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Impact of gut microbiota in chronic kidney disease: natural polyphenols as beneficial regulators

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ABSTRACT

Chronic kidney disease (CKD) poses a severe health risk with high morbidity and mortality, profoundly affecting patient quality of life and survival. Despite advancements in research, the pathophysiology of CKD remains incompletely understood. Growing evidence links CKD with shifts in gut microbiota function and composition. Natural compounds, particularly polyphenols, have shown promise in CKD treatment due to their antioxidant and anti-inflammatory properties and their ability to modulate gut microbiota. This review discusses recent progress in uncovering the connections between gut microbiota and CKD, including microbiota changes across different kidney diseases. We also examine metabolite alterations,such as trimethylamine-N-oxide, tryptophan derivatives, branched-chain amino acids, short-chain fatty acids, and bile acids,which contribute to CKD progression. Further, we outline the mechanisms through which polyphenols exert therapeutic effects on CKD, focusing on signaling pathways like nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR), NOD-like receptor thermal protein domain associated protein 3 (NLRP3), phosphatidylin-ositol-3-kinase (PI3K)/protein kinase B (Akt), and toll like receptors (TLR), as well as their impact on gut microbiota. Lastly, we consider how dietary polyphenols could be harnessed as bioactive drugs to slow CKD progression. Future research should prioritize multi-omics approaches to identify patients who would benefit from polyphenolic interventions, enabling personalized treatment strategies to enhance therapeutic efficacy.

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1. Introduction

Chronic kidney disease (CKD) is a major disease that seriously endangers human health and life. A 2020 study published in *The Lancet* examined global CKD trends from 1990 to 2017 and found that by 2017, approximately 697.5 million individuals worldwide were living with CKD, accounting for 9.1% of the global population [1]. The huge number of sick people has caused a heavy economic and medical burden to the country, society, and families and has become a major public health problem worldwide [2]. Currently, the main treatment for CKD is renin-angiotensin-aldosterone system inhibitors, supplemented by symptomatic treatment with drugs and dietary restrictions. However, the above therapeutic measures only delay the progression of CKD and do not block or reverse the patient's progression to the stage of end-stage renal disease (ESRD). As longer evidence-based medical studies are conducted, adverse effects such as aldosterone escape and hyperkalemia limit the clinical use of the drugs [3–5]. Recently, a growing body of data suggests that CKD progression and its complications are associated with gut microbiota disorders in CKD patients [6,7].

The human gut microbiota is a complex ecosystem essential for maintaining health and preventing disease. The number of microorganisms residing in the human body is approximately 3.8×10^{13}, higher than that of human cells, which is 3.0×10^{13} [8]. Microorganisms are commonly distributed in various parts of the human body, such as the skin, respiratory tract, gastrointestinal tract (GIT), genitourinary system, among others, with the most distributed in the GIT [9]. In healthy individuals, microbial communities and their metabolites perform various physiological functions through bacterial-host and bacterial-bacterial

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interactions that are essential for maintaining human health [10]. The function of the gut microbiota is associated with alterations in many environmental factors, such as dietary habits, medications, and disease states [6,11]. Kidney diseases, such as IgA nephropathy (IgAN), diabetic kidney disease (DKD), and ESRD, can disrupt the gut microbial ecology, a condition known as ecological dysregulation [6,12]. Dysfunction of gut microbiota promotes the production of gut-derived uremic toxins such as Indoxyl sulfate (IS) and p-cresyl sulfate (p-CS), and increased intestinal permeability allows bacterial products, such as lipopolysaccharides (LPSs), to enter the circulation, inducing systemic inflammation and renal and cardiovascular injuries, which in turn promotes CKD progression [13]. Modifying the gut-kidney axis may offer a promising therapeutic strategy to prevent renal fibrosis and slow CKD progression. The gut-kidney axisspecifically referring to the two-way communication between the intestines and kidneys under health and disease conditions[14]. The bidirectional communication of the gut-kidney axis is mainly mediated by metabolites produced by the gut microbiota, which have the ability to regulate host physiological functions[15]. For example, *Lactobacilli* and *Prevoelaceae* are bacterial families with the ability to synthesize short-chain fatty acids (SCFA) with phosphate transbutyrylase and butyrate kinase activities, which are reduced in ESRD patients [16].

Many factors can influence the composition and function of the gut microbiota in CKD patients. Among the factors inherent to the body, the disease type and the course of disease progression significantly influence microbial composition [12]. External factors include infections, medication management (including antibiotics and phosphate binders), environmental stresses, and dietary restrictions associated with CKD, particularly low-fiber diets leading to slow intestinal transport, impaired protein assimilation, metabolic acidosis, and constipation [17,18]. In this context, dietary polyphenols have been recognized as potential therapeutic/nutritional agents for treating kidney diseases. Polyphenols, which are available in foods of plant origin, are promising antioxidants, especially for the kidney, because of their ability to regulate adenosine triphosphate (ATP) production, scavenge free radicals, reduce apoptosis and inflammation, and exert antioxidant and anti-inflammatory properties. It also protects the structure and function of renal mitochondria and directly up-regulates the antioxidant defense system, which positively affects the homeostasis of renal mitochondria [19]. Furthermore, studies have also demonstrated that dietary polyphenols act on the kidneys directly or indirectly through modulation of the microbiota and the gut-kidney axis [20,21].

In this review, we focus on current knowledge of the role of microbiota and microbiome-derived metabolites related to the progression of CKD. Besides, we describe the beneficial effects of some natural polyphenolic compounds on CKD by influencing the composition of gut microbiota, which provides a useful basis for further research and design, and elucidates the potential for the development of polyphenols as adjunctive therapeutic products to improve the prognosis of patients with CKD. Based on a new perspective of the gut microbiota, we provide interesting insights into the mechanism of action of polyphenols in CKD therapy.

2. Impact of gut microbiome on CKD

A significantly lower level of relative abundance and composition of gut microbiota was observed in patients with CKD than in healthy individuals [22]. Table 1 summarizes recent studies on changes in gut microbiota composition and relative abundance in different types of CKD.

2.1. IgA nephropathy

IgAN is the most prevalent primary glomerular disease worldwide and the principal cause of ESRD [40]. It is reported that overproduction of aberrantly glycosylated IgA1, largely due to mucosal immune dysregulation, is the triggering factor in IgAN, with growing focus on the pathogenic contribution of intestinal mucosal immune imbalance [41]. When the immune function of the intestinal mucosa becomes abnormal, the body's immune tolerance to the gut microbiota decreases, which leads to a decrease in intestinal barrier function, and an increase in blood entry of intestinal endotoxins, leaving the body in a pro-inflammatory state. As a result, a large amount of galactose-deficient immunoglobulin A1 (Gd-IgA1) is produced [25,41]. Gd-IgA1-containing immune complexes (ICs) in IgAN mediate glycocalyx loss in endothelial cells, loss of glycocalyx results in hyperpermeability of the endothelium [42]. Additionally, Makita et al. found that Gd-IgA1-IgG ICs accelerated the production of adhesion factors and proinflammatory cytokines in glomerular endothelial cells. The glomerular endothelial cell injury induced by Gd-IgA1-containing ICs may enhance the permeability of Igs in the mesangial region and subsequent inflammatory response [43].

In recent years, some studies have found that IgAN patients have different gut microbiota from normal people. Wang et al. found that *Actinobacteria*, *Erysipelotrichaceae*, *Butyrivibrio*, *Phascolarctobacterium*, *Lachnospira*, and *Erysipelotrichales* are associated with the high risk of IgAN. In contrast, *Parabacteroides* and *Ruminococcus* are associated with a low risk of IgAN. Among them, *Actinobacteria* performed well in distinguishing IgAN from other glomerular diseases, and there may be a positive correlation between the abundance of *Actinobacteria* and the degree of renal damage in IgAN patients [23]. Similarly, Zhao et al. found through clinical studies that the gut microbiota of IgAN is characterized by significant enrichment of *Escherichia-Shigella,* which is expected to be used as a biomarker and therapeutic target for IgAN [24]. A two-way Mendelian randomization study conducted by Ren et al. found that *Enterobacter* and *Prevotellaceae* are protective factors for IgAN and conjectured that gene-microbiome interactions and butyrate synthesis are the mechanisms by which these bacterial groupings combat IgAN [25]. *Bifidobacterium spp.* is the most important probiotic in the human body. It plays an important role in preventing pathogen invasion, maintaining mucosal homeostasis, enhancing intestinal integrity, and regulating host immunity [44]. Gut microbiota dysbiosis is seen in both IgAN patients

Table 1. Changes in the composition and abundance of gut microbiota in different types of CKD.

CKD	Research subject	Change in the relative abundance of gut microbiota		Ref.
		Increase	Reduction	
IgA nephropathy (IgAN)	A large-scale multi-ethnic genome-wide association studies (GWAS) meta-analysis of 18,340 individuals from 24 cohorts	*Actinobacteria, Erysipelotrichaceae, Phascolarctobacterium Lachnospira, Erysipelotrichales*	*Parabacteroides, Ruminococcus*	[23]
	127 patients with IgAN who were treatment naive	*Escherichia-Shigella, Pseudomonas, Erysipelatoclostridium, Ruminococcaceae_UBA1819, Ruminococcaceae_CAG-352*	*Lachnospira, Lachnospiraceae_ND3007_group, Fusicatenibacter, Lachnospiraceae_NC2004_group, Lachnospiraceae_UCG-001, Lachnospiraceae_UCG-004, Lachnospiraceae_UCG-010, Lachnospiraceae_unclassified, Agathobacter, Romboutsia*	[24]
	IgAN GWAS data from the FinnGen research	genus: *Butyricicoccus*	genus: *Enterorhabdus*, Family *Peptococcaceae*, Family *Prevotellaceae*	[25]
	35 IgAN patients	*Bacteroides*	*Bifdobacterium, Prevotella 9*	[26]
Diabetic kidney diseases (DKD)	432 cases of incident diabetes	*Clostridium citroniae, Clostridium bolteae, Tyzzerella nexilis, Ruminococcus gnavus*	*Alistipes putredinis, Sutterella wadsworthensis, Alistipes indistinctus*	[27]
	180 DKD patients	phyla: *Proteobacteria, Actinobacteriota, Synergistota, Euryarchaeota, Patescibacteria, Verrucomicrobiota, Cyanobacteria* genus: *Escherichia-Shigella Subdoligranulum, Enterobacteriaceae_unclassified, Akkermansia, Bifidobacterium, [Eubacterium]_siraeum_group, Negativibacillus, Acetanaerobacterium*	phyla: *Bacteroidota, Bacteria_unclassified,* genus: *Bacteroides,Faecalibacterium*	[28]
	A meta-analysis included 578 patients with DKD	phylum: *Proteobacteria, Actinobacteria, Bacteroidetes* family: *Coriobacteriaceae, Enterobacteriaceae, Veillonellaceae* genus: *Enterococcus, Citrobacter, Escherichia, Klebsiella, Akkermansia, Sutterella, Acinetobacter,species E. coli*	phylum: *Firmicutes* family: *Lachnospiraceae* genus: *Roseburia, Prevotella, Bifidobacterium*	[29]
	15 patients with DKD	*Bacteroides stercoris, Prevotella sp. MSX73, Barnesiella, Alistipes ihumii, Bacteroides stercoris CAG_120, Tannerella sp. CAG_51, Parabacteroides sp. 20_3*	*Clostridium, Eubacterium, Roseburia intestinalis, Lachnospira, Intestinibacter*	[30]
Lupus nephritis (LN)	A meta-analysis included 138 LN patients and 5 different types of LN mouse models	phylum: *Proteobacteria,* genus: *Streptococcus,* species: *Ruminococcus gnavus,*	*Firmicutes/Bacteroidetes*	[31]
	16 systemic lupus erythematosus (SLE) patients	*Ruminococcus gnavus*	/	[32]
	Female NZBWF1 (SLE) mice	phylum: Bacteroidetes, Proteobacteria family: *Porphyromonadaceae, Sphingobacteriaceae* genus: *Parabacteroides, Pedobacter, Olivibacter, Clostridium*	phylum: *Firmicutes*	[33]
	B6SKG mice	*Bacteroidales species, Candidatus Arthromitus, segmented filamentous bacteria*	family: *Bifidobacteriaceae, Ruminococcaceae*	[34]
Membranous nephropathy (MN)	8 MN patients	phylum: *Fusobacteria, Proteobacteria* genus: *Providencia, Myroides, Parabacteroides*	phylum: *Firmicutes* genus: *Lachnospira, Roseburia, Megamonas, Megasphaera, Fusobacterium, Akkermansia*	[35]
	A meta-analysis included involving 290 patients with idiopathic membranous nephropathy (IMN)	phylum: *Proteobacteria* genus: *Streptococcus, Peptostreptococcaceae_incertae_sedis*	phylum: *Firmicutes* genus: *Lachnospira*	[36]
Hypertensive renal disease	Male spontaneously hypertensive rats (SHR)	phylum: *Firmicutes* family: *Clostridiales*	phylum: *Bacteroidetes* family: *Bacteroidaceae* genus: *Prevotella-9, Lactobacillaceae, Bifidobacteriaceae*	[37]
Hyperuricemic Nephropathy (HN)	Male Kunming mice with HN	*Firmicutes/Bacteroidetes* genus: *Staphylococcus*	genus: *Bacteroides, Alloprevotella, Kneothrix, Ruminococcus, Eisenbergiella*	[38]
	Male C57BL/6 J mice with HN	phylum: *Actinobacteria, Proteobacteria, Saccharibacteria* family: *Lachnospiraceae, Coriobacteriaceae, Rikenellaceae* genus: *Desulfovibrio, Enterobacter, Faecalibaculum, Helicobacter, Lactobacillus, Parabacteroides*	phylum: *Bacteroidetes* family: *Ruminococcaceae* genus: *Ruminococcaceae UCG 013, Streptococcus*	[39]

and IgAN mouse models, with notably reduced levels of *Bifidobacterium spp*. Moreover, the proportion of *Bifidobacterium spp.* in the gut microbiota was negatively correlated with proteinuria and hematuria levels. IgAN mice supplemented with probiotics contain *Bifidobacterium spp.* Probiotics and their SCFA metabolites may alleviate the pathological and clinical manifestations of IgAN by inhibiting the NLRP3/ASC/Caspase-1 signal pathway [26].

2.2. Diabetic kidney disease

Diabetic kidney disease (DKD) is the main microvascular complication of diabetes mellitus (DM), and it has also become the main cause of ESRD [45]. Even though the pathogenesis of DKD is more complicated than other CKD, new research has demonstrated the involvement of gut microbes in the disease's progression. Ruuskanen MO et al. found in a prospective cohort study that 4 strains (*Clostridium citroniae*, *Clostridium bolteae*, *Ruminococcus gnavus,* and *Tyzzerellanexilis*) and two clusters (cluster 1 and 5) consistently had a significant positive association with the risk of type 2 diabetes mellitus (T2DM) [27]. Patients with DKD have microecological disorders of gut microbiota in the early stage of the disease. With the progression of the disease, there is an accumulation of harmful metabolites, destruction of intestinal barrier function, and chronic inflammation [30,46]. Studies have shown that the flora richness of most DKD patients is significantly lower than that of non-DKD [28,29]. At the genus level, conditional pathogens *Escherichia-Shigella* is significantly enriched in DKD, while beneficial bacteria such as SCFAs-producing *Prevotella* and *Blautia* decrease. At the same time, gut microbiota characteristics are present in different stages of DKD. Shang et al. divided 180 patients with DKD into four groups according to clinical stage and observed significant differences in gut microbiota among the four groups. With the deterioration of DKD, the diversity of gut microbiota of patients increased significantly. The three most enriched genera in stage 5 DKD were *[Eubacterium]_siraeum_group*, *Ruminococcaceae_incertae_sedis,* and *Acetanaerobacterium* [28]. Studies suggest that elevated levels of LPS may contribute to the progression of DKD [47]. In late DKD, the proliferation of Gram-negative bacteria such as *Verrucomicrobia* and *Fusobacteria*, accompanied by elevated LPS levels, accelerated macrophage/monocyte and neutrophil activation to induce inflammation. This study also found that *Agathobacter* had high AUC and ROC values in distinguishing DKD from DM, early DKD from DM, and late DKD from early DKD, which may be the most promising microbial biomarkers for DKD [48].

2.3. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the archeotype of the systemic autoimmune diseases, characterized by the production of pathogenic autoantibodies and immune complexes, resulting in damage to various organs and tissues [49]. Lupus nephritis (LN) is a major cause of morbidity and mortality in SLE [50]. So far, the etiology of SLE and LN is not completely clear, and it is considered to be related to genetic and environmental factors [51]. In recent years, researchers have tried to explore the characteristics of gut microorganisms and their role in the pathogenesis of LN [52]. Disturbance of gut microbiota and destruction of intestinal mucosal barrier leads to the production of toxins that cause renal damage by gut microorganisms [53], as well as abnormal immune cell activation, excessive production of antibodies, immune complexes, inflammatory factors, and inflammatory cell infiltration, all of which can damage the renal parenchyma directly or indirectly [31,54]. Clinical studies have found that the α diversity of gut microbiota in patients with LN is significantly decreased, characterized by the expansion of certain types of bacteria (such as *Blautia* and *Odoribacter*) and strains represented by Gram-negative bacteria [55,56]. In addition, as a common strain of human gut microbiota, *Ruminococcusgnavus* is overexpressed in inflammatory bowel disease and nervous system diseases [57]. Azzouz et al. found that the increase of *Ruminococcus gnavus* abundance may be one of the causes of recurrent lupus erythematosus, and *Ruminococcus gnavus* strains with potential pathogenicity were isolated from the feces of LN patients [32]. *Segmented filamentous bacteria* (SFB) is an important intestinal bacterium related to immunity, which has been proven to be very important in the LN model. Intra-intestinal transplantation of SFB in mice accelerates the progression of LN and promotes the infiltration of M2 macrophages in the kidney and the dysfunction of gut microbiota [34]. On the contrary, SLE mice treated with broad-spectrum antibiotics could inhibit the progression of renal inflammation and renal injury, improve vascular endothelial dysfunction and oxidative stress, and reduce Th17 cell infiltration in the aorta [33]. *L.plantarum* is a promising probiotic that benefits a variety of diseases. In the SLE mouse model, the administration of *L.plantarum* helps to regulate the inflammatory environment by reducing interleukin (IL)-6 and IL-17 and increasing circulating IL-10 levels. Treatment with *L.plantarum* reduced IgG deposition in the kidneys and significantly improved kidney function. Furthermore, the strain restored the integrity of the intestinal barrier to varying degrees [58]. Notably, a study by Zegarra-Ruiz showed that *Lactobacillus reuteri* promotes lupus progression by aggravating glomerular inflammation, activating plasmacytoid dendritic cells, and interferon I expression, which is inconsistent with other studies that have shown positive effects of *Lactobacilli* [59]. It is suggested that gut microbiota may show adverse effects under some genetic and specific environmental conditions, and it may cause harm to the body once the homeostasis of the host is destroyed [60]. In addition, the potential difference of strains used in different studies may also be an important factor leading to the inconsistency of experimental results.

2.4. Other types of CKD

Studies have found significant differences in α and β diversity of idiopathic membranous nephropathy (IMN) patients compared with CKD and healthy populations. At the phylum level, *Fusobacteria* and *Proteobacteria* increased in IMN patients, but *Firmicutes* decreased. At the genus level, the levels of *Akkermansia*, *Megamonas*, and SCFAs-producing bacteria *Roseburia*, *Fusobacterium*, and *Lachnospira* in healthy people were higher than in CKD and IMN patients. *Parabacteroides* were significantly increased in patients with CKD and IMN, while *Providencia* and *Myroides* were more prevalent in patients with IMN [35]. The results of the meta-analysis of Zhang et al. show that the enrichment of *Proteobacteria* and the depletion of *Lachnospira* may be the key characteristics of the changes of gut microbiota in patients with IMN and may play an important

role in the pathogenesis of IMN. The above conclusions are expected to provide bacterial targets for diagnosing and treating IMN [36]. Guan et al. established a spontaneously hypertensive (SHR) mouse model to explore the relationship between gut microbiota and the progression of hypertensive renal injury. At the phylum level, the relative abundance of *Firmicutes* in SHR increased significantly, while the relative abundance of *Bacteroidetes* decreased significantly. At the family level, the relative abundance of *Bacteroidaceae* in the SHR group decreased, while that of *Clostridiales* increased. *Clostridiaceae* is a kind of indole-positive bacteria that is positively correlated with indole, and indole has a negative effect on the kidney. At the genus level, the abundance of beneficial bacteria such as *Prevotella-9*, *Bifidobacteriaceae,* and *Akkermansia* decreased [37]. Hyperuricemic nephropathy (HN) is a common clinical complication of hyperuricemia (HUA). Differences in gut microbiota composition were detected between healthy individuals and HUA patients [38,61]. HN mouse model was established using potassium oxazinate combined with adenine. The α diversity of gut microbiota was significantly reduced, and β diversity differed significantly from the normal and treatment groups. At the phylum level, the relative abundance of *Firmicutes* and *Bacteroidetes* and the ratio of *Firmicutes*/*Bacteroidetes* (F/B) changed slightly. At the genus level, *Bacteroidetes*, *Alloprevotella*, *Knethrix*, *Ruminococcus gnavus,* and *Eisenbergiella* in the HN group with decreased abundances were negatively correlated with HN phenotype. *Staphylococcus* with increased relative abundance was positively correlated with HN fibrosis biomarkers (transforming growth factor-β (TGF-β), fibronectin, collagen I) [38]. In another study, *Enterobacter*, *Helicobacter*, and *Desulfovibrio* were enriched in the intestines of HN mice. *Enterobacter* is rich in urease, which can hydrolyze urea into ammonia and ammonium hydroxide and induce intestinal inflammation and barrier damage. *Helicobacter* and *Desulfovibrio* mediate tryptophan metabolism and catalyze the production of indole, the precursor of uremic toxin indole sulfate [39].

The composition of gut microbiota exhibits substantial variability across different research studies. This heterogeneity can be attributed to two primary factors: Firstly, the inherent complexity of gut microbial ecosystems, influenced by diverse lifestyle factors and numerous confounding variables, frequently results in inconsistent findings among studies. Secondly, substantial methodological disparities in research design, including variations in sample size, collection protocols, therapeutic interventions, geographical distribution, and analytical methodologies, may significantly impact the comparability and interpretation of microbiota research outcomes. The causal relationship between CKD and gut dysbiosis remains unclear. Until now, experimental interventions involving fecal microbiota transplantation (FMT) from ESRD or CKD patients into germ-free animal models have failed to yield conclusive evidence demonstrating a detrimental impact on renal function. Therefore, future research should focus on the precise identification of specific bacterial species and the analysis of their functions, in order to elucidate the potential causal relationship between gut microbiota dysbiosis and CKD.

3. Effects of gut-derived metabolites on CKD

The metabolites mediated by gut microbiota are closely related to CKD, which affects the progress and prognosis of CKD. Intestinal inflammation and epithelial barrier destruction lead to the imbalance of intestinal flora and produce excessive urotoxins, including trimethylamine-N-oxide (TMAO), tryptophan metabolites indole and indole-3-acetic acid (IAA) [12]. These toxins occur at the distal end of the colon and reversibly bind to serum proteins in a free form, maintaining a balanced cycle between free and binding states. Elevated levels of urotoxin indicate impaired renal function [62]. In addition, beneficial bacteria in the intestinal tract produce some metabolites that benefit kidney health, mainly divided into three categories: branched-chain amino acids (BCAA), SCFAs, and bile acids (BAs). These metabolites have pharmacological activities such as promoting protein synthesis, reducing inflammation and oxidative stress, and improving renal fibrosis.

3.1. TMAO

TMAO is derived primarily from a diet rich in choline, phosphatidylcholine, and L-carnitine, which are first metabolized by the intestinal flora in the colon into trimethylamine (TMA). Then, it is produced by oxidation of flavin-containing monooxygenase 3 (FMO3) in the liver [63]. The gene clusters responsible for TMA production are commonly found in the colon in obligate anaerobic *Clostridia* under *Firmicutes* and facultative anaerobic *Enterobacteriaceae* under *Proteobacteria* [64]. In recent years, studies have found a link between TMAO and CKD. TMAO accelerates the age-related decline in renal function, triggers the transformation of renal fibroblasts into myofibroblasts, and promotes the occurrence of renal fibrosis [65]. Metabolomics studies have also confirmed TMAO as a potential biomarker for CKD [66]. The formation of TMAO by gut microbiota contributes to the development and progression of chronic kidney disease. A single-center prospective cohort study of 521 patients with CKD found that elevated TMAO in patients with CKD predicted lower survival rates. Subsequently, animal experiments in this study showed a continuous dose-dependent relationship between dietary supplementation with choline and TMAO and renal tubulointerstitial fibrosis and renal impairment [67]. In addition, inhibiting the production of TMAO in the adenine-induced CKD model significantly reduced the area of renal cortical scarring and fibrosis, thereby reducing the expression of multiple inflammatory and fibrotic genes and attenuating the development of CKD and cardiac hypertrophy. TMAO promotes CKD, and the mechanism may be related to activating the NF-κB signaling pathway and increasing the expression of inflammatory genes in renal tubular epithelial cells (TEC) [68].

3.2. Tryptophan metabolite

Tryptophan is an essential aromatic amino acid for the human body and is considered to be an important component of the crosstalk metabolite between the gut microbiota

and the host [69]. Intestinal microbiota produces a variety of metabolites such as kynurenine (KYN), indole-3-acetic acid (IAA), and IS through the tryptophan metabolic pathway. These metabolites increase in acute renal injury (AKI) or CKD and can be used as potential biomarkers for early disease identification [70]. A cohort study showed that the ratio of KYN to tryptophan was positively correlated with the risk of ESRD. Researchers suggest that an imbalance between tryptophan-KYN metabolism might be associated with progressive renal impairment in patients with type 2 diabetes and propose a new method for slowing the progression of DKD by switching the KYN pathway to the kynurenic acid pathway [71]. On the other hand, tryptophan metabolites interact with AHR and pregnane X receptors (PXR) *in vivo* as ligands [72]. AHR is a helix-loop-helix transcription factor that binds to various ligands *in vivo*. It is one of the main receptors of renal injury induced by tryptophan metabolites. IS and KYN induce and aggravate renal injury by activating AHR signal transduction [73,74]. However, the effects of AHR receptor activation on CKD seem to vary significantly. Tryptophan metabolite methyl 2-(1H-indole-3-carbonyl)-1,3-thiazole-4-carboxylate (ITE) and 6-formylindolo [3,2-b] carbazole (FICZ) as ligands of AHR can inhibit collagen I production induced by TGF- β1 and delay fibrosis [75]. PXR is important as a transcription factor in endogenous metabolism and homeostasis [76]. Indole, Indolacrylic acid (IA) and indole 3-propionic acid (IPA) are the main ligands of PXR. They activate PXR to enhance intestinal mucosal integrity and induce an anti-inflammatory response [77].

3.3. BCAA

BCAA, composed of leucine, isoleucine, and valine, is an essential amino acid for the human body, usually obtained from diet or produced by intestinal microbial community metabolism [78]. BCAAs are involved in the metabolic/synthetic pathways of many intestinal microorganisms, among which *Escherichia coli* and *Corynebacterium glutamicum* are the most widely studied [79]. As the signal molecule and direct fuel of the citric acid cycle intermediate, BCAA is very important for human health [80]. Moreover, BCAA catabolism is an important source of amino acid synthesis of nitrogen, which is based on the transamination of branched-chain amino acid transaminase (BCAT) to synthesize glutamic acid, aspartic acid, and other amino acids to promote protein synthesis [81]. However, excessive BCAA participates in the mechanism of renal fibrosis by promoting the proliferation of glomerular mesangial cells and the deposition of extracellular matrix (ECM) secreted by proliferative mesangial cells [82]. It has been reported that the level of branched-chain amino acids (including valine and isoleucine) in fecal metabolic species and the gene level of biological metabolism in patients with DKD are significantly increased [83]. BCAAs in patients with insulin resistance are mainly produced by *Prevotella copri* and *Bacteroides vulgaris* [84]. Another mechanism by which dysregulation of BCAA metabolism promotes kidney injury is that deletion of BCAA gene expression leads to reduced mitochondrial respiration and ATP production, which reduces cellular energy sources and exacerbates de-differentiation and apoptosis of TECs [85]. During chronic renal failure, the contents of BCAA in plasma and valine in muscle decreased significantly [86]. Supplementation of BCAA and other amino acids can normalize plasma branched-chain amino acids during renal failure, maintain protein balance, minimize uremic toxins, and delay the progress of CKD [87]. Therefore, a precise balance must be maintained between the intake and metabolism of BCAA, and its metabolic imbalance is a potential risk factor for chronic kidney disease.

3.4. SCFAs

SCFAs refer to straight-chain saturated fatty acids with less than 6 carbon atoms, including acetate, propionate, and butyrate. Dietary fibers such as non-starch polysaccharides, oligosaccharides, and resistant starch are difficult to digest and are fermented by microorganisms to produce SCFAs in the colon [88]. The main species of bacteria involved in the production of SCFAs are *Roseburia spp.*, *Butyricicoccus spp.*, *Faecalibacterium prausnitzii*, *Bacterioides spp.* and *Bifidobacterium* [89]. SCFAs have many beneficial effects, such as improving metabolic function, inhibiting insulin resistance, and regulating immune inflammation [90]. A high-fiber diet and SCFAs supplementation can improve a variety of acute and chronic kidney diseases, including CKD (DKD, ESRD) and ischemia-reperfusion injury, contrast agent and gentamicin-induced nephrotoxic injury, ureteritis, and hydronephro-induced postrenal injury and other conditionally-induced AKI [91]. SCFAs act as a signal molecule to bind to G-protein coupled receptor41 (GPR41), G-protein coupled receptor43 (GPR43), G-protein coupled receptor109A (GPR109A), or inhibit histone deacetylase (HDACs) [92]. The gut-enriched bacterium *Faecalibacterium prausnitzii* (*F. prausnitzii*) is a major producer of butyrate [93]. *F. prausnitzii* plays a protective role in the kidney by regulating butyrate-GPR43 signal transduction to remodel intestinal homeostasis and delay CKD progress [94]. The study reports propionic acid attenuates adenine-induced renal failure *via* GPR41 and GPR43 [95]. In addition, SCFA activates the GPR receptor (GPR43 or GPR109A) to prevent the occurrence of DKD. Meanwhile, SCFAs have an anti-renal fibrosis effect and delay the development of DKD to ESRD, and its mechanism involves inhibiting the activation of the TGF-β pathway, HDAC activity, and reducing the phosphorylation of extracellular regulated protein kinases (ERK) [96]. SCFAs affect the transcription of nuclear factor NF-κB and its downstream pro-inflammatory cytokine-related genes by inhibiting HDAC [89]. However, excessive SCFAs can induce inflammation in the body, leading to hydronephrosis and kidney damage [92].

3.5. BAs

BAs is an amphiphilic cholesterol metabolite. Intestinal flora, represented by *Bacterioides spp.*, *Firmicutes,* and *Actinobacteria*, metabolizes BAs secreted to the duodenum into secondary BAs through various modifications and bile salt hydrolase (BSH) hydrolysis [97]. The metabolic process is divided into four different ways: the uncoupling of amino acid glycine or

taurine and the dehydroxylation, dehydrogenation, and differential isomerization of cholesterol core [98]. For example, primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) undergo 7α-dehydroxylation in intestinal flora to produce secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), which are rich in the human body [99]. BAs metabolism can improve the balance of glucose and lipid metabolism in the kidney. Studies have shown that maintaining the level of serum BAs above 2.8 mmol/L in patients with DKD is beneficial in improving renal prognosis and delaying the development of ESRD [100]. BAs act as a ligand to activate the nuclear hormone receptor-farnesol X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), which plays an important protective role in renal physiology and disease [101]. It is reported that BAs and their analogues activate FXR and TGR to improve proteinuria and prevent podocyte injury, Mesangial dilatation, and tubulointerstitial fibrosis, as well as the prevention and treatment of DKD and obesity-related nephropathy. However, BAs overload is not a good event for the kidneys. When BAs silting is accompanied by increased concentration of systemic BAs circulation, proximal renal tubular epithelial cells (TECs) reabsorb and enrich BAs through apical sodium-dependent bile acid transporter (ASBT), leading to oxidative stress of TECs, cell death, and glomerular cyst, resulting in cholemic nephropathy (CN) [102,103].

3.6. Other uremic toxins

Tyrosine is metabolized by gut microbes, which produce protein uremic toxins such as pCS, p-Cresol Glucuronide (pCG), and Phenyl Sulfate (PS). The bacteria involved in the metabolism include *Clostridiaceae*, *Enterococcaceae*, *Bacteroidaceae*, *Bifidobacteriaceae*, *Staphylococcaceae*, etc [104]. It is reported that the levels of pCS and pCG in individual plasma increase with the progression of CKD, which is due to the accumulation of this kind of protein uremic toxin in the blood caused by the decrease of glomerular filtration rate [105]. Interestingly, compared with pCG, pCS plays a dominant role in kidney disease. PCS can promote apoptosis and inflammation of TECs, while pCG tends to enhance the inflammatory response of pCS [106]. Moreover, the total and free serum levels of pCS in patients with CKD were significantly higher than those in pCG [107]. Adenine-induced and fecal bacteria transplantation end-stage renal disease microbiota increases blood pCS levels, aggravating renal fibrosis and oxidative stress [108,109]. PS seems to have a close relationship with DKD. The level of PS increases with the progression of diabetes, which leads to podocyte injury and albuminuria, which can be used as a marker for early diagnosis of DKD and a predictor of progressive risk, as well as a therapeutic target for reducing albuminuria [110,111].

Hippuric acid (HA) is another gut-derived protein that binds to uremic toxins. Dietary epicatechin and chlorogenic acid are metabolized by intestinal microorganisms to form benzoic acid and glycine to form hippuric acid [112]. Another pathway of hippuric acid production is the metabolite of phenylalanine produced by the intestinal bacterium *Clostridium sporogenes* [113]. The accumulation of HA is closely related to the disease of CKD patients, especially in polycystic kidney disease [114]. It has been found that HA may promote redox imbalance and renal fibrosis of CKD by activating the TGF-β/SMAD signal mediated by reactive oxygen species (ROS) and destroying NRF2-driven antioxidant capacity [115].

4. Modulation of CKD by polyphenols *via* the gut microbiota

Intestinal dysbiosis disrupts the symbiotic relationship between the host and associated microorganisms, leading to CKD. Some studies have suggested that increasing the intake of certain dietary components can regulate the gut microbiota by interacting with the gut microbiota before reaching the kidneys [116]. As a major dietary component of antioxidant effects, polyphenols are natural compounds specially synthesized by plants with specific chemical characteristic [117]. When polyphenols are obtained from food, more than 90% of dietary polyphenols reach the large intestine without being absorbed by the small intestine. The gut microbiota effectively digests polyphenols, producing active metabolites that cross the intestinal barrier to reach the kidneys, where they help mitigate oxidative stress, inflammation, and fibrosis [118]. Conversely, polyphenols directly affect the composition of gut microbiota by affecting the growth and metabolism of bacteria in the gut, which is conducive to increasing beneficial bacteria and inhibiting the proliferation of pathogenic bacteria [119,120]. Polyphenol compounds and their metabolites ameliorate gut microbiota disturbances and delay the progression of CKD (Figure 1 and Table 2).

4.1. Punicalagin

Punicalagin (PU) is the most abundant ellagitannin in pomegranate peel and has a high antioxidant effect [147]. Studies have shown that PU not only has strong antioxidant capabilities but also has a beneficial effect on colitis [148], nonalcoholic fatty liver [149], and obesity [150] by regulating gut microbiota. Han et al. [121] reported that PU reduced hyperuric-induced renal impairment by improving gut microbiota dysfunction in HUA mice. At the phylum level, PU significantly increased the abundance of *Bacteroidota* and decreased the abundance of Firmicutes and the F/B ratio. At the genus level, PU treatment significantly reduced the abundance of pro-inflammatory bacteria *Parabacteroides*, *Oscillibacter*, *Desulfovirio*, and *Tuzzerella*. In addition, PU significantly enhanced the relative abundance of SCFA-producing bacteria *Prevotellaceae_UCG-001* and *Muribaculaceae*. KEGG pathway analysis predicted potential functional changes associated with alterations in the intestinal flora. Notably, pathways involved in the renin-angiotensin system, arachidonic acid metabolism, and lipopolysaccharide biosynthesis closely linked to inflammation and HUA were significantly activated in hyperuricemic mice and decreased following PU administration.

Hua et al. [122] analyzed the effect of PU intake on renal function in DM mice induced by a high-fat diet. They found that PU altered the gut microbiota composition of DM mice, reducing the F/B ratio and weakening the relative abundance of *Proteobacteria*. At the genus level, the abundance of SCFA bacteria (*Akkermansia*, *Eubacterium_coprostanoligenes_group,* and *Lachnospiraceae*) in the PU group was higher than that in the DM group. These SCFA bacteria were negative correlation with disease-related serum index, such as lipopolysaccharide (LPS), diamine oxidase (DAO), blood urea nitrogen (BUN), creatinine (Cre), insulin (INS), uric acid (UA), among others. Moreover, the level of *Desulfovibrio* (an endotoxin-producing bacteria) showed an increased relative abundance in the DM group. In contrast, some pathogenic bacteria, including *Rikenellaceae RC9 gut group*, *Alistipes*, *Helicobacter*, *Dorea,* and *Ruminococcus_torques_group* displayed a strong positive association with CKD phenotypes. In addition, the study also found that propionic acid, butyric acid, isobutyric acid, isovaleric acid, and valeric acid in the cecum increased in mice treated with PU, and PU reduced expression of inflammatory cytokines and chemokines such as ACOD1, SERPINB2, CCL22, CCL22, and CCL28, providing strong neuroprotection in DM.

4.2. Resveratrol

Resveratrol (RES) is a natural polyphenol compound widely found in grapes, mulberries, red wine, and peanut skins [151]. Several *in vitro*, *in vivo*, and clinical studies have demonstrated that RES has potential antioxidant, anti-inflammatory, cardioprotective, neuroprotective [152], and renal protective effects [153]. Hsu et al. [123] evaluated the effects of RES and its purified product resveratrol butyrate ester (RBE) on the gut microbiota of adenine-induced CKD rats. They found that intake of RES and RBE protected adenine-fed rats from hypertension and kidney damage. Interestingly, the protective effect of RES on hypertension was accompanied by an increase in the number of SCFAs-producing bacteria, including *Alistipes*, *Blautia*, and *Parabacteroides*. The beneficial effects of high-dose RBE were related to reducing the renal expression of GPR41 and olfactory receptor 78 (Olfr78), antagonizing the AHR signaling pathway, and increasing the abundance of beneficial bacteria such as *Akkermansia*, *Blautia* and *Enterococcus*. In a follow-up study, Tian et al. [124] used the same modeling method to evaluate the effects of RES and its purified 3-Opropanoylresveratrol (RPE2) and 3,4 '-di-O-propanoylresveratrol (RPE4) on the changes of gut microbiota in a juvenile rat adenine-induced CKD model. They observed that RES and its purified RPE and RPE4 can resist CKD-induced hypertension, increase the availability of NO, decrease plasma ADMA and SDMA levels, and increase plasma SCFA levels. After intaking RPE2 and RPE4, gut microbiota composition of juvenile rats significantly changed. The protective effects of RES on kidneys may be closely related to increased *Eubacterium*, *Bacteroides* and *Allobaculum* abundance, and decreased abundances of *Parabacteroides*, *Peptococcus* and *Turicibacter*. After the RPE4 intervention, the abundance of

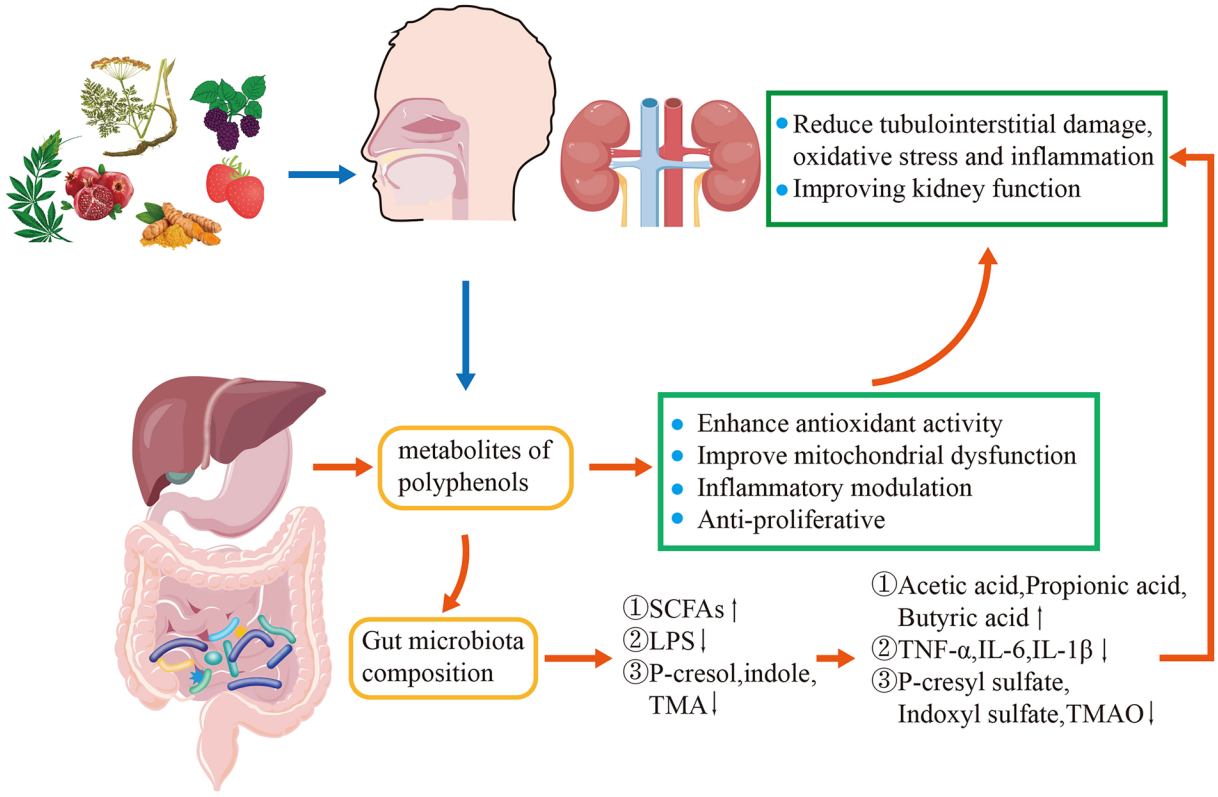

Figure 1. Effects of polyphenols on CKD by gut microbiota metabolism.

Table 2. A review of studies that examined the effect of polyphenols on NAFLD *via* gut microbiota.

Authors	Dose & duration	Population	Effect	Changes in gut microbiota
Punicalagin				
Han et al. [121]	Punicalagin(100, 200, and 300 mg/kg/d) p.o. 12 weeks	Male Kunming mice	↓ The expression of UA resorption protein URAT1 and GLUT9 ↑ The expression of UA excretion protein ABCG2 and OAT1 ↓ Activation of MAPK/NF-κB in the kidney and intestine of hyperuricemia mice ↓ UA excretion protein expression in the intestine	↓ *Firmicutes and Firmicutes/Bacteroidetes ratio* ↑ *Bacteroidota* ↓ *Parabacteroides*, *Oscillibacter*, *Desulfovibrio and Tuzzerella* ↑ *Prevotellaceae_UCG-001*, *Muribaculaceae*
Hua et al. [122]	Punicalagin (50 and 100 mg/kg/d) p.o. 8 weeks	Male C57BL/6J mice	↓ CREA, UA, and BUN ↑ propionic acid, butyric acid, iso butyric acid, isovaleric acid and valeric acid on the cecal contents ↑ The expression of ZO-1 and Occludin ↓ The serum levels of DAO and LPS ↓ The expression of inflammation related genes (ACOD1, SERPINB2, CCL22, CCL28 et al.)	↓ *Proteobacteria* and *Firmicutes/Bacteroidetes ratio* ↑ *Akkermansia*, *Eubacterium_coprostanoligenes_group and Lachnospiraceae* ↓ *Desulfovibrionaceae* ↓ *Rikenellaceae RC9 gut group, Alistipes,Helicobacter, Dorea* and *Ruminococcus_torques_group*
Resveratrol				
Hsu et al. [123]	10 mg/kg/d Resveratrol p.o. 6 weeks	Sprague Dawley (SD) rats	↓ Renal GPR43 and Olfr78 expression ↓ AhR-relating AHRR and CYP1A1	↑ *Alistipes*, *Blautia*, and *Parabacteroides* ↑ *Akkermansia*, *Blautia*, and *Enterococcus* ↓ *Butyricicoccus*, *Ruminococcus_1*
Tian et al. [124]	10 mg/kg/d Resveratrol p.o. 6 weeks	Sprague Dawley (SD) rats	↑NO availability, arginine-to-ADMA ratio ↓The levels of ADMA and SDMA	↑ *Eubacterium*, *Bacteroides*, and *Allobaculum* ↓ *Parabacteroides*, *Peptococcus*, and *Turicibacter* ↑ *Ruminococcus*, *Ligilactobacillus*, *Bacteroides*, and *Allobaculum*
Zhou et al. [125]	100 mg/kg/day Resveratrol p.o. 8 weeks	C57BL/6J male mice	↓ Renal Injury and Inflammation ↑ Intestinal UA Metabolism	↑ *Faecalibaculum*, *Bifidobacterium*, *Clostridium*, and *Lactococcus* ↓ *Bacteroides*, *Helicobacter*, and *Prevotella* ↑ *Lactobacillus*_sp._*ESL0791*, *Lacticaseibacillus_rhamnosus*, *Bifidobac* *terium_colobi*, *Ligilactobacillus_hayakitensis*, and *Limosilactobacillus_vaginalis* ↓ *g Eisenbergiella_tayi*, *Desulfovibrionaceae_bacterium*, and Bacteroides_sp.AF35-22
Hsu et al. [126]	Resveratrol (50 mg/L) in drinking water 6 weeks	Virgin Sprague-Dawley (SD) rats	↓ TMA-to-TMAO conversion ↑ The L-arginine-to-ADMA ratio ↓ The levels of renal 8-OHdG expression	↓*Firmicutes/Bacteroidetes* ratio, *Deferribacteres* and *Verrucomicrobia* ↓ *Akkermansia* ↑ *Lactobacillus* and *Bifidobacterium* ↑ *BacteroidesBifidobacterium*, *Roseburin,* and *Ruminococcaceae*
Yan et al. [127]	0.4% Resveratrol p.o. 12 weeks	*db/db* mice	↓ The oral glucose tolerance test and insulin tolerance test ↓ The protein expressions of a-SMA、TGF-β1 and E-cadherin in the kidney ↑ Fecal acetate acid	↑ *Firmicutes* ↑*Lactobacillaceae* ↓ *Lachnospiraceae* and *Oscillospiraceae* ↑ *Lactobacillus* and *Faecalibaculum* ↓ *Lachnospiraceae_NK4A136_group*
Cai et al. [128]	10 mg/kg/day Resveratrol p.o. 12 weeks	*db/db* mice	↑ Tight-junction proteins ZO-1 and claudin-1 protein expression ↓ The plasma levels of LPS, IFN-γ, TNF-a, and IL-6 ↓ Serum creatinine, blood urea nitrogen and urine 24-h microalbuminuria	↓ *Firmicutes* and *Firmicutes/Bacteroidetes* ratio ↑ *Bacteroidetes* ↑ *Bacteroides*, *Alistipes* and *Parabacteroides*

(*Continued*)

Table 2. Continued.

Authors	Dose & duration	Population	Effect	Changes in gut microbiota
Emodin				
Zeng et al. [129]	5ml (1 mg/day) Emodin *via* colonic irrigation	Sprague-Dawley (SD) rats	↓ Urea concentrations and urinary protein excretion	↑ *Tenericutes*
	4 weeks		↓ Uremic toxin IS	↓ The unclassified genera from *S24-7 family*, *Clostridium* ↑ *Adlercreutzia*, *Bacteroides*, unclassified genera from *RF39 order* and *Ruminococcaceae family*
Xu et al. [130]	gavage of Deoxycholic acid-chitosan coated liposomes (30 mg/kg/d) and enema of Emodin-loaded *in situ* colonic gel (10 mg/kg/d)	Sprague Dawley (SD) rats	↓ The expression of α-SMA, collagen I, and TGF-β in rat renal tissues	↓ *Proteobacteria*, *Firmicutes*
	28 days		↓ TNF-α, IFN-γ, and IL-6 in rat serum	↑ *Fusicatenibacter*, *Elusimicrobium*, *Ruminococcaceae*, *Bifidobacterium*
			↓ DAO, D-LA, ET, IS and TMAO in rats serum	↓ *Escherichia*, *Shigella*, *Clostridium*, *Alistipes*, and *Streptococcus*
Lu et al. [131]	low-dose emodin-NP (1.15 mg/kg emodin) *via* colonic irrigation every two days	Male Sprague Dawley rats	↓ IL-1β, IL-6, TNF-α, IFN-γ, and LPS in the serum or renal tissues samples	↑ *Clostridium* and *Barnesiella*. *Butyricicoccus* and *Romboutsia*
	high-dose emodin-NP (4.6 mg/kg emodin) *via* colonic irrigation every two days		↓ The key proteins (TLR4, MyD88, and NF-κB) expression in intestinal TLR4 signaling pathway	↓ *Alloprevotella*, *Eubacterium*, and *Fusicatenibacter*
	8 weeks			
Magnesium lithospermate B				
Zhu et al. [132]	Magnesium lithospermate B (30 mg/kg/day) p.o.	Male DBA/2J mice and ICR mice	↓ IL-1β、MCP-1、TGF-β和TNF-α mRNA in the kidney	↓ *Bifidobacterium*, *Lachnospiraceae*, *Aerococcus*, *Bacteroidales_S24- 7_group*
	8 weeks		↑ SCFAs levels	↑ *Alistipes*, *Lachnospiraceae_NK4A136_group*
			↑ Alanine, threonine, glycine, lysine, glutamine, glutamate, methionine, citrulline, tyrosine, and phenylalanine	↓ *Clostridium*, *Bifidobacterium*, *Fusobacterium*
			↓ IS, PCS, HA, PhS, and TMAO	
			↓ 4-hydroxyphenylacetate convert to PC	
Epigallocatechin gallate				
Yu et al. [133]	Epigallocatechin gallate (50 mg/kg/day) p.o.	ICR mice	↑ UA secretion transporter genes (Oat1 and Oct1)	↑ *Actinobacteriota*, *Bacteroidota*, *Bifidobacterium*, *Coriobacteriaceae UCG- 002*, *norank f Muribaculaceae*, *Lactobacillus* and *Faecalibaculum*
	7 days		↓ UA reabsorption transporter genes (Urat1 and Glut9)	↓ *Lactobacillus, Erysipelatoclostridium*
			↑*Igfbp5 in the intestinal epithelium* ↓*Gucy1a1*, *Gucy1b1*, *Gpd1*, *Akap6*, *and Slc25a4 in the intestinal epithelium*	
Unno et al. [134]	a 0.2% Epigallocatechin gallate diet	Male ICR mice	↓Plasma and urinary concentrations of p-Cresol	↓ *Firmicutes*, *Clostridiales* ↑ *Bacteroidetes*, *Verrucomicrobia*
	2 weeks			↑ *Bacteroidales*, *Verrucomicrobiales*
Chlorogenic acid				
Zhou et al. [135]	Chlorogenic Acid (40 mg/kg/day) p.o.	Male Sprague–Dawley rats	↓ GSH-Px, CAT, SOD, MDA	↓ *Firmicutes*, *Actinobacteria*
	2 weeks		↓ TNF-α, IL-1β, IL-6, ICAM-1, MCP-1, and NF-κB and the protein expression of NF-κB p65	↑ *Bacteroidetes*
			↓ Serum TMAO	↑ *Lachnospiraceae* NK4A136 group, *Butyricimonas* and *Phascolarctobacterium*

(*Continued*)

Table 2. Continued.

Authors	Dose & duration	Population	Effect	Changes in gut microbiota
			↓ PI3K/AKT/mTOR Pathway	↓ *Blautia*, *Coriobacteriaceae* UCG-002, *Dubosiella*, *Faecalibaculum*, *Holdemania*, *Enterococcus* and *Eisenbergiella*
Zhou et al. [136]	Chlorogenic Acid((both 30 and 60 mg/kg/day) p.o. 19 days	Male Kunming mice	↓ XOD activity ↑ The renal mRNA expression of ABCG2, OAT1 and the mRNA levels of ileal ABCG2 ↓ The serum LPS and TLR4/MyD88/NF-κB in kidneys ↑ The total SCFA levels ↑ The mRNA expression of zonula occludens-1 and occludin in the ileum	↓ *Firmicutes* ↑ *Bacteroidetes* ↑ *Bacteroides*, *Alistipes*, *Prevotellaceae UGC-001*, *Butyricimonas* ↓ *Muribaculum*, *Faecalibaculum* and *Aeromonas*
Ding et al. [137]	Acute experiment: intraperitoneal injection of Chlorogenic Acid (500 mg/kg bw) Sub-chronic experiment: gavage of Chlorogenic Acid (30 mg/kg bw) once a day Acute experiment: 24h Sub-chronic experiment:8 weeks	Kunming mice	↓ Cd accumulation in tissues ↓ AST, ALT, BUN and Cr ↓ The levels of MDA, SOD and CAT ↓ The protein expressions of TLR4, NF-κB, and MyD88 ↓ NO and MPO expression	↓ *Firmicutes* and *Firmicutes/Bacteroidetes* ratio ↑ *Bacteroidetes* ↑ *Ruminiclostridium_9*, *Alloprevotella*, *and Rikenella*
Cheng et al. [138]	Chlorogenic Acid (30 mg/kg/day) p.o. 8 weeks	Male Kunming mice	↓ AST, ALT, BUN and Cr ↓ MDA and AOPP ↑ glutathione ↓ SOD, GSH-PX and CAT ↓ Pb accumulation in tissues ↓ The levels of the proteins NF-κB, Bax, Bcl-2, cytochrome C and caspase-9 in kidneys	↓ *Lachnospiraceae_NK4A136_group* ↑ *Helicobacter*
Fisetin				
Ren et al. [139]	Fisetin (100 mg/kg/day) p.o. 29 days	C57BL/6J mice	↓ The mRNA expression levels of KIM-1 and NGAL ↓ The mRNA expression levels of Col1a1, Fn, and a-SMA ↑ The serum levels of L-tryptophan ↓ The serum levels of L-kynurenine ↓ The expression of AHR, ARNT, and CYP1b1 genes	↓ *Firmicutes* ↑ *Bacteroidetes* and *Epsilonbacteraeota* ↓ *Lactobacillus* and *Insolitispirillum*
Luteolin				
Pan et al. [140]	HGGG (100 mg/kg/day) p.o. 8 weeks	Male Sprague-Dawley (SD) rats	↓UACR, BUN, and urine NAG levels ↓ Collagen IV, Fibronectin, Vimentin and α-SMA ↓ TNF-α, IL-6,Caspase-1, IL-1β and NLRP3 in renal tissues ↑ The expression of tight-junction proteins Claudin-1 and ZO-1	↓ *Firmicutes* ↑ *Bacteroidetes* and *Actinobacteria* ↑ *Bifidobacteriaceae* and *Ruminococcaceae* ↑ *Ruminococcus*, *Barnesiella_sp*, *Anaerovoracaceae* and *Prevotellaceae_NK3B31* ↓ *Oscillospira*
Yuan et al. [141]	Isoorientin(15 mg/kg/day) p.o.	BALB/c mice	↑ The digestibility of crude proteins and utilization of the gross energy	↓ *Acinetobacter*, *Alistipes*, *Anaerotruncus*, *Bifidobacterium*, *Desulfovibrio*, *Faecalibaculum*, *Helicobacter*, *Kurthia*, *Lachnoclostridium*, *Lactobacillus*, *Odoribacter*, *Oscillibacter*, *Ruminiclostridium*

(*Continued*)

Table 2. Continued.

Authors	Dose & duration	Population	Effect	Changes in gut microbiota
	30 days		↑ The activities of T-SOD and GSH-Px	↑ *Bacteroides*, *Enterococcus*, *Alloprevotella*, *Enterorhabdus*, *Mucispirillum*, *Parabacteroides*, *Parabacteroides*, *Parasutterella*, *Caproiciproducens*, *Roseburia*, *Anaeroplasma and Pantoea*
			↓ H2O2 and MDA levels	
			↑ Lipid metabolism and Vitamin B6 metabolism	
Sun et al. [142]	Low-Dose YQHG group (1.4 g/kg);Middle-Dose YQHG (2.8 g/kg); High-Dose YQHG (5.6 g/kg)	Male Sprague Dawley (SD) rats	↓ Scr, BUN, and urinary protein	↓ *Firmicutes/Bacteroidota* Ratio
	8 weeks		↓ Glomerular fibrosis area and tubulointerstitial fibrosis area	
			↓ The Expression of PTGS2, P53 and IL-6 in kidney tissue	
Curcumin				
Xu et al. [143]	Curcumin(200 mg/kg/day) p.o.	Male Wistar rats	↓ The levels of serum creatinine, BUN and uric acid level	↓ *Proteobacteria*
	8 weeks		↓ Brown-black uric acid crystals in the renal tubules and interstitium	↓ *Escherichia-Shigella*, *Bacteroides*
			↑ The expression levels of ZO-1, occludin and claudin-1 in the ileum	↑ *Lactobacillus*, *Ruminococcaceae*
Pivari et al. [144]	Meriva® 500 mg/tablet twice in a day p.o.	CKD patients and non-CKD subjects	↓ MCP-1 or CCL-2, IL-4 and IFN-γ plasma levels	↓ *Verrucomicrobia*
	6 months		↓ Plasma TBARS levels	↓ *Enterobacter*, *Escherichia-Shigella*
			↓ Total and free PCS levels	↑ *Lachnospiraceae*, *Lachnoclostridium*
Salarolli et al. [145]	2.5 g of turmeric (95% Curcumin) 3 times per week at the end of each HD session	Hemodialysis patients	↓ The p-CS plasma levels	
	12 weeks			
Reis et al. [146]	500 mg of Curcumin longa powder (98.42 % curcuminoids total) three times a day (1.5 g/day)	Peritoneal dialysis patients	↓ The p-CS and MDA plasma levels	
	12weeks			

UA: uric acid; URAT1: urate transporter 1; GLUT9: glucose transporter 9; ABCG2: ATP binding cassette subfamily G member 2; OAT1: organic anion transporter 1; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappa-B; CREA (or Cr): creatinine; BUN: blood urea nitrogen; ZO-1: zonula occludens-1; DAO: diamine oxidase; ACOD1: aconitate decarboxylase 1; SERPINB2: serpin peptidase inhibitor, clade B (ovalbumin), member 2; CCL22: chemokine (C-C motif) ligand 22; GPR43: G protein-coupled receptor 43; Olfr78: olfactory receptor 78; AHRR: Aryl hydrocarbon receptor repressor; CYP1A1: cytochrome P450, family 1, subfamily A, polypeptide 1; NO: nitric oxide; ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; TMA: trimethylamine; TMAO: trimethylamine oxide; 8-OHdG : 8-hydroxy-2-deoxyguanosine; a-SMA: α-smooth muscle actin; TGF-β1: transforming growth factor beta 1; E-cadherin: epithelial cadherin; LPS: lipopolysaccharide; INF-γ: interferon gamma; IS: Indoxyl sulfate; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; D-LA: D(+)-Lactide; ET: ethanol; IL-1β:interleukin-1β; TLR4: toll-like receptor 4; MyD88: myeloid differentiation factor 88; MCP-1: monocyte chemoattractant protein-1; SCFAs: short-chain fatty acids; PCS: p-cresyl sulfate; HA: hippuric acid; PhS: phenyl sulfate; PC: p-cresyl; Oat1: organic anion transporter 1; Oct1: organic cation transporter 1; Igfbp5: insulin-like growth factor binding protein 5; Gucy1a1: guanylate cyclase 1 soluble subunit alpha 1; Gucy1b1: guanylate cyclase 1 soluble subunit beta 1; Gpd1: glycerol-3-phosphate dehydrogenase 1; Akap6: A-kinase anchoring protein 6; Slc25a4: solute carrier family 25 member 24; GSH-Px: glutathione peroxidase; CAT: catalase; SOD: superoxide dismutase; MDA: malondialdehyde; ICAM-1: vascular cell adhesion molecule-1; PI3K: Phosphatidylinositol 3-kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; XOD: xanthine oxidase; Cd: Cadmium; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AOPP: advanced oxidation protein products; Bcl-2: B-cell lymphoma/Leukemia-2; Bax: BCL2-associated X; caspase-9: cysteine-requiring aspartate protease 9; KIM-1: kidney injury molecule 1; NGAL: neutrophil gelatinase-associated lipocalin; Col1a1: collagen, type I; Fn: fibronectin; AHR: aryl hydrocarbon receptor; ARNT: aryl hydrocarbon receptor nuclear translocator; CYP1b1: cytochrome P450 1B1; UACR: urinary albumin/creatinine ratio; NAG :N-acetyl-β-D- glucosaminidase; NLRP3: NOD-like receptor protein 3; SCr: serum creatinine; PTGS2: prostaglandin-endoperoxide synthase 2; P53: Protein 53; TBARS: thiobarbituric acid reactive substances.

Ruminococcus, *Ligilactobacillus*, *Bacteroides* and *Allobaculum* was increased.

Zhou et al. [125] further employed metagenomic sequencing to investigate the effect of RES supplementation on the gut microbiota composition in mice with high-fat diet (HFD)-induced HUA and observed that RES normalized the intestinal microbiota composition in the studied mice. At the species level, the RES group had higher levels of beneficial bacteria, such as *Lactobacillus_sp._ESL0791*, *Lacticaseibacillus_rhamnosus*, *Ligilactobacillus_hayakitensis*, *Ligilactobacillus_hayakitensis*, and *Limosilactobacillus_vaginalis*, while the opportunistic pathogens such as *Eisenbergiella_tayi*, *Desulfovibrionaceae_bacterium* and *Bacteroides_sp._AF35-22* showed to be relatively less abundant in the RES group. The FMT experiment further confirmed gut microbiota's vital role in mediating the therapeutic effect of RES. The sequencing results revealed that *o_Lactobacillales* and *g_Ligilactobacillus* were common biomarkers in the RES intervention group and the FMT group, suggesting that Lactobacillus is vital for the effect of RES.

Another interesting question is whether maternal CKD-induced offspring kidney disease/hypertension is associated with alterations in the microbiome and microbial metabolites. Hsu et al. [126] found that administering RES treatment during the perinatal period increased bacterial alpha diversity and decreased the ratio of F/B and the abundance of *Deferribacteres* and *Verrucomicrobia* at the phylum level. Genus-level analysis showed that RES induced a higher abundance of Lactobacillus, *Bacteroides*, *Bifidobacterium*, *Roseburia,* and *Ruminococcaceae,* and a lower abundance of *Akkermansia* in maternal CKD rats. Regarding intestinal microbiota metabolites, RES significantly reduced the conversion of TMA to TMAO and increased the level of GPR41 protein in the offspring's kidneys. In addition, RES therapy during pregnancy and the lactation period increased plasma levels of L-arginine and the L-arginine-to-ADMA ratio in offspring. It reduced the expression of oxidative stress damage marker 8-OHdG, protecting the offspring's kidneys against damage caused by hypertension.

Yan et al. [127] found that after 12 weeks of RES supplementation, the expression of fibrosis gene (a-SMA and TGF-β) in the kidneys of db/db mice was significantly reduced, and increased the expression of anti-fibrosis genes such as E-cadherin, suggesting that RES could reduce fibrosis in *db/db* mice. The study found that RES administration increased Firmicutes abundance at the microbial level. At the genus level, RES increased the relative abundance of *Lactobacillus* and *Faecalibaculum* and inhibited the relative abundance of *Lachnospiraceae_NK4A136_group*. They further transplanted the gut microbiota of *db/db* and *db/db*+RES mice into mice with depleted microbiota. They found that renal function-related measures, including blood creatinine, urea nitrogen, and proteinuria levels, were lower in recipients of microbiota from the resveratrol-fed mice. More importantly, the beneficial effect of RES on renal tubulointerstitial fibrosis is partly achieved by modulating the gut microbiota-SCFAs axis in *db/db* mice. In another study, Cai et al. [128] evaluated the protective effect of RES on intestinal barrier function in *db/db* mice. Their study confirmed that RES treatment significantly decreased the level of 4 kDa FITC-dextran in *db/db* mice and restored the expression of intestinal tight-junction proteins ZO-1 and claudin-1. The levels of IFN-γ and TNF-α in the small intestine and plasma levels of LPS, IFN-γ, TNF-α, and IL-6 were significantly decreased. In addition, they found that transplantation of the RES-modified fecal microbial community was sufficient to antagonize renal dysfunction, reshape the gut microbiome, and improve intestinal permeability and inflammation in recipient db/db mice.

4.3. Emodin

As a natural polyphenol, emodin (EMO) is an active ingredient of many traditional Chinese herbs, such as *Rhubarb*, *Aloe vera*, *Polygonum cuspidatum,* and *Polygonum multiflorum*, which has anti-inflammatory, antioxidant, anti-apoptotic and neuroprotective effects [154]. In addition, EMO has been shown to improve intestinal flora structure and repair intestinal barrier function [155]. Zeng et al. [129] found that EMO *via* colonic irrigation decreased urea, IS, and urinary protein excretion in rats with CKD. Regarding gut microbiota, EMO enriched the relative abundance of *Tenericutes* at the phylum level. At the genus level, the relative abundance of *Adlercreutzia*, *Bacteroides*, unclassified genera from *RF39* order, and *Ruminococcaceae* family showed an increasing trend after EMO treatment, the abundance of the unclassified genera from *S24-7* family and *Clostridium* displayed an opposite trend. Xu et al. [130] established a UUO rats followed by EMO-loaded in sim colonic gel (EMO-IGE) and found that, compared with EMO alone, EMO-IGE had better anti-fibrosis effect, which was manifested in reducing the expression of α-SMA, collagen I and TGF-β, decreasing the levels of intestinal damage biomarkers, such as DAO, D-LA, and ET, as well as uremic toxins, such as IS and TMAO. More importantly, the gut microbial dysbiosis was restored by EMO-IGE. Especially on the phylum level, the EMO-IGE group had mainly reduced *Proteobacteria* and *Firmicutes*; on the genus level, the EMO-IGE group had mainly increased the abundance of 15 beneficial bacteria such as *Fusicatenibacter*, *Elusimicrobium*, *Ruminococcaceae,* and *Bifidobacterium*. The increase in *Escherichia_Shigella* and *Streptococcus* damaged the intestinal mucosal barrier and increased plasma TMAO concentration, thereby increasing the production of inflammatory cytokines. In addition, Alistipes are potent producers of harmful metabolites, including cresol and indole, which are further metabolized to pCS and IS. Their findings demonstrated that the EMO-IGE inhibited the reproduction of these pathogenic bacteria. Lu et al. [131] constructed a novel colon-targeted drug delivery system of EMO-nanoparticles to study their efficacy in delaying CKD progression. EMO-nanoparticles *via* colonic irrigation remarkably reduced interleukin-1β (IL-1β), IL-6, and LPS levels in serum, improved intestinal barrier function, and down-regulated the expression of key proteins in the intestinal toll like receptors 4 (TLR4) signaling pathway , Myeloid Differentiation Primary Response Protein 88 (MyD88), and

nuclear factor kappa-B (NF-κB). In terms of the microbial community composition, their results revealed that treatment with EMO-nanoparticles increased the abundance of *Romboutsia*, *Butyricicoccus*, *Parabacteroides,* and *Clostridium*. Furthermore, after the treatment of CKD rats with high- and low-dose EMO-nanoparticles, the gut microbiota was changed to a different extent, *Bacteroides*, *Phascolarctos bacterium*, and *Ruminococcus* increased in the low-dose EMO-nanoparticle group, while *Akkermansia* increased in the high-dose EMO-nanoparticle group.

4.4. Magnesium lithospermate B

Danshen, a commonly used Chinese herbal medicine, is the dried root of *Salvia miltiorrhiza* Bunge, which has many pharmacological activities, such as promoting blood circulation, reducing oxidative stress injury, and anti-apoptosis. Magnesium lithospermate B (Mlb) is the main water-soluble active ingredient of Danshen. Due to its anti-apoptotic and antioxidant properties, it has been clinically used to treat cardiovascular diseases [156]. Recent studies have shown that Mlb not only plays a role in cardiovascular diseases but also possesses beneficial effects against renal disease [157]. Zhu et al. [132] evaluated the effects of Mlb on the intestinal microbiota structure in STZ-induced diabetic rats. They discovered that Mlb treatment down-regulated the levels of IL-1β, monocyte chemoattractant protein-1 (MCP-1), TGF-β, and TNF-α at mRNA levels in the rat kidney. After Mlb treatment, the relative abundances of 6 OTUs were significantly altered, the relative abundances of *Bifidobacterium*, *Lachnospiraceae*, *Aerococcus,* and *Bacteroidales_S24-7_group* were decreased, and the relative abundances of *Alistipes* and L*achnospiraceae_NK4A136_group* were significantly increased. Regarding gut microbiota-derived metabolites, Mlb might partially ameliorate the renal injury caused by STZ by modulating the levels of 10 amino acids, such as alanine, threonine, and glycine. In addition, Mlb significantly reduced plasma and fecal levels of uremic toxin p-CS by inhibiting the bacteria-mediated conversion of 4-hydroxyphenylacetic acid to p-cresol. They further confirmed that Mlb and its metabolite danshensu inhibited the formation of p-Cresol mediated by the genus *Clostridium*, *Bifidobacterium,* and *Fusobacterium*, respectively.

4.5. Epigallocatechin gallate

Epigallocatechin gallate (EGCG), a green tea polyphenol, has been shown to possess anti-obesity, anti-bacterial, anti-cancer, and anti-inflammatory activities. Studies have found that EGCG could modulate the gut microbiome by promoting the growth of beneficial species and suppressing potentially harmful ones [158]. Yu et al. [133] used male ICR mice to establish a HUA model. Their study revealed that EGCG promoted the expression of UA (Uric acid) secretion transport genes (*Oat1* and *Oct1*) and inhibited the expression of UA reabsorption transport genes (*Urat1* and *Glut9*) in the kidney. They found that EGCG might regulate uric acid metabolism by regulating the composition of gut microbiota. The results of transcriptomic analysis of the intestinal epithelium showed that 191 differentially expressed genes (DEGs) were found in EGCG-treated mice, including 8 purine-related genes (*Gucy1a1*, *Gucy1b1*, *Gpd1*, *Akap6*, *Slc25a4*, *Per1*, *Igfbp5,* and *Sparc*). By 16S rDNA sequencing, EGCG was found to significantly increase the abundance of *Actinobacteriota*, *Bacteroidota*, *Bifidobacterium*, *Coriobacteriaceae UCG-002*, and *norank f Muribaculaceae*, *Lactobacillus* and *Faecalibaculum*. The abundance of *Coriobacteriaceae*, *Bifidobacterium*, and *norank f Muribaculaceae* were significantly correlated with high *Oat1* expression. Conversely, the expression of *Oct1* was negatively correlated with the relative abundance of *Lactobacillus*, *norank f norank o RF39*, but positively correlated with the abundance of *Faecalibaculum*. Metabolomics analysis suggested that modified cations in bacterial metabolites induced by EGCG might contribute to the alleviation of HUA. EGCG-induced bacterial metabolites such as prostaglandin E2, acetylcholine, L-lysine, etc., might contribute to the remission of HUA.

Unno's study also confirmed that EGCG supplements altered the structure of microbial communities and the composition of intestinal bacteria [134]. By administering ICR mice with three different concentration gradients of EGCG dietary formulas, they found that the intake of EGCG decreased the plasma and urinary concentrations of p-Cresol in a concentration-dependent manner. However, such beneficial effects almost completely disappeared once EGCG was enzymatically hydrolyzed to EGC and gallic acid. In terms of gut microbiota, intake of EGCG significantly decreased the abundance of *Firmicutes* at the phylum level and *Clostridiales* at the order level, which has been confirmed that bacteria belonging to the *Clostridiales* order are the main intestinal bacteria in producing p-Cresol in the gut [159], and it has been confirmed that bacteria belonging to the order of *Clostridiales* are the main producers of p-Cresol. On the other hand, EGCG increases the abundance of *Bacteroidetes* and *Verrucomicrobia*. At the order level, the relative abundance of *Bacteroidales,* a member of the phylum *Bacteroidetes*, increased after EGCG treatment.

4.6. Chlorogenic acid

Chlorogenic acid (CGA), also known as coffee tannic acid and coffee ellagic acid, is a water-soluble phenolic acid synthesized by plants during aerobic breathing. Empirical research has emphasized that CGA could alleviate kidney diseases caused by inflammation and oxidative stress, thus having a renal protective effect [160]. In addition, CGA can change the composition of the gut microbiota, regulating the barrier function of intestinal epithelium [161,162]. Zhou et al. [135] revealed the positive effect of CGA in a "plant-based" diet on hyperuricate-induced UA nephropathy. These analyses indicated that consuming CGA reduced the inflammatory response and oxidative stress, inhibiting the PI3K/AKT signaling pathway. Moreover, dietary CGA can regulate gut microbiota in the HUA mouse model. At the phylum level, CGA

treatment significantly reduced the relative abundance of *Firmicutes* and *Actinobacteria* yet increased that of *Bacteroidetes*. At the genus level, the abundance of potential probiotics such as *Blautia*, *Coriobacteriaceae UCG-002*, *Dubosiella*, *Faecalibaculum*, *Holdemania*, *Enterococcus* and *Eisenbergiella* were significantly decreased, while the relative abundances of *Lachnospiraceae NK4A136 group*, *Butyricimonas* and *Phascolarctobacterium* were increased after HUA model establishment. However, most of these alterations were effectively reversed by CGA treatment. In addition, CGA regulates the cascade reaction of the microbial-TMAO signaling pathway and reverses the increase of serum TMAO. Another study published by Zhou et al. [136] found that CGA could significantly upregulate low expression levels of renal *mOAT1* and *mABCG2* as well as ileal *mABCG2* in HUA mice to promote blood uric acid excretion. At the same time, CGA lowered the serum LPS level, downregulated the gene expression of proinflammatory cytokines, and inhibited the activation of the TLR4/MyD88/NF-κB signaling pathway in kidneys. In addition, CGA restored the structural and compositional shifts of the HUA-induced gut microbial community. At the genus level, the relative abundances of SCFA-producing bacteria *Bacteroides*, *Alistipes*, *Prevotellaceae UGC-001*, and *Butyricimonas* increased after CGA treatment, the abundances of *Muribaculum*, *Faecalibaculum*, and *Aeromonas* declined. Predicted metagenome functional analyses showed CGA reversed purine metabolism and glutamate metabolism of microbiota.

Ding et al. [137] reported the effect of CGA against cadmium-induced hepatorenal injury and its effect on the gut microbiome profiles in cadmium (Cd)-exposed mice. Their result indicated that CGA therapy led to a decrease in cadmium accumulation in the kidneys and liver. In a sub-chronic exposure Cd exposure experiment, CGA treatment was indicated to prevent Cd-induced oxidative damage in the liver and kidney tissues by reducing the production of NO and MPO. Meanwhile, the CGA treatment also caused a significant decrease in the protein expressions of TLR4, NF-κB, and MyD88 in the liver and kidney. Regarding the composition of the microbial community, there was no significant difference in bacterial richness and diversity among the CGA group and the control group. At the phylum level, the relative abundance of *Firmicutes* decreased significantly, and the abundance of *Bacteroides* increased in Cd-exposed mice after CGA treatment. At the genus level, the abundance of *Ruminiclostridium_9*, *Alloprevotella,* and *Rikenella* in Cd-exposed mice was lower compared with the control group, and all of these alterations were effectively reversed by CGA treatment. In a mice model of lead-induced hepato-renal damage, Cheng et al. [138] found that CGA significantly inhibited lead-induced increase of cytoplasmic NF-κB, Bax, cytochrome C, and caspase-9 protein expressions. Moreover, CGA regulated lead-induced dysbiosis of the gut microbiota. The lead treatment produced a significant change in the phylum-level proportional abundance, as the proportion of *Helicobacter* decreased from 8.22% (control) to 2.95% (lead), and the proportion of *Lachnospiraceae_NK4A136_group* increased from 7.09% (lead) to 1.85% (control). After CGA treatment, the proportion of *Helicobacter* increased to 11.24%, while the proportion of *Lachnospiraceae_NK4A136_group* decreased to 2.68%. The CGA-treatment and control groups showed similar community structures of gut microbiota. In addition, CGA significantly increased the acetic acid, propionic acid, and butyric acid levels in the feces of lead-exposed mice.

4.7. Fisetin

Fisetin is a natural polyphenol widely found in vegetables and fruits, with strawberries (160 μg/g) having the highest concentration, followed by apples (26.9 μg/g) and persimmons (10.5 μg/g) [163]. Recently, fisetin has been reported to regulate gut microbiota in mouse models of Parkinson's disease [164] and colitis [165]. Ren et al. [166] found in the adenine/potassium oxonate-induced HUA in mice, fisetin administration was found to dose-dependently improve renal tubular interstitial fibrosis, which manifested as reduced KIM-1, NGAL, Col1A1, Fn, and α-SMA expressions. Moreover, fisetin altered the abundance and composition of gut microbiota in HUA-induced CKD mice. At the phylum level, hyperuricemic mice displayed an increase in the relative abundance of *Firmicutes* and a decrease in the relative abundance of *Bacteroidetes* and *Epsilonbacteraeota*, which recovered after fisetin treatment. At the genus level, fisetin restored the altered abundance of 47 genera in hyperuricemic mice, of which 44 were associated with creatinine, urea nitrogen, and uric acid. Regarding gut microbiota metabolism, fisetin restored the change of 17 significant plasma metabolites involved in tryptophan metabolism. Accordingly, serum L-tryptophan levels in CKD mice were significantly decreased, while its metabolites L-kynurenine and serotonin levels were significantly increased, and administration of fisetin reversed the changes of L-tryptophan and L-kynurenine. Additionally, *in vivo* and *in vitro* results of their study showed that fisetin inhibited AHR activation and attenuated L-kynurenine-induced renal fibrosis [139].

4.8. Luteolin

Luteolin (LUT), a flavonoid polyphenolic compound, is widely found in fruits, vegetables, flowers, and herbs. It is worth noting that LUTs have multiple beneficial pharmacological properties, including anti-coronavirus and renoprotective activities against kidney injury induced by sepsis, renal ischemia, and diverse nephrotoxic agents [167]. The potential impact of gut microbiota on LUT metabolism and the influence of LUT on microbiota composition indicate that the interaction between LUT and host microbiota plays an important role in therapeutic efficacy [168,169].

Red ginseng fruit (HGGG) is a kind of novel berry with high nutritional value and a delicious taste. Pan et al.'s [140] research identified LUT was the predominant flavonoid identified in HGGG. In DN rats induced by STZ, the reno protective effects in HGGG-treated DN rats were linked to reducing the expressions of renal fibrosis markers such as collagen IV,

fibronectin, vimentin, and α-SMA, as well as inhibition of NLRP3 inflammasome. Further analysis showed that HGGG administration improved gut barrier integrity, as indicated by enhanced expression of the tight-junction proteins Claudin-1 and ZO-1. Additionally, supplementation with HGGG resulted in restructuring the microbial community in DN rats. At the phylum level, the microbial composition was marked by a lower abundance of *Bacteroidetes* and a higher abundance of *Verrucomicrobia* in DN rats. HGGG treatment significantly enhanced the levels of *Actinobacteria* and regulated the abundances of *Bacteroidetes* and *Firmicutes*. At the family level, HGGG treatment promoted the presence of *Bifidobacteriaceae* and *Ruminococcaceae*. At the genus level, HGGG administration increased the relative abundance of beneficial bacteria known for regulating polyamines and producing SCFAs, including *Ruminococcus, Barnesiella_sp, Anaerovoracaceae,* and *Prevotellaceae_NK3B31*. Meanwhile, HGGG decreases the abundance of *Oscillospira*, potential pathogens producing LPS. Yishen Qingli Heluo granule (YQHG) is representative of traditional Chinese medicine (TCM) for the clinical treatment of CKD, and Quercetin is the core compound of this TCM remedy. In the 5/6 nephrectomized rats model, they demonstrated that YQHG treatment effectively reshaped the composition of the gut microbiota, such as increasing the abundance of *Bacteroidota* and decreasing the abundance of *Firmicutes*. In addition, YQHG treatment reduces the proportion of *Firmicutes*/*Bac*teroidota in a dose-dependent manner [142].

Isoflavone (ISO) is a 6-C-glucoside of LUT, Yuan et al. [141] investigated the effects of ISO on antioxidant capacity and gut microbiota of BALB/c mice. ISO supplementation strengthened the activity of T-SOD and GSH-Px, decreased the levels of H_2O_2 and MDA, and increased the crude proteins and the gross energy digestibility. In terms of gut microbiota composition, ISO treatment inhibited the growth of inflammation-induced pathogens, such as *Acinetobacter*, *Alistipes*, *Anaerotruncus*, *Bifidobacterium*, *Desulfovibrio*, *Faecalibaculum*, *Helicobacter*, *Kurthia*, *Lachnoclostridium*, *Lactobacillus*, *Odoribacter*, *Oscillibacter*, *Ruminiclostridium*. Contrarily, *Bacteroides*, *Enterococcus*, *Alloprevotella*, *Enterorhabdus*, *Mucispirillum*, *Parabacteroides*, *Parabacteroides*, *Parasutterella*, *Caproiciproducens*, *Roseburia*, *Anaeroplasma* and *Pantoea* significantly enriched after ISO supplementation. In addition, ISO altered the metabolic pathways of the gut microbiota, and they found that the metabolic pathways of the gut microbiota were mainly enriched in antioxidant, anti-inflammatory, and antibacterial functions along with the ISO application.

4.9. Curcumin

Curcumin (CUR), a natural polyphenol compound extracted from turmeric, possesses diverse beneficial properties for cancer, cardiovascular disease, diabetes, liver, and neurodegenerative diseases and is relatively safe and inexpensive [170]. Research has shown that CUR also regulates the composition and metabolism of the gut microbiota, promoting the growth of beneficial gut bacteria to improve gut health and related diseases [171]. In Xu et al. [143] research, a uric acid nephropathy rat model was established using adenine and potassium oxonate to investigate the effects of CUR on gut microbiota. This study showed that supplementation of CUR promoted the integrity of the intestinal barrier, increasing the expression of ZO-1, occludin, and claudin-1 proteins. In addition, CUR supplementation reduced plasma LPS levels. In terms of gut microbiota, CUR therapy protected the overgrowth of opportunistic pathogens conditional pathogens in uric acid nephropathy, including *Escherichia-Shigella* and *Bacteroides*, and increased the relative abundance of bacteria producing SCFAs, such as *Lactobacillus* and *Ruminococcaceae*.

Pivari et al. [144] conducted a prospective randomized clinical controlled study to observe the beneficial effect of CUR on inflammation, lipid peroxidation, and intestinal microbiota in patients with CKD. This study showed that after three months of CUR supplementation, monocyte chemotactic protein 1 (MCP-1 or CCL-2) levels, IL-4, and IFN-γ decreased significantly in patients with CKD. Thiobarbituric-acid-reactive substances (TBARS) are a well-established method for assessing lipid peroxidation levels. They found that TBARS levels decreased by approximately 25% after six months of CUR supplementation. Interestingly, after 3 and 6 months of CUR supplementation, a decreasing trend could be noted for total and free PCS levels. About gut microbiota, *Escherichia-Shigella* significantly decreased after 6 months of CUR supplementation, while *Lachnoclostridium* significantly increased. Notably, at family level, *Lactobacillace spp*. was significantly elevated in the last 3 months of supplementation. Salarolli et al. [145] conducted a double-blind, randomized controlled clinical study to evaluate the effect of CUR supplementation on uremic toxins plasma levels produced by gut microbiota in hemodialysis patients. CUR supplementation significantly reduced p-CS plasma levels but did not affect IS and IAA levels. Reis et al. [146] conducted a longitudinal, randomized, single-blind, placebo-controlled trial to evaluate the effects of curcuminoid supplementation on oxidative stress, inflammatory status, and uremic toxins produced by gut microbiota in patients undergoing peritoneal dialysis. Their study found that the plasma MDA and p-CS levels decreased after 12 weeks in the CUR group. However, the concentration of protein thiols inflammatory markers such as Nrf2, NF-κB, HOX-1, TNF-a, IL-6, and hs-CRP did not change significantly.

5. Toxicity

Although natural polyphenols have shown potential therapeutic benefits in the treatment of CKD, and their toxicity can not be neglected. Research has shown that when Gallic Acid and CGA are administered at doses exceeding 200 mg/kg, they form polyphenol glutathione conjugates in a dose-dependent manner, leading to kidney injury characterized by glomerular hyperplasia and tubular necrosis. Mechanism studies have found that these two polyphenolic substances can significantly inhibit the activity of complexes II, III, and IV of the electron transport chain from kidney

mitochondria, leading to mitochondrial dysfunction characterized by increased ROS generation and decreased ATP synthesis, inducing acute kidney injury [172]. A Mexican study indicated that when the dose of *Flourensia cernua* DC polyphenol extract reached 2000 mg/kg, BALB/c female mice exhibited toxic reactions characterized by glomerular atrophy without affecting liver and brain tissues [173]. Zhao et al. reported for the first time that treatment male CF-1 mice with high dose of EGCG (1500 mg/kg) could induce hepatotoxic effects, and the mechanism of toxicity might be related to the induction of oxidative stress in the liver. Further *in vitro* experiments confirmed that EGCG caused DNA damage in both human lymphocytes and Nalm6 cells in a dose-dependent manner. Based on this, it was speculated that this oxidative damage to EGCG could be considered as a potential predisposing factor for EGCG carcinogenicity [174]. The above research indicates that polyphenols have two-way pharmacological effects. Polyphenols induce therapeutic effects at low doses and exerts toxicity at high doses. Dosage of Polyphenols may require strict control in animal experiments and clinical trials.

6. Summary and outlook

This study reviewed recent experimental and clinical research on the role of gut microbiota and its metabolites in the pathogenesis of CKD. Additionally, we explored the beneficial effects of dietary polyphenols in CKD, both through their direct actions and by modulating gut microbiota and its metabolites. From a microbiota perspective, the enrichment of specific bacterial taxa—*Desulfovibrio*, *Lachnospiraceae*, *Helicobacter, Escherichia, and Erysipelatoclostridium*—has been identified as a potential biomarker for CKD. Furthermore, serum L-carnitine, produced *via* the L-tryptophan pathway influenced by gut microbiota and associated with polyphenol metabolism, has recently been linked to a heightened risk of CKD and cardiovascular complications. In addition, dietary polyphenols are metabolized into low molecular weight phenolic metabolites by the gut microbiota. For example, polyphenols such as flavanan-3-ol monomers (also known as catechins), flavonols, anthocyanins, and phenolic acids are modified by the microbiota in the colon and converted into small-molecule metabolites such as benzaldehyde, benzene derivatives (pyrocatechol and pyrogallol, Phenyl-γ-valerolactones) and phenolic acids (benzoic acid, phenylacetic acid, phenylpropanoic acid, cinnamic acid and hippuric acid) [175,176]. A review has shown that human fecal bacterial species have a corresponding phenolic metabolite, such as *Flavonifractor plautii* have been shown to produce 5-(phenyl) -γ-valerolactone. *Eubacterium ramulus*, *Clostridium butyricum*, *Flavonifractor plautii*, *Catenibacillus scindens* and *E. ramulus* participate in the formation of phenylpropionic acid. *E. ramulus* and *F. plautii* were shown to generate phenylacetic acid. *Escherichia coli*, *Bifidobacterium animalis subs*, *Lactis* and *Lactobacillus gasseri* are known to generate cinnamic acid, etc [177]. These phenolic metabolites can cross the intestinal epithelial barrier and enter the systemic circulation, and are distributed in the kidneys and urine. Therefore, they may provide important clues for studying the mechanism of polyphenol compounds regulating CKD through intestinal flora. Among them, trans-cinnamic acid has been shown to attenuate HDF-induced oxidative stress and inflammation in HK-2 cells and delay obesity-related CKD [178]. These findings suggest that the gut microbiome could serve as a clinically relevant biomarker for CKD, and natural compounds like polyphenols may hold promise in CKD prevention and treatment.

A diet rich in polyphenolic compounds is believed to have at least some degree of kidney protection. Therefore, studying their role in the gut-kidney axis has become a central issue in the field of kidney disease research. However, converting dietary polyphenols into therapeutic drugs can be challenging. This challenging area of research may involve several issues: 1) Adverse reactions: Polyphenols and certain drugs may interact with each other, affecting their absorption, distribution, metabolism, and excretion in the body, which may affect treatment efficacy or lead to adverse reactions. 2) Drug metabolism: Polyphenols can affect the metabolism and clearance rate of drugs by affecting the activity of drug-metabolizing enzymes such as cytochrome P450 enzymes. Especially in the middle and late stages of CKD, the glomerular filtration rate decreases, which may lead to fluctuations in drug concentration in the body, increasing toxicity or reducing efficacy. 3) Dosage issue: The selection of polyphenol dosage is crucial for treatment efficacy and safety, and inappropriate dosage may reduce the therapeutic effect. 4) Long-term safety: the evidence to support the beneficial effects of polyphenol gut microbial metabolites and their associated gut microbiota is still unclear, especially in the treatment of CKD. The following solutions are proposed to address these challenges. Firstly, microencapsulation technology, nanotechnology, and the development of prodrugs that can be converted into active polyphenols *in vivo* can be used to enhance the bioavailability of polyphenols. Secondly, establishing standardized dosing regimens for polyphenolic mixtures and polyphenolic monomers will help ensure patients receive the most appropriate dosage based on their disease status. Finally, large-scale clinical studies are encouraged to systematically evaluate the safety of various structurally diverse (poly) phenolic compounds and their metabolites in the treatment of CKD, and to identify drugs with favorable safety profiles through evidence-based medical methods. The application of cutting-edge multi-omics technologies such as immunohistochemistry, transcriptomics, metabolomics, and lipidomics will be needed to identify patients who may benefit the most from polyphenol therapy and develop personalized treatment plans to improve their treatment outcomes. In the future, more research is needed to thoroughly evaluate the immunomodulatory effects of polyphenols and the efficacy of their metabolites in enhancing preventive and therapeutic capacity, as well as the role of gut microbiota in polyphenol metabolism and its further impact on CKD.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

[1] Collaboration GBDCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709–733. doi:10.1016/S0140-6736(20)30045-3.

[2] Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Adv Exp Med Biol. 2019;1165:3–15. doi:10.1007/978-981-13-8871-2_1.

[3] Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–869. doi:10.1056/NEJMoa011161.

[4] Shunan F, Jiqing Y, Xue D. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events in patients with diabetes and overt nephropathy: a meta-analysis of randomised controlled trials. J Renin Angiotensin Aldosterone Syst. 2018;19(4):1470320318803495. doi:10.1177/1470320318803495.

[5] Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385(24):2252–2263. doi:10.1056/NEJMoa2110956.

[6] Koppe L, Soulage CO. The impact of dietary nutrient intake on gut microbiota in the progression and complications of chronic kidney disease. Kidney Int. 2022;102(4):728–739. doi:10.1016/j.kint.2022.06.025.

[7] Amini Khiabani S, Asgharzadeh M, Samadi Kafil H. Chronic kidney disease and gut microbiota. Heliyon. 2023;9(8):e18991. doi:10.1016/j.heliyon.2023.e18991.

[8] Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533. doi:10.1371/journal.pbio.1002533.

[9] Juarez VM, Montalbine AN, Singh A. Microbiome as an immune regulator in health, disease, and therapeutics. Adv Drug Deliv Rev. 2022;188:114400. doi:10.1016/j.addr.2022.114400.

[10] Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med. 2016;375(24):2369–2379. doi:10.1056/NEJMra1600266.

[11] Kim C-S. Roles of diet-associated gut microbial metabolites on brain health: cell-to-cell interactions between gut bacteria and the central nervous system. Adv Nutr. 2024;15(1):100136. doi:10.1016/j.advnut.2023.10.008.

[12] Chen YY, Chen DQ, Chen L, et al. Microbiome-metabolome reveals the contribution of gut-kidney axis on kidney disease. J Transl Med. 2019;17(1):5. doi:10.1186/s12967-018-1756-4.

[13] Huang Y, Xin W, Xiong J, et al. The intestinal microbiota and metabolites in the gut-kidney-heart axis of chronic kidney disease. Front Pharmacol. 2022;13:837500. doi:10.3389/fphar.2022.837500.

[14] Chen J, Tsim KWK, Gao K, et al. Editorial: the gut-kidney axis: a potential drug target for treating kidney diseases. Front Pharmacol. 2022;13:1012890. doi:10.3389/fphar.2022.1012890.

[15] Yang T, Richards EM, Pepine CJ, et al. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. Nat Rev Nephrol. 2018;14(7):442–456. doi:10.1038/s41581-018-0018-2.

[16] Huang HW, Chen MJ. Exploring the preventive and therapeutic mechanisms of probiotics in chronic kidney disease through the gut-kidney axis. J Agric Food Chem. 2024;72(15):8347–8364. doi:10.1021/acs.jafc.4c00263.

[17] Meijers B, Evenepoel P, Anders HJ. Intestinal microbiome and fitness in kidney disease. Nat Rev Nephrol. 2019;15(9):531–545. doi:10.1038/s41581-019-0172-1.

[18] Mao ZH, Gao ZX, Liu DW, et al. Gut microbiota and its metabolites - molecular mechanisms and management strategies in diabetic kidney disease. Front Immunol. 2023;14:1124704. doi:10.3389/fimmu.2023.1124704.

[19] Ashkar F, Bhullar KS, Wu J. The effect of polyphenols on kidney disease: targeting mitochondria. Nutrients. 2022;14(15):3115. doi:10.3390/nu14153115.

[20] Guerreiro I, Ferreira-Pego C, Carregosa D, et al. Polyphenols and their metabolites in renal diseases: an overview. Foods. 2022;11(7):1060. doi:10.3390/foods11071060.
[21] Bao N, Chen F, Dai D. The regulation of host intestinal microbiota by polyphenols in the development and prevention of chronic kidney disease. Front Immunol. 2019;10:2981. doi:10.3389/fimmu.2019.02981.
[22] Rukavina Mikusic NL, Kouyoumdzian NM, Choi MR. Gut microbiota and chronic kidney disease: evidences and mechanisms that mediate a new communication in the gastrointestinal-renal axis. Pflugers Arch. 2020;472(3):303–320. doi:10.1007/s00424-020-02352-x.
[23] Wang F, Li N, Ni S, et al. The effects of specific gut microbiota and metabolites on IgA nephropathy-based on mendelian randomization and clinical validation. Nutrients. 2023;15(10):2407. doi:10.3390/nu15102407.
[24] Zhao J, Bai M, Ning X, et al. Expansion of Escherichia-Shigella in gut is associated with the onset and response to immunosuppressive therapy of IgA nephropathy. J Am Soc Nephrol. 2022;33(12):2276–2292. doi:10.1681/ASN.2022020189.
[25] Ren F, Jin Q, Liu T, et al. Causal effects between gut microbiota and IgA nephropathy: a bidirectional Mendelian randomization study. Front Cell Infect Microbiol. 2023;13:1171517. doi:10.3389/fcimb.2023.1171517.
[26] Tan J, Dong L, Jiang Z, et al. Probiotics ameliorate IgA nephropathy by improving gut dysbiosis and blunting NLRP3 signaling. J Transl Med. 2022;20(1):382. doi:10.1186/s12967-022-03585-3.
[27] Ruuskanen MO, Erawijantari PP, Havulinna AS, et al. Gut microbiome composition is predictive of incident type 2 diabetes in a population cohort of 5,572 Finnish adults. Diabetes Care. 2022;45(4):811–818. doi:10.2337/dc21-2358.
[28] Shang J, Cui W, Guo R, et al. The harmful intestinal microbial community accumulates during DKD exacerbation and microbiome-metabolome combined validation in a mouse model. Front Endocrinol (Lausanne). 2022;13:964389. doi:10.3389/fendo.2022.964389.
[29] Wang Y, Zhao J, Qin Y, et al. The specific alteration of gut microbiota in diabetic kidney diseases-a systematic review and meta-analysis. Front Immunol. 2022;13:908219. doi:10.3389/fimmu.2022.908219.
[30] Zhang L, Wang Z, Zhang X, et al. Alterations of the gut microbiota in patients with diabetic nephropathy. Microbiol Spectr. 2022;10(4):e0032422. doi:10.1128/spectrum.00324-22.
[31] Wang A, Zhao J, Qin Y, et al. Alterations of the gut microbiota in the lupus nephritis: a systematic review. Ren Fail. 2023;45(2):2285877. doi:10.1080/0886022X.2023.2285877.
[32] Azzouz DF, Chen Z, Izmirly PM, et al. Longitudinal gut microbiome analyses and blooms of pathogenic strains during lupus disease flares. Ann Rheum Dis. 2023;82(10):1315–1327. doi:10.1136/ard-2023-223929.
[33] de la Visitación N, Robles-Vera I, Toral M, et al. Gut microbiota contributes to the development of hypertension in a genetic mouse model of systemic lupus erythematosus. British J Pharmacol. 2021;178(18):3708–3729. doi:10.1111/bph.15512.
[34] Shirakashi M, Maruya M, Hirota K, et al. Effect of impaired T cell receptor signaling on the gut microbiota in a mouse model of systemic autoimmunity. Arthritis Rheumatol. 2022;74(4):641–653. doi:10.1002/art.42016.
[35] Zhang J, Luo D, Lin Z, et al. Dysbiosis of gut microbiota in adult idiopathic membranous nephropathy with nephrotic syndrome. Microb Pathog. 2020;147:104359. doi:10.1016/j.micpath.2020.104359.
[36] Zhang Y, Zhao J, Qin Y, et al. Specific alterations of gut microbiota in patients with membranous nephropathy: a systematic review and meta-analysis. Front Physiol. 2022;13:909491. doi:10.3389/fphys.2022.909491.
[37] Guan Y, Chen K, Quan D, et al. The combination of Scutellaria baicalensis Georgi and Sophora japonica L. ameliorate renal function by regulating gut microbiota in spontaneously hypertensive rats. Front Pharmacol. 2020;11:575294. doi:10.3389/fphar.2020.575294.
[38] Li Y, Li L, Tian J, et al. Insoluble fiber in barley leaf attenuates hyperuricemic nephropathy by modulating gut microbiota and short-chain fatty acids. Foods. 2022;11(21):3482. doi:10.3390/foods11213482.
[39] Lin X, Zou X, Hu B, et al. Bi Xie Fen Qing Yin decoction alleviates potassium oxonate and adenine induced-hyperuricemic nephropathy in mice by modulating gut microbiota and intestinal metabolites. Biomed Pharmacother. 2024;170:116022. doi:10.1016/j.biopha.2023.116022.
[40] Stamellou E, Seikrit C, Tang SCW, et al. IgA nephropathy. Nat Rev Dis Primers. 2023;9(1):67. doi:10.1038/s41572-023-00476-9.
[41] Barratt J, Rovin BH, Cattran D, et al. Why target the gut to treat IgA nephropathy? Kidney Int Rep. 2020;5(10):1620–1624. doi:10.1016/j.ekir.2020.08.009.
[42] Zhang H, Deng Z, Wang Y. Molecular insight in intrarenal inflammation affecting four main types of cells in nephrons in IgA nephropathy. Front Med (Lausanne). 2023;10:1128393. doi:10.3389/fmed.2023.1128393.
[43] Makita Y, Suzuki H, Nakano D, et al. Glomerular deposition of galactose-deficient IgA1-containing immune complexes via glomerular endothelial cell injuries. Nephrol Dial Transplant. 2022;37(9):1629–1636. doi:10.1093/ndt/gfac204.
[44] Gavzy SJ, Kensiski A, Lee ZL, et al. Bifidobacterium mechanisms of immune modulation and tolerance. Gut Microbes. 2023;15(2):2291164. doi:10.1080/19490976.2023.2291164.
[45] Wang X, Zhao J, Li Y, et al. Epigenetics and endoplasmic reticulum in podocytopathy during diabetic nephropathy progression. Front Immunol. 2022;13:1090989. doi:10.3389/fimmu.2022.1090989.
[46] Wu H, Tremaroli V, Schmidt C, et al. The gut microbiota in prediabetes and diabetes: a population-based cross-sectional study. Cell Metab. 2020;32(3):379–390 e373. doi:10.1016/j.cmet.2020.06.011.
[47] Linh HT, Iwata Y, Senda Y, et al. Intestinal bacterial translocation contributes to diabetic kidney disease. J Am Soc Nephrol. 2022;33(6):1105–1119. doi:10.1681/ASN.2021060843.
[48] Zhang L, Lu QY, Wu H, et al. The intestinal microbiota composition in early and late stages of diabetic kidney disease. Microbiol Spectr. 2023;11(4):e0038223. doi:10.1128/spectrum.00382-23.
[49] Barber MRW, Drenkard C, Falasinnu T, et al. Global epidemiology of systemic lupus erythematosus. Nat Rev

Rheumatol. 2021;17(9):515–532. doi:10.1038/s41584-021-00668-1.
[50] Davidson A, Aranow C, Mackay M. Lupus nephritis: challenges and progress. Curr Opin Rheumatol. 2019;31(6):682–688. doi:10.1097/BOR.0000000000000642.
[51] Woo JMP, Parks CG, Jacobsen S, et al. The role of environmental exposures and gene-environment interactions in the etiology of systemic lupus erythematous. J Intern Med. 2022;291(6):755–778. doi:10.1111/joim.13448.
[52] Choi SC, Brown J, Gong M, et al. Gut microbiota dysbiosis and altered tryptophan catabolism contribute to autoimmunity in lupus-susceptible mice. Sci Transl Med. 2020;12(551):eaax2220. doi:10.1126/scitranslmed.aax2220.
[53] Chi M, Ma K, Wang J, et al. The immunomodulatory effect of the gut microbiota in kidney disease. J Immunol Res. 2021;2021:5516035–5516016. doi:10.1155/2021/5516035.
[54] Speer T, Dimmeler S, Schunk SJ, et al. Targeting innate immunity-driven inflammation in CKD and cardiovascular disease. Nat Rev Nephrol. 2022;18(12):762–778. doi:10.1038/s41581-022-00621-9.
[55] Yaigoub H, Fath N, Tirichen H, et al. Bidirectional crosstalk between dysbiotic gut microbiota and systemic lupus erythematosus: what is new in therapeutic approaches? Clin Immunol. 2022;244:109109. doi:10.1016/j.clim.2022.109109.
[56] Kalayci FNC, Ozen S. Possible role of dysbiosis of the gut microbiome in SLE. Curr Rheumatol Rep. 2023;25(12):247–258. doi:10.1007/s11926-023-01115-8.
[57] Vacca M, Celano G, Calabrese FM, et al. The controversial role of human gut lachnospiraceae. Microorganisms. 2020;8(4):573. doi:10.3390/microorganisms8040573.
[58] Guo M, Lu M, Chen K, et al. Akkermansia muciniphila and Lactobacillus plantarum ameliorate systemic lupus erythematosus by possibly regulating immune response and remodeling gut microbiota. mSphere. 2023;8(4):e0007023. doi:10.1128/msphere.00070-23.
[59] Zegarra-Ruiz DF, El Beidaq A, Iniguez AJ, et al. A diet-sensitive commensal lactobacillus strain mediates TLR7-dependent systemic autoimmunity. Cell Host Microbe. 2019;25(1):113–127 e116. doi:10.1016/j.chom.2018.11.009.
[60] Yoon K, Kim N. Roles of sex hormones and gender in the gut microbiota. J Neurogastroenterol Motil. 2021;27(3):314–325. doi:10.5056/jnm20208.
[61] Zhao ZX, Tang XH, Jiang SL, et al. Astragaloside IV improves the pharmacokinetics of febuxostat in rats with hyperuricemic nephropathy by regulating urea metabolism in gut microbiota. Front Pharmacol. 2022;13:1031509. doi:10.3389/fphar.2022.1031509.
[62] Al Khodor S, Shatat IF. Gut microbiome and kidney disease: a bidirectional relationship. Pediatr Nephrol. 2017;32(6):921–931. doi:10.1007/s00467-016-3392-7.
[63] Zixin Y, Lulu C, Xiangchang Z, et al. TMAO as a potential biomarker and therapeutic target for chronic kidney disease: a review. Front Pharmacol. 2022;13:929262. doi:10.3389/fphar.2022.929262.
[64] Yoo W, Zieba JK, Foegeding NJ, et al. High-fat diet-induced colonocyte dysfunction escalates microbiota-derived trimethylamine N-oxide. Science. 2021;373(6556):813–818. doi:10.1126/science.aba3683.
[65] Andrikopoulos P, Aron-Wisnewsky J, Chakaroun R, et al. Evidence of a causal and modifiable relationship between kidney function and circulating trimethylamine N-oxide. Nat Commun. 2023;14(1):5843. doi:10.1038/s41467-023-39824-4.
[66] Cañadas-Garre M, Anderson K, McGoldrick J, et al. Proteomic and metabolomic approaches in the search for biomarkers in chronic kidney disease. J Proteomics. 2019;193:93–122. doi:10.1016/j.jprot.2018.09.020.
[67] Tang WH, Wang Z, Kennedy DJ, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res. 2015;116(3):448–455. doi:10.1161/CIRCRESAHA.116.305360.
[68] Zhang W, Miikeda A, Zuckerman J, et al. Inhibition of microbiota-dependent TMAO production attenuates chronic kidney disease in mice. Sci Rep. 2021;11(1):518. doi:10.1038/s41598-020-80063-0.
[69] Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease. Nat Commun. 2018;9(1):3294. doi:10.1038/s41467-018-05470-4.
[70] Hui Y, Zhao J, Yu Z, et al. The role of tryptophan metabolism in the occurrence and progression of acute and chronic kidney diseases. Mol Nutr Food Res. 2023;67(21):e2300218. doi:10.1002/mnfr.202300218.
[71] Liu JJ, Ching J, Wee HN, et al. Plasma tryptophan-kynurenine pathway metabolites and risk for progression to end-stage kidney disease in patients with type 2 diabetes. Diabetes Care. 2023;46(12):2223–2231. doi:10.2337/dc23-1147.
[72] Dvořák Z, Sokol H, Mani S. Drug mimicry: promiscuous receptors PXR and AhR, and microbial metabolite interactions in the intestine. Trends Pharmacol Sci. 2020;41(12):900–908. doi:10.1016/j.tips.2020.09.013.
[73] Liu JR, Miao H, Deng DQ, et al. Gut microbiota-derived tryptophan metabolism mediates renal fibrosis by aryl hydrocarbon receptor signaling activation. Cell Mol Life Sci. 2021;78(3):909–922. doi:10.1007/s00018-020-03645-1.
[74] Shimizu H, Yisireyili M, Higashiyama Y, et al. Indoxyl sulfate upregulates renal expression of ICAM-1 via production of ROS and activation of NF-kappaB and p53 in proximal tubular cells. Life Sci. 2013;92(2):143–148. doi:10.1016/j.lfs.2012.11.012.
[75] Shi Y, Tang B, Yu J, et al. Aryl hydrocarbon receptor signaling activation in systemic sclerosis attenuates collagen production and is a potential antifibrotic target. Int Immunopharmacol. 2020;88:106886. doi:10.1016/j.intimp.2020.106886.
[76] Lv Y, Luo YY, Ren HW, et al. The role of pregnane X receptor (PXR) in substance metabolism. Front Endocrinol (Lausanne). 2022;13:959902. doi:10.3389/fendo.2022.959902.
[77] Ye X, Li H, Anjum K, et al. Dual role of indoles derived from intestinal microbiota on human health. Front Immunol. 2022;13:903526. doi:10.3389/fimmu.2022.903526.
[78] Neinast M, Murashige D, Arany Z. Branched chain amino acids. Annu Rev Physiol. 2019;81(1):139–164. doi:10.1146/annurev-physiol-020518-114455.
[79] Hao Y, Pan X, You J, et al. Microbial production of branched chain amino acids: advances and perspectives. Bioresour Technol. 2024;397:130502. doi:10.1016/j.biortech.2024.130502.

[80] McCann JR, Rawls JF. Essential amino acid metabolites as chemical mediators of host-microbe interaction in the gut. Annu Rev Microbiol. 2023;77(1):479–497. doi:10.1146/annurev-micro-032421-111819.

[81] Sciacovelli M, Dugourd A, Jimenez LV, et al. Dynamic partitioning of branched-chain amino acids-derived nitrogen supports renal cancer progression. Nat Commun. 2022;13(1):7830. doi:10.1038/s41467-022-35036-4.

[82] Miao T, Li M, Shao T, et al. The involvement of branched-chain amino acids (BCAAs) in aromatic trihalogenated DBP exposure-induced kidney damage in mice. Chemosphere. 2022;305:135351. doi:10.1016/j.chemosphere.2022.135351.

[83] Kim JE, Nam H, Park JI, et al. Gut microbial genes and metabolism for methionine and branched-chain amino acids in diabetic nephropathy. Microbiol Spectr. 2023;11(2):e0234422. doi:10.1128/spectrum.02344-22.

[84] Pedersen HK, Gudmundsdottir V, Nielsen HB, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016;535(7612):376–381. doi:10.1038/nature18646.

[85] Piret SE, Guo Y, Attallah AA, et al. Kruppel-like factor 6-mediated loss of BCAA catabolism contributes to kidney injury in mice and humans. Proc Natl Acad Sci USA. 2021;118(23):e2024414118. doi:10.1073/pnas.2024414118.

[86] Dimou A, Tsimihodimos V, Bairaktari E. The critical role of the branched chain amino acids (BCAAs) catabolism-regulating enzymes, branched-chain aminotransferase (BCAT) and branched-chain alpha-keto acid dehydrogenase (BCKD), in human pathophysiology. Int J Mol Sci. 2022;23(7):4022. doi:10.3390/ijms23074022.

[87] Cano NJ, Fouque D, Leverve XM. Application of branched-chain amino acids in human pathological states: renal failure. J Nutr. 2006;136(1 Suppl):299S–307S. doi:10.1093/jn/136.1.299S.

[88] Deehan EC, Yang C, Perez-Munoz ME, et al. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. Cell Host Microbe. 2020;27(3):389–404 e386. doi:10.1016/j.chom.2020.01.006.

[89] Magliocca G, Mone P, Di Iorio BR, et al. Short-chain fatty acids in chronic kidney disease: focus on inflammation and oxidative stress regulation. Int J Mol Sci. 2022;23(10):5354. doi:10.3390/ijms23105354.

[90] Rekha K, Venkidasamy B, Samynathan R, et al. Short-chain fatty acid: an updated review on signaling, metabolism, and therapeutic effects. Crit Rev Food Sci Nutr. 2024;64(9):2461–2489. doi:10.1080/10408398.2022.2124231.

[91] Li L, Ma L, Fu P. Gut microbiota-derived short-chain fatty acids and kidney diseases. Drug Des Devel Ther. 2017;11:3531–3542. doi:10.2147/DDDT.S150825.

[92] He M, Wei W, Zhang Y, et al. Gut microbial metabolites SCFAs and chronic kidney disease. J Transl Med. 2024;22(1):172. doi:10.1186/s12967-024-04974-6.

[93] Miquel S, Martín R, Rossi O, et al. Faecalibacterium prausnitzii and human intestinal health. Curr Opin Microbiol. 2013;16(3):255–261. doi:10.1016/j.mib.2013.06.003.

[94] Li HB, Xu ML, Xu XD, et al. Faecalibacterium prausnitzii attenuates CKD via butyrate-renal GPR43 axis. Circ Res. 2022;131(9):e120–e134. doi:10.1161/CIRCRESAHA.122.320184.

[95] Mikami D, Kobayashi M, Uwada J, et al. Short-chain fatty acid mitigates adenine-induced chronic kidney disease via FFA2 and FFA3 pathways. Biochim Biophys Acta Mol Cell Biol Lipids. 2020;1865(6):158666. doi:10.1016/j.bbalip.2020.158666.

[96] Tao P, Ji J, Wang Q, et al. The role and mechanism of gut microbiota-derived short-chain fatty in the prevention and treatment of diabetic kidney disease. Front Immunol. 2022;13:1080456. doi:10.3389/fimmu.2022.1080456.

[97] Collins SL, Stine JG, Bisanz JE, et al. Bile acids and the gut microbiota: metabolic interactions and impacts on disease. Nat Rev Microbiol. 2023;21(4):236–247. doi:10.1038/s41579-022-00805-x.

[98] Guzior DV, Quinn RA. Review: microbial transformations of human bile acids. Microbiome. 2021;9(1):140. doi:10.1186/s40168-021-01101-1.

[99] Funabashi M, Grove TL, Wang M, et al. A metabolic pathway for bile acid dehydroxylation by the gut microbiome. Nature. 2020;582(7813):566–570. doi:10.1038/s41586-020-2396-4.

[100] Xiao X, Zhang J, Ji S, et al. Lower bile acids as an independent risk factor for renal outcomes in patients with type 2 diabetes mellitus and biopsy-proven diabetic kidney disease. Front Endocrinol (Lausanne). 2022;13:1026995. doi:10.3389/fendo.2022.1026995.

[101] Li S, Li C, Wang W. Bile acid signaling in renal water regulation. Am J Physiol Renal Physiol. 2019;317(1):F73–F76. doi:10.1152/ajprenal.00563.2018.

[102] Ghallab A, González D, Strängberg E, et al. Inhibition of the renal apical sodium dependent bile acid transporter prevents cholemic nephropathy in mice with obstructive cholestasis. J Hepatol. 2024;80(2):268–281. doi:10.1016/j.jhep.2023.10.035.

[103] Fickert P. Detour of bile acid routes as therapeutic roadmap for cholemic nephropathy. J Hepatol. 2024;80(2):188–190. doi:10.1016/j.jhep.2023.11.008.

[104] Fang Q, Liu N, Zheng B, et al. Roles of gut microbial metabolites in diabetic kidney disease. Front Endocrinol (Lausanne). 2021;12:636175. doi:10.3389/fendo.2021.636175.

[105] Gryp T, De Paepe K, Vanholder R, et al. Gut microbiota generation of protein-bound uremic toxins and related metabolites is not altered at different stages of chronic kidney disease. Kidney Int. 2020;97(6):1230–1242. doi:10.1016/j.kint.2020.01.028.

[106] Poveda J, Sanchez-Nino MD, Glorieux G, et al. p-cresyl sulphate has pro-inflammatory and cytotoxic actions on human proximal tubular epithelial cells. Nephrol Dial Transplant. 2014;29(1):56–64. doi:10.1093/ndt/gft367.

[107] Poesen R, Evenepoel P, de Loor H, et al. Metabolism, protein binding, and renal clearance of microbiota-derived p-cresol in patients with CKD. Clin J Am Soc Nephrol. 2016;11(7):1136–1144. doi:10.2215/CJN.00160116.

[108] Kim K, Anderson EM, Thome T, et al. Skeletal myopathy in CKD: a comparison of adenine-induced nephropathy and 5/6 nephrectomy models in mice. Am J Physiol Renal Physiol. 2021;321(1):F106–F119. doi:10.1152/ajprenal.00117.2021.

[109] Wang X, Yang S, Li S, et al. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents. Gut. 2020;69(12):2131–2142. doi:10.1136/gutjnl-2019-319766.

[110] Fiaccadori E, Cosola C, Sabatino A. Targeting the gut for early diagnosis, prevention, and cure of diabetic kidney disease: is the phenyl sulfate story another step forward? Am J Kidney Dis. 2020;75(1):144–147. doi:10.1053/j.ajkd.2019.07.001.

[111] Kikuchi K, Saigusa D, Kanemitsu Y, et al. Gut microbiome-derived phenyl sulfate contributes to albuminuria in diabetic kidney disease. Nat Commun. 2019;10(1):1835. doi:10.1038/s41467-019-09735-4.

[112] Ticinesi A, Guerra A, Nouvenne A, et al. Disentangling the complexity of nutrition, frailty and gut microbial pathways during aging: a focus on hippuric acid. Nutrients. 2023;15(5):1138. doi:10.3390/nu15051138.

[113] Pruss KM, Chen H, Liu Y, et al. Host-microbe co-metabolism via MCAD generates circulating metabolites including hippuric acid. Nat Commun. 2023;14(1):512. doi:10.1038/s41467-023-36138-3.

[114] Grams ME, Tin A, Rebholz CM, et al. Metabolomic alterations associated with cause of CKD. Clin J Am Soc Nephrol. 2017;12(11):1787–1794. doi:10.2215/CJN.02560317.

[115] Sun B, Wang X, Liu X, et al. Hippuric acid promotes renal fibrosis by disrupting redox homeostasis via facilitation of NRF2-KEAP1-CUL3 interactions in chronic kidney disease. Antioxidants (Basel). 2020;9(9):783. doi:10.3390/antiox9090783.

[116] Mafra D, Borges N, Alvarenga L, et al. Dietary components that may influence the disturbed gut microbiota in chronic kidney disease. Nutrients. 2019;11(3):496. doi:10.3390/nu11030496.

[117] Rana A, Samtiya M, Dhewa T, et al. Health benefits of polyphenols: a concise review. J Food Biochem. 2022;46(10):e14264. doi:10.1111/jfbc.14264.

[118] Ondrussek-Sekac M, Navas-Carrillo D, Orenes-Piñero E. Intestinal microbiota alterations in chronic kidney disease and the influence of dietary components. Crit Rev Food Sci Nutr. 2021;61(9):1490–1502. doi:10.1080/10408398.2020.1761771.

[119] Mithul Aravind S, Wichienchot S, Tsao R, et al. Role of dietary polyphenols on gut microbiota, their metabolites and health benefits. Food Res Int. 2021;142:110189. doi:10.1016/j.foodres.2021.110189.

[120] Corrêa TAF, Rogero MM, Hassimotto NMA, et al. The two-way polyphenols-microbiota interactions and their effects on obesity and related metabolic diseases. Front Nutr. 2019;6:188. doi:10.3389/fnut.2019.00188.

[121] Han QQ, Ren QD, Guo X, et al. Punicalagin attenuates hyperuricemia via restoring hyperuricemia-induced renal and intestinal dysfunctions. J Adv Res. 2025;69:449–461. doi:10.1016/j.jare.2024.03.029.

[122] Hua Q, Han Y, Zhao H, et al. Punicalagin alleviates renal injury via the gut-kidney axis in high-fat diet-induced diabetic mice. Food Funct. 2022;13(2):867–879. doi:10.1039/d1fo03343c.

[123] Hsu CN, Hou CY, Chang CI, et al. Resveratrol butyrate ester protects adenine-treated rats against hypertension and kidney disease by regulating the gut-kidney axis. Antioxidants (Basel). 2021;11(1):83. doi:10.3390/antiox11010083.

[124] Tain YL, Chang CI, Hou CY, et al. Resveratrol propionate ester supplement exerts antihypertensive effect in juvenile rats exposed to an adenine diet via gut microbiota modulation. Nutrients. 2024;16(13):2131. doi:10.3390/nu16132131.

[125] Zhou Y, Zeng Y, Wang R, et al. Resveratrol improves hyperuricemia and ameliorates renal injury by modulating the gut microbiota. Nutrients. 2024;16(7):1086. doi:10.3390/nu16071086.

[126] Hsu CN, Hou CY, Chang-Chien GP, et al. Perinatal resveratrol therapy prevents hypertension programmed by maternal chronic kidney disease in adult male offspring: implications of the gut microbiome and their metabolites. Biomedicines. 2020;8(12):567. doi:10.3390/biomedicines8120567.

[127] Yan H, Zhang Y, Lin X, et al. Resveratrol improves diabetic kidney disease by modulating the gut microbiota-short chain fatty acids axis in db/db mice. Int J Food Sci Nutr. 2024;75(3):264–276. doi:10.1080/09637486.2024.2303041.

[128] Cai TT, Ye XL, Li RR, et al. Resveratrol modulates the gut microbiota and inflammation to protect against diabetic nephropathy in mice. Front Pharmacol. 2020;11:1249. doi:10.3389/fphar.2020.01249.

[129] Zeng YQ, Dai Z, Lu F, et al. Emodin via colonic irrigation modulates gut microbiota and reduces uremic toxins in rats with chronic kidney disease. Oncotarget. 2016;7(14):17468–17478. doi:10.18632/oncotarget.8160.

[130] Xu Z, Hou Y, Sun J, et al. Deoxycholic acid-chitosan coated liposomes combined with in situ colonic gel enhances renal fibrosis therapy of emodin. Phytomedicine. 2022;101:154110. doi:10.1016/j.phymed.2022.154110.

[131] Lu Z, Ji C, Luo X, et al. Nanoparticle-mediated delivery of emodin via colonic irrigation attenuates renal injury in 5/6 nephrectomized rats. Front Pharmacol. 2020;11:606227. doi:10.3389/fphar.2020.606227.

[132] Zhu N, Duan H, Feng Y, et al. Magnesium lithospermate B ameliorates diabetic nephropathy by suppressing the uremic toxin formation mediated by gut microbiota. Eur J Pharmacol. 2023;953:175812. doi:10.1016/j.ejphar.2023.175812.

[133] Yu H, Lou Z, Wu T, et al. Mechanisms of epigallocatechin gallate (EGCG) in ameliorating hyperuricemia: insights into gut microbiota and intestinal function in a mouse model. Food Funct. 2024;15(11):6068–6081. doi:10.1039/d4fo01606h.

[134] Unno T, Ichitani M. Epigallocatechin-3-gallate decreases plasma and urinary levels of p-cresol by modulating gut microbiota in mice. ACS Omega. 2022;7(44):40034–40041. doi:10.1021/acsomega.2c04731.

[135] Zhou X, Zhang B, Zhao X, et al. Chlorogenic acid prevents hyperuricemia nephropathy via regulating TMAO-related gut microbes and inhibiting the PI3K/AKT/mTOR pathway. J Agric Food Chem. 2022;70(33):10182–10193. doi:10.1021/acs.jafc.2c03099.

[136] Zhou X, Zhang B, Zhao X, et al. Chlorogenic acid supplementation ameliorates hyperuricemia, relieves renal inflammation, and modulates intestinal homeostasis. Food Funct. 2021;12(12):5637–5649. doi:10.1039/d0fo03199b.

[137] Ding Y, Li X, Liu Y, et al. Protection mechanisms underlying oral administration of chlorogenic acid against cadmium-induced hepatorenal injury related to regulating intestinal flora balance. J Agric Food Chem. 2021;69(5):1675–1683. doi:10.1021/acs.jafc.0c06698.

[138] Cheng D, Li H, Zhou J, et al. Chlorogenic acid relieves lead-induced cognitive impairments and hepato-renal damage via regulating the dysbiosis of the gut microbiota in mice. Food Funct. 2019;10(2):681–690. doi:10.1039/c8fo01755g.
[139] Ren Q, Cheng L, Guo F, et al. Fisetin improves hyperuricemia-induced chronic kidney disease via regulating gut microbiota-mediated tryptophan metabolism and aryl hydrocarbon receptor activation. J Agric Food Chem. 2021;69(37):10932–10942. doi:10.1021/acs.jafc.1c03449.
[140] Pan S, Jiang SS, Li R, et al. Hong Guo Ginseng Guo (HGGG) protects against kidney injury in diabetic nephropathy by inhibiting NLRP3 inflammasome and regulating intestinal flora. Phytomedicine. 2024;132:155861. doi:10.1016/j.phymed.2024.155861.
[141] Yuan L, Li X, He S, et al. Effects of natural flavonoid isoorientin on growth performance and gut microbiota of mice. J Agric Food Chem. 2018;66(37):9777–9784. doi:10.1021/acs.jafc.8b03568.
[142] Sun X, Huang Y, Zhu S, et al. Yishen Qingli Heluo granule in the treatment of chronic kidney disease: network pharmacology analysis and experimental validation. Drug Des Devel Ther. 2022;16:769–787. doi:10.2147/DDDT.S348335.
[143] Xu X, Wang H, Guo D, et al. Curcumin modulates gut microbiota and improves renal function in rats with uric acid nephropathy. Ren Fail. 2021;43(1):1063–1075. doi:10.1080/0886022X.2021.1944875.
[144] Pivari F, Mingione A, Piazzini G, et al. Curcumin supplementation (Meriva((R))) modulates inflammation, lipid peroxidation and gut microbiota composition in chronic kidney disease. Nutrients. 2022;14(1):231. doi:10.3390/nu14010231.
[145] Salarolli RT, Alvarenga L, Cardozo L, et al. Can curcumin supplementation reduce plasma levels of gut-derived uremic toxins in hemodialysis patients? A pilot randomized, double-blind, controlled study. Int Urol Nephrol. 2021;53(6):1231–1238. doi:10.1007/s11255-020-02760-z.
[146] Reis D, Alvarenga L, Cardozo L, et al. Can curcumin supplementation break the vicious cycle of inflammation, oxidative stress, and uremia in patients undergoing peritoneal dialysis? Clin Nutr ESPEN. 2024;59:96–106. doi:10.1016/j.clnesp.2023.11.015.
[147] Xu J, Cao K, Liu X, et al. Punicalagin regulates signaling pathways in inflammation-associated chronic diseases. Antioxidants (Basel). 2021;11(1):29. doi:10.3390/antiox11010029.
[148] Liu H, Yan C, Teng Y, et al. Gut microbiota and D-ribose mediate the anti-colitic effect of punicalagin in DSS-treated mice. Food Funct. 2024;15(13):7108–7123. doi:10.1039/d4fo00741g.
[149] Sánchez-Terrón G, Martínez R, Morcuende D, et al. Pomegranate supplementation alleviates dyslipidemia and the onset of non-alcoholic fatty liver disease in Wistar rats by shifting microbiota and producing urolithin-like microbial metabolites. Food Funct. 2024;15(14):7348–7363. doi:10.1039/d4fo00688g.
[150] Yin Y, Martínez R, Zhang W, et al. Crosstalk between dietary pomegranate and gut microbiota: evidence of health benefits. Crit Rev Food Sci Nutr. 2024;64(27):10009–10035. doi:10.1080/10408398.2023.2219763.
[151] Meng T, Xiao D, Muhammed A, et al. Anti-inflammatory action and mechanisms of resveratrol. Molecules. 2021;26(1):229. doi:10.3390/molecules26010229.
[152] Shaito A, Posadino AM, Younes N, et al. Potential adverse effects of resveratrol: a literature review. Int J Mol Sci. 2020;21(6):2084. doi:10.3390/ijms21062084.
[153] Den Hartogh DJ, Tsiani E. Health benefits of resveratrol in kidney disease: evidence from in vitro and in vivo studies. Nutrients. 2019;11(7):1624. doi:10.3390/nu11071624.
[154] Dong X, Fu J, Yin X, et al. Emodin: a review of its pharmacology, toxicity and pharmacokinetics. Phytother Res. 2016;30(8):1207–1218. doi:10.1002/ptr.5631.
[155] Xun W, Ji M, Ma Z, et al. Dietary emodin alleviates lipopolysaccharide-induced intestinal mucosal barrier injury by regulating gut microbiota in piglets. Anim Nutr. 2023;14:152–162. doi:10.1016/j.aninu.2023.05.004.
[156] Cheng TL, Lin ZY, Liao KY, et al. Magnesium lithospermate B attenuates high-fat diet-induced muscle atrophy in C57BL/6J mice. Nutrients. 2021;14(1):104. doi:10.3390/nu14010104.
[157] Shen D, Guo M, Geng X, et al. Magnesium lithospermate B protects against cisplatin-induced acute kidney injury via alleviating mitochondrial dysfunction. Drug Des Devel Ther. 2022;16:2293–2304. doi:10.2147/DDDT.S358830.
[158] Han X, Fu Y, Wang K, et al. Epigallocatechin gallate alleviates osteoporosis by regulating the gut microbiota and serum metabolites in rats. Food Funct. 2023;14(23):10564–10580. doi:10.1039/d3fo03233g.
[159] Saito Y, Sato T, Nomoto K, et al. Identification of phenol- and p-cresol-producing intestinal bacteria by using media supplemented with tyrosine and its metabolites. FEMS Microbiol Ecol. 2018;94(9):125. doi:10.1093/femsec/fiy125.
[160] Jiao H, Zhang M, Xu W, et al. Chlorogenic acid alleviate kidney fibrosis through regulating TLR4/NF-κB mediated oxidative stress and inflammation. J Ethnopharmacol. 2024;335:118693. doi:10.1016/j.jep.2024.118693.
[161] Chen J, Song Z, Ji R, et al. Chlorogenic acid improves growth performance of weaned rabbits via modulating the intestinal epithelium functions and intestinal microbiota. Front Microbiol. 2022;13:1027101. doi:10.3389/fmicb.2022.1027101.
[162] Hu X, Zhen W, Bai D, et al. Effects of dietary chlorogenic acid on cecal microbiota and metabolites in broilers during lipopolysaccharide-induced immune stress. Front Microbiol. 2024;15:1347053. doi:10.3389/fmicb.2024.1347053.
[163] Arangia A, Marino Y, Fusco R, et al. Fisetin, a natural polyphenol, ameliorates endometriosis modulating mast cells derived NLRP-3 inflammasome pathway and oxidative stress. Int J Mol Sci. 2023;24(6):5076. doi:10.3390/ijms24065076.
[164] Chen TJ, Feng Y, Liu T, et al. Fisetin regulates gut microbiota and exerts neuroprotective effect on mouse model of Parkinson's disease. Front Neurosci. 2020;14:549037. doi:10.3389/fnins.2020.549037.
[165] Ashiqueali SA, Chaudhari D, Zhu X, et al. Fisetin modulates the gut microbiota alongside biomarkers of senescence and inflammation in a DSS-induced murine model of colitis. Geroscience. 2024;46(3):3085–3103. doi:10.1007/s11357-024-01060-z.

[166] Ren Q, Tao S, Guo F, et al. Natural flavonol fisetin attenuated hyperuricemic nephropathy via inhibiting IL-6/JAK2/STAT3 and TGF-beta/SMAD3 signaling. Phytomedicine. 2021;87:153552. doi:10.1016/j.phymed.2021.153552.

[167] Zhu M, Sun Y, Su Y, et al. Luteolin: A promising multifunctional natural flavonoid for human diseases. Phytother Res. 2024;38(7):3417–3443. doi:10.1002/ptr.8217.

[168] Guo W, Luo L, Meng Y, et al. Luteolin alleviates methionine-choline-deficient diet-induced non-alcoholic steatohepatitis by modulating host serum metabolome and gut microbiome. Front Nutr. 2022;9:936237. doi:10.3389/fnut.2022.936237.

[169] Ge X, Wang C, Chen H, et al. Luteolin cooperated with metformin hydrochloride alleviates lipid metabolism disorders and optimizes intestinal flora compositions of high-fat diet mice. Food Funct. 2020;11(11):10033–10046. doi:10.1039/d0fo01840f.

[170] Dei Cas M, Ghidoni R. Dietary curcumin: correlation between bioavailability and health potential. Nutrients. 2019;11(9):2147. doi:10.3390/nu11092147.

[171] Shabbir U, Rubab M, Daliri EB, et al. Curcumin, quercetin, catechins and metabolic diseases: the role of gut microbiota. Nutrients. 2021;13(1):206. doi:10.3390/nu13010206.

[172] Hurtado-Nuñez G-E, Cortés-Rojo C, Sánchez-Ceja S-G, et al. Gallic, ellagic acids and their oral combined administration induce kidney, lung, and heart injury after acute exposure in Wistar rats. Food Chem Toxicol. 2022;170:113492. doi:10.1016/j.fct.2022.113492.

[173] Aguirre-García YL, Castillo-Manzanares A, Palomo-Ligas L, et al. Toxicity evaluation of a polyphenolic extract from Flourensia cernua DC through artemia lethality assay, hemolytic activity, and acute oral test. J Toxicol. 2024;2024(1):2970470. doi:10.1155/2024/2970470.

[174] Zhao T, Li C, Wang S, et al. Green tea (Camellia sinensis): a review of its phytochemistry, pharmacology, and toxicology. Molecules. 2022;27(12). doi:10.3390/molecules27123909.

[175] Tosi N, Favari C, Bresciani L, et al. Unravelling phenolic metabotypes in the frame of the COMBAT study, a randomized, controlled trial with cranberry supplementation. Food Res Int. 2023;172:113187. doi:10.1016/j.foodres.2023.113187.

[176] Mena P, Bresciani L, Brindani N, et al. Phenyl-gamma-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: synthesis, analysis, bioavailability, and bioactivity. Nat Prod Rep. 2019;36(5):714–752. doi:10.1039/c8np00062j.

[177] Carregosa D, Pinto C, Ávila-Gálvez MÁ, et al. A look beyond dietary (poly)phenols: the low molecular weight phenolic metabolites and their concentrations in human circulation. Compr Rev Food Sci Food Saf. 2022;21(5):3931–3962. doi:10.1111/1541-4337.13006.

[178] Jia K, Shi P, Zhang L, et al. Trans-cinnamic acid alleviates high-fat diet-induced renal injury via JNK/ERK/P38 MAPK pathway. J Nutr Biochem. 2025;135:109769. doi:10.1016/j.jnutbio.2024.109769.