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REVIEW

Gut Microbiota Dysbiosis and Metabolite Imbalance Mediate Diabetic Kidney Disease Inflammation: Mechanisms and Intervention Strategies Targeting Gut-Kidney Axis and NF-κB/NLRP3 Pathways

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Objective: Chronic unresolved inflammation is a core driver of diabetic kidney disease (DKD) progression, with gut microbiota dysbiosis and metabolite imbalance (via gut-kidney axis) as key pathogenic triggers. This review systematically elucidates the pathological link between gut microbiota-metabolite-axis dysfunction and DKD-related inflammation (centered on NF-κB/NLRP3 pathways) and summarizes multi-target intervention strategies—including traditional Chinese medicine (TCM), SGLT2 inhibitors, probiotics/prebiotics—targeting this axis.

Methods: Literature search was conducted on PubMed using keywords ["Gut microbiota" or "Gut microflora" or "Gut microbiota metabolites"], ["Diabetic kidney disease" or "Diabetic nephropathy" or "DKD"], ["immune regulation"], ["intestinal barrier"], [inflammation"], ["Traditional Chinese Medicine" or "TCM"], without date restrictions. Articles that do not meet the requirements are excluded.

Results: Gut microbiota dysbiosis in DKD is characterized by reduced SCFA-producing bacteria (Ruminococcaceae, Lachnospiraceae) and enriched pathogenic Proteobacteria, leading to metabolite imbalance: insufficient beneficial metabolites (SCFAs, IPA) and accumulation of harmful metabolites (TMAO, phenyl sulfate, BCAAs). This imbalance impairs intestinal barrier (ZO-1/Occludin downregulation), promotes endotoxin (LPS) translocation, and activates NF-κB (p65 phosphorylation) and NLRP3 inflammasome (NLRP3/ASC/caspase-1 complex), exacerbating renal inflammation via pro-inflammatory cytokines (IL-1β, TNF-α, IL-6). Intervention strategies (including TCM) suppress this cascade: TCM (eg, Astragalus membranaceus, Xiaoyaosan) reshapes microbiota, strengthens intestinal barrier, and inhibits NF-κB/NLRP3; SGLT2 inhibitors and probiotics/prebiotics complement via SCFA elevation and TMAO reduction. Clinically, these interventions lower UACR, improve eGFR, and correlate with reduced serum IL-1β/TNF-α.

Conclusion: Gut microbiota-metabolite-intestinal barrier axis dysfunction is a pivotal pathological mechanism of DKD inflammation, mediated by NF-κB/NLRP3 pathways. Multi-pronged interventions targeting this axis effectively resolve inflammation, providing promising therapeutic approaches for DKD.

Keywords: inflammation, diabetic kidney disease, intestinal microecology, traditional Chinese medicine, immune function, bacterial communities

Introduction

Diabetic kidney disease (DKD) is the most common microvascular complication of Type 2 diabetes mellitus (T2DM) and the leading cause of end-stage renal disease (ESRD) worldwide, accounting for approximately 40–50% of ESRD cases.[1–3]

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Currently, the treatment of DKD primarily focuses on blood glucose control (eg, sodium-glucose cotransporter 2 [SGLT2] inhibitors), blood pressure management (eg, renin-angiotensin-aldosterone system [RAAS] inhibitors), and metabolic disorder improvement. However, it still cannot fully halt disease progression—even with strict glycemic and blood pressure control, more than 30% of diabetic patients will develop DKD. Moreover, after progressing to ESRD, patients' quality of life declines significantly and the medical burden increases sharply.[4,5] This current situation suggests that there are key links in the pathogenesis of DKD that have not been fully explored.

In recent years, the proposal of the "Gut-Kidney Axis" theory has provided a new perspective for DKD research. As an important "organ" of host metabolism, gut microbiota dysbiosis (structural and functional disorders) can regulate kidney injury through metabolite-mediated inflammatory responses.[6–9] Clinical cohort studies have confirmed that DKD patients exhibit significantly reduced gut microbiota α/β diversity, decreased abundance of beneficial bacteria (eg, Bifidobacterium, short-chain fatty acid (SCFA)-producing bacteria), and increased abundance of pathogenic bacteria (eg, Escherichia coli, phylum Proteobacteria).[10,11] This dysbiosis is closely correlated with the levels of inflammatory factors (IL-1β, TNF-α) and the degree of renal function impairment (urinary albumin-to-creatinine ratio [UACR] estimated glomerular filtration rate [eGFR]).[3,12–15] More importantly, gut microbiota metabolites (eg, SCFAs, trimethylamine N-oxide [TMAO], phenyl sulfate) can act as "messengers" to directly or indirectly regulate the renal inflammatory microenvironment by activating or inhibiting key inflammatory pathways such as the NLRP3 inflammasome and NF-κB.[16]

While existing reviews have explored the association between gut microbiota and DKD, most focus on changes in microbial composition, lacking systematic integration of the "microbiota-metabolite-inflammation-renal injury" axis as well as insufficient collation of clinical translation evidence.[7,17,18] This review systematically analyzes the mechanisms of action of gut microbial metabolism in DKD-related inflammation, summarizes therapeutic strategies targeting gut microbial metabolism, and identifies the limitations of current research and future directions. It aims to provide theoretical support for mechanistic research and clinical intervention of DKD.

Microenvironment of Intestinal Flora and Inflammation of Diabetes Nephropathy

Characteristics of Gut Microbiota in Healthy and DKD States

The pathogenesis of DKD is complex, involving multiple factors such as glucose metabolic disorders, intestinal microecological imbalance, oxidative stress, and inflammatory responses. We have summarized the pathogenesis of DKD, as shown in Figure 1. Imbalance of gut microbiota plays an important role in the occurrence of DKD.

Approximately 10^{14} microorganisms colonize the intestinal tract of healthy individuals, predominantly belonging to the phyla Bacteroidetes and Firmicutes, supplemented by Proteobacteria, Actinobacteria, and other phyla. Its core functions include. First, participating in dietary fiber fermentation to produce beneficial metabolites such as SCFAs. Second, synthesizing vitamins (eg, B vitamins). Third, maintaining intestinal barrier integrity by upregulating the expression of tight junction proteins ZO-1 and Occludin. Fourth, inhibiting pathogenic bacterial colonization.[18] This homeostasis is termed "gut microecological balance", which serves as a crucial guarantee for host metabolic and immune homeostasis. The gut microecological balance is significantly disrupted in patients with DKD, and the degree of dysbiosis correlates with DKD staging. Multiple cohort studies have shown that the Shannon index and Chao1 index of fecal microbiota in DKD patients are significantly lower than those in healthy controls and diabetic patients without nephropathy, indicating decreased microbial richness and evenness.[14,15] Meanwhile, the intestinal microbial composition also changes, characterized by reduced abundance of beneficial bacteria (eg, Ruminococcaceae, Lachnospiraceae, Bifidobacterium), which are the main producers of SCFAs. In addition, the abundance of pathogenic and opportunistic pathogens (eg, phylum Proteobacteria, Escherichia coli-Shigella, Haemophilus) is increased, and their metabolites (eg, lipopolysaccharide [LPS], trimethylamine N-oxide [TMAO]) possess pro-inflammatory activity.[15,19] Notably, DKD patients also exhibit site-specific gut microbiota dysbiosis. A high-fat diet (HFD)/streptozotocin (STZ)-induced diabetic rat model showed that the Bacteroidetes/Firmicutes ratio in the jejunal microbiota (not just the colonic microbiota) was decreased, and this ratio was negatively correlated with renal interleukin (IL)-1β and tumor necrosis factor (TNF)-α

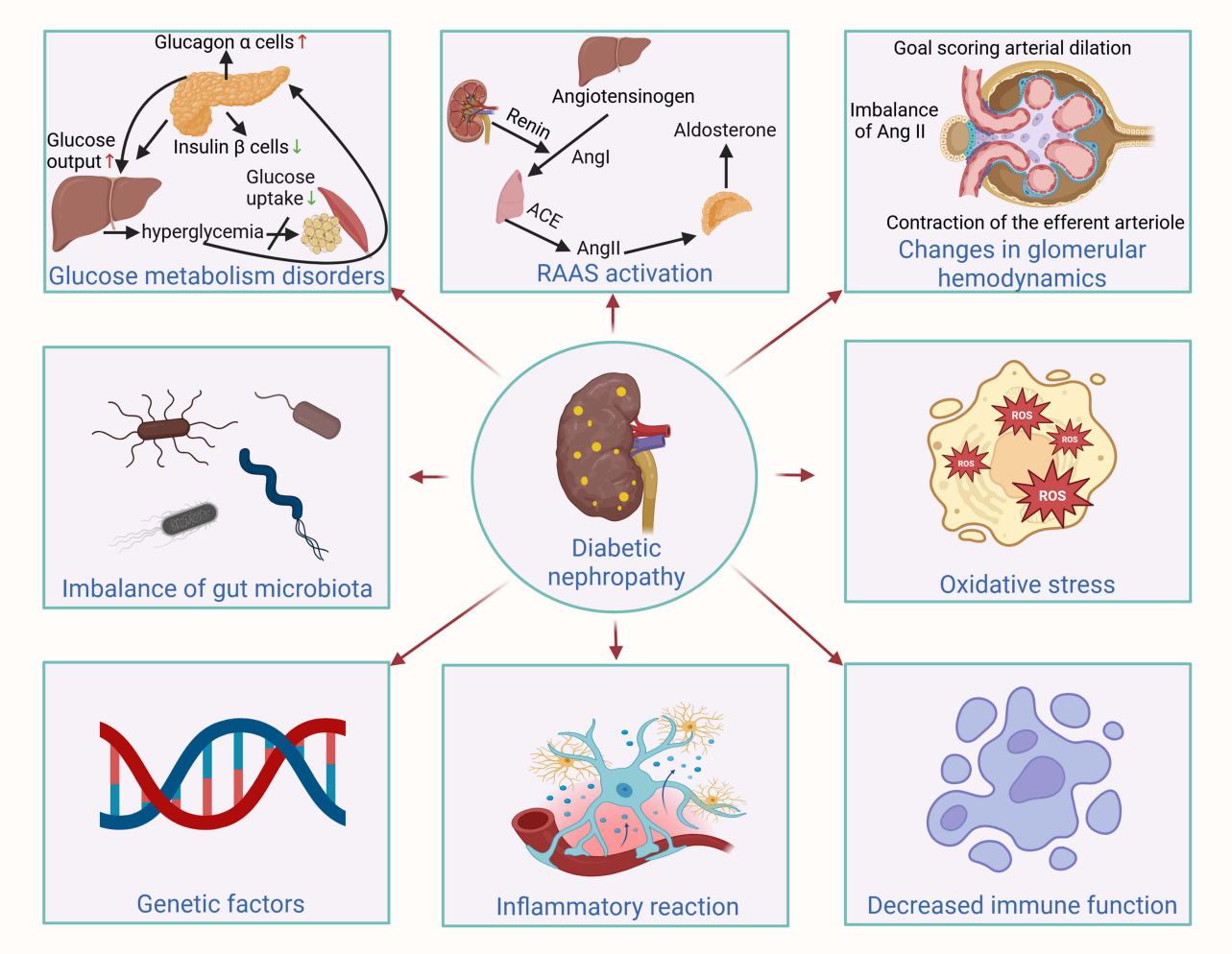

Figure 1 The main pathophysiological mechanism of DKD. This figure illustrates the interconnected core pathophysiological drivers of diabetic nephropathy (DKD), with DKD centered as the target pathological condition. Surrounding it are eight synergistic mechanisms: glucose metabolism disorders (dysregulated pancreatic islet cell function induces persistent hyperglycemia); RAAS activation (renin/ACE-mediated Ang II production and aldosterone secretion drive renal injury); glomerular hemodynamic changes (imbalanced Ang II signaling disrupts intraglomerular pressure homeostasis); oxidative stress (excessive ROS accumulates to damage renal parenchymal cells); decreased immune function (impaired renal immune cell activity fails to clear pro-inflammatory mediators); inflammatory reaction (renal inflammatory infiltration promotes fibrosis and functional decline); genetic factors (gene polymorphisms increase DKD susceptibility); and gut microbiota imbalance (dysbiosis disrupts the gut-kidney axis to exacerbate renal injury. These mechanisms form an interactive network that synergistically drives the pathological progression of DKD.

levels, suggesting that small intestinal microbiota dysbiosis may be involved in the initiation of DKD-related inflammation at an earlier stage.[20]

The "Bridge" Linking Microbiota-Inflammation-Renal Injury

The intestinal barrier—composed of epithelial cells, tight junction proteins (ZO-1, Occludin), a mucus layer, and immune cells—serves as a key structure preventing translocation of gut microbiota and their metabolites. Key DAMPs released during intestinal barrier disruption (eg, high-mobility group box 1 [HMGB1], ATP, and fragmented epithelial cytoskeletons) amplify systemic inflammation and renal injury. HMGB1, released from damaged intestinal epithelial cells, binds to TLR4 on renal tubular epithelial cells and macrophages, activating NF-κB signaling and promoting pro-inflammatory cytokine (IL-1β, TNF-α) secretion.[21] In DKD, intestinal barrier dysfunction is the core link connecting gut microbiota dysbiosis and renal inflammation. Gut microbiota dysbiosis directly impairs the barrier: toxins (eg, hemolysin) from pathogenic bacteria (eg, Escherichia coli) degrade tight junction proteins, increasing intestinal permeability.[5]

Metabolite imbalance further exacerbates barrier impairment: TMAO induces mitochondrial reactive oxygen species (mROS) production, damaging intestinal epithelial cell mitochondria, while SCFA deficiency impairs epithelial repair

capacity.[22] Notably, inflammatory activation forms a vicious cycle: IL-6 and TNF-α from renal inflammation act on the intestine via the circulatory system, further downregulating tight junction protein expression and aggravating "intestinal injury-inflammation-renal injury" crosstalk.[23]

Immune cells including macrophages, neutrophils, and mucosal-associated invariant T (MAIT) cells mediate this crosstalk. Intestinal barrier disruption allows translocation of LPS and DAMPs, which recruit circulating monocytes/macrophages to the kidney, polarizing them into pro-inflammatory M1 phenotypes that exacerbate renal interstitial inflammation.[24,25] Neutrophil infiltration into the intestine and kidney further damages barrier integrity and renal parenchyma via reactive oxygen species (ROS) and neutrophil extracellular traps (NETs).[26]

Clinical evidence shows that serum endotoxin (lipopolysaccharide [LPS]) levels are significantly elevated in DKD patients and positively correlated with UACR and IL-1β.[8,12] Animal experiments have confirmed that antibiotic-mediated gut microbiota depletion can reduce serum LPS and renal inflammatory factor levels, alleviate tubulointerstitial injury, directly verifying the pathological significance of intestinal barrier dysfunction.[5]

The "Effector Molecules" of Gut Microbiota in Regulating DKD-Related Inflammation

Gut microbiota metabolites are core mediators of crosstalk between gut microbiota and renal inflammation. Based on their effects on DKD-related inflammation, they can be classified into "beneficial metabolites" (eg, SCFAs, indole-3-propionic acid [IPA]) and "harmful metabolites" (eg, TMAO, phenyl sulfate, branched-chain amino acids [BCAA]). These metabolites regulate renal inflammation through three mechanisms: First, direct action on renal cells: they reach the kidneys via the blood circulation, bind to specific receptors (eg, GPR43) or activate signaling pathways (eg, NLRP3 inflammasome), thereby regulating inflammatory responses.[18] Second, modulation of systemic immunity: they influence macrophage polarization (M1→M2) and T cell differentiation, indirectly improving the renal inflammatory microenvironment.[27] Third, regulation of renal metabolism: for example, BCAA accumulation can exacerbate podocyte insulin resistance, indirectly promoting the secretion of inflammatory factors.[28,29]

Notably, the effects of metabolites are "concentration-dependent": for instance, low concentrations of acetate can protect the kidneys via GPR43, while high concentrations of acetate activate the renin-angiotensin system (RAS) and promote the progression of early-stage DKD.[12] This complexity suggests that precise regulation of metabolite levels is required to achieve therapeutic effects.

