toxin-producing bacteria. This shift, on the one hand, accelerates the fermentation of tryptophan and tyrosine into precursors of indole sulfate (IS) and p-cresol sulfate (pCS); on the other hand, a decline in the abundance of bacteria possessing bile salt hydrolase (BSH) and 7α-dehydroxylase activity leads to impaired secondary bile acid production and altered proportions of conjugated bile acids [62]. Serum metabolomics studies in the same CKD cohort simultaneously observed a progressive increase in IS, pCS, and TMAO alongside a concurrent rise in conjugated bile acids (such as GCDCA), suggesting that bile acid abnormalities and the accumulation of uremic toxins in CKD are co-products of the same microbial niche remodeling [63]. IS is an endogenous agonist of the aryl hydrocarbon receptor (AhR); in CKD, it continuously activates AhR and upregulates pro-inflammatory and pro-fibrotic genes. Exposure to IS reduces the mRNA expression of CYP7A1-the rate-limiting enzyme in the classical bile acid synthesis pathway-in primary human hepatocytes; simultaneously, the expression of bile acid uptake transporters such as NTCP and OATP1B3 is also downregulated [64]. This implies that IS not only amplifies inflammation via AhR but also reduces the capacity for bile acid pool formation at the synthetic end.

4.4. Bile Acids and Cardiovascular Complications of CKD: Vascular Calcification

In chronic kidney disease (CKD), impaired renal clearance combined with persistent intestinal overproduction leads to significantly elevated circulating bile acid levels and an increased enterohepatic circulation. These phenomena have consistently been associated with endothelial dysfunction, oxidative stress, vascular calcification, and accelerated progression of renal and cardiovascular diseases. Cardiovascular disease is the leading cause of death among CKD patients , and medial vascular calcification is the most characteristic pathological change [65]. Elevated serum DCA levels in patients with CKD directly act on vascular smooth muscle cells (VSMCs), promoting their transdifferentiation from a contractile phenotype to an osteogenic/chondrogenic phenotype.Central to this transdifferentiation is the abnormal activation of the transcription factor Msx2; together, these factors drive VSMCs to express osteopontin, osteocalcin, and alkaline phosphatase, providing a matrix for hydroxyapatite crystal deposition [66].

With regard to the DCA-FXR axis, FXR agonists can selectively reduce circulating DCA levels, thereby protecting CKD mice from medial calcification and atherosclerotic

calcification. The mechanism involves blocking the endoplasmic reticulum stress-mediated ATF4 pathway and inhibiting the osteogenic differentiation of VSMCs [67]. FXR activation also upregulates the expression of vascular endothelial growth factor A (VEGF-A) and endothelial nitric oxide synthase (eNOS), improving nitric oxide production and reducing reactive oxygen species, thereby protecting endothelial function [68]. However, the role of FXR is not unidirectional: in a model of intermittent hypoxia-hypercapnia, FXR deficiency actually disrupted the coupling between gut microbiota changes and vascular pathology, sparing the aorta from atherosclerosis [69]. This suggests that the effects of FXR may be opposite in different vascular beds and under different pathological conditions; the inference that activating FXR protects blood vessels must distinguish between tissue types and disease stages.

In contrast, the effects of TGR5 on the vascular wall are more consistent. In age-related coronary artery disease, attenuated TGR5 signaling weakens endogenous inhibition of macrophage activation and VSMC phenotypic transformation, promoting vascular calcification and plaque instability;conversely, TGR5 activation inhibits M1 polarization, promotes M2 conversion, and-via the cAMP-PKA pathway-suppresses NF-κB-mediated inflammation, blocks the osteoblast-like transformation of VSMCs, and reduces Runx2 and osteopontin expression as well as calcium salt deposition [70]. Notably, atorvastatin promotes the production of DCA and LCA by increasing the proportion of gut bacteria expressing 7α-dehydroxylase, thereby upregulating the expression of TGR5-regulated genes in white adipose tissue and the colon and alleviating liver and vascular damage [71].

