

Gut-kidney axis in chronic kidney disease: Dysbiosis, uremic metabolites and therapeutic opportunities (Review)

YINDING WANG¹, HANYU ZENG¹, NALI LIU¹ and DONG YANG²

¹Department of Nephrology, The Third Affiliated Hospital of Gansu University of Chinese Medicine, Baiyin, Gansu 730900, P.R. China;

²Department of Nephrology, Baiyin Hospital of Integrated Traditional Chinese and Western Medicine, Baiyin, Gansu 730900, P.R. China

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Abstract. Chronic kidney disease (CKD) poses a notable global health burden. Beyond traditional pathways, the gut-kidney axis has emerged as a potential contributor to disease progression. In the present narrative review, current evidence on the role of intestinal dysbiosis, characterized by reduced microbial diversity, depletion of beneficial short-chain fatty acid producers and expansion of uremic toxin-generating bacteria, in the accumulation of nephrotoxic metabolites (such as indoxyl sulfate, p-cresyl sulfate and trimethylamine N-oxide) is summarized. These toxins promote oxidative stress, inflammation and fibrosis, accelerating renal decline. By contrast, microbially derived short-chain fatty acids exert protective effects. Although therapeutic strategies targeting the gut microbiome (including probiotics, prebiotics and adsorbents) and fecal microbiota transplantation (targeting the gut microbiome) exhibit potential in modulating toxin levels, evidence for clinical endpoint benefit remains insufficient. In the present review, mechanistic insights were critically evaluated, clinical intervention studies are systematically summarized in tabulated form and a roadmap for personalized, microbiota-informed therapeutic strategies is proposed.

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1. Introduction

Chronic kidney disease (CKD) represents a notable global public health challenge, affecting >800 million individuals worldwide and imposing a burden of morbidity and mortality, primarily from cardiovascular complications (1,2). In accordance with the KDIGO 2024 clinical practice guidelines, CKD is defined as the presence of abnormalities in the kidney structure or function present for >3 months. It has implications for health, which can be classified according to the cause, estimated glomerular filtration rate (eGFR) category (G1-G5) and albuminuria category (A1-A3) (1). The traditional pathophysiological focus of CKD progression has been on hemodynamic factors, including the renin-angiotensin-aldosterone system and metabolic abnormalities. Conventional therapies, such as renin-angiotensin-aldosterone system blockade and solute carrier family 5 member 2 inhibition, remain the mainstay of renoprotection but only partially delay CKD progression (2,3). Therefore, the limitations of conventional therapies in curbing disease progression have encouraged the investigation of novel pathogenic pathways. The ‘gut-kidney axis’ has emerged as a concept that can provide an important conceptual framework for understanding the intricate crosstalk between the host gut microbial ecosystem and renal physiology (3-5). This axis posits that disruptions in gut microbial homeostasis, known as dysbiosis and the subsequent production of gut-derived metabolites can serve notable roles in the initiation and aggravation of CKD and its associated complications.

The premise of the gut-kidney axis in CKD is supported by a growing body of evidence demonstrating consistent alterations in the gut microbiota of patients with renal impairment. Studies utilizing advanced sequencing technologies have

Correspondence to: Dr Dong Yang, Department of Nephrology, Baiyin Hospital of Integrated Traditional Chinese and Western Medicine, 479 Chang'an Road, Baiyin, Gansu 730900, P.R. China
E-mail: mowenyd2000@163.com

Abbreviations: AKI, acute kidney injury; AST-120, spherical activated carbon adsorbent; CKD, chronic kidney disease; CRP, C-reactive protein; DMB, 3,3-dimethyl-1-butanol; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FMT, fecal microbiota transplantation; GPR, G protein-coupled receptor; H₂S, hydrogen sulfide; IS, indoxyl sulfate; LPS, lipopolysaccharide; NLRP3, NOD-like receptor family pyrin domain containing 3; PBUTs, protein-bound uremic toxins; PCS, p-cresyl sulfate; RCT, randomized controlled trial; SCFAs, short-chain fatty acids; TMA, trimethylamine; TMAO, trimethylamine N-oxide

Key words: chronic kidney disease, gut-kidney axis, dysbiosis, uremic toxins, short-chain fatty acids, indoxyl sulfate, therapeutic strategies, microbiome

reproducibly documented a decline in microbial diversity and a shift in certain bacterial populations in CKD cohorts (6-8). A landmark integrative metagenomic and metabolomic analysis by Wu *et al* (6) established severity-specific signatures of gut microbiota, linking the depletion of beneficial, short-chain fatty acid (SCFA)-producing families, such as *Lachnospiraceae* and *Ruminococcaceae*, with the accumulation of uremic toxins. Further reinforcing these findings, Gryp *et al* (9) reported a lower abundance of the butyrate-producing genus *Butyricicoccus* in patients with advanced CKD, suggesting a progressive loss of protective microbial elements as renal function declines. This dysbiotic state is exacerbated by factors inherent to CKD, such as dietary protein and phosphate restrictions, uremic milieu and frequent antibiotic use, which collectively create a cycle that perpetuates gut barrier dysfunction and systemic inflammation (2,10,11).

The most direct mechanistic link between gut dysbiosis and renal damage is the accumulation of gut-derived uremic toxins. These compounds, which are normally excreted by healthy kidneys, reach toxic levels in CKD and directly promote oxidative stress, inflammation and fibrosis (12,13). Amongst the most extensively studied are protein-bound uremic toxins (PBUTs), such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS) and trimethylamine N-oxide (TMAO). IS and PCS are generated from the bacterial fermentation of dietary aromatic amino acids tryptophan and tyrosine, respectively (14,15). Previous studies by Gryp *et al* (15,16) demonstrated that the gut microbiota capacity to generate these toxins remains active or is altered at different CKD stages, with specific uremic toxin precursor-generating bacteria (such as *Bacteroides* species) being isolated and quantified in patients. The pathogenicity of these toxins is well-established. Serum IS levels have been prospectively associated with the progression of CKD in both adult and pediatric populations (17,18), whilst mechanistic studies showed they can directly induce endothelial dysfunction, renal tubular damage and fibroblast activation (12,19,20).

Concurrently, TMAO, a metabolite derived from dietary choline and L-carnitine through gut microbial conversion to TMA and subsequent hepatic oxidation, has garnered notable attention (21,22). Elevated plasma TMAO levels are associated with an increased risk of atherosclerotic cardiovascular disease, a leading cause of mortality in patients with CKD (23-25). Furthermore, a large prospective study by Wang *et al* (26) provided evidence that higher plasma TMAO concentrations are associated with incident CKD and a more rapid decline in kidney function, supporting its role as both a biomarker and a potential mediator of renal disease. The consistency of these findings across diverse populations, from children with CKD to adult cohorts, underscores the broad relevance of this metabolic pathway (27,28).

In response to these aforementioned pathophysiological insights, targeting the gut microbiome has emerged as a promising therapeutic frontier. Strategies range from dietary interventions and pre/pro/synbiotics to more direct approaches, such as adsorbents and fecal microbiota transplantation (FMT) (29-31). Supplementation with resistant starch or other dietary fibers has been shown to increase the production of beneficial SCFAs (such as butyrate, which can ameliorate inflammation), improve gut barrier integrity and

directly protect against renal injury in animal models (32-34). A randomized controlled trial (RCT) by Cosola *et al* (35) demonstrated that a synbiotic formulation containing *Lactobacillus casei* LC4P1 [2.4×10^9 colony forming units (CFU)], *Bifidobacterium animalis* BLC1 (2.4×10^9 CFU), fructo-oligosaccharides (2.5 g), inulin (2.5 g) and a natural antioxidant blend (quercetin 0.064 g, resveratrol 0.023 g and proanthocyanidins 0.013 g), known as NATURENG[®], successfully decreased free serum IS and improved gastrointestinal symptoms in patients with stage IIIb-IV CKD, providing clinical proof-of-concept. However, it is crucial to critically evaluate the heterogeneity in therapeutic outcomes. Although some interventions, such as spherical activated carbon adsorbent (AST-120), do show promise in altering microbial composition and metabolite profiles (36), others, such as some probiotic trials, have yielded highly heterogeneous results on hard clinical endpoints (37-39). Specifically, the probiotic trials reviewed by Favero *et al* (37) and Tian *et al* (38) tested numerous *Lactobacillus* (including *L. acidophilus*, *L. casei* and *L. plantarum*), *Bifidobacterium* (such as *B. breve* and *B. longum*) and *Streptococcus thermophilus* strains, either alone or in combination; however, these trials reported inconsistent effects on uremic toxin levels, inflammatory markers and renal outcomes, with the evidence for hard clinical endpoints remaining insufficient (39). This highlights the need for a deeper understanding of the precise microbial mechanisms and the development of more personalized, microbiome-targeted therapies.

Although numerous reviews have addressed the gut-kidney axis in CKD (3-5,29), these earlier syntheses have largely focused on isolated mechanistic or therapeutic aspects rather than integrating metagenomic, metabolomic and interventional evidence. The present review distinguishes itself by integrating these three evidence streams, drawing on the most recent evidence (search period: January 2015-April 2026), with a particular emphasis on therapeutic translation. Specifically, the present review aims to achieve the following: i) Critically assess severity-specific microbial signatures across diverse populations, including novel data on TMAO causality and acute kidney injury (AKI)-to-CKD transition; ii) systematically evaluates the landscape of microbiome-targeted interventions, presenting a comprehensive summary of clinical studies in tabulated form (Tables I-III); and iii) identifies key research gaps and proposes a roadmap for personalized, microbiota-informed therapeutic strategies. Therefore, the present review comprehensively compiled current available evidence on the gut-kidney axis in CKD, whilst critically analyzing the mechanisms of dysbiosis-induced metabolite toxicity, including the roles of PBUTs, TMAO and the protective effects of SCFAs. Furthermore, it systematically evaluated the landscape of novel therapeutic strategies aimed at manipulating the gut microbiome, discussing both the compelling preclinical data and the translation of these findings into clinical practice. By integrating findings from mechanistic animal studies, observational human cohorts and interventional trials, the present review aimed to provide the most up-to-date perspective on how harnessing the gut-kidney axis can open new avenues for mitigating the progression and complications of CKD.

Table I. Key characteristics of gut microbiota dysbiosis in patients with chronic kidney disease.

Study (author, year)	Population and sample size	Sequencing method	Observed microbial alterations	Key metabolite changes	Clinical/functional correlates	(Refs.)
Sato <i>et al</i> , 2021	Early CKD (G1-G3a) and HC; n=150	16S rRNA sequencing	Decreased Microbial richness in early CKD. Increased Enterobacteriaceae (Proteobacteria).	Not assessed in detail.	Reduced richness associated with increased serum creatinine.	(7)
Gryp <i>et al</i> , 2021	CKD (stages 3-5) and HC; n=140	16S rRNA sequencing	Decreased Abundance of butyrate-producing Butyricicoccus. Increased Proteobacteria/Firmicutes ratio in advanced CKD.	Decreased Fecal butyrate.	Progressive loss of butyrate producers with declining eGFR.	(9)
Cosola <i>et al</i> , 2021 (Intervention)	Stage IIIb-IV CKD; n=30 (RCT)	16S rRNA sequencing (subset)	Synbiotic intervention decreased Bacteroides by 18%.	Decreased Free serum IS (-26%) and PCS (-21%).	Improved GI symptoms and intestinal permeability.	(35)
Chen <i>et al</i> , 2021 (Meta-analysis)	>1,200 fecal samples (CKD vs. HC)	Aggregated 16S rRNA data	Progressive decrease in Shannon/Simpson indices from CKD G2. Greatest drop in ESKD.	Increased Uremic toxins (associated with decreased diversity).	α -diversity inversely associated with serum creatinine	(40)
Wu <i>et al</i> , 2024	Advanced CKD (G4-5) and HC; n=100	Shotgun metagenomics and immune profiling	41% of species in HC undetectable or <10% abundant in CKD G4-5.	Increased IS, PCS. Altered immune and metabolic pathways.	Dysbiosis linked to impaired host immunity and metabolite clearance.	(41)
Peters <i>et al</i> , 2023	Multi-ethnic US cohort (HCHS/SOL); n=2,300+	16S rRNA sequencing	Increased Proteobacteria, decreased Firmicutes (Clostridia) associated with decreased eGFR and increased albuminuria.	Not assessed.	Gut microbiome composition associated with kidney function and damage cross-sectionally.	(42)
Lin <i>et al</i> , 2021	Hemodialysis patients; n=180	16S rRNA sequencing	Decreased Microbial diversity. Increased Proteobacteria. Increased Plasma LPS.	Increased Serum LPS. Positive association with zonulin.	Low diversity predicted all-cause mortality (HR 1.18 per 100-unit decrease in Chao1).	(47)
Georgopoulou <i>et al</i> , 2024	CKD (non-dialysis) and HC; n=80	qPCR & immunohistochemistry	Not primary focus. Assessed gut barrier.	Serum LPS increased, association with increased zonulin.	Confirmed gut barrier disruption and endotoxemia in CKD.	(48)
McFarlane <i>et al</i> , 2022	CKD (stages 3-5); n=150	16S rRNA sequencing	Increased Butyrate-producing genera associated with decreased inflammation.	Inverse association between butyrate producers and hs-CRP.	Every 10% increased in butyrate producers associated with decreased hs-CRP by 0.07 ng/ml.	(49)
Hellman <i>et al</i> , 2025	Population-based cohort; n=6,000+	Shotgun metagenomics	Baseline dysbiosis signature predicted future CKD risk.	Not assessed.	Preservation of butyrate producers linked to 24% decreased in 3-year CV events (HR 0.76).	(50)

CKD, chronic kidney disease; HC, healthy controls; ESKD, end-stage kidney disease; SCFA, short-chain fatty acid; IS, indoxyl sulfate; PCS, p-Cresyl sulfate; LPS, lipopolysaccharide; hs-CRP, high-sensitivity C-reactive protein; GI, gastrointestinal; RCT, randomized controlled trial; HR, hazard ratio; CV, cardiovascular disease; rRNA, ribosomal RNA; eGFR, estimated glomerular filtration rate; qPCR, quantitative PCR.

Table II. Key studies elucidating the role of the gut-kidney axis in kidney disease progression.

Author and year	Study design	Population/model	Key intervention/ exposure	Main findings related to gut-kidney axis	(Refs.)
Wang <i>et al</i> , 2024	Prospective cohort (human)	3,854 adults free of CKD at baseline	Plasma TMAO measurement	Highest TMAO quartile ($\geq 8.3 \mu\text{M}$) associated with 2.2-fold higher risk of incident CKD over 10 years, independent of traditional risk factors.	(26)
Lee <i>et al</i> , 2024	Experimental (mouse)	Murine IRI model	Antibiotic-induced microbiota depletion vs. conventional microbiota	Depletion of butyrate-producing bacteria worsened AKI severity and fibrosis; <i>Lactobacillus acidophilus</i> KBL409 restored butyrate and attenuated injury.	(83)
Gharaie <i>et al</i> , 2023	Prospective cohort (human)	Patients in the ICU (n=88)	Plasma IS measured within 6h of admission	Early IS levels associated with tubular injury (KIM-1) and predicted persistent CKD at 6 months, independent of illness severity.	(85)
Gupta <i>et al</i> , 2020	Experimental (mouse)	5/6 nephrectomy CKD model	Inhibition of TMA production (DMB) or FMO3 knockout	TMAO reduction attenuated renal fibrosis by 38% and preserved peritubular capillaries, supporting mechanistic plausibility.	(90)
Kim <i>et al</i> , 2023	Experimental (mouse)	Aged vs. young mice with unilateral IRI	Aging + IRI	Aged mice showed sustained gut dysbiosis (Increased Enterobacteriaceae, Increased LPS) and exacerbated fibrosis post-IRI, linking aging microbiome to AKI-to-CKD transition.	(84)
Tungsanga <i>et al</i> , 2022	Experimental (mouse)	5/6 nephrectomy model	Post-IRI administration of <i>Lactocaseibacillus rhamnosus</i> L34	Probiotic restored gut barrier (claudin-1), reduced LPS and halved renal fibrosis, demonstrating modulation of AKI-to-CKD continuum.	(91)
Chen <i>et al</i> , 2020	Longitudinal cohort (human)	CRIC study (n=2,391)	Serum IS levels	Each 1-SD higher IS associated with faster eGFR decline (-0.24 ml/min/year), independent of proteinuria and BP.	(92)
Watanabe <i>et al</i> , 2020	Experimental (mouse)	UUO model	Gut microbiota depletion via antibiotics	Microbiota depletion reduced renal inflammation and injury, highlighting gut-immune crosstalk in obstructive nephropathy.	(93)

AKI, acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FMO3, flavin-containing monooxygenase 3; HR, hazard ratio; IRI, ischemia/reperfusion injury; IS, indoxyl sulfate; LPS, lipopolysaccharide; OR, odds ratio; SD, standard deviation; TMA, trimethylamine; TMAO, trimethylamine N-oxide; UUO, unilateral ureteral obstruction; ICU, intensive care unit. KIM-1, kidney injury molecule 1.

Table III. Summary of clinical studies investigating gut microbiome-targeted interventions in CKD.

Author, year	Intervention type	Study design	Population (CKD stage; n)	Intervention details	Duration	Key findings	(Refs.)
Cosola <i>et al.</i> , 2021	Synbiotic	RCT, pilot	Stage IIIb-IV; n=20	<i>Lactiplantibacillus plantarum</i> + resistant dextrin	6 weeks	Decreased free IS by 26%, decreased free PCS by 21%; improved intestinal permeability	(35)
Cruz-Mora <i>et al.</i> , 2014	Synbiotic	Open-label	ESKD on HD; n=15	Multi-strain synbiotic	4 weeks	Decreased plasma PCS; increased fecal Bifidobacteria	(94)
Guida <i>et al.</i> , 2014	Synbiotic	RCT	CKD (non-dialysis); n=41	Synbiotic (probiotic + FOS)	4 weeks	Decreased plasma PCS by 15-20%	(95)
Natarajan <i>et al.</i> , 2014	Probiotic	RCT	Peritoneal dialysis; n=42	Renady TM (specific probiotic mix)	6 months	Decreased serum IS by 25%; improved quality-of-life scores	(96)
Rossi <i>et al.</i> , 2016 (SYNERGY)	Synbiotic	RCT, double-blind, crossover	Stage 3b-4; n=30	Synbiotic yogurt	6 weeks	Decreased free IS by 14%; no change in total (protein-bound) IS	(97)
Borges <i>et al.</i> , 2018	Probiotic	RCT, double-blind	Non-dialysis CKD; n=46	Multi-strain probiotic	8 weeks	No significant change in IS, PCS or inflammatory markers	(100)
Esgalhado <i>et al.</i> , 2018	Prebiotic (resistant starch)	RCT, pilot	Hemodialysis; n=30	Resistant starch type 2 (HAM-RS2), 20 g/day	6 weeks	Increased fecal butyrate by 60%; decreased plasma IS (21.4 to 16.8 μ M); no change in PCS	(102)
Li <i>et al.</i> , 2020	Prebiotic (inulin)	RCT, crossover	Peritoneal dialysis; n=40	Inulin-type fructan, 15 g/day	8 weeks	Decreased fecal IS by 18%; increased <i>Faecalibacterium prausnitzii</i> 2.3-fold	(103)
Ramos <i>et al.</i> , 2019	Prebiotic (FOS)	RCT	Non-dialysis CKD (Stage 3-4); n=50	FOS, 12 g/day	12 weeks	No significant change in IS or PCS	(105)
Schulman <i>et al.</i> , 2015 (EPIC)	Oral adsorbent (AST-120)	RCT, multi-center	Stage 3-4; n>1,500	AST-120 (spherical activated carbon)	12 months	Decreased serum IS by 15%; no difference in composite renal endpoint (doubling Cr, dialysis and death)	(108)
Cha <i>et al.</i> , 2016	Oral adsorbent (AST-120)	RCT	Advanced CKD (eGFR 15-60); n=203	AST-120	12 months	Trend toward slower eGFR decline in AST-120 group (not statistically significant)	(109)
Kee <i>et al.</i> , 2021	Oral adsorbent (AST-120)	RCT, Phase IV	Stage 3b-4; n=210	AST-120 (6 g/day vs. 9 g/day)	12 weeks	6 g/day: Decreased IS by 30%; 9 g/day: no additional benefit; increased GI adverse events dose-dependently	(111)
Hung <i>et al.</i> , 2025	Oral adsorbent (novel)	Pilot RCT	CKD (stage not specified); n=45	Bamboo-derived activated charcoal	4 weeks	Decreased PCS by 22% (unblinded study)	(112)

Table III. Continued.

Author, year	Intervention type	Study design	Population (CKD stage; n)	Intervention details	Duration	Key findings	(Refs.)
Kimber <i>et al</i> , 2020	Small molecule (Rifaximin)	RCT, placebo-controlled	Stage 3-4 CKD; n=45	Rifaximin 550 mg twice daily	4 weeks	Decreased fecal TMAO formation by 18%; increased Enterobacteriaceae abundance	(113)
Arteaga-Muller <i>et al</i> , 2024	Fecal Microbiota transplantation (FMT)	Phase I, open-label	Stage 4 CKD; n=12	Single nasoduodenal infusion from lean healthy donor	1 week (assessment)	Increased butyrate producers (Faecalibacterium, Roseburia) from 4 to 15%; decreased serum IS by 19%; transient increase in TMAO in 2 recipients	(114)

CKD, chronic kidney disease; ESKD, end-stage kidney disease; HD, hemodialysis; IS, indoxyl sulfate; PCS, p-Cresyl sulfate; TMAO, trimethylamine N-oxide; RCT, randomized controlled trial; FOS, fructooligosaccharides; DMB: 3,3-dimethyl-1-butanol; FMT, fecal microbiota transplantation; GI, gastrointestinal; CrCl, creatinine clearance; BP, blood pressure; eGFR, estimated glomerular filtration rate.

Literature search strategy. The present narrative review was conducted following the Scale for the Assessment of Narrative Review Articles guidelines for quality and transparency (40). A systematic literature search was performed in the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and MEDLINE (<https://www.nlm.nih.gov/>) database for articles published in English between January 2015 and April 2026. The search strategy combined the following key words and Medical Subject Headings (MeSH) terms: ‘chronic kidney disease’ OR ‘CKD’ OR ‘renal insufficiency’ AND ‘gut microbiota’ OR ‘microbiome’ OR ‘dysbiosis’ AND ‘uremic toxins’ OR ‘indoxyl sulfate’ OR ‘p-cresyl sulfate’ OR ‘trimethylamine N-oxide’ OR ‘TMAO’ AND ‘short-chain fatty acids’ OR ‘SCFAs’ AND ‘probiotics’ OR ‘prebiotics’ OR ‘synbiotics’ OR ‘fecal microbiota transplantation’ OR ‘FMT’. Studies were included if they reported original data or comprehensive reviews on the gut-kidney axis in CKD, with a focus on mechanistic insights, metabolite toxicity or therapeutic interventions. *In vitro* cell studies, preclinical animal studies, human observational cohorts and interventional trials were all considered for inclusion. Articles were excluded if they were not published in English, lacked original data or substantive synthesis, or focused on non-CKD populations.

2. Gut microbiota dysbiosis in CKD

A consistent reduction in microbial richness and diversity is now recognized as a hallmark of CKD, irrespective of underlying etiology (6,40). A meta-analysis of 16S ribosomal RNA (rRNA) sequencing from >1,200 fecal samples revealed a progressive decline in Shannon and Simpson indices from stage G2 onward, with the greatest drop in advanced CKD and end-stage kidney disease (ESKD) (40). Reduced α -diversity was inversely associated with serum creatinine and inversely with uremic toxin concentration (7). Parallel shotgun metagenomics also showed that 41% of the species-level operational taxonomic units detected in healthy individuals were either undetectable or present at <10% abundance of healthy individuals in patients with stage G4-5 CKD (41). Collectively, these data indicate that loss of microbial richness is not merely an epiphenomenon but tracks the severity of renal impairment (Table I). The core features of CKD-associated dysbiosis, including loss of diversity, phylum-level shifts and functional changes in metabolite production, are illustrated in Fig. 1.

Phylum-level shifts: Proteobacteria expansion and butyrate-producer depletion. At the phylum level, three independent Chinese (40), European (9) and US multi-ethnic cohorts (42) documented a uniform proportional increase in Proteobacteria (mean relative abundance 28-37% in CKD vs. 4-9% in controls), which is accompanied by a contraction of Firmicutes, particularly the Clostridia class. Within Firmicutes, the butyrate-synthesizing families *Lachnospiraceae* and *Ruminococcaceae* were consistently under-represented, where pooled random-effects analysis estimated a standardized mean difference of -0.78 [95% confidence interval (CI), -1.02 to -0.54] for *Lachnospiraceae* abundance in CKD vs. controls (40). *Butyricoccus*, a genus that converts dietary fiber to butyrate, fell below the limit of detection in 64% ESKD samples, whereas it was present in 92% of healthy controls (9).

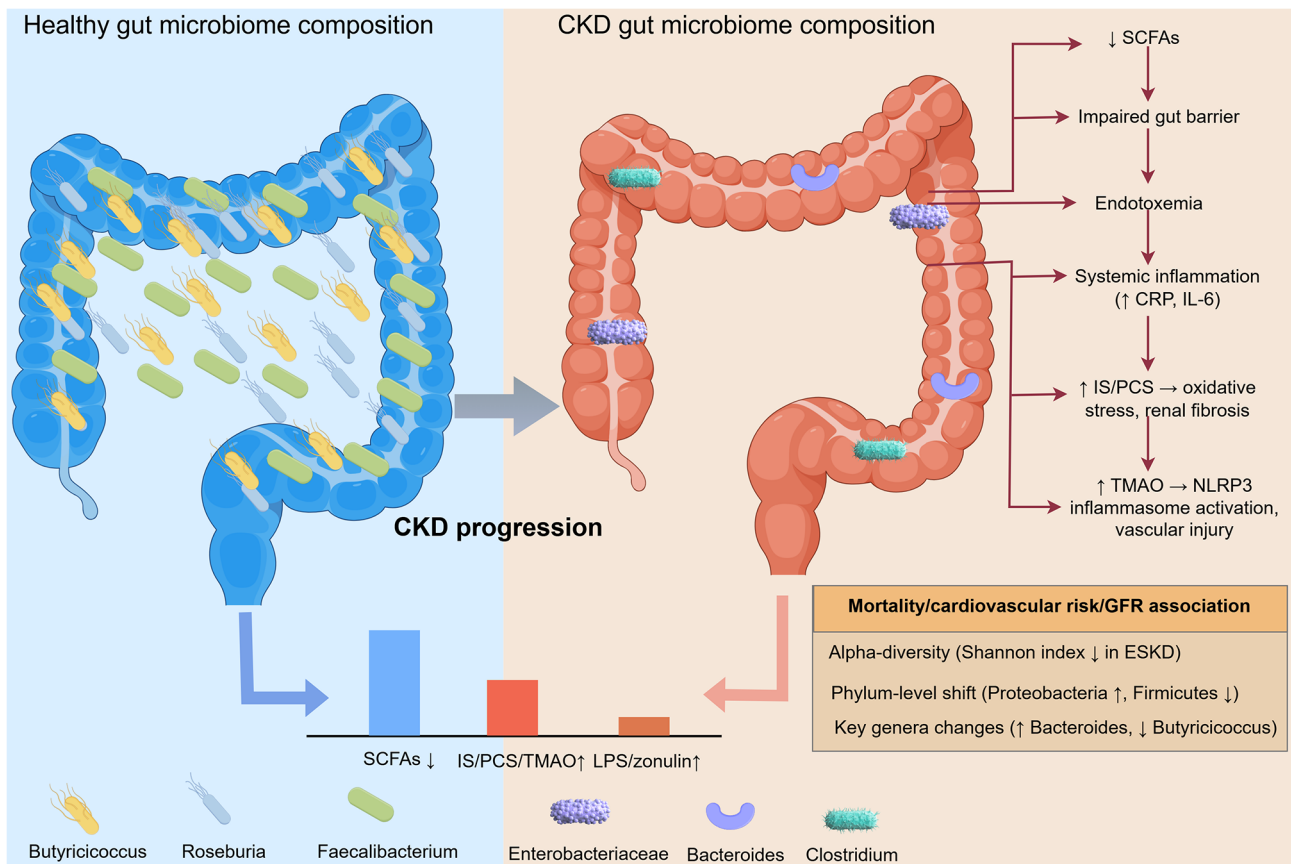


Figure 1. Gut microbiota dysbiosis in CKD. In CKD, the gut microbiome exhibits reduced diversity, with a characteristic shift toward Proteobacteria and uremic toxin-producing genera (such as *Bacteroides*), alongside depletion of butyrate-producing Firmicutes. These changes lead to decreased SCFAs production, increased generation of protein-bound toxins (IS and PCS) and TMAO, elevated endotoxemia and impaired intestinal barrier integrity. The resulting systemic inflammation and direct renal toxicity accelerate CKD progression and associate with adverse clinical outcomes, such as cardiovascular events and increased mortality. Figure created using Figdraw (<https://www.figdraw.com/>). CKD, chronic kidney disease; SCFAs, short chain fatty acid; IS, indoxyl sulfate; PCS, p-cresyl sulfate; TMAO, trimethylamine N-oxide; ESKD, end-stage kidney disease; CRP, C reactive protein; LPS, lipopolysaccharide; NLRP3, nod-like receptor family pyrin domain containing 3.

The functional consequence is a reduction in fecal butyrate (-38%) and propionate (-29%), metabolites that normally maintain epithelial barrier integrity (33) and suppress renal inflammation through G protein-coupled receptor (GPR) 43/109A signaling (32).

Uremic toxin-generating taxa: Concordant enrichment. Culture-independent quantification demonstrated that bacteria possessing tryptophanase or tyrosine-phenol-lyase genes, predominantly *Bacteroides*, *Clostridium* and some pathogenic *Klebsiella*, are selectively expanded in CKD (43). Whole-genome sequencing of 452 *Bacteroides* isolates recovered from patients showed a 2.3-fold higher copy number of the tryptophanase operon compared with that of control strains, suggesting genetic as well as numerical over-representation (43). Consequently, fecal and serum concentrations of the PBUTs IS and PCS rise in parallel with the abundance of these genera (44). A randomized controlled synbiotic trial provided further support for the biological plausibility of this association (35). An 8-week intervention with the synbiotic NATUREN G® (containing *Lactobacillus casei* LC4P1, *Bifidobacterium animalis* BLC1, fructo-oligosaccharides, inulin and a natural antioxidant blend of quercetin, resveratrol and proanthocyanidins) that reduced *Bacteroides* by 18%,

simultaneously lowered free serum IS by 26% and PCS by 21%, corroborating earlier observational findings (35).

TMAO pathway: Divergent findings explained by diet and geography. TMA producers, including *Anaerococcus*, *Prevotella* and certain *Clostridium* cluster XIVa, are generally more abundant in CKD, yet reported plasma TMAO concentrations vary widely. A pooled analysis previously revealed that median TMAO was 4.5 μM in European cohorts but 12.8 μM in East-Asian cohorts (45). Follow-up metabolomic tracing showed that the difference disappeared when dietary L-carnitine/choline was restricted to <5 mg/kg/day, indicating that substrate availability rather than microbial capacity drives the inter-study discordance (46). Once dietary confounders are accounted for, renal function remains an independent predictor of TMAO (45), supporting kidney clearance as a critical modulator.

Gut-immune interface: Endotoxin, barrier integrity and inflammation. Expansion of Gram-negative Proteobacteria translates into elevated fecal and serum lipopolysaccharide (LPS) (47,48). Mean serum LPS levels in CKD (0.56 EU ml^{-1}) exceeded control values (0.21 EU ml^{-1}) by >2.5-fold (47), whereby circulating LPS was positively associated with zonulin,

a marker of tight-junction disruption (48). Experimental data corroborate this causality; specifically, LPS infusion in germ-free mice (animals completely devoid of all microorganisms, maintained in sterile isolators) reproduced systemic IL-6 and TNF- α surges, further determining that LPS-driven inflammation occurs independently of the resident microbiota, whereas butyrate supplementation (a short-chain fatty acid that upregulates tight junction proteins and attenuates LPS-induced NF- κ B signaling) restored occludin expression and reduced renal macrophage infiltration by 34% (33). These findings align with human studies showing that every 10% increment in butyrate-producing genera was associated with a 0.07 ng/ml decrease in high-sensitivity C-reactive protein (CRP) (49). This inverse association is mechanistically attributable to butyrate, which reinforces intestinal barrier function by upregulating tight junction proteins such as occludin and claudin-1, thereby limiting lipopolysaccharide translocation and systemic CRP elevation (33).

Clinical and prognostic implications. Low microbial diversity predicted all-cause mortality in a longitudinal ESKD cohort [hazard ratio (HR), 1.18 per 100-unit decrease in Chao1 index; 95% CI, 1.05-1.33] (47). Conversely, preservation of butyrate producers conferred a 24% reduction in 3-year cardiovascular events (HR 0.76; 95% CI, 0.59-0.97) (50). Taken together, current evidence positions gut dysbiosis not merely as a biochemical curiosity but as an independent, modifiable risk factor that tracks CKD progression and amplifies systemic inflammation through toxin generation and barrier dysfunction.

Confounders and limitations in microbiome interpretation. Interpretation of CKD-associated microbiome signatures is complicated by multiple confounding factors, including dietary restrictions, diabetes, constipation, antibiotic exposure, phosphate binders, iron supplementation, dialysis modality and geographic variation (38,51,52). Dietary protein and fiber intake can directly modulate the abundance of toxin-producing and SCFA-producing bacteria, respectively (53,54). In addition, phosphate binders and iron supplements can alter gut microbial composition and metabolite profiles (11,51). Furthermore, constipation, which is prevalent in patients with CKD, promotes the retention and bacterial fermentation of urea and other nitrogenous substrates, including dietary aromatic amino acids (including tryptophan and tyrosine/phenylalanine) that serve as precursors for indoxyl sulfate and p-cresyl sulfate generation, as well as choline, L-carnitine and betaine that are converted by gut microbiota to trimethylamine and subsequently oxidized to trimethylamine N-oxide, potentially amplifying uremic toxin generation (10,16). The heterogeneity in sequencing methodologies and analytical pipelines across studies also complicates direct comparisons (8,40). Therefore, future studies should systematically control for these variables and report detailed medication with the full dietary dataset to enable the more robust interpretation of gut microbiota alterations in CKD.

In summary, whilst phylum-level shifts (Proteobacteria expansion and Firmicutes contraction) are consistently observed across cohorts, genus-level findings vary markedly, as evidenced by the aforementioned discordant reports regarding *Bacteroides* and *Clostridium* species. Namely, *Bacteroides*

has been reported as selectively expanded in Taiwanese CKD cohorts (43), yet no significant difference in *Bacteroidaceae* family composition between CKD/ESKD patients and healthy controls was found in a separate Iranian cohort (8); similarly, *Clostridium* species abundance has been shown to be virtually identical between CKD/ESRD and healthy groups in one study (5), whereas separate analysis has implicated *Clostridium* cluster XIVa as a TMA producer enriched in CKD (45). These discrepancies reflect differences in sequencing platforms, analytical pipelines and population characteristics. The predominance of cross-sectional designs and inadequate control for dietary and medication confounders remain the principal limitations. Furthermore, the clinical significance of these microbial alterations, particularly whether they represent causal drivers of CKD progression or merely bystander phenomena, remains uncertain in the absence of longitudinal intervention studies that modulate specific microbial targets.

3. Gut-derived metabolites and their toxic effects on the kidneys

The accumulation of gut-derived metabolites in CKD has emerged as a pivotal pathogenic mechanism linking intestinal dysbiosis to renal injury. As renal clearance declines, microbial metabolites that are normally excreted by the kidneys accumulate in the systemic circulation, exerting direct nephrotoxicity and amplifying systemic inflammation. This section critically reviews the most clinically relevant gut-derived uremic toxins, IS, PCS and TMAO, with a focus on their biochemical behavior, renal handling and toxicological impact across the CKD spectrum. The contrasting pathogenic and protective mechanisms of key gut-derived metabolites within the kidney are summarized in Fig. 2.

PBUT: IS and PCS. IS and PCS are prototypical PBUTs generated through the bacterial fermentation of dietary tryptophan and tyrosine, respectively. Their accumulation begins in early CKD stages and increases exponentially with declining glomerular filtration rate (55-57). Due to high albumin binding (>90%), their renal clearance is limited, where conventional dialysis modalities achieve only modest reductions in their plasma levels (58-60).

Mechanistically, IS and PCS exert toxicity through multiple pathways. IS induces the expression of NADPH oxidase 4 and activates NADPH oxidase activity, triggering oxidative stress and activating NF- κ B-mediated inflammatory cascades in tubular epithelial cells (61). By contrast, PCS can disrupt endothelial integrity by phosphorylating Vascular endothelial-cadherin, increasing vascular permeability and promoting atherogenesis (62,63). Furthermore, both toxins can stimulate fibroblast proliferation and extracellular matrix deposition, accelerating tubulointerstitial fibrosis (64,65). Notably, IS has been shown to suppress hypoxia-inducible factor-dependent erythropoietin expression through activation of the aryl hydrocarbon receptor pathway, thereby contributing to inadequate erythropoietin production and erythropoiesis-stimulating agent hyporesponsiveness in CKD (66).

Clinical studies have consistently associated elevated IS and PCS levels with adverse renal outcomes. In a prospective pediatric CKD cohort, IS predicted a faster decline in eGFR,

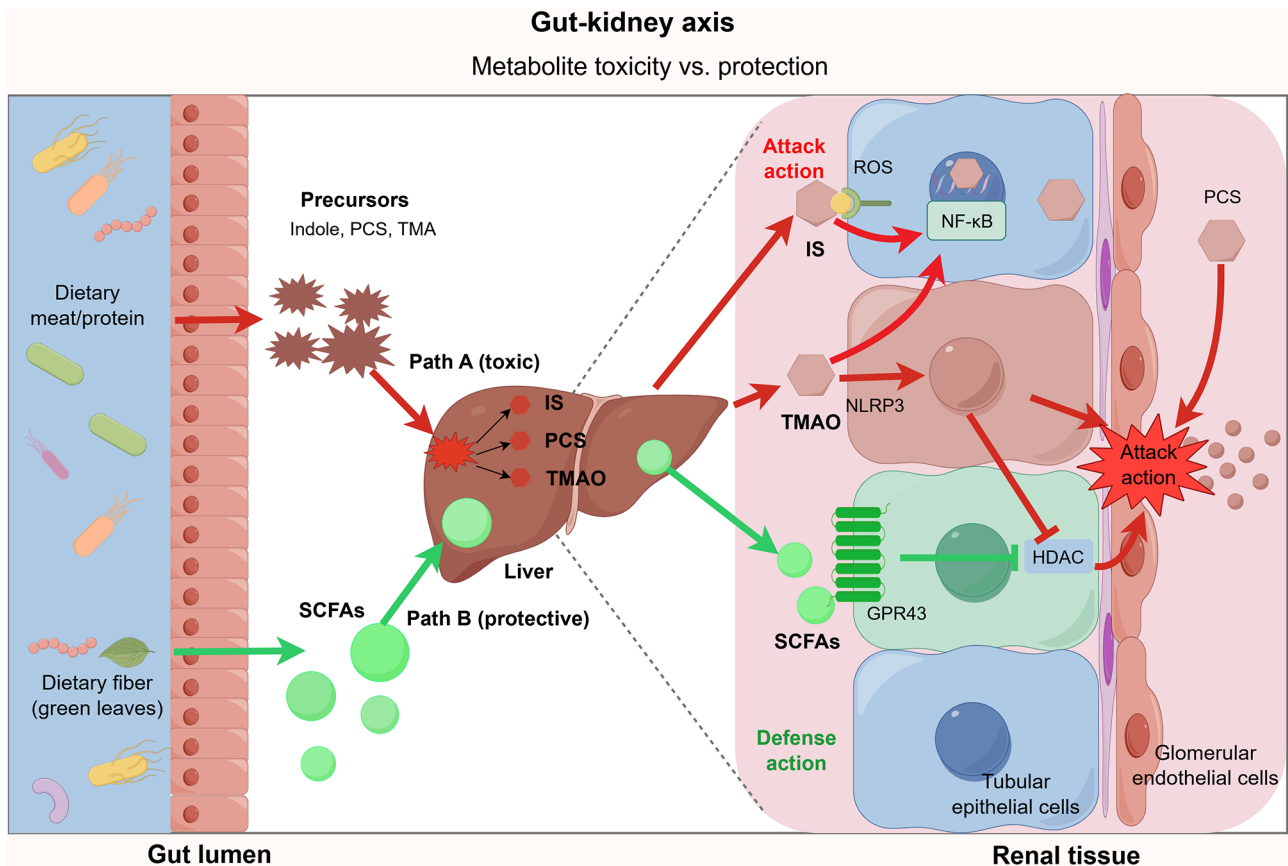


Figure 2. Gut-kidney axis metabolite toxicity vs. protection. Dietary protein is fermented by gut microbiota and transformed in the liver into uremic toxins (PCS, TMAO and IS). In the kidney, PCS disrupts glomerular endothelial junctions. In tubular epithelial cells, IS induces ROS and NF-κB activation, whilst TMAO activates NLRP3. By contrast, dietary fiber-derived SCFAs exert protective effects on tubular cells by GPR43 binding and HDAC inhibition to block inflammatory signals. Figure created using Figdraw (<https://www.figdraw.com/>). SCFAs, short chain fatty acid; IS, indoxyl sulfate; PCS, p-cresyl sulfate; TMAO, trimethylamine N-oxide; TMA, trimethylamine; HDAC, histone deacetylase; ROS, reactive oxygen species; GPR, G-protein coupled receptor; NLRP3, nod-like receptor family pyrin domain containing 3.

independent of proteinuria and blood pressure (17). Similarly, PCS levels have been shown to promote vascular calcification by inducing osteogenic conversion of vascular smooth muscle cells through reactive oxygen species (ROS)-dependent activation of the MAPK/NF-κB signaling pathway and upregulation of runt-related transcription factor 2 and alkaline phosphatase. In addition, higher PCS levels have been shown to be independently associated with increased arterial stiffness in non-dialysis CKD stages 3-5 (67,68). However, a number of interventional studies have also yielded ambiguous results. While synbiotic therapy reduced free IS and PCS levels by ~20-25% (30,35), these reductions did not consistently translate into improved hard renal endpoints (including easing of eGFR decline, progression to ESKD, initiation of dialysis or kidney transplantation), possibly due to the persistence of protein-bound fractions and the short follow-up durations.

TMAO: A gut-derived cardiorenal toxin. TMAO is typically formed from a two-step microbial-host pathway: Gut bacteria convert dietary choline and L-carnitine into TMA, which is then oxidized by hepatic flavin monooxygenases to TMAO (55,69). Plasma TMAO levels rise markedly in CKD, not only due to impaired renal excretion but also because of increased microbial TMA production (26,70). Unlike PBUTs, TMAO is not protein-bound and is therefore more efficiently

cleared by dialysis. However, its levels remain elevated in patients undergoing hemodialysis, suggesting sustained microbial generation (46,71).

The renal toxicity of TMAO is multifaceted. In rodent models, TMAO administration exacerbated renal fibrosis by activating the nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and enhancing macrophage M2 polarization through histone H4K12 lactylation (72,73). It also promotes endothelial dysfunction by inhibiting endothelial nitric oxide (NO) synthase to reduce NO bioavailability (74). Clinically, elevated TMAO predicts incident CKD and accelerates eGFR decline in large multi-ethnic cohorts (26). In children with CKD, TMAO pathway activity has been associated with subclinical vascular abnormalities, including increased arterial stiffness and abnormal ambulatory blood pressure profiles, supporting its potential role in early vascular remodeling (27).

Dietary interventions targeting TMAO precursors have shown promise in healthy populations (1,75). This finding establishes that circulating TMAO may be responsive to dietary precursor availability, providing a rationale for investigating whether restricting dietary choline and L-carnitine intake could lower TMAO burden in patients with CKD (75). In patients with CKD, the strong association between plasma TMAO and renal function provides a rationale for investigating

dietary strategies to modulate this pathway (75). However, such diets are challenging to sustain and may compromise nutritional status. Pharmacological inhibition of microbial TMA production using 3,3-dimethyl-1-butanol (DMB) was found to attenuate renal fibrosis in CKD mice (46). However, human efficacy data for DMB remain limited to *in vitro* studies demonstrating that DMB inhibits TMA formation in human fecal cultures (37), with to the best of our knowledge, no published clinical trials evaluating its safety or efficacy in patients with CKD. The absence of human interventional data represents a key translational gap for this therapeutic approach.

SCFAs: Protective counter-regulators. Compared with the aforementioned toxins, SCFAs (particularly butyrate, propionate and acetate) are microbial metabolites with documented nephroprotective effects. SCFAs are produced by the fermentation of dietary fiber by Firmicutes (such as *Lachnospiraceae* and *Ruminococcaceae*), both of which are depleted in CKD (76). Butyrate enhances gut barrier integrity by upregulating tight junction proteins (such as occluding and claudin-1) and suppressing the systemic translocation of LPS (77).

Experimental data indicate that butyrate attenuates renal inflammation through GPR43/109A signaling and inhibits histone deacetylase activity, reducing NF- κ B-mediated cytokine release (32,78). In an RCT, supplementation with resistant starch increased fecal butyrate levels and reduced serum IS and PCS concentrations in patients with stage 3b-4 CKD (54). However, the translational potential of SCFA-augmenting strategies is constrained by inter-individual variability in microbiota response and the rapid absorption and metabolism of SCFAs by colonic epithelial cells, which limits their local availability and systemic delivery (1,5).

Ammonia and hydrogen sulfide (H_2S): Emerging tubular toxins. Beyond the classical PBUTs and TMAO, emerging evidence implicates ammonia and H_2S in CKD-associated tubular injury. Ammonia is generated by bacterial urease activity that has been shown to exacerbate tubulointerstitial inflammation by activating the complement cascade and increasing ammoniogenesis in residual nephrons (79). H_2S is traditionally viewed as cytoprotective, with endogenous H_2S deficiency implicated in the pathogenesis of CKD (80). However, emerging evidence indicates that the uremic toxin IS can impair H_2S formation in renal tubular cells by down-regulating H_2S -producing enzymes, including cystathionine β -synthase, cystathionine γ -lyase and 3-mercaptopyruvate sulfurtransferase, through aryl hydrocarbon receptor activation. This in turn compromises the glutathione-mediated antioxidant defense and contributes to tubular cell damage (81). Recent metabolomic profiling identified a marked increase in fecal and serum H_2S levels in CKD stages 4-5, associating with urinary kidney injury molecule-1 (KIM-1) excretion, a validated marker of tubular damage (82). However, human data remain sparse, where the therapeutic modulation of these metabolites is exploratory at present.

Across these metabolites, the strength of evidence is strongest for IS and PCS (consistent mechanistic and cohort data), intermediate for TMAO and weakest for SCFAs (largely preclinical). Single-time-point measurements, geographic dietary confounders and the scarcity of studies examining

combined metabolite effects represent pervasive limitations. Notably, the modest magnitude of toxin reductions achieved by current interventions (including synbiotics/probiotics and oral adsorbents such as AST-120; typically 15-30%) raises the question as to whether such decreases are sufficient to markedly alter disease trajectory or whether more notable metabolite modulation is required for clinical benefit (30,35).

4. Role of the gut-kidney axis in kidney disease progression

Accumulating evidence is framing the gut-kidney axis as a self-amplifying circuit rather than a passive uremic toxin conduit. Intestinal dysbiosis, barrier breakdown and metabolite accumulation operate sequentially and in parallel to initiate AKI, propel CKD progression and accelerate the transition to ESKD. Whilst the primary focus of the present review is CKD, the inclusion of AKI is justified by the growing recognition that acute injury can leave a fibrotic legacy that accelerates long-term CKD progression, where gut dysbiosis induced during AKI can persist beyond the acute phase, creating a permissive microbiome that fuels kidney injury persistence (83,84). Key studies from both experimental models and human cohorts that have elucidated the causal and progressive role of the gut-kidney axis are summarized in Table II.

Dysbiosis as an instigator of AKI. AKI has traditionally been attributed to ischemia, nephrotoxins or sepsis (3,7). However, the pre-morbid microbial configuration can independently govern both injury severity and the fibrotic memory, which can in turn determine the long-term outcome. Lee *et al* (83) depleted murine microbiota with broad-spectrum antibiotics for 3 weeks before inducing bilