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REVIEW

Gut microbiota regulates oxidative stress and inflammation: a double-edged sword in renal fibrosis

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Abstract

Gut microbiota is a complex and dynamic system that plays critical roles in human health and various disease. Progressive chronic kidney disease (CKD) suggests that patients irreversibly progress to end-stage kidney disease and need renal replacement treatments, including dialysis and transplantation. Ample evidence indicates that local oxidative stress and inflammation play pivotal roles in the pathogenesis and progression of CKD and dysbiosis of gut microbiota. CKD is always accompanied by intestinal inflammation and oxidative stress, which lead to rapid systemic translocation of bacterial-derived uraemic toxins, including indoxyl sulphate, phenyl sulphate and indole-3-acetic acid, and the consequent development and aggravation of renal fibrosis. Although inflammation and oxidative stress have been extensively discussed, there is a paucity of reports on the effects of gut microbiota on renal fibrosis and gut microbiota mediation of oxidative stress and inflammation. This review provides an overview of gut microbiota on inflammation and oxidative stress in renal fibrosis, briefly discusses regulation of the gut flora using microecological preparations and natural products, such as resveratrol, curcumin and emodin as treatments for CKD, and provides a clear pathophysiological rationale for the design of promising therapeutic strategies.

Keywords Chronic kidney disease · Inflammation · Oxidative stress · Gut-kidney axis · Microecological preparations · Natural products

Introduction

Chronic kidney disease (CKD) is a global public health problem whose the prevalence and mortality rate are rapidly increasing all over the world [1, 2]. CKD affects approximately 15–20% of the adult population and a considerable proportion of patients progress to end-stage renal disease (ESRD) [1, 3]. Renal fibrosis, characterized by tubulointerstitial fibrosis and glomerulosclerosis, is the typical outcome of CKD, and represents a growing public health burden and is the leading cause of ESRD [4, 5]. As the most common histopathological type of CKD, renal fibrosis is associated with uncontrolled fibrogenesis, which may be activated by various kidney injuries that lead to CKD and ESRD [6]. Therefore, the effective management of renal dysfunction due to renal fibrosis is essential for the treatment of CKD. Despite the high prevalence of renal fibrosis, there are few effective strategies to reverse kidney fibrosis beyond blood pressure regulation and glycaemic control [7].

Renal fibrosis is accompanied by activated oxidative stress and inflammation, which are prominent pathological features of progressive kidney disease [8]. Oxidative stress and inflammation play a central role in CKD progression and outcome. However, the link between disease initiation and inflammation is controversial [9]. The concept of a gut-kidney axis has been proposed and, there is renewed interest in modification of gut microbiota and activation of inflammatory pathways [10]. The dysbiosis of gut microbiota is characterised by a decrease in microbiome diversity and richness of various taxa, and it is commonly observed in CKD patients [11]. Studies have shown that CKD leads

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to intestinal inflammation and impairment of the epithelial barrier, which result in an expedited systemic translocation of bacteria-derived uraemic toxins [12]. This process triggers a cascade of inflammatory response, apoptotic development, and progressive fibrogenesis, which further exacerbates renal fibrosis [10]. Therefore, gut microbial dysbiosis and chronic inflammation constitute risk factors for CKD progression [13]. An abnormal gut microbiota in patients with ESRD leads to metabolite disorder and finally worsens clinical outcomes [14, 15]. Therefore, altering gut-kidney axis may be a promising therapeutic target for suppressing oxidative stress and inflammation.

The available information on gut microbiota-associated oxidative stress and inflammation in renal fibrosis was searched by several database such as Web of Science, Pubmed, Springer Nature, Wiley, ScienceDirect, etc. In this review, we highlight previous knowledge of oxidative stress, inflammation and functional features of gut microbiota in CKD, and review the role of microbial-derived metabolites in regulating inflammatory processes in CKD. We also discuss future directions in "gut-kidney" study and consider the benefits and drawbacks.

Oxidative stress and inflammation in renal fibrosis

Renal fibrosis is a common pathological alteration in kidneys that leads to excessive accumulation of extracellular matrix (ECM) components [16, 17]. Tubular epithelial cells play a crucial role in the initiation and progression of renal fibrosis [18]. The excessive buildup of ECM components, such as collagen, fibronectin, laminin, glycoproteins, proteoglycans, and various polysaccharides, in the tubulointerstitial space during fibrosis progression disrupt kidney structure, reduce blood supply, and impair renal function, which ultimately leads to irreversible kidney failure [7]. This process is primarily driven by myofibroblasts, which originate from resident fibroblasts exposed to fibrogenic factors, such as transforming growth factor beta (TGF-β1), or other ECM components. Activation of TGF-β1 mediated renal injury. However, latent TGF-β1 showed a beneficial effect role in the inhibition of renal fibrosis and inflammation [19]. Renal fibrosis affects all compartments of the kidney from tubulointerstitial area to vascular system and glomeruli and leads to arteriosclerosis and glomerulosclerosis, which are common pathological pathways in most chronic kidney diseases [5].

Renal fibrosis is a complex process involving various cell types and molecular pathways [20, 21]. These factors promote the activation of fibroblasts and the excessive production of ECM components. Notably, kidney proximal tubular cells are particularly sensitive to hypoxic injury, and the degree of tubular damage is a key determinant of kidney disease prognosis [22]. Oxidative stress and inflammation are widely recognized pivotal factors in the development of renal fibrosis [9, 23]. Under normal conditions, oxidative stress leads to increasing antioxidant and cytoprotective enzymes to prevent tissue damage. This response is related to the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), which induces basal activity and coordinates inducing genes encoding antioxidant enzymes [9, 23]. This process triggers a vicious cycle in which oxidative stress evokes inflammation by various mechanisms, such as nuclear factor kappa B (NF-ƙB) activation, that results in activation and recruitment of immune cells [9, 23]. Inflammation mediates oxidative stress by producing reactive nitrogen and oxygen species, which mediate renal injury via apoptosis, necrosis and fibrosis [9, 23]. Mitochondria-produced reactive oxygen species (ROS) contribute to oxidative stress, which arises from an imbalance between ROS production and cellular antioxidant defences and leads to DNA, protein, and lipid damage in renal cells [24].

Acute kidney injury (AKI) is a clinical syndrome that results in aberrant kidney structure and function that is associated with various underlying molecular mechanisms [25–30]. Oxidative stress is a significant etiological and exacerbating factor in the development of renal diseases, including AKI and CKD, as well as in the transition and progression from AKI to CKD and ESRD [31, 32]. Clinical studies demonstrated that oxidative stress emerged in the early stages of CKD and increased with worsening renal function, and it was intensified in hemodialysis patients [9]. Oxidative stress plays a pivotal role in podocyte injury, proteinuria, segmental glomerulosclerosis, and tubulointerstitial fibrosis by activating specific pathways and interacting with the TGF-β/Smad signaling pathway to drive renal fibrosis [33]. The kelch-like ECH-associated protein 1 (Keap1)/Nrf2 signalling pathway plays a crucial role in the antioxidant response, and it has been extensively studied. The dissociation of the Keap1-Nrf2 complex during oxidative stress allows Nrf2 to translocate to the nucleus and bind to antioxidant response elements and enhance the expression of cytoprotective genes and antioxidant enzymes, such as catalase, nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), haem oxygenase-1 (HO-1), and glutathione peroxidase 1 [34]. Despite its protective role, excessive ROS production may lead to diminished Nrf2 activity and exacerbation of kidney damage vulnerability. The upregulation of Nrf2 using antioxidant therapies has shown promising results in many studies, which support its therapeutic potential [35]. Collectively, these findings emphasize that various factors beyond oxidative stress influence renal fibrosis.

Fibrosis progression often involves the infiltration of inflammatory cells and increased levels of inflammatory

factors, such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β). Inflammation is the natural response to external stimuli, uremia, oxidative stress, and endotoxins, and it aids tissue repair after injury. However, persistent inflammation is a primary driver of fibrotic disease development [36]. Oxidative stress promotes inflammation via generation of proinflammatory oxidized lipids, activation of NF-ƙB, and induction of expression of proinflammatory cytokines in prooxidant environment, which culminates in recruitment of proinflammatory cells and activation of fibroblasts [37]. Inflammatory cells, such as neutrophils and macrophages, are recruited during an inflammatory response. The accumulation of macrophages in kidney leads to production of cytokines, including interleukin-1 (IL-1), TNF-α, and ROS, which stimulate renal tubular epithelial cells to release profibrotic growth factors and the possible induction of epithelial–mesenchymal transition in tubular cells. The recruited macrophages directly transform into myofibroblasts, which promotes fibrosis progression in kidneys via several processes, including macrophage-myofibroblast transition [38, 39].

Although TGF-β1 is a key mediator of renal fibrosis, which is widely known for its role in promoting renal fibrosis, it is typically considered unrelated to inflammation. However, recent studies showed that TGF-β1 was an anti-inflammatory cytokine that regulated renal inflammation [38]. The anti-inflammatory effect of TGF-β1 partially explains the failure of TGF-β1 antibodies to alleviate the progression of diabetic kidney disease (DKD) in clinical settings [40]. The complement system is an important upstream inducer for inflammation, but it is also regulated by inflammatory responses. Studies have found that complement C5 is upregulated in type 2 diabetes and is accompanied by dysbiosis of gut microbiota. Measurement of the changes in renal C5a/C5a receptor expression in patients with type 2 diabetes mellitus and *db/db* mice revealed that excessive activation of C5 promoted the progression of renal fibrosis in DKD by activating signal transducer and activator of transcription 3 in glomerular endothelial cells and impairing the gut–kidney axis [41]. Another study reported that treatment with a C5a inhibitor in *db/db* mice reduced tubulointerstitial fibrosis by inhibiting intrarenal lipid accumulation and TGF-β-driven fibrosis [42].

Inflammation exacerbates oxidative stress to further compromise renal function. The NOD-like receptor protein 3 (NLRP3) inflammasome is a member of the NOD-like receptor family with three pyrin domains that contributes to diverse kidney diseases by impacting inflammation, pyroptosis, apoptosis, and fibrosis [43, 44]. Recent studies suggested that NLRP3 induced mitochondrial ROS production and fibrosis in podocytes, which exacerbated a decline in renal function [45].

In summary, oxidative stress and inflammation are major drivers of development and progression of renal fibrosis, and their interaction amplifies renal damage. Various factors induce oxidative stress and inflammation, and the gut-kidney axis has emerged as a novel perspective for understanding the complexities of renal fibrosis (Fig. 1).

Gut microbiome

Trillions of microorganisms inhabit human gastrointestinal tract that are collectively known as gut microbiota [46, 47]. These microorganisms have a symbiotic relationship with hosts and provide a broad range of benefits, including the

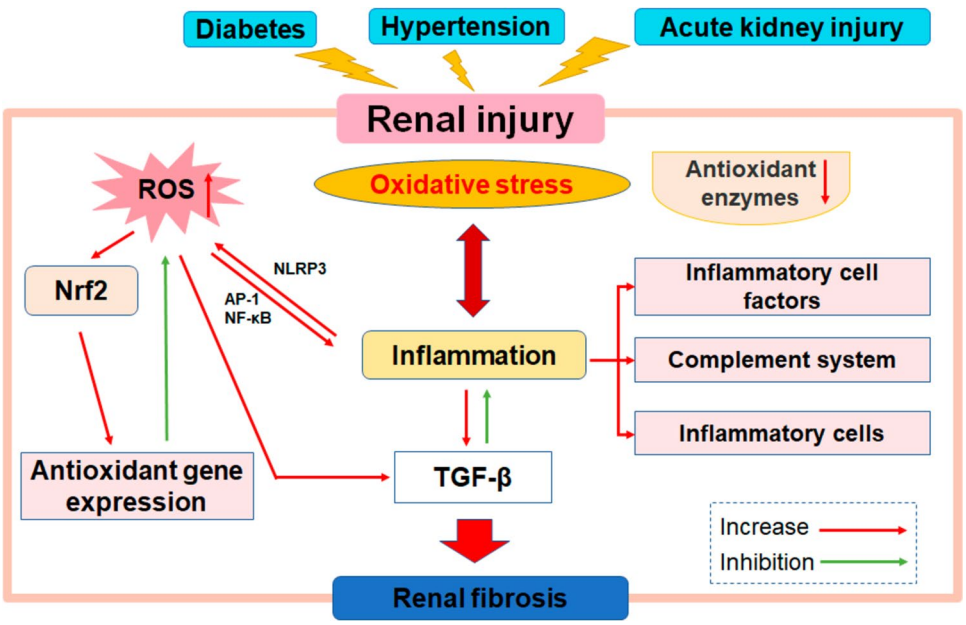

Fig. 1 Oxidative stress and inflammation mediate renal fibrosis. Kidney injury induces the production of ROS. As the balance between ROS and the antioxidant system is disrupted, oxidative stress and inflammation occur, leading to inflammation-related reactions that ultimately promote fibrosis. These pathways intricately link and reinforce each other. *AP-1* activator protein 1

production of vitamins and secondary bile acids and the metabolism of dietary proteins and carbohydrates, which are essential for host health [48]. Research in the microbiome often uses bioinformatics and microbiome sequencing to explore the functions and varieties of the gut microbiome [49].

Gut microbiome in health

The dominant bacteria are Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobia and Actinobacteria in healthy individuals. Bacteroidetes and Firmicutes account for 90% of the microbiome [50]. The number of bacterial species reported in the human gut differs between studies. Species can also differ between individuals due to differences in enterotype, body mass index, exercise frequency, lifestyle, and cultural and dietary habits [51]. However, there is a remarkable commonality among individuals. Arumugam et al. grouped human colonies of gut microbiota into three different enterotypes that were characterized by a high relative abundance of a single microbial genus: *Bacteroides*, *Ruminococcus* or *Prevotella* [52]. The Bacteroides enterotype was previously related to high-fat or high-protein diets, and Prevotella enterotype was associated with high-carbohydrate diets [53].

Gut microbiome in CKD

Mounting evidence indicates that kidney and gut microbiota have a complicated and bidirectional relationship [14, 54, 55]. Declining renal function leads to an accumulation of circulating uremic toxins that may lead to that may lead to local and systemic inflammation and induce profibrotic effects [56–58]. Ample evidence suggests that dysbiosis of gut microbiota is involved in renal disease [59, 60]. The latest study demonstrated that an elongation taxonomic chain Bacilli-Lactobacillales-Lactobacillaceae-*Lactobacillus*-*Lactobacillus johnsonii* correlated with patients with CKD progression, whose relative abundance strongly correlated with estimated glomerular filtration rate and serum levels of creatinine, urea and cystatin C [14]. Similarly, the relative abundance of *L. johnsonii* was significantly decreased in adenine-induced CKD rats. Further study showed that *L. johnsonii* supplementation attenuated renal injury [14]. Another study showed that *Escherichia coli* showed a higher abundance in patients with immunoglobulin A nephropathy than that in healthy control and altered *Enterococcaceae*, *Moraxella, Moraxella, and Acinetobacter* were associated with renal function injury, which were implicated in primarily bile acid metabolism [61]. In addition, *Coprococcus catus* and *Bacteroides stercoris* showed more and less abundant in patients with CKD respectively [62]. The bacteria were isolated and cultured from fecal samples of CKD patients, and lower relative abundances of short-chain fatty acid (SCFAs)-generating bacteria, such as *Bifidobacterium* spp. and *Streptococcus* spp., and higher relative abundances of Enterobacteriaceae and *Escherichia coli* with impaired kidney function, which confirm alterations in gut microbial composition in CKD patients [63]. Abnormalities in the intestinal microbiota of patients with ESRD can result in harmful metabolic pathways that encode functions involved in toxin and secondary bile acid synthesis, thereby exacerbating clinical outcomes. Two bacterial species, *Fusobacterium nucleatum* and *Eggerthella lenta* increase the production of uremic toxins and promote the development of kidney disease in CKD rats. In conclusion, the balance of intestinal functions is closely related to host health. An imbalance in intestinal microbiota composition and microbial function may play critical roles in intestinal and extraintestinal disease pathophysiology. The potential restoration of "healthy microbiota" to recover intestinal, immune, and metabolic homeostasis was safe and tolerable in previous clinical trials [64, 65]. However, the precise mechanisms are unknown and require further exploration.

Gut microbiota-mediated oxidative stress and inflammation in renal fibrosis

CKD patients exhibit persistent systemic inflammation, and a myriad of factors promote this state, such as uremic toxins, oxidative stress and infections. The dysbiosis of gut microbiota is an essential mechanism of CKD. The latest omics studies in CKD models revealed an increase in Enterobacteriaceae, *Eggerthella lenta* and *Clostridium* spp. and a decrease in *Bacteroides eggerthii*, *Roseburia faecis* and *Prevotella* spp. [66]. The relative abundances and compositions of the gut microflora alter the metabolic state, and reversing these changes inhibited inflammation, maintained intestinal barrier integrity, and enhanced intrarenal antioxidant capacity [67, 68]. The latest study showed that *Akkermansia*, *Lactococcus* and *Butymonas* were associated with renal function decline, aberrant metabolites, oxidative stress and mitophagy [69].

Generally, the dysbiosis of gut microbiota contributes to oxidative stress and inflammation via several mechanisms (Fig. 2), such as excessive accumulation of uremic toxins, decreased production of SCFAs, and leakage of gut barrier.

Uremic toxins in CKD

In the context of CKD, microbial metabolism transfers from carbohydrate to protein metabolism, which leads to an increase in the levels of protein fermentation metabolites in plasma. This results in an increase in a number of major microbial-derived uremic toxins (Table 1), including

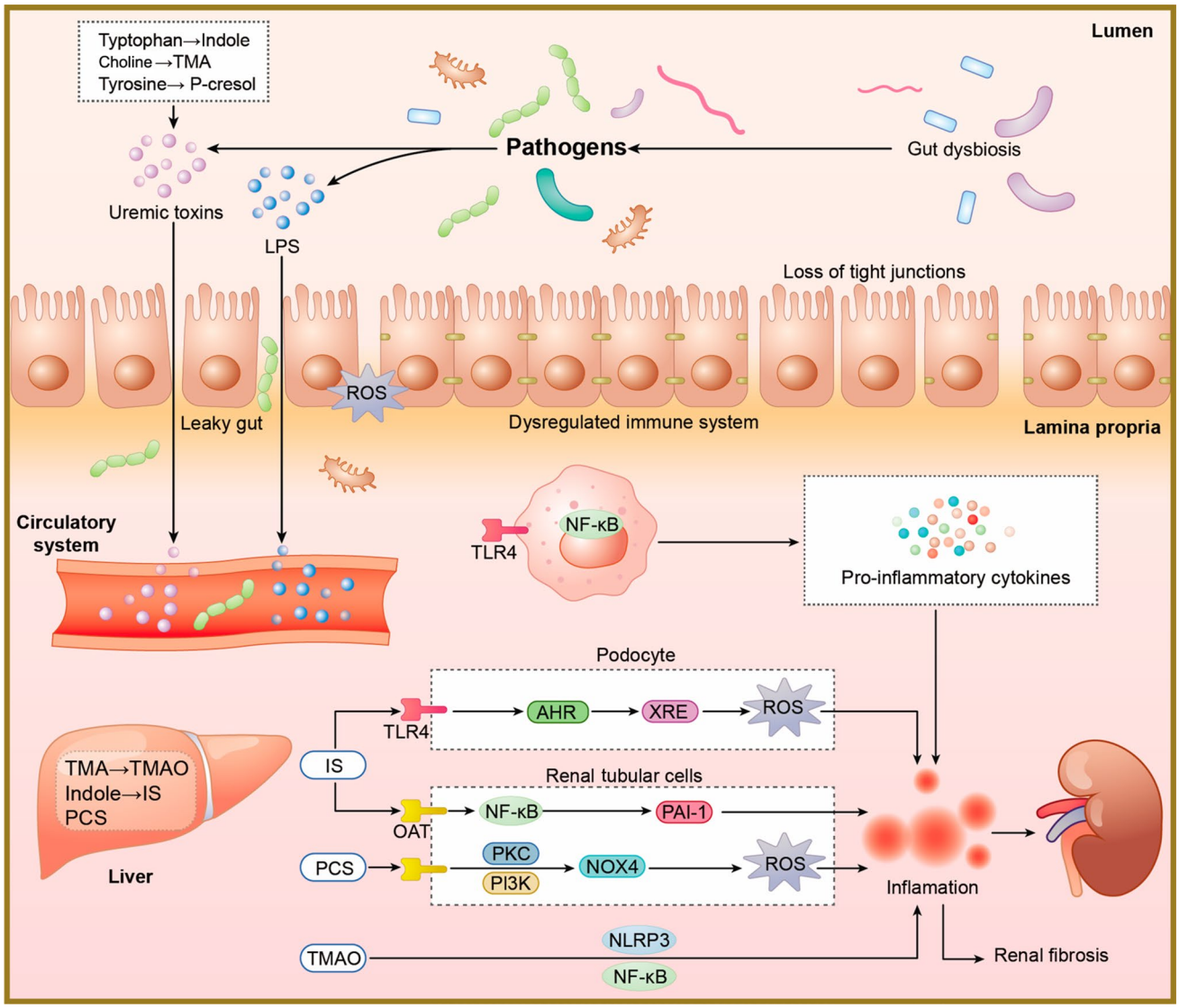

Fig. 2 Overview of the effect of gut microbiota dysbiosis in renal fibrosis. In the intestines, microbial dysbiosis leads to an increase in pathogens, resulting in elevated levels of LPS and gut-derived uremic toxins. These substances compromise the intestinal barrier, leading to "leaky gut," impairing mucosal immunity, and causing oxidative stress and inflammation in the intestinal mucosa. This stimulates the activation of immune cells that produce pro-inflammatory factors. Gut-derived uremic toxins are produced in the intestines and enter the circulatory system through the "leaky gut". They are metabolized by the liver and ultimately promote the development of renal fibrosis through the promotion of inflammation and oxidative stress. *OAT* organic anion transporter, *PAI-1* plasminogen activator inhibitor-1, *TLR4* Toll-like receptor 4

indoxyl sulphate (IS), indole-3-acetic acid (IAA), p-cresyl sulphate (PCS) and trimethylamine-N-oxide (TMAO) [15, 70, 71]. Typically, these metabolites are eliminated through glomerular filtration and tubular secretion [72]. However, these compounds accumulate in the body when the renal excretory capacity decreases, which creates a toxic milieu in the bloodstream [73]. The variation in plasma levels of protein-bound uremic toxins across different stages of CKD is not fully explained by differences in the rate of gut bacterial production alone. This finding implies that retention resulting from impaired kidney function is the major contributor to the elevated plasma levels [72]. The toxic metabolites retained as a result of altered kidney function contribute to the inflammatory state and drive fibrosis in kidneys, which is why patients with CKD must undergo dialysis. Unfortunately, protein-bound metabolites are difficult to remove using classical dialysis due to their protein-binding solid capabilities [74, 75]. In clinical studies, patients with hemodialysis exhibited higher inflammatory marker and uremic toxin levels than non-dialysis patients [76]. An increase in the serum levels of IS and PCS in stage 3–4 CKD patients also

Table 1 The metabolite, pathways, underlying molecular mechanism, primary outcome and possible pathway in renal fibrosis