4.5. Strategies for Modulating Metabolites in the Gut Microbiota

Changes in dietary patterns can alter the composition of the gut microbiota within as little as one day. In patients with chronic kidney disease (CKD), Bifidobacteria within the Actinobacteria phylum are depleted; supplementation with Bifidobacteria in a CKD-specific diet reduces serum creatinine, blood urea nitrogen, and p-cresol sulfate (pCS), demonstrating their role in reducing the accumulation of these uremic toxins [72]. A growing body of research suggests that increasing plant-based dietary intake may help slow the progression of CKD, reduce the risk of cardiovascular disease, diabetes, and obesity, and lower inflammatory responses and cholesterol levels, thereby delaying renal failure and dialysis [73-74]. Furthermore, combining a low-protein diet with prebiotics appears to further reduce the burden of uremic toxins while enhancing microbiota-dependent renal/enteric protective mechanisms [75]. Makki K et al. found that the soluble dietary fiber OFS promotes glucose homeostasis by stimulating microbial production of 6α-hydroxycholic acid, thereby facilitating TGR5 activation and GLP-1 secretion [76].

Probiotics are a cost-effective, non-invasive intervention with few side effects, typically consisting of live bacterial strains such as Bifidobacterium, Lactobacillus, and Streptococcus. These probiotics exert antimicrobial effects by producing bacteriocins [77]. Probiotics, prebiotics, and synbiotics improve renal function by modulating the gut-kidney axis, thereby alleviating uremic toxicity and systemic inflammation [78]. Furthermore, studies have shown that treatment with Bifidobacterium animalis subsp. A6 can alleviate renal fibrosis and glomerulosclerosis by reducing the relative abundance of toxin-producing bacteria (such as Bacteroides ovatus and Fusobacterium) and lowering serum levels of uremic toxins, creatinine, and urea in rats with chronic kidney disease [79]. Animal studies further support the potential of synbiotics to improve gut microbiota composition, reduce uremic toxins, and prevent renal function decline in CKD models [80]. In summary, probiotics, prebiotics, and synbiotics are promising therapeutic approaches for the management of chronic kidney disease, providing mechanistically grounded interventions targeting the gut-kidney axis.

Obecholic acid (OCA) can influence the enterohepatic circulation and metabolic profile of bile acids by regulating the structure of the gut microbiota; OCA is expected to indirectly improve CKD-related metabolic disorders and inflammatory states [81]. Studies have shown that natural products alleviate CKD by reshaping microbial dysbiosis. Liu et

al. found that the decoction of Zicuiyin reduced serum creatinine levels in patients with diabetic kidney disease (DKD), accompanied by increased abundances of the Bacteroidetes and Lactobacillaceae families and decreased abundances of Enterobacteriaceae, Fusobacteriaceae, and Micrococcaceae [82]. Zhou W et al. reported that medecassoside (an oxolane-type triterpenoid glycoside) improves renal function and reduces fibrosis while promoting the growth of Bacteroides fragilis [83].

Fecal microbiota transplantation (FMT) primarily involves transferring a microbial extract from the feces of a healthy donor to an affected recipient to restore the integrity of the gut microbiota and its function; it is recommended in treatment guidelines for Clostridioides difficile infection [84]. FMT modulates the immune response by suppressing inflammation and metabolic dysfunction associated with chronic kidney disease [85]. Preclinical studies have shown that in DKD models, FMT restores gut microbiota composition, enhances microbial diversity, and reduces tubulointerstitial damage and inflammatory cytokines [86]. However, caution is still warranted when applying FMT to patients with clinical kidney disease. Furthermore, FMT technology requires extensive in-depth research, such as donor selection, long-term stability of donor feces, safety, and processing methods.

5. Conclusion and Perspectives

CKD remains one of the leading causes of death worldwide. In recent years, the role of enteric BAs in kidney disease has emerged as a new field of research,and the interaction between the gut microbiota and BAs plays a multifaceted role in chronic kidney disease. Although the current focus of CKD treatment is on slowing disease progression and preserving renal function, understanding the link between the gut microbiota and CKD holds promise for opening new research horizons in future kidney disease management, providing opportunities to identify BAs as new therapeutic targets for chronic kidney disease, and paving the way for future preventive and therapeutic approaches.Although research on the bile acid pathway in CKD has made progress, scientific questions remain to be addressed. Most studies are limited to cellular and animal experiments, and there is a lack of sufficiently reliable clinical efficacy studies. Therefore, further research is necessary to fully understand the specific mechanisms of action and to develop optimal application strategies.Future research should include comprehensive evaluations of larger and more diverse cohorts, taking lifestyle and/or dietary factors into account, and employing a multi-omics approach to define the clinical significance of CKD-specific changes and their value in the management of chronic kidney disease.

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