The Mechanism Module of Intestinal Flora Metabolites Regulating Inflammation in Diabetes Nephropathy

Short Chain Fatty Acids (SCFAs)

SCFA-Mediated Anti-Inflammatory Effects

SCFAs are the major metabolites produced by gut microbiota fermenting dietary fiber, including acetate (60%), propionate (25%), and butyrate (15%). Their producer bacteria mainly belong to Ruminococcaceae and Lachnospiraceae of the phylum Firmicutes, as well as Bacteroidaceae of the phylum Bacteroidetes.[30] SCFAs (acetate, propionate, butyrate) exhibit dose-dependent effects, with physiological concentrations (10–100 μmol/L in serum, 10–100 mmol/L in colonic lumen) mediating anti-inflammatory effects in DKD. In clinical cohorts, DKD patients have serum SCFA levels (20–60 μmol/L) lower than healthy controls (40–90 μmol/L),[31] within the physiological range where GPR43/GPR109A activation inhibits NLRP3.[18] However, pharmacological concentrations (>200 μmol/L) of acetate activate renal RAS,[12] which is rarely observed in clinical practice (DKD patients' acetate levels rarely exceed 80 μmol/L).[15] This indicates that SCFA supplementation in DKD should target physiological concentrations to avoid adverse effects, aligning with clinical observations that moderate SCFA elevation (to ~70 μmol/L) correlates with improved eGFR.[31] SCFAs exert anti-inflammatory effects mainly by activating GPR43/GPR109A receptors, inhibiting the NLRP3 inflammasome, and regulating macrophage polarization. GPR43 (predominantly expressed on macrophages and podocytes) and GPR109A (mainly expressed on intestinal epithelial cells and renal interstitial cells) are specific receptors for SCFAs. Upon binding to these receptors, SCFAs can activate the AMPK signaling pathway, inhibit mTOR activity, and reduce the secretion of IL-1β and TNF-α.[32] Clinical studies have shown that GPR43 expression is increased

in renal tissues of DKD patients and negatively correlated with podocyte injury markers (nephrin, podocin), verifying the pathological significance of the receptor-mediated pathway.[33]

Butyrate can downregulate the expression of NLRP3, ASC, and caspase-1, block inflammasome assembly, and reduce the release of mature IL-1β. Animal experiments have confirmed that butyrate supplementation can reduce renal NLRP3 expression by 40% and IL-1β levels by 35% in DKD mice.[20] In addition, SCFAs can promote the polarization of macrophages from pro-inflammatory M1 to anti-inflammatory M2 phenotype, increase IL-10 secretion, and decrease the TNF-α/IL-10 ratio. In vitro experiments have shown that propionate treatment can increase macrophage IL-10 expression by 2.5-fold and M2 marker (CD206) expression by 3-fold.[34]

Stage-Specific SCFA Actions

In early-stage DKD (UACR: 30–300 mg/g), SCFAs exert protective effects primarily by inhibiting renal RAS activation,[14] a phenomenon distinct from their core anti-inflammatory mechanisms.[18] Acetate supplementation reduces Ang II and IL-6 levels, while GPR43 deficiency abrogates these benefits by impairing AMPKα-mediated podocyte insulin resistance.[14]

In advanced-stage DKD (eGFR < 30 mL/min/1.73m^2), SCFAs primarily act by inhibiting renal fibrosis. Cai et al[31] confirmed that butyrate supplementation could activate the AMPK/mTOR pathway, promote autophagy of renal tubular epithelial cells, and reduce collagen deposition. Clinical data showed that fecal butyrate levels in advanced DKD patients were negatively correlated with the degree of renal interstitial fibrosis.[23]

In elderly DKD patients, SCFAs can protect the kidneys by inhibiting "inflammaging". Rong et al[22] found that the abundance of SCFA-producing bacteria was further reduced in elderly DKD patients, accompanied by elevated levels of inflammaging markers (p16INK4a, IL-6). SCFA supplementation could downregulate the mTOR-p16INK4a pathway, reduce the senescence-associated secretory phenotype (SASP), and improve renal function in elderly DKD mice.

Trimethylamine N-oxide (TMAO)

TMAO is a key representative of harmful metabolites, produced by gut microbiota metabolizing choline and carnitine. First, gut microbiota converts choline into trimethylamine (TMA), which is then oxidized to TMAO by hepatic flavin-containing monooxygenase 3 (FMO3).[35] TMAO exhibits dose-dependent pathogenicity: physiological serum concentrations (0–4 μmol/L) are harmless, while concentrations >8 μmol/L (observed in 60% of advanced DKD patients[36]) significantly activate mROS-NLRP3 signaling.[37] Clinical cohort studies confirm that TMAO levels >12 μmol/L increase ESRD risk by 2.3-fold,[38] defining a clinically relevant pathogenic threshold. Notably, TMAO concentrations in early DKD (4–8 μmol/L) show no significant correlation with renal inflammation,[39] highlighting dose-dependent clinical relevance—only supraphysiological concentrations drive disease progression.

Activation of the "mROS-NLRP3" axis by TMAO to promote DKD-related inflammation represents its core pathogenic mechanism. TMAO can enter renal tubular epithelial cells, bind to the mitochondrial membrane, inhibit the activity of mitochondrial respiratory chain complex IV, and induce increased mROS production, ultimately leading to mitochondrial damage.[19] Elevated mROS activates the NLRP3 inflammasome: mROS oxidizes the cysteine residues of the NLRP3 protein, promoting its oligomerization and assembly, activating caspase-1, and releasing mature IL-1β.[40] In addition, NLRP3 activated by TMAO can further induce pyroptosis of renal tubular epithelial cells (characterized by cellular swelling and membrane rupture), releasing inflammatory factors and recruiting immune cell infiltration.[41] Animal experiments have confirmed that inhibiting TMAO production (eg, using FMO3 inhibitors) can reduce renal mROS levels by 45%, NLRP3 expression by 50%, and UACR by 30% in DKD mice.[42] Clinical data show that serum TMAO levels in DKD patients are positively correlated with IL-1β and caspase-1, directly verifying the clinical relevance of this mechanism.[38]

TMAO does not act alone but synergizes with other harmful metabolites to exacerbate DKD-related inflammation. Both TMAO and phenyl sulfate can activate the mROS-NLRP3 axis, and the inflammatory effect is enhanced by 1.8-fold when combined.[43] In addition, TMAO can also synergize with BCAAs. TMAO exacerbates BCAA-induced podocyte insulin resistance, indirectly promoting IL-6 secretion.[44] This synergistic effect suggests that targeting a single harmful

metabolite may not be sufficient to fully block inflammatory progression, and multi-targeted intervention should be considered.

Amino Acids and Their Derivatives

Direct interaction between intestinal epithelial cell (IEC) receptors and renal cells has not been definitively demonstrated, but indirect crosstalk is mediated by immune cells and signaling molecules. IECs express receptors such as TLR4, GPR43, and AhR, which bind gut microbiota metabolites (eg, LPS, SCFAs, IPA) and trigger secretion of chemokines (CCL2, CXCL10).[45,46] These chemokines recruit circulating immune cells (eg, monocytes, dendritic cells) to the intestine, which then migrate to the kidney and release cytokines (TNF-α, IL-6) that act on renal interstitial cells and podocytes.[47] For example, LPS binding to IEC TLR4 induces CCL2 secretion, recruiting CCR2+ monocytes to the intestine; these monocytes subsequently traffic to the kidney, differentiating into M1 macrophages that promote podocyte apoptosis.[48] While direct receptor-receptor interaction between IECs and renal cells is speculative, immune cells serve as critical intermediaries in gut-kidney crosstalk.

Serum BCAA levels are significantly elevated in DKD patients and positively correlated with UACR and IL-8.[49] Its pro-inflammatory mechanisms include the following three aspects. First, exacerbating podocyte insulin resistance: BCAA accumulation can activate the mTOR signaling pathway, inhibit AMPK activity, induce podocyte cytoskeletal disorganization, and indirectly promote IL-6 secretion.[22] Second, promoting macrophage inflammation: BCAAs can activate the GCN2 signaling pathway, induce macrophages to secrete IL-8 and monocyte chemoattractant protein-1 (MCP-1), and recruit inflammatory cells to the renal interstitium.[15] Third, regulating gut microbiota: elevated BCAAs can further inhibit the abundance of SCFA-producing bacteria, forming a "metabolic dysregulation-microbiota dysbiosis-inflammation" vicious cycle.[50]

Machine learning analysis has shown that BCAAs, together with TMAO and phenyl sulfate, form a "microbiota-metabolite module" that can accurately predict the degree of DKD-related inflammation (AUC = 0.832). Its predictive value is second only to that of eGFR and UACR, suggesting that BCAAs may serve as potential biomarkers for DKD-related inflammation.[37]

Phenyl sulfate is a derivative produced by gut microbiota metabolizing tyrosine. Its levels are increased by 2–3 fold in DKD patients and positively correlated with the degree of glomerulosclerosis. Studies have shown that phenyl sulfate can bind to the leucine-rich repeat (LRR) domain of NLRP3, promote its interaction with ASC, and activate caspase-1.[51] In addition, phenyl sulfate can induce podocyte apoptosis, downregulate nephrin expression, and increase proteinuria.[52,53] More importantly, phenyl sulfate can compete for organic anion transporter 1 (OAT1), reduce the excretion of other toxins, and exacerbate renal injury.[54] Clinical studies have shown that the combined detection of phenyl sulfate and TMAO can increase the AUC of DKD diagnosis from 0.713 to 0.751, suggesting its potential as a biomarker.[54]

IPA is a derivative produced by gut microbiota metabolizing tryptophan. Similar to SCFAs, its levels are decreased in DKD patients.[9,55] IPA can activate the aryl hydrocarbon receptor (AhR), downregulate the phosphorylation level of NF-κB p65, reduce the secretion of IL-6 and TNF-α, thereby inhibiting the NF-κB pathway.[9] In addition, IPA can upregulate the expression of mucus layer protein (MUC2), reduce gut microbiota translocation, and thus protect the intestinal barrier. Furthermore, IPA can activate the SIRT1/PGC-1α pathway, improve mitochondrial function of renal cells, and decrease mROS production.[56] Although research on IPA is relatively limited, existing evidence suggests that it may be a potential protective factor against DKD-related inflammation, which warrants further investigation.[9]

Other Metabolites

Besides the aforementioned core metabolites, valeric acid, caproic acid, and bile acid derivatives produced by gut microbiota are also involved in the regulation of DKD-related inflammation, but relevant research remains relatively limited. As homologs of SCFAs, valeric acid and caproic acid can inhibit the NLRP3 inflammasome through similar mechanisms. However, their abundance is more significantly reduced in DKD patients and negatively correlated with the risk of ESRD. In addition, microbiota-mediated secondary bile acids (eg, lithocholic acid) can inhibit renal inflammation via the TGR5 receptor. Levels of secondary bile acids are decreased in DKD patients and negatively correlated with IL-1β.[56] The mechanisms of action and clinical significance of these metabolites still require further research for verification.

Microbial Metabolism and Inflammatory Characteristics in Different Clinical Scenarios of Diabetes Nephropathy

Early-Stage DKD (eGFR ≥ 60 mL/min/1.73m^2, UACR: 30–300 mg/g)

The core feature of early-stage DKD is "microbiota dysbiosis initiating inflammation, with inflammation not yet causing significant renal function impairment". Its characteristics of gut microbiota metabolism and inflammation include. First, microbiota dysbiosis is dominated by a mild reduction in beneficial bacteria. The abundance of SCFA-producing bacteria (eg, Ruminococcaceae) is decreased by 10%–20%, the abundance of pathogenic bacteria (eg, Escherichia coli) is increased by 15%–25%, and α diversity is slightly reduced.[57] Second, metabolite imbalance is characterized by a mild decrease in SCFAs and abnormal elevation of acetate. Serum acetate levels are increased (possibly associated with altered intestinal fermentation patterns), while propionate and butyrate levels are decreased, and TMAO levels have not yet significantly elevated.[39] Third, inflammation is centered on local renin-angiotensin system (RAS) activation. Gut microbiota dysbiosis is hypothesized to activate the renal RAS system—supported by correlational evidence that reduced SCFA-producing bacteria abundance correlates with elevated renal Ang II and IL-6 levels.[14,58] Animal experiments have confirmed that early intervention (eg, propionate supplementation) can significantly delay DKD progression: after 8 weeks of propionate supplementation in HFD/STZ-induced diabetic rats, UACR was reduced by 28% and renal Ang II levels by 32%, highlighting the importance of targeting gut microbiota metabolism in the early stage.[39]

Advanced-Stage DKD (eGFR < 30 mL/min/1.73m^2, UACR > 300 mg/g)

A well-documented vicious cycle between inflammation and fibrosis characterizes advanced DKD.[37] Exacerbated gut microbiota dysbiosis (reduced SCFAs, elevated TMAO) directly contributes to this cycle—TMAO-induced mROS-NLRP3 inflammasome activation is an established pathway,[37] with FMO3 inhibition reducing renal NLRP3 expression and fibrosis.[35] However, the direct link between microbiota dysbiosis and enhanced renal fibro-inflammatory marker (α-SMA) expression remains hypothesized, as it relies on indirect evidence of microbial metabolite translocation.[59] First, the abundance of SCFA-producing bacteria is decreased by 40%–50%, the abundance of pathogenic bacteria (eg, Haemophilus, Megasphaera) is increased by 50%–60%, and α diversity is significantly reduced. Meanwhile, levels of TMAO, phenyl sulfate, and BCAAs are significantly elevated, while levels of SCFAs and IPA are remarkably decreased—this metabolite imbalance is positively correlated with renal function impairment.[39] In addition, systemic inflammatory factor (IL-1β, IL-18, TNF-α) levels are increased, pyroptosis of renal tubular epithelial cells and macrophage infiltration are prominent, and the expression of fibrosis markers (α-SMA, collagen I) is upregulated. Clinical evidence shows that serum TMAO levels in advanced DKD patients are negatively correlated with eGFR ($r = -0.42$, $P < 0.001$), and NLRP3 expression levels can predict the risk of ESRD progression.[19] This suggests that targeting NLRP3 and TMAO may be important intervention directions for advanced-stage DKD.

Elderly DKD (Age ≥ 65 Years)

The core feature of elderly DKD is the "superimposition of microbiota dysbiosis and inflammaging", with more prominent characteristics.[60] First, microbiota dysbiosis is more severe: the abundance of SCFA-producing bacteria is further decreased by 20–30% compared with non-elderly DKD patients, while the abundance of inflammaging-related bacteria (eg, Christensenella) is increased. Second, metabolite imbalance is associated with inflammaging: insufficient SCFAs fail to inhibit the mTOR-p16INK4a pathway, leading to elevated levels of inflammaging markers (p16INK4a, IL-6, SASP). Third, inflammation is characterized by "chronic low-grade inflammation": systemic inflammatory factor levels are slightly elevated but persist, accelerating renal aging and functional decline. Animal experiments have confirmed that SCFA supplementation can improve renal function in elderly DKD mice by inhibiting inflammaging.[61]

Therapeutic Strategies Targeting Gut Microbiota Metabolism in DKD

Therapeutic strategies for DKD targeting gut microbiota metabolism can be classified into "pharmacological synergistic regulation" (TCM), "gut microbiota modulation" (probiotics, prebiotics, fecal microbiota transplantation [FMT]),

"metabolite regulation" (supplementation of beneficial metabolites, inhibition of harmful metabolites), and "dietary intervention". The mechanisms, experimental evidence, and translational prospects of different strategies are as follows.

Pharmacological Synergistic Regulation

In the treatment of DKD, many individual herbs or herbal extracts have shown significant therapeutic effects. We have summarized the research on DKD treatment based on individual herbs or herbal extracts, and the results are shown in Table 1. Commonly used herbs include Huangqi, *Salvia miltiorrhiza* (Danshen), *Poria cocos* (Fuling), and *Lycium barbarum* (Gouqi) etc. The active components of these herbs possess multiple biological activities and can improve renal function through various mechanisms.[62] For example, astragaloside, the main component in Huangqi, has been found to exert antioxidant, anti-inflammatory effects and improve renal tubular cell function, which can significantly reduce urinary protein excretion and serum creatinine levels in diabetic mice.[12] In addition, tanshinone from Salvia miltiorrhiza also shows renoprotective effects, which can alleviate renal injury by regulating oxidative stress and inflammatory responses.[63] The combined use of these herbs can produce a synergistic effect, thereby enhancing the therapeutic efficacy.

Chinese herbal formulas have shown unique advantages in the treatment of DKD.[77] We have summarized the research on DKD treatment based on Chinese herbal formulas, and the results are shown in Table 2. Through multi-component and multi-target mechanisms of action, Chinese herbal formula can effectively improve patients' clinical symptoms and biochemical indicators. For example, studies have demonstrated that the compound preparation combining Astragali Radix and Salvia miltiorrhiza can significantly reduce the urinary protein excretion rate and serum creatinine levels in DKD patients, with its efficacy being superior to that of single-drug administration.[17] In addition, Chinese herbal formula can regulate the intestinal microecology, improve intestinal barrier function, and further influence systemic inflammatory responses and metabolic status, thereby providing new approaches for the treatment of DKD.[7] The synergistic effect of such compounds not only enhances the therapeutic effect but also reduces potential side effects that may be caused by single components, offering a safer treatment option for patients.

SGLT2 inhibitors (eg, dapagliflozin) are first-line therapeutic agents for DKD. Recent studies have shown that they can regulate gut microbiota metabolism via the "gut-kidney axis" to enhance anti-inflammatory effects.[4] Studies have demonstrated that SGLT2 inhibitors can increase the abundance of SCFA-producing bacteria (eg, Ruminococcaceae) and decrease the abundance of pathogenic bacteria (eg, Escherichia coli).[4] They can also elevate serum SCFA levels, reduce TMAO levels, upregulate the expression of ZO-1 and Occludin, and decrease gut microbiota translocation, thereby regulating intestinal metabolite levels and protecting the intestinal barrier.[5] In addition, through the aforementioned mechanisms, SGLT2 inhibitors inhibit the NF-κB pathway and reduce the levels of IL-17 and TNF-α, thus improving the renal inflammatory state. Dapagliflozin can increase gut microbiota α diversity by 25%, serum SCFA levels by 30%, and reduce urinary albumin-to-creatinine ratio (UACR) by 35% in db/db mice.[4] In a clinical study, after 6 months of dapagliflozin administration in 120 DKD patients, serum TMAO levels decreased by 20% and IL-17 levels by 18%, and these changes were associated with improved eGFR.[4,92]

Probiotic Supplementation

Probiotics refer to live microorganisms beneficial to the host. Those extensively studied in DKD include Bifidobacterium, Lactobacillus, and Faecalibacterium. Probiotics can directly improve gut microbiota dysbiosis by increasing the abundance of SCFA-producing bacteria and inhibiting the colonization of pathogenic bacteria. Studies have shown that probiotics can secrete bacteriocins (eg, nisin) to inhibit the activation of the NLRP3 inflammasome, thereby reducing inflammatory responses.[9,54] In addition, probiotics can upregulate the expression of tight junction proteins and reduce gut microbiota translocation to protect the intestinal barrier.

Multiple studies have confirmed that probiotic supplementation can improve renal function in DKD mice. Lactobacillus plantarum GMNL-263 can reduce hemoglobin A1c (HbA1c) levels and inhibit renal fibrosis in STZ-induced diabetic rats.[9] A probiotic cocktail (Lactobacillus + Bifidobacterium) can decrease renal IL-1β levels by 35% and UACR by 28% in db/db mice.[93] Clostridium butyricum can reduce the apoptosis of renal tubular epithelial cells by activating the AMPK pathway.[94] In a randomized controlled trial, 100 DKD patients (UACR: 30–300 mg/g) received

Table 1 Research Progress on Individual Herb or Herbal Extracts for the Treatment of DN

Herb	Extract	Research Model	Signaling Pathway	Main Indicators	Results	Reference
Ginkgo biloba L. (Yin Xing Ye)	Isoquercitrin	db/db mice	JAK-STAT	IL-6, IL-1β, MCP-1, TGF-β, STAT3, TNF-α↓	Alleviates DKD by inhibiting STAT3 activity.	Xuan 2025,[64]
Penthorum chinense Pursh (Che Gen Cai)	Thonningianin A	STZ-induced DN mice	NLRP3/ASC/ Caspase-1	IL-1β, IL-6↓ Claudin-1, Occludin, ZO-1↑	Thonningianin A may improve renal interstitial fibrosis in DN mice by regulating the NLRP3/ ASC/Caspase-1 signaling pathway.	Zhang 2024,[62]
Astragalus membranaceus (Huangqi)	Astragalus polysaccharide	STZ injection-induced DN rats	Sirt1/FoxO1	IL-1β, IL-6, MDA↓ SOD, GSH↑	Astragalus polysaccharide mitigated DN under hyperglycemic conditions by activating the Sirt1/FoxO1 autophagy pathway.	Xu 2024,[65]
Salvia miltiorrhiza (Dan Shen)	Salvianolic acid B, Tanshinone IIA	STZ injection-induced DN rats	PI3K/Akt/NF-κB	IL-6, IL-1β, MCP-1, TNF-α↓	Salvianolic acid B and tanshinone IIA may improve glucose and lipid disorders in early DN rats by regulating the PI3K/Akt/NF - κ B signaling pathway.	Xu 2024,[66]
Mori Folium (Sang Ye)	Quercetin	STZ injection-induced DN rats	Nrf2	GPX4, MDA↓ GSH↑	Quercetin treats diabetes nephropathy by inhibiting iron death in rat models.	Zhang 2024,[67]
Astragalus membranaceus (Huangqi)	Astragalus polysaccharide	STZ injection-induced DN rats	TLR4/NF-κB	IL-1β, IL-6, MCP-1↓	Astragalus polysaccharide ameliorated DN renal injury, and the mechanisms perhaps related to relieving inflammatory responses and attenuating the TLR4/NF-κB signaling pathway.	Guo 2023,[68]
Astragalus membranaceus (Huangqi)	Astragaloside IV	Immortalized mouse podocytes	Nrf2-ARE/TFAM	Bcl-2↓ BAX↑	AS-IV can resist oxidative stress induced renal injury and podocyte apoptosis in diabetes by improving the function of mitochondria.	Shen 2023,[69]
Camomile (Gan Ju)	Fisetin	STZ-induced DN mice	Nrf2/HO-1/GPX4	MDA↓ SOD, GSH, Podocin↑	Fisetin could enhance the antioxidative stress capacity of DN mice by promoting the activation of the Nrf2/HO-1/GPX4 signaling pathway in renal tissues.	Qian 2023,[70]
Mori Folium (Sang Ye)	Quercetin	STZ-induced DN mice	Nrf2/HO-1	TFR-1, FTH-1, GPX4↓	Quercetin inhibits the ferroptosis of renal tubular epithelial cells by regulating the Nrf2/ HO-1 signaling pathway.	Feng 2023,[71]
Aloe (Lu Hui)	Aloe-emodin	STZ injection-induced DN rats	——	Collagen I, Notch 1, p-AKT, IL-1β, IL-7, IRF4↓	Aloe-emodin could ameliorate DN by targeting IRF4.	Lu 2022,[72]
Cordyceps cicadae (Jin Chan Hua)	Cordyceps cicadae polysaccharides	STZ injection-induced DN rats	TLR4/NF-κB; TGF-β1/Smad	IL-1β, IL-6↓	Cordyceps cicadae polysaccharides has a beneficial effect on renal tubulointerstitial fibrosis in DN rats by blocking the TLR4/NF - κ B and TGF - β 1/Smad signaling pathways.	Yang 2020,[73]

(*Continued*)

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Table 1 (Continued).

Herb	Extract	Research Model	Signaling Pathway	Main Indicators	Results	Reference
Belamcanda chinensis (She Gan)	Tectorigenin	db/db mice	AdipoR1/2	TGF-β1, SMAD4↓	Tectorigenin have a potently effect for retarding type 2 diabetes-associated DN.	Yang 2020,[74]
Astragalus membranaceus (Huangqi)	Astragaloside IV	STZ injection-induced DN rats	——	NO, eNOS acetylation↓	Astragaloside IV improves the functional abnormalities of DN by inhibiting the acetylation of eNOS.	Fan 2019,[75]
Coptis chinensis (Huang Lian)	Berberine	STZ injection-induced DN rats	TLR4/NF-κB	IL-1β, IL-6, MCP-1↓	Berberine ameliorated DN through relieving STZ-induced renal injury via inactivating TLR4/NF-κB pathway.	Zhu 2018,[76]

Abbreviations: IRF4, interferon regulatory factor 4; TFR-1, transferrin receptor 1; FTH-1, ferritin heavy chain 1; GPX4, glutathione peroxidase 4; MCP-1, monocyte chemoattractant protein-1; ↑, Increased expression/level; ↓, Decreased expression/level.

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Table 2 Research Progress on Chinese Herbal Formulas for the Treatment of DN

Chinese Herbal Formulas	Research Model	Signaling Pathway	Main Indicators	Results	Reference
Tangshen Formula	Right uninephrectomy and STZ injection-induced DN rats	JNK/NF-κB	MCP-1, TNF-α↓	Orally administered Tangshen Formula significantly inhibited diabetic renal injury, and modulated gut microbiota, which decreased levels of lipopolysaccharide and indoxyl sulfate, and attenuated renal inflammation.	Zhao, 2020[78]
Qing Re Xiao Zheng formula	HFD and STZ injection-induced DN mice	TLR4/NF-κB	LPS↓ Zo-1↑	The reno-protective effects of Qing Re XiaoZheng formula was probably associated with modulating gut microbiota and inhibiting inflammatory responses in the kidney.	Gao 2021,[79]
Shenyan Kangfu tablet	db/db mice	NF-κB	HbA1c, TNF-α, IL-1β↓	Shenyan Kangfu tablet alleviates DN by regulating the cascade of renal inflammatory signaling and gut microbiota	Chen 2021,[80]
QiDiTangShen granules	db/db mice	——	TBA, β-MCA, TCA, Tβ-MCA, DCA↓	QiDiTangShen granules significantly alleviated renal injuries in mice with DN. The gut microbiota-bile acid axis may be an important target for the reno-protection of QiDiTangShen granules in DN.	Wei 2021,[81]
San-Huang-Yi-Shen capsule	HFD and STZ-induced DN mice	——	MDA, IL-6, IL-1β, TNF-α↓ SOD, GSH↑	San-Huang-Yi-Shen capsule has various improvement effects on DN, including alleviating hyperglycemia and improving renal function, renal pathological changes, oxidative stress, and inflammatory response.	Su 2022,[82]
Jowiseungki decoction	STZ-induced DN mice	PKCα/PI3K/Akt; NF-κB/α-SMA	PKC-α, TGF-β1, α-SMA, iNOS, COX-2↓ IRS-1, PI3K, JSD↑	Jowiseungki decoction can improve symptoms in STZ-induced DN mice through the inhibition of kidney dysfunction.	Meng 2021,[83]
Bekhogainsam decoction	STZ-induced DN mice	PI3K/Akt; MAPK	PKCα, TGF-β1, α-SMA↓	Bekhogainsam decoction treats diabetes nephropathy by preventing structural damage and renal dysfunction.	Meng 2020,[84]
Zicuiyin decoction	DN patients based on Chinese DN guidelines	——	HbA1c, SCr↓	Zicuiyin decoction had better efficacy in improving and protecting kidney function, especially those who decline eGFR and gut microbiota dysbiosis.	Liu 2022,[85]
Huang Lian Jie Du Decoction	db/db mice	AGEs/RAGE/Akt/Nrf2	MDA↓ SOD, GSH, HO-1↑	Huang Lian Jie Du Decoction ameliorates DN by regulating the AGEs/RAGE/Akt/Nrf2 pathway and metabolic profiling.	Tang 2022,[86]
Jinlida granules	db/db mice	AMPK/PGC-1α	BAX, Caspase-3↓ BCL2↑	Jinlida granules could improve mitochondrial homeostasis and reduce cell apoptosis in podocytes via activating the AMPK/PGC-1α pathway.	Sun 2025,[87]
Shen-Qi-Jiang-Tang granule	STZ-induced DN mice	TNF/JNK/p38	IL-1, TNF-α, IL-6, IL-12↓	Shen-Qi-Jiang-Tang granule exerts a kidney protective effect in DN mice via modulating TNF signaling pathways.	Chen 2023,[88]
Fuxin Granules	db/db mice	TGF-β1/Smad; VEGF/VEGFR2	TGF-β1, Smad2/3, VEGFA, VEGFR2↓ eNOS↑	Fuxin Granules treats DN by regulating the TGF - β1/Smad and VEGF/VEGFR2 signaling pathways.	Zheng 2021,[89]

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Table 2 (Continued).

Chinese Herbal Formulas	Research Model	Signaling Pathway	Main Indicators	Results	Reference
Chaihuang-Yishen granule	Right uninephrectomy and STZ injection-induced DN rats	NF-κB	MCP-1, TNF-α, TGF-β1↓	Chaihuang-Yishen granule ameliorates renal injury in diabetic rats through reduction of inflammatory cytokines and their intracellular signaling.	Zhang 2014,[90]
Sanziguben	db/db mice	TLR4/NF-κB/NLRP3	IL-18, IL-1β↓	Sanziguben improved intestinal flora disorder and inhibited the TLR4/NF-κB/NLRP3 pathway to alleviate DN.	Wang 2023,[91]

Abbreviations: HFD, high-fat diet; STZ, streptozotocin; TBA, total bile acid; β-MCA, β-muricholic acid; TCA, taurocholic acid; Tβ-MCA, tauro β-muricholic acid; DCA, deoxycholic acid; PKC-α, protein kinase C-alpha; TGF-β1, transforming growth factor beta-1; α-SMA, α-smooth muscle actin; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; IRS-1, insulin receptor substrate 1; Glycosylated hemoglobin A1c, HbA1c; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; eNOS, endothelial nitric oxide synthase; ↑, Increased expression/level; ↓, Decreased expression/level.

soybean milk containing Lactobacillus plantarum A7 for 8 weeks. After intervention, cystatin C (a renal function marker) decreased by 12% and progranulin (an inflammatory adipokine) decreased by 18%, but there was no significant effect on UACR.

Probiotics and Dietary Fiber

Probiotics refer to dietary fibers fermentable by gut microbiota (eg, fructooligosaccharides [FOS], inulin, resistant starch). Their core mechanism is to promote the proliferation of beneficial bacteria and increase SCFA production.[95] Studies have shown that FOS can increase the abundance of SCFA-producing bacteria by 40%, serum propionate levels by 35%, and reduce UACR by 32% in streptozotocin (STZ)-induced diabetic rats.[96] Inulin-type fructans can modulate the gut microbiota of db/db mice, elevate acetate levels, and ameliorate glomerulosclerosis. Resistant starch can decrease serum phenyl sulfate levels and inhibit the NLRP3 inflammasome in STZ-induced diabetic rats. In a study involving diabetic patients, supplementation with FOS for 12 weeks resulted in a 25% increase in serum SCFA levels and a 15% decrease in IL-6.[9,97]

Probiotics and their metabolites (eg, SCFAs) are generally renoprotective in DKD, but emerging evidence suggests that dysregulated metabolite levels may induce mild renal stress. For example, high concentrations of acetate (a SCFA) activate the renal renin-angiotensin system (RAS), leading to podocyte cytoskeletal disorganization via AT1R signaling.[98] Mechanistically, probiotic metabolites impact podocytes by regulating cell survival (eg, butyrate inhibits podocyte apoptosis via AMPK activation) and permeability (eg, propionate upregulates nephrin expression).[99]

Apolipoproteins (eg, ApoE) may indirectly mediate probiotic effects: gut microbiota modulates ApoE expression in the liver, and ApoE deficiency exacerbates podocyte injury by impairing lipid metabolism in the kidney.[100] However, direct links between probiotics/metabolites and apolipoproteins in DKD are scarce. Regarding K+ channels, no studies have confirmed their involvement in probiotic-mediated podocyte regulation; this represents a knowledge gap requiring future investigation.

Mechanism of TCM on Intestinal Microecology in Treating DKD

The gut-liver-kidney axis drives renal injury through three key mediators. First, gut microbiota-derived choline is metabolized to trimethylamine (TMA) by intestinal bacteria, which is oxidized to TMAO by hepatic flavin-containing monooxygenase 3 (FMO3). TMAO then accumulates in the kidney, activating mROS-NLRP3 signaling and inducing tubular epithelial cell pyroptosis.[101] Second, intestinal microbiota modulate bile acid composition (eg, deoxycholic acid, DCA); impaired enterohepatic circulation leads to bile acid accumulation in the liver and kidney, activating farnesoid X receptor (FXR) and exacerbating renal fibrosis.[98] Third, inflammatory mediators: Gut-derived LPS and pro-inflammatory cytokines (TNF-α, IL-6) induce hepatic inflammation, which enhances liver production of acute-phase proteins (eg, C-reactive protein) and pro-fibrotic factors (eg, TGF-β1); these molecules are released into the circulation, promoting renal interstitial fibrosis.[102]

The Impact of TCM on Gut Microbiota

TCM plays an important role in regulating intestinal microecology, particularly in the treatment of DKD.[103] Studies have shown that TCM can promote overall health by improving the composition and function of the gut microbiota.[104,105] For instance, certain TCM components such as Astragali Radix and Salvia miltiorrhiza have been confirmed to regulate the intestinal microbial community, increase the abundance of beneficial bacteria, and inhibit the growth of harmful bacteria, thereby improving the balance of intestinal microecology.[12] Additionally, TCM compound preparations such as Yiqi Yangyin Huayu Tongluo Formula (YT Formula) have exhibited significant renoprotective effects in DKD models, and part of their mechanisms may be related to the regulation of gut microbiota.[106]

What's more, TCM modulates gut microbiota, but the specific microbial targets vary due to formula heterogeneity. For example, Yiqi Yangyin Huayu Tongluo Formula enriches Bifidobacterium and Ruminococcaceae,[106] while Qing-Re-Xiao-Zheng Formula primarily reduces Proteobacteria. These differences arise from distinct ingredient combinations—qi-invigorating herbs (eg, A. membranaceus) tend to promote SCFA-producing bacteria,[12] whereas heat-clearing herbs

(eg, Coptis chinensis) inhibit pathogenic taxa.[76] Such variability underscores that TCM's microbiota-modulating effects are formula-specific, requiring tailored research to validate mechanism-consistent outcomes.

Bioactive components of TCM regulate gut microbiota through multiple mechanisms.[107,108] For example, studies have found that the active components in Astragali Radix can promote the growth of beneficial intestinal bacteria and inhibit the proliferation of pathogenic bacteria by regulating the production of SCFAs.[7] In addition, certain TCM components such as *Fagopyrum esculentum* (buckwheat) and *Lycium barbarum* (wolfberry) have also shown potential in regulating gut microbial communities, improving intestinal barrier function, and reducing intestinal inflammatory responses.[63] These mechanisms not only contribute to the treatment of DKD but also provide new insights for the intervention of other metabolic diseases.

The application of TCM in improving intestinal microecological imbalance has been increasingly reported.[109] For example, studies have shown that decoctions containing multiple TCM components can effectively improve the intestinal microecology of patients with DKD, reduce urinary protein excretion rate, and enhance renal function.[110] In clinical practice, TCM compound formulas such as Yiqi Yangyin Formula can significantly alleviate patients' symptoms, and regulate intestinal microbial communities to enhance immune function and exert renoprotective effects.[111] These studies indicate that TCM not only has potential in the treatment of DKD but also provides an effective intervention for regulating intestinal microecology.[112]

Repair of Intestinal Barrier Function by TCM

The intestinal barrier is a crucial component for maintaining intestinal health, primarily composed of intestinal epithelial cells, a mucus layer, and gut microbiota.[113] Intestinal epithelial cells form a physical barrier through tight junctions (eg, ZO-1, Occludin) to prevent the invasion of harmful substances and pathogens while allowing the absorption of nutrients.[114] The functions of the intestinal barrier include defending against external pathogens, maintaining the homeostasis of the intestinal environment, and regulating immune responses.[115] Studies have demonstrated that the integrity of the intestinal barrier is closely associated with various diseases (such as diabetes and inflammatory bowel disease), and its damage may lead to intestinal leakage, exacerbate systemic inflammatory responses, and thereby affect overall health.[12]

TCM has demonstrated unique advantages in protecting the intestinal barrier.[116] Many TCM components possess anti-inflammatory, antioxidant, and reparative properties, which can enhance the integrity of the intestinal barrier.[117] For instance, astragalus polysaccharides have been found to increase the expression of tight junction proteins in intestinal epithelial cells, thereby strengthening intestinal barrier function.[12,118] In addition, certain TCM herbs such as Dracaena cochinchinensis and Coptis chinensis can regulate gut microbiota, promote the growth of beneficial bacteria, and inhibit the reproduction of harmful bacteria, further improving intestinal barrier function.[119] These effects not only help maintain the intestinal physical barrier but also enhance the overall health of the body by regulating immune responses and reducing intestinal inflammation.

In recent years, there has been a growing number of studies on the role of TCM in repairing intestinal barrier damage. Research has shown that TCM compound formulas such as syndrome-specific decoctions and Sijunzi Decoction can effectively reduce intestinal inflammation and promote the regeneration of intestinal epithelial cells. For example, studies have found that Sijunzi Decoction significantly improves intestinal barrier function and promotes the repair of intestinal mucosa by regulating gut microbiota.[12] In addition, modern research has also revealed the mechanisms of action of TCM components such as baicalin and *Paeonia lactiflora* (white peony root) in repairing the intestinal barrier, including inhibiting the NF-κB signaling pathway and enhancing the expression of intestinal tight junction proteins.[120] These studies provide an important theoretical basis and practical guidance for the application of TCM in intestinal barrier damage repair, demonstrating the potential value of TCM in modern medicine.

The Mechanism of TCM Improving Immune Function

Peripheral immunity contributes to DKD progression via three core mechanisms. First, T cell subset imbalance: Reduced Treg cell frequency and function in DKD lead to impaired anti-inflammatory capacity, while expanded Th17 cells secrete IL-17, which promotes renal mesangial cell proliferation and extracellular matrix deposition.[121] Second, cytokine

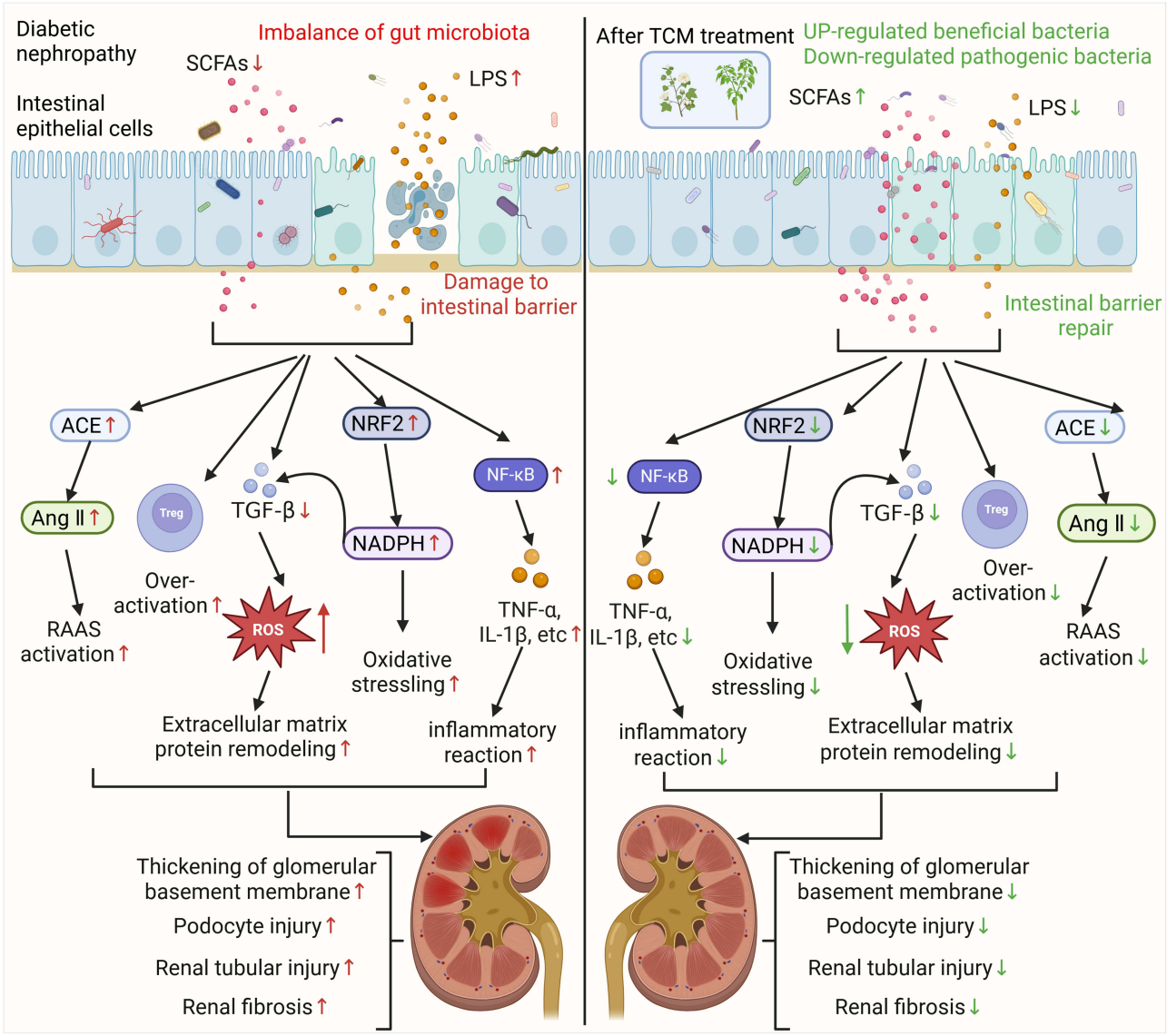

Figure 2 The mechanism of TCM regulating intestinal ecology in the treatment of DKD. This figure delineates the multi-targeted, holistic regulatory mechanism through which traditional Chinese medicine (TCM) mitigates diabetic kidney disease (DKD) by modulating intestinal ecology via the gut-kidney axis. TCM interventions—encompassing single herbs (eg, Astragalus membranaceus, Salvia miltiorrhiza), compound formulas (eg, Yiqi Yangyin Huayu Tongluo Formula, Yishen Qingli Huoluo Granule), and active components (eg, astragaloside IV)—exert synergistic effects across three interconnected core processes. Gut microbiota homeostasis is restored through augmented abundance of beneficial SCFA-producing taxa (eg, Lactobacillus, Ruminococcus, Bifidobacterium) alongside diminished levels of pathogenic bacteria (eg, Enterobacteriaceae, Proteobacteria). Intestinal barrier integrity is strengthened via enhanced expression of tight junction proteins (ZO-1, Occludin), which mitigates intestinal permeability (commonly termed "leaky gut") and curtails translocation of endotoxins (LPS) and uremic toxins (indoxyl sulfate, p-cresyl sulfate, TMAO). Microbial metabolite balance is reestablished with elevated levels of protective short-chain fatty acids (SCFAs: acetate, propionate, butyrate) and reduced concentrations of harmful metabolites (TMAO, BCAAs). Collectively, these regulatory actions dampen downstream pro-inflammatory and pro-fibrotic signaling pathways (NF-κB, NLRP3 inflammasome, TGF-β/Smad), diminish secretion of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), and attenuate renal oxidative stress and fibrosis. Ultimately, TCM-driven modulation of intestinal ecology disrupts the vicious cycle of gut dysbiosis, intestinal barrier impairment, toxin accumulation, and subsequent renal damage, yielding renoprotective benefits including enhanced eGFR, reduced albuminuria, and alleviated glomerular and tubulointerstitial injury in DKD.

network dysregulation. Peripheral pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) translocate to the kidney, activating renal resident immune cells and inducing podocyte injury.[122] Third, immune cell trafficking. Gut-derived inflammatory monocytes (CD11b+Ly6C+) migrate to the kidney via the circulation, differentiating into M1 macrophages that exacerbate tubulointerstitial fibrosis.[123]

TCM has shown significant potential in regulating immune cells.[124] Studies have demonstrated that TCM can influence the function of immune cells through multiple mechanisms. For instance, certain TCM components can promote the proliferation and differentiation of T cells, enhancing their anti-tumor activity. Moreover, TCM can inhibit

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the excessive activation of regulatory T cells (Treg), thereby improving the function of effector T cells and optimizing immune responses. Specifically, some Chinese herbs such as Huangqi and Danshen have been proven to enhance the body's immune response by regulating signaling pathways in immune cells (eg, NF-κB and MAPK pathways), thereby increasing resistance to diseases.[125] Additionally, TCM can indirectly regulate the activity of immune cells by improving the intestinal microecology, promoting the enhancement of overall immune function.[126]

TCM in regulating inflammatory responses is equally noteworthy. For example, certain TCM components can alleviate the body's inflammatory response by inhibiting the expression of inflammatory factors such as TNF-α and IL-6, thereby protecting tissues from damage.[111,127] In addition, TCM can also alter the inflammatory microenvironment and promote tissue repair by regulating the activity of immune cells. For instance, Chinese herbs like Huangqi and Danshen can enhance the phagocytic function of macrophages, promote the resolution of inflammation, and thus improve the prognosis of diseases.[128] This multi-target regulatory mechanism endows TCM with unique advantages in the treatment of inflammation-related diseases.

The mechanism of action of TCM is closely related to various immunoregulatory factors. Studies have shown that TCM can influence the function of immune cells by regulating the expression of cytokines and chemokines. For example, TCM can achieve immune balance by upregulating the levels of anti-inflammatory factors such as IL-10 and inhibiting the release of pro-inflammatory factors such as IL-1β and IL-6.[12] In addition, TCM can also enhance the body's immune capacity by affecting the gut microbiota and altering the production of immunoregulatory factors. The balance of gut microbiota is crucial for maintaining the normal function of the immune system, and the role of TCM in regulating intestinal microecology provides new insights into its application in improving immune function.[129] This multi-faceted mechanism through the regulation of immunoregulatory factors enables TCM to show promising application prospects in the treatment of diseases related to immune dysfunction (as shown in Figure 2).

Conclusion

The progression of inflammation in DKD is closely associated with gut microbiota metabolic dysbiosis, and its core mechanism involves the vicious cycle of "gut microbiota dysbiosis - intestinal barrier injury - metabolite imbalance - renal inflammation". Insufficiency of beneficial metabolites (SCFAs, IPA) exacerbates inflammation by inhibiting GPR43 and activating mTOR, while accumulation of harmful metabolites (TMAO, phenyl sulfate, BCAAs) promotes inflammation via the mROS-NLRP3 axis and NF-κB pathway. Notably, this association exhibits stage-specific characteristics across different phases of DKD (early-stage, advanced-stage, and elderly DKD), highlighting the need for tailored interventions.

Based on existing research evidence, therapeutic strategies targeting gut microbiota metabolism—including TCM, probiotics, prebiotics, fecal microbiota transplantation (FMT), SGLT2 inhibitors, and dietary intervention—have demonstrated anti-inflammatory and renoprotective effects in animal experiments. Among these, TCM possesses unique advantages rooted in its holistic regulatory mechanism: unlike single-target interventions (eg, probiotics supplementing specific bacteria or SGLT2 inhibitors regulating metabolic pathways), TCM (including individual herbs such as Astragalus membranaceus, Salvia miltiorrhiza, and formulas like Yiqi Yangyin Huayu Tongluo Formula, Tangshen Formula) exerts multi-component, multi-dimensional effects. It simultaneously reshapes gut microbiota homeostasis (increasing SCFA-producing bacteria, reducing pathogenic Proteobacteria), repairs intestinal barrier integrity (upregulating ZO-1, Occludin), inhibits NF-κB/NLRP3-mediated inflammatory cascades, and modulates immune function—aligning with the "gut-kidney axis" holistic pathogenesis of DKD. This integrated regulation allows TCM to break the vicious cycle of DKD inflammation at multiple nodes, which is distinct from the relatively focused effects of other interventions.

Preliminary clinical evidence supports the efficacy of TCM, SGLT2 inhibitors, and probiotics, but further verification through multicenter randomized controlled trials (RCTs) is required—especially for TCM, which needs standardized protocols (eg, syndrome differentiation-based formula selection, unified dosage and course) to validate its clinical translation. Future research should prioritize causal validation through conducting metabolite supplementation and neutralization experiments, employing receptor or gene knockout models (eg, GPR43, NLRP3), performing fecal

microbiota transplantation (FMT) combined with metabolite profiling, and integrating multi-omics approaches (metagenomics, metabolomics, transcriptomics) to identify direct regulatory cascades. Besides, current evidence primarily supports short-term improvements in UACR and eGFR, but data on long-term prognostic outcomes (eg, ESRD incidence, cardiovascular mortality, overall survival) are scarce.

In conclusion, gut microbiota metabolism is a key regulatory node in DKD-related inflammation. Based on preclinical evidence and preliminary clinical data, TCM may suppress DKD inflammation via gut-kidney axis modulation and core inflammatory pathway inhibition, suggesting potential as an adjunct anti-inflammatory strategy for DKD. However, its clinical efficacy remains heterogeneous, and conclusions are limited by small-scale, short-term studies. Large-scale, standardized RCTs with uniform syndrome differentiation and dosage are essential to validate its consistency and generalizability.

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

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