Metabolites	Sample sources	Disease models	Molecular mechanisms	Primary outcomes	Signalling pathways	Ref(s)
TMAO	Kidney	CKD mice and TMAO-induced HK-2 cells	Increasing α-SMA protein expression	Decreased kidney mass and cell viability	Unknown	[71]
TMAO	Kidney	TMAO or choline diet mice	Increasing mRNA expression of *Col1A1*, *TIMP1*, *TGF-β* and *α-SMA*	Inducing renal function impairment and tubulointerstitial fibrosis	Unknown	[80]
TMAO	Kidney	NX rats	Increasing protein expression of MCP-1, TNF-α, IL-6, IL-1β, IL-18, NLRP3 and NOX4, decreasing SOD2 protein expression	Inducing renal failure, inflammatory cell infiltration and oxidative stress	p38/MAPK and NF-ƙB pathways	[87]
TMAO	Kidney	Diabetic rats	Increasing expression of TGF-β1, NLRP3 and IL-18	Inducing DKD, renal dysfunction and fibrosis	NLRP3 inflammasome	[84]
TMAO	Kidney	CKD mice, TMAO-induced RPTEC and MDCK II cells	Increasing expression of *IL-8*, *CCL2*, *CCL20*, NF-ƙB p65 and TNF-α	Increasing TMAO production and inflammatory response	Activating NF-ƙB pathway	[197]
IAA	Blood vessel	CKD patients and IAA-induced endothelial cells	Protein expression of decreasing cytoplasm AHR and increasing nuclei AHR and increasing mRNA expression of *CYP1A1*, *CYP1B1*, *tissue factor* and *COX-2*	Increasing *COX-2* and *tissue factor* expression and thrombotic risk in CKD patients	Activating AHR/p38MAPK/NF-ƙB pathway	[98, 99]
IAld	Serum	UUO and NX rats, CKD patients and 1-hydroxypyrene-induced HK-2 cells	Decreasing mRNA expression of *AHR*, *CYP1A1*, *CYP1A2*, *CYP1B1* and *COX-2* as well as Increasing cytoplasm and decreasing nuclei AHR protein expression	Improving renal function, inhibiting inflammation and attenuating renal fibrosis	Ameliorating AHR pathway	[14]
IS	T cells	IS-induced human peripheral T cells	Increasing expression of *CYP1A1*, *CYP1B1*, *AhRR*, *TNF-α* and *interferon-γ*	Modulating inflammatory response and cell cycle regulation in T cells	Activating AHR pathway	[100]
IS	Macrophages	IS-induced human monocyte-derived macrophages	Increasing expression of *TNF-α*, *CYP1A1*, *CYP1B1,* NF-ƙB, and SOCS2, decreasing AHR expression	Inducing macrophages to produce TNF-α	Activating AHR, NF-ƙB and SOCS2 pathways	[102]
IS	Plasma	Human plasma and hemolysate	Decreasing protein expression of catalase and SOD2	Inducing oxidative stress damage to hemolysate and shortened lifespan of red blood cells in the bloodstream	Impaired Nrf2 pathway	[104]
IS	Colon	IS-induced IEC-6 Cells	Decreasing mRNA expression of *Nrf2*, *HO-1*, *NQO1* and *SOD2*	Inducing oxidative stress and damage to intestinal epithelial cell monolayer integrity	Impaired Nrf2 pathway	[105]

Table 1 (continued)

Metabolites	Sample sources	Disease models	Molecular mechanisms	Primary outcomes	Signalling pathways	Ref(s)
IS	Colon and macrophages	IEC-6 cells and mice treated by IS	Increasing protein expression of COX-2, ROS, TNF-α, iNOS, IL-6 and IL-1β while decreasing protein expression of HO-1 and SOD2	Modulation of intestinal homeostasis, immune response and inducing systemic pro-inflammatory state	Activating NF-ƙB and impaired Nrf2 pathways	[106]
IS and kynurenic acid	Muscles and capillaries	Adenine-induced CKD mice	Decreasing protein expression of β-catenin and VEGFA	circulating IS and kynurenic acid in blood and AHR activity	Regulating tryptophan metabolite/AHR/β-catenin axis	[126]
PCS	Kidney	NX rats and PCS-induced HK-2 cells	Increasing mRNA expression of *p22*, *NOX4*, *TGF-β1* and *TIMP-1*	Increasing NADPH oxidase activity and ROS production	Activating NADPH oxidase via PKC or PI3K pathways	[109]
PS	Kidney	CKD mice, diabetic rats and PS-induced podocytes	Increasing mRNA expression of *TNF-α* and *MCP-1*	Increasing albuminuria levels, podocyte damage and inflammatory response	Inflammation-associated pathways	[110]

α-SMA alpha smooth muscle actin, *CCl* CC motif chemokine ligand, *COL1A1* collagen type I alpha 1 chain, *NOX4* nicotinamide adenine dinucleotide phosphate oxidase 4, *PKC* protein kinase C, *SOCS2* suppressor of cytokine signaling 2, *TIMP1* tissue inhibitor of metalloproteinase 1, *VEGFA* vascular endothelial growth factor A

correlated with increased levels of inflammatory biomarkers [77].

Uremic toxins, such as IS, IAA, PCS, and TMAO, play pathogenic roles in the stimulation of glomerular and tubular damage and the promotion of inflammation, oxidative stress and fibrosis [63]. Therefore, a low-protein diet is an effective therapeutic strategy to slow or prevent the progression of CKD [78].

TMAO

TMAO, a free water-soluble low-molecular-weight uremic toxin, is synthesized in the liver from trimethylamine, a metabolite derived from food components like choline, lecithin, betaine, and carnitine by gut microbiota [79]. 16S rRNA sequence analysis demonstrated that administering a high choline diet to mice increased the relative abundance of *Lactobacillus* and *Lachnospiraceae_UCG-002*, while decreasing the proportion of *Bacteroides*. These findings suggest the influence of TMAO on gut microbiota [80]. As a free water-soluble low-molecular-weight uremic toxin, TMAO can accumulate in plasma of CKD patients and is effectively removed by dialytic clearance [81].

While existing research mainly focuses on cardiovascular effects of TMAO, recent studies also suggest a correlation between elevated TMAO levels and renal fibrosis, specifically in animal models. Prolonged consumption of a high TMAO diet has been directly linked to progressive renal fibrosis and dysfunction [82]. Patients with type 2 diabetes and CKD were found to have a higher relative abundance of trimethylamine-producing gut bacteria than healthy subjects [83].

The onset and progression of TMAO-mediated CKD primarily involve inflammation mechanisms. In vivo studies indicate that TMAO stimulates the activation of the NLRP3 inflammasome, resulting in the release of IL-1 and IL-18, accelerating renal inflammation and fibrosis [84]. TMAO is also known to activate NF-ƙB signaling pathway [85]. Recent studies have found that inhibition of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/NF-ƙB signaling pathway mediated by lipopolysaccharide (LPS) and TMAO can significantly suppress inflammation, cell apoptosis, and oxidative stress in AKI [86]. Interestingly, Lai et al. found that TMAO could activate NLRP3 inflammasome and aggravate oxidative stress by upregulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 and downregulating SOD2 [87]. TMAO has also been suggested to aggravate hyperoxaluria-induced kidney injury by triggering protein kinase RNA-like endoplasmic reticulum kinase/ROS signaling pathway, thus enhancing autophagy, apoptosis, and inflammation [88]. While the direct impact of TMAO on fibrosis is not fully understood,

further investigations are warranted to explore its potential role in this context.

tryptophan metabolites

Genome analysis indicated that tryptophan metabolism was closely associated with protein-bound uremic toxins in CKD rats [89]. This finding emphasizes the role of tryptophan metabolism in CKD. Many bacteria are closely related to tryptophan metabolites, such as indole, tryptamine, IAA, indole-3-lactic acid, indole-3-aldehyde, and indole-3-propionic acid (IPA) [90]. After metabolism by gut microbiota, they play a beneficial role in intestinal mucosal stability and anti-inflammatory properties [91]. Aryl hydrocarbon receptor (AHR) is a typical ligand-activated transcription factor that were implicated in renal disease [92, 93]. These metabolites serve as ligands for the AHR, leading to direct or indirect exacerbation of renal fibrosis progression through underlying mechanisms (Fig. 3).

IS and IAA have been extensively studied in renal fibrosis. As a protein-binding uremic toxin, IS is poorly cleared by dialysis. Therefore, the decreased ability to eliminate IS

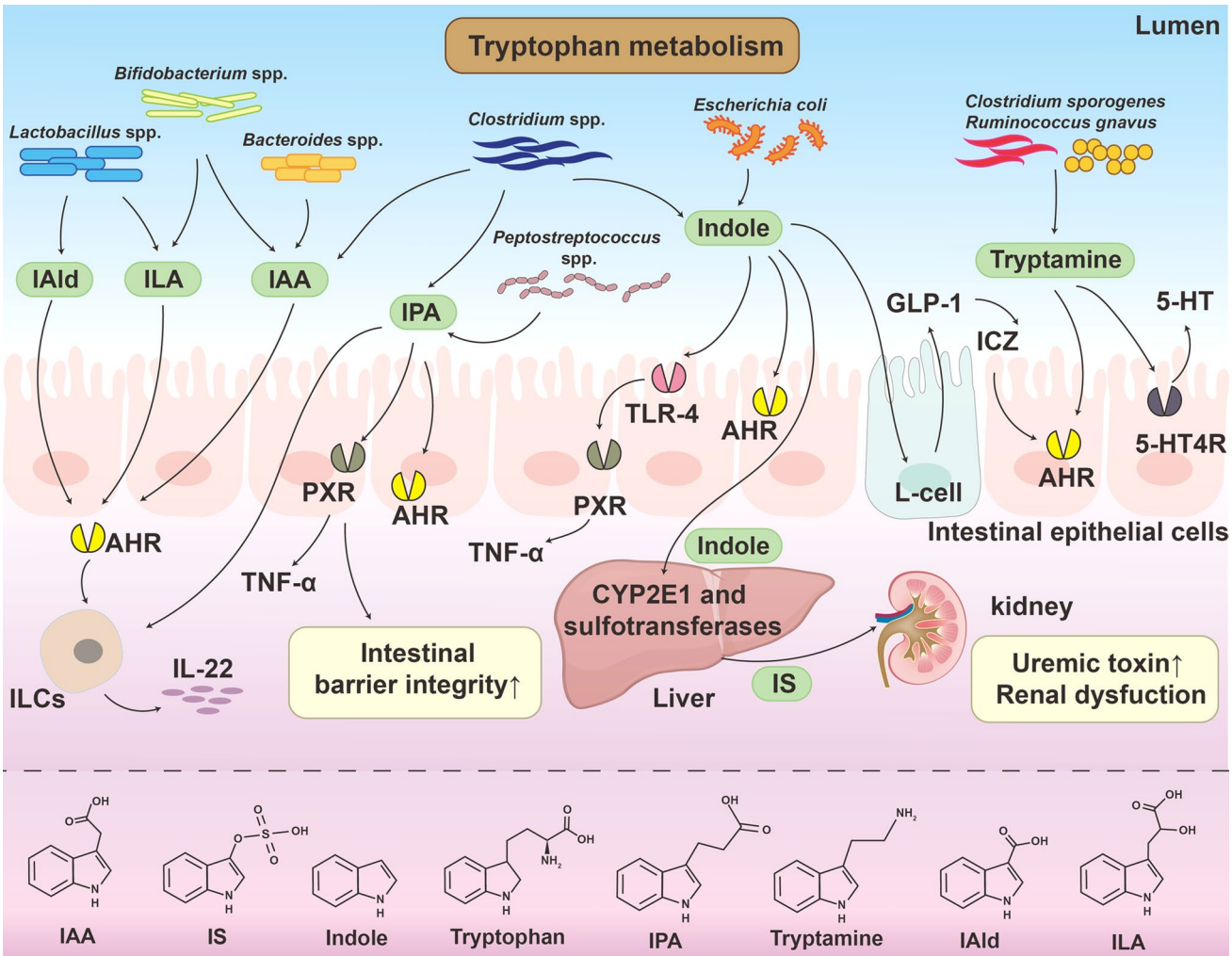

Fig. 3 Tryptophan-derived metabolites of intestinal microorganisms and their effects on host physiology and disease. The intestinal microbiota metabolizes tryptophan and produces specific metabolites. Here are shown 6 kinds of tryptophan-derived microbial metabolites that are capable of directly or indirectly activating AHR receptors, thereby triggering immune cells such as ILCs to promote inflammatory status. Indole and IPA may both mediate PXR to secrete TNF-α, with IPA being shown to enhance the stability of the intestinal mucosal barrier, while indole may regulate PXR via activation of toll-like receptors. Indole is metabolized into IS by CYP2E1 and sulfotransferases in the liver, which leads to uremic toxin accumulation and renal dysfunction. Indole also induces the release of GLP-1 in enteroendocrine L-cells, promoting the production of ICZ, which also activates AHR. Several tryptophan catabolites activate AHR in intestinal immune cells to alter innate and adaptive immune responses that maintain mucosal reactivity. Tryptophan serves as a ligand for 5-HT receptors to stimulate 5-HT secretion, thereby stimulating gastrointestinal motility. *5-HT* serotonin, *GLP-1* glucagon-like peptide-1, *ICZ* indole[3,2-b] carbazole, *ILA* indole-3-lactic acid, *ILCs* innate lymphocyte cells, *PXR* pregnane X receptor

in CKD leads to increased serum IS levels. Once IS is transported into renal tubular cells via organic anion transporters in the basolateral membrane of basal cells, it mediates renal tubular cells to produce TGF-β1 and chemokines, which induce free radicals in renal tubular cells and endothelial cells, trigger oxidative stress, and enhance cytokine expression and inflammatory responses via the induction of plasminogen activator inhibitor-1 and activation of NF-ƙB [94, 95].

Indole-3-aldehyde (IAld) is one of tryptophan metabolites by *L. johnsonii* [14]. The latest study demonstrated that decreasing serum IAld level in rats induced by unilateral ureteral obstruction (UUO) and 5/6 nephrectomy (NX) as well as CKD patients [14]. IAld attenuated renal injury by inhibiting the mRNA expression of AHR and its downstream target gene cyclooxygenase-2 (COX-2) in rats with CKD or UUO, and in cultured 1-hydroxypyrene-induced HK-2 cells [14]. Renoprotective effect of IAld was partially diminished in AHR deficiency mice and HK-2 cells [14]. The findings demonstrated that *L. johnsonii* mitigated renal injury by inhibiting AHR signalling pathway via increasing serum IAld level.

Furthermore, IS and IAA, as typical AHR ligands, can bind to cytoplasmic AHR, and the IS/AHR complex translocates to the nucleus, where it binds to AHR nuclear translocation via heat shock protein 90 exchange and serves as a transcriptional activator by binding to specific xenobiotic response elements in promoter regions of enzymes that generate ROS [96]. Current research on IAA primarily focuses on its ability to damage vascular endothelial cells. Clinical studies have shown a positive correlation between AHR protein expression in CKD patients and IAA plasma levels [97]. IAA activates the AHR/mitogen-activated protein kinases (MAPK) pathway and regulates cell proliferation, differentiation, and immune function in ESRD patients, and it induces cardiovascular disease [98]. In vitro experiments, previous studies have shown that IAA activated AHR/p38 MAPK/NF-ƙB pathway and upregulated COX-2 expression and activity to induce oxidative stress and inflammation [98, 99]. These findings suggest that prooxidative and proinflammatory effects of IAA contribute to the progression of CKD.

Recent studies indicated that IS played a crucial role in the activation of AHR and the progression of CKD. Notably, IS can activate the AHR pathway in CKD, resulting in the upregulation of its target genes, *cytochrome P450 family 1 subfamily A member 1* (*CYP1A1*), *cytochrome P450 family 1 subfamily A member 2* (*CYP1A2*), *cytochrome P450 family 1 subfamily B member 1* (*CYP1B1*), *COX-2* and *aryl hydrocarbon receptor repressor* (*AhRR*) [100]. AHR activation by IS caused podocyte and glomerular injury. The intrarenal IS levels in rats with chronic renal failure were increased sixfold, and mice induced by IS for 8 weeks exhibited glomerular and vascular injury with increased CYP1A1 expression. IS also induces AHR nuclear translocation in mice, which elevated CYP1A1 expression and decreased the size and viability of podocytes [101]. IS-mediated AHR binds to NF-ƙB p65 subunit and leads to mutual inhibition of AHR and NF-ƙB, which suppresses the production of TNF-α in macrophages of CKD patients. IS-activated AHR is translocated to the nucleus and binds to xenobiotic response element sites, which inhibits NF-ƙB activation and mitigation of the mutual inhibition of AHR and NF-ƙB. Once released from suppression, the IS-activated AHR is recruited to the nucleus at later time points where it mediates TNF-α expression by interacting with the AHR binding site in the TNF-α gene [102]. A recent study showed that IS increased the expression of interferon regulatory factor 1, which is a downstream AHR gene, and alleviated CKD-associated intestinal dysfunction [103]. IS also inhibits antioxidant enzyme activity. A recent study showed that IS induced oxidative damage by changing oxidative stress in plasma, which suggested that it decreased erythrocyte lifespan in the bloodstream of CKD patients [104]. IS contributes to intestinal alterations associated with CKD primarily by inducing ROS release, reducing antioxidative responses, and influencing nuclear translocation of Nrf2 and its downstream antioxidant enzymes, which amplify oxidative cell damage [105]. IS also affects gut homeostasis and immune responses and induces a systemic pro-inflammatory state, which supports its use as a therapeutic option for CKD patients [106]. Several studies demonstrated that IS increased TNF-α and IL-6 levels to exacerbate inflammatory state and oxidative stress [107].

Although metabolic products of tryptophan have been extensively studied in the intestinal environment, the effects of other products on renal fibrosis have not been widely reported. For example, IPA has antiinflammatory and antioxidant effects, and Sun et al. reported that elevated serum IPA levels negatively correlated with CKD development, which indicates that IPA may be a key biomarker and protective factor for CKD [108]. Therefore, this pathway may be a promising direction for future investigations of renal fibrosis.

PS and PCS

Phenol is synthesized from tyrosine and phenylalanine by tyrosine phenol-lyase and further modified to produce PS or PCS, which are also highly conjugated with proteins. IS and PCS are often studied together due to their similarities, but comparatively less research has been performed on how PCS leads to renal fibrosis. Previous studies reported that PCS caused damage to renal tubular cells [109]. PCS activates NADPH oxidase and the production of ROS via the protein kinase C and PI3K signaling pathways, which lead to the expression of inflammatory cytokines in renal tubular cells and the mediation of renal fibrosis [109]. In the context of DKD, PS is a predictor of incipient albuminuria.

Kikuchi et al. used murine models of mild and severe DKD and demonstrated an active role of PS in DKD [110]. PS triggered albuminuria by eliciting podocyte injury and pro-inflammatory. A previous study revealed that *Adlercreutzia* and unclassified *Erysipelotrichaceae* in feces were positively associated with plasma PS levels, which indicated that these minor taxa may contribute to changes in PS levels [110].

Intestinal mucosal barrier

The dysbiosis of gut microbiota and gastrointestinal barrier disruption contribute to sustained and systemic inflammation in CKD patients. The gastrointestinal tract is lined by a single epithelial cell layer, which is essential for nutrient absorption and acts as an important barrier that prevents or hinders pathogen and antigen translocation [111]. It is primarily comprised of enterocytes with interspersed specialized cell types, such as goblet and neuroendocrine cells.

The dysbiosis of gut microbiota increases the population of pathogenic bacteria that are more strongly associated with the production of LPS and uremic toxins, which damage epithelial cells. Damage to epithelial cells leads to a marked loss of barrier function, and the intestinal mucus layer plays a crucial role in this context. The core of maintaining the colonic mucus layer is the mucins produced by goblet cells. Bacteria that synthesize mucus help restore mucus layer by producing SCFAs [112]. Any alteration in gut microbiota can disrupt mucin synthesis and impair the integrity and defensive function of the mucus barrier [113]. This disorder exacerbates the translocation of bacteria and their harmful by-products, which worsens systemic inflammation and the progression of CKD [114]. The shift of bacteria and their products from intestinal lumen to circulatory system activates pattern-recognition receptors on various cell types. Epithelial cells bind to each other via tight junctions, adherens junctions, and desmosomes, but tight junctions are essential structures. Tight junction integrity defects are a significant cause of increased permeability and intestinal dysfunction. Tight junctions are further composed of claudin, occludin, junctional adhesion protein molecule-A, as well as intracellular plaque proteins, such as zonula occludens and cingulin [115]. Breakdown of intestinal barrier leads to leukocyte infiltration and local inflammation, which induce retraction and endocytosis of transcellular tight junction proteins, such as claudins and occludin. This pathological condition is known as "leaky gut" and leads to chronic systemic inflammation [116]. Intestinal tight junction protein expression is always lower and systemic microinflammation occurs in CKD-fecal microbiota transplantation mice [117]. Previous research focused on urea because it can be metabolized by intestinal bacterial urease to ammonia, which leads to tight junction breakdown [118]. In addition, current studies indicate that a low-potassium diet, low LPS levels, and uremic toxins also increase intestinal permeability, which leads to bacterial translocation [103, 114].

As the largest lymphoid organ in the body, the gut mucosal immune system is richly endowed with immune cells, which recognize and process ingested antigens, thereby inducing tolerance and protective immunity against intestinal pathogens. This system regulates inflammation by activating innate and acquired immunity. When tight junctions of the intestinal epithelium are damaged, bacteria and endotoxins are transported through the intestinal wall to the underlying tissue compartment, which may lead to increased antigen exposure and dysregulation of mucosal immune system, which triggers a local inflammation that leads to persistent intestinal barrier damage [9]. Microbial–derived metabolites, especially LPS, lead to an enhanced inflammatory response, which further promotes CKD progression [119]. Research indicates that LPS, in conjunction with other microbial-derived toxins, can synergistically enhance inflammatory responses. (1 → 3)-β-D-glucan, a major component of the Candida cell wall, together with LPS, further exacerbates inflammation in bilateral nephrectomy mice and liver injury [120]. Meanwhile, an in vitro study also showed that combination of LPS and (1 → 3)-β-D-glucan increased expression of IL-6 and TNF-α in supernatant of HK-2 cells and upregulation expression of genes including Dectin-1 and Toll-like receptor 4, which promote inflammatory and fibrotic processes [121]. This evidence supports the hypothesis that gut leakage exacerbates fibrotic progression by promoting renal inflammation. Heat shock protein 70 is constitutively expressed and functions as a tight junction stabilizer. "Leaky gut" was accompanied by decreased claudin-1 and heat shock protein 70 expression [122]. Yang et al. reported that the expression of cytokines and the ratio of pro-inflammatory-to-resident macrophages in colon of CKD mice were increased in association with "Leaky gut" [122]. In addition to immune cells, the innate immune system also plays an important role in this process. Mitochondrial antiviral signaling proteins are part of the innate immune system that suppresses inflammatory responses and maintains intestinal integrity. The presence of enteric *Clostridium* spp. and elevated interleukin-17 levels were observed in the bloodstream and kidney in diabetic mice, especially diabetic mitochondrial antiviral signaling protein-knockout mice [123].

Therefore, any disruption of the microbiome in CKD can lead to intestinal barrier disruption and result in mucosal immune dysregulation, systemic immunological imbalance, and chronic inflammation, which lead to the progression of renal fibrosis, and the restoration of intestinal dysbiosis may improve this condition [124]. Therefore, it is necessary to further research the potential mechanisms by which the gut microbiome leads to intestinal barrier disruption and how to effectively prevent subsequent mucosal immune dysregulation.

SCFAs

As previously described, gut microbiota substantially contributes to the production of uremic solutes and disruption of the intestinal barrier, but growth without microbiota has more harmful effects on CKD. Because SCFAs and amino acid utilization show a renoprotective effect, the loss of these factors may explain the exacerbation of renal damage in germ-free mice with renal failure [125]. SCFAs are produced by intestinal microbial fermentation from undigested dietary fiber [126, 127]. The most abundant SCFAs are acetate, propionate and butyrate. These metabolites have beneficial effects and act as signaling molecules in several pathways.

However, SCFAs are reduced in the different stages of CKD and in dialysis patients [128]. This decrease is associated with the dysbiosis of gut microbiota, and the reduced production of SCFAs exacerbates the progression of CKD [10]. This finding indicates that in addition to being a source of nutrients, SCFAs produced by the gut flora act on oxidative stress and inflammation via complex regulatory mechanisms (Fig. 4). SCFAs inhibit inflammation in several organs by suppressing the migration and proliferation of immune cells and cytokine levels [41]. Supplementation

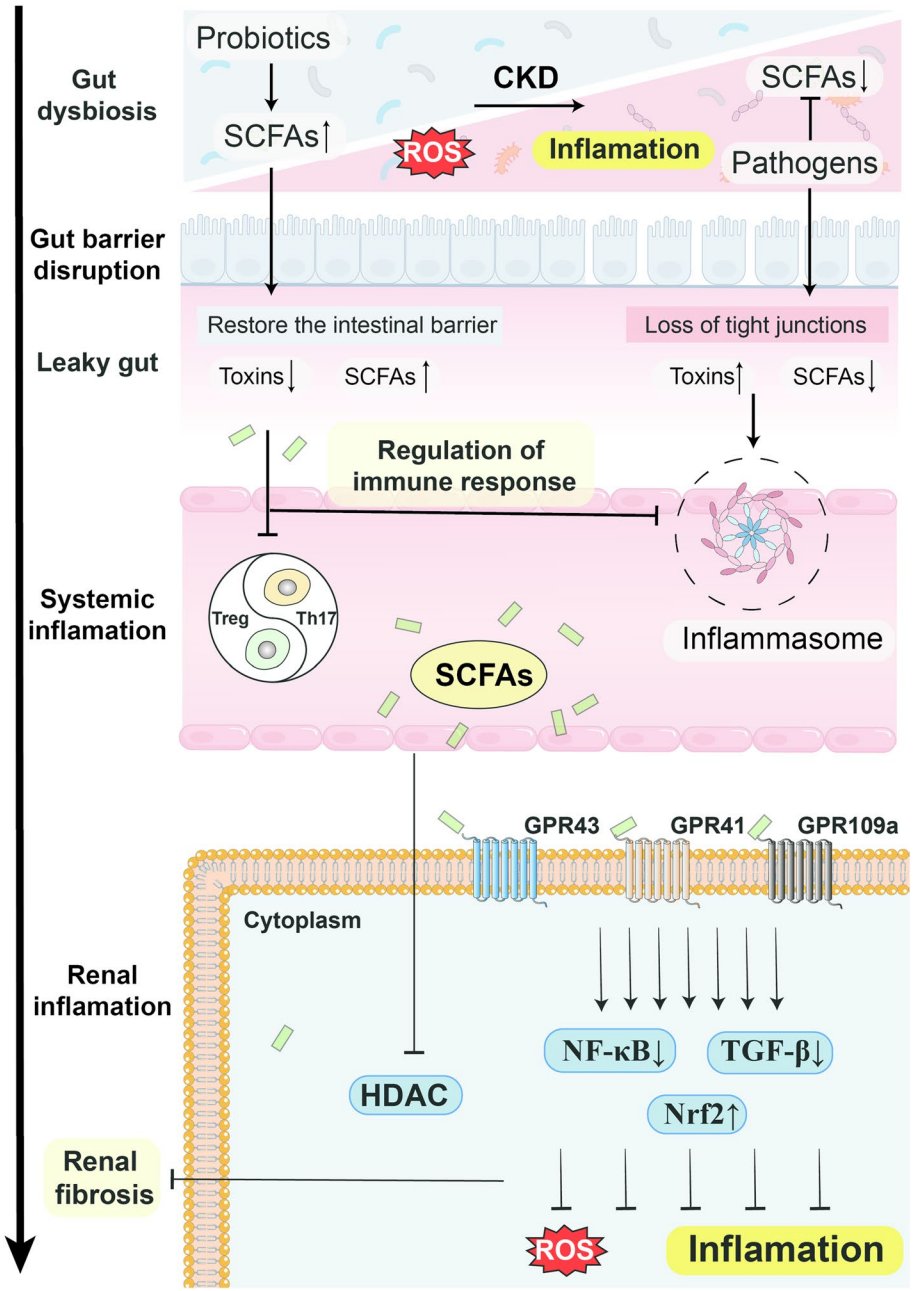

Fig. 4 Regulatory role of SCFAs on oxidative stress and inflammation in gut microbiota dysbiosis during CKD. In the context of CKD, there is a disruption of the gut microbiota, which leads to an increase in toxins and a decrease in SCFAs. These changes compromise the intestinal barrier, leading to "leaky gut," impairing mucosal immunity, causing oxidative stress, and triggering systemic inflammation, ultimately promoting renal fibrosis. Supplementing with probiotics can increase the production of SCFAs. SCFAs help repair the intestinal barrier, promote the balance between Treg and Th17 cells, and reduce the production of uremic toxins and endotoxins, thereby inhibiting oxidative stress and inflammation. SCFAs can inhibit HDAC or bind to receptors such as GPR41, GPR43, and GPR109A, downregulating NF-ƙB and TGF-β, and promoting the expression of Nrf2 to suppress oxidative stress and inflammation, ultimately reducing the occurrence of renal fibrosis

with bicarbonates restore oxidant-antioxidant balance in T cells [129]. SCFAs reduce intestinal inflammation by restoring the balance of Treg/Th17 cells [130].

The ability of SCFAs can modulate oxidative stress and the inflammation reported by in vivo and in vitro experiments, and it correlates with many secondary complications. Acetate improved glomerular injury and renal fibrosis by ameliorating mitochondrial dysfunction [131], but not cisplatin-induced fibrosis [132]. SCFAs improved inflammation in podocytes and renal tubular cells under hyperglycemic conditions [133]. Dong et al. showed that butyrate supplementation in a standard diet inhibited the expansion of glomerular and mesangial areas, interstitial fibrosis and oxidative injury in DKD in an Nrf2-dependent manner [134]. Butyrate salts also reduced the overexpression of TGF-β induced by persistent low-grade inflammation [135]. The levels of SCFAs are reduced in CKD patients, and butyrate ameliorates renal fibrosis by reducing production of trimethylamine (TMA) and TMAO [136]. Sodium propionate reduced oxidative stress and inflammation, which suppressed important gut-derived uremic toxins, including IS and PCS in hemodialysis patients [137]. The protective effects of SCFAs on the intestinal mucosa should not be overlooked. Butyrate strengthens the intestinal barrier by modulating intestinal permeability and mucin expression and inhibits LPS influx into the blood, which attenuates the progression of CKD [114, 138].

Mechanistically, SCFAs regulate local renal inflammation and ROS via binding to free fatty acid receptors orphan G-protein coupled receptor (GPCR) family, such as GPR43, GPR41, GPR109a, and olfactory receptor 78 (Olfr78), or by acting as histone deacetylase (HDAC) inhibitors [37, 139]. GPR43 and GPR41 are majorly expressed in distal renal and collecting tubules, and podocytes express GPR109a. However, how SCFAs alleviate oxidative stress and inflammation in CKD via binding to GPCRs remains controversial. Li et al. demonstrated that SCFAs-treated diabetic mice showed amelioration of renal fibrosis and inflammation, but not in the absence of GPR43 or GPR109A [133]. Interestingly, SCFAs activated GPR41 and GPR109a but not GPR43 in a folate-induced CKD model to reduce interstitial fibrosis and chronic inflammation, which slowed the progression of CKD [140]. A high-fiber diet is often associated with the production of SCFAs, and high-fiber diets effectively reduced renal fibrosis in a deoxycorticosterone acetate salt model. However, GPR43 and other GPCRs, such as Olfr78, are not expressed in the kidney [141]. The type of SCFAs and disease model we studied likely affect the receptors activated by SCFAs. Butyrate partially improves renal function via GPR43-mediated suppressing oxidative stress and NF-ƙB signaling pathway and inhibits mesangial matrix accumulation and renal fibrosis [142]. Butyrate also binds to GPR109a. It improved proteinuria by retaining podocytes and reduced tissue inflammation and glomerulosclerosis [143]. A recent study revealed that propionate suppressed expression of intrarenal proinflammatory factors and fibrosis-related genes in mouse induced by adenine, and these protective effects of propionate were associated with GPR43 and GPR41 as propionate receptors [139]. The greatest SCFAs secreted by gut commensal bacteria in the large intestine is acetate, which is more selective for the GPR43 receptor, which was critical for acetate-mediated renoprotection and tolerance in murine models of DKD and kidney transplantation, respectively [133].

In addition to GPCRs, SCFAs are also inhibitors of intracellular HDACs, which attenuate the progression of renal fibrogenesis, ROS generation, and inflammation [144]. In mice with ischemic nephropathy, gene expression analysis of receptors of SCFAs revealed that acetate treatment modulated epigenetic modifications and upregulated GPR43 expression. However, acetate mitigated the production of proinflammatory cytokines, cellular oxidative stress, and apoptosis independent of GPR43 and GPR41 by suppressing HDAC expression [145], Similar results were observed in sepsis-induced AKI [129]. These studies indicated that intrarenal GPR signaling may not be involved in the inhibition of HDACs by SCFAs. In contrast, HDAC inhibition in colonic tissue partially depends on GPR43 [132]. Therefore, the precise mechanisms involved should be further investigated. Notably, acetate, propionate, and butyrate bind to Olfr78 receptor, which regulates T lymphocyte function by increasing Th1 and Th17 cells to improve immunity [37]. The role of Olfr78 in renal fibrosis remains unclear, and further elucidation of its function in renal fibrosis may be a promising field.

Current research suggests that SCFAs are associated with oxidative stress and inflammation in CKD patients. However, all these studies are preliminary or controversial because determining the exact mechanisms of SCFAs in the enteric-renal axis is a significant challenge. Due to stimulation intensity and differences in animal models, these mechanisms may differ between and within tissues. Therefore, the specific mechanisms require further exploration.

CKD treatment by regulating gut microbiota

Microecological preparations

Modulation of the gut-kidney axis may be a good strategy for patients to slow the progression of CKD, and many current therapeutic strategies target this vital aspect [146, 147]. Notably, gut microbiota has the innate ability to resist external influences, but it is susceptible to the external environment. Modulation of the intestinal environment may be used as a beneficial therapeutic effect for CKD. Microecological

preparations, faecal microbiota transplant (FMT), long-term dietary interventions and nutritional supplements have been the primary focus of research on modulating CKD-related gut microbiota strategies.

Microecological preparations, including probiotics, prebiotics and symbiotics, aim to mitigate oxidative stress and inflammation, reduce the reversion of dysbiotic microbiota, effectively alter producers of SCFAs, and attenuate renal fibrosis [148]. Recent research also revealed that oral administration of Bacteroides fragilis reduced LPS production and improved renal fibrosis via modulation of 1,5-anhydroglucitol levels. As an activator of TGR5, 1,5-anhydroglucitol attenuated renal fibrosis by inhibiting oxidative stress and inflammation [149].

Although animal model studies and clinical trials showed a beneficial effect of biotic supplements for CKD [68], some studies failed to confirm these benefits [150, 151]. This failure is likely due to the confounding effects of many other factors. Therefore, more evidence is needed to support the use of microecological preparations as an effective treatment option in these settings [152–154]. FMT is a beneficial therapeutic option that is validated only by recurrent *Clostridium difficile* infection, ulcerative colitis and metabolic syndrome [155]. Although FMT failed to alter kidney function in CKD patients, it reduced the accumulation of uremic toxins generated via intestinal cresol pathway and had a beneficial influence on gut microbiota diversity [156]. A recent metagenomic investigation revealed that FMT treatment in mice regulated tryptophan metabolism and lysine levels to delay the malignant development of CKD [89]. Therefore, strategies to reverse microbial dysbiosis using FMT remain promising therapies for CKD [157].

Long-term dietary interventions have been shown to overcome microbial resistance and alter composition and metabolism in gut microbiota [158, 159]. Therefore, the beneficial effect of CKD diets is based on controlling protein, phosphate, sodium and intake while keeping nutritional status via essential amino acid supplementation and supplying a high energy intake [160, 161]. Other patterns of dietary control, such as the Mediterranean and Dietary Approaches to Stop Hypertension diets, show a positive effect on gut microbiome and inhibiting oxidative stress [162]. The Mediterranean diet, which includes abundant fruits, vegetables, olive oil and whole grains, is loaded with dietary fiber, polyphenols, and unsaturated fatty acids, which improve beneficial bacteria growth, such as butyrate producers, including *Clostridium leptum* and *Eubacterium rectale*, and reduce the growth of pro-inflammatory bacteria such as *Firmicutes*. These changes improve inflammation, oxidative states, and oxidative stress parameters [162], and may also benefit kidney function [163]. The Dietary Approaches to Stop Hypertension diet, which includes low-salt and plant-rich foods, has shown potential for reducing the risk of type 2 diabetes, metabolic syndrome, and CKD, although some controversies remain [164]. Nutritional supplements, such as fiber supplements, bioactive compounds, and fermented foods also regulate gut microbiota [165]. Notably, the mechanism of their action is similar to microecological preparations. It is not surprising that the above-mentioned therapeutic strategies aim to modulate the intestinal environment by supplementing beneficial bacteria in the intestine or providing nutrient compounds for beneficial bacteria. The functional plasticity of gut microbiota in response to changes in diet presents an opportunity to use food as a medicine in CKD [166].

Carbon adsorbent

AST-120, as a chelator, can adsorb uremic toxins and their precursors in the gastrointestinal tract, which allows the excretion of these factors in feces before absorption into bloodstream [167]. Recent research suggests that AST-120 ameliorates renal function by restoring terminal and tight junctions via the Toll-like receptor pathway, which mitigates systemic inflammation and contributes to its renoprotective effects [168]. The scavenging of IS precursors by AST-120 markedly ameliorated IS-induced oxidative stress and rescued antioxidant glutathione activity in tubular epithelial cells, which protected against tubular injury and ultimately slowed renal functional decline [169].

Natural products

There is an increasing interest in traditional Chinese medicine or natural products for treatment of CKD based on the advantages of multiple ingredients, multiple links and multiple targets [170–174]. A variety of natural components are attractive for renal fibrosis treatment and rehabilitation [175–180]. They showed the effectiveness in regulating intestinal flora and alleviating renal fibrosis in patients and animal models with CKD [181, 182].

The latest study showed that The Yi-Shen-Hua-Shi granule reduced proteinuria associated with improving dysbiosis of gut microbiota in CKD patients [183]. In addition, Sanziguben polysaccharides alleviate DKD by improving dysbiosis of gut microbiota and inhibited TLR4/NF-κB/NLRP3 pathway [182]. Moreover, combining *Bifidobacterium bifidum* tetragonum tablets and Jin Gui Ren Qi Pill improved microbial dysbiosis and metabolism disorder in patients with DKD [184]. Resveratrol has been widely studied for its potent antiinflammatory, antioxidative and antiglycation properties in CKD [185–187]. Research has shown that resveratrol effectively lowered serum urea, creatinine, and 24-h urinary total protein levels in db/db mice and reduced intestinal permeability while increasing the abundance of beneficial bacteria, such as *Bacteroides*, *Alistipes*, and *Parabacteroides*, which are associated with antiinflammatory

factors and display antiinflammatory effects. Studies have also found that faecal transplantation from mice treated with resveratrol into *db/db* mice produced similar results [124]. To enhance the bioavailability of resveratrol, another study synthesized resveratrol butyrate via esterification with butyric acid. High doses of resveratrol butyrate were linked to reduced renal expression of GPR41 and Olfr78, which counteracted the AHR signaling pathway, and increased the abundance of beneficial bacteria such as *Akkermansia*, *Blautia*, and *Enterococcus* genera [188]. Curcumin is a natural polyphenol compound and one of the main components of turmeric with renoprotective effects [189, 190]. Clinical investigations have found that, after 6 months of curcumin supplementation in CKD patients, the abundance of *Shigella* was lower while that of *Lactobacillus* was higher, as well as decreased plasma pro-inflammatory mediators and lipid peroxidation [191]. Similarly, another study showed that treatment with a docosahexaenoic acid-acylated curcumin diester significantly reduced the relative abundance of *Proteobacteria*, *Bacteroides*, *Bilophila*, and *Succinivibrio*, which are closely associated with LPS and TMAO/TMA metabolism [86]. Alginate oligosaccharides are extracted from brown algae. Alginate oligosaccharides increase the relative abundances of *Lactobacillus johnsonii* and *Lactobacillus reuteri*, improving cisplatin-induced kidney oxidative damage [192]. In addition, punicalagin, *Rehmannia glutinosa* leaves total glycoside, and *Cordyceps cicadae* polysaccharides have also shown promising effects in improving renal function [193–195]. The most common changes related to natural product are changes in the abundance of *Lactobacillus*, *Akkermansia*, and *Bacteroides* which have positive effects on CKD. However, most of these studies were conducted in animal models, and clinical studies are limited. Furthermore, there is a lack of correlation between the experimental results and changes in microbiota. Therefore, to gain a more comprehensive understanding of the underlying mechanisms by which natural products regulate gut microbiota and their potential role in CKD, further research should prioritize human clinical studies and consider establishing fecal transplantation groups as well as utilizing metagenomic analysis to provide more compelling evidence.

Conclusion

As detailed in this review, it has been increasingly acknowledged that homeostasis between the host and gut microbiota plays a crucial role in renal fibrosis. The interaction between gut microbiota and kidney is bidirectional. On the one hand, the uremic milieu affects the composition and function of gut microbiota, and on the other hand, ecological disruption is associated with an increase in uremic toxins and microinflammation derived from the microbial population, both of which promote the progression of kidney disease. Inhibitors of bacterial enzymes that produce uremic metabolites, including iodomethylcholine, which inhibits bacterial TMA formation and lowered systemic creatinine levels, is a promising area of research. Oxidative stress and chronic inflammation play critical roles in the progression of kidney disease. Current research into the roles of the gut-kidney axis in the progression of renal fibrosis via oxidative stress and chronic inflammation has focused on metabolic products of gut microbiota, including uremic toxins and SCFAs. These factors mediate the gut-mucosal barrier, control inflammatory mediators, modulate immune cells, and ultimately shape the overall environment to promote or disrupt the process. In theory, restoring balance to the gut-kidney axis using rational therapeutics represents an exciting avenue for the treatment of CKD. Although the exact underlying mechanisms must be further explored, therapeutic strategies based on modulating the gut–kidney axis have begun to emerge. Nefecon regulated local immunity in the intestinal mucosa and improve kidney function. Therefore, the gut-directed drug medication Nefecon is on track to become the first agent for specifical treatment of immunoglobulin A nephropathy [196]. Future research should further explore the underlying mechanisms of this potential therapeutic strategy and its applications in clinical practice.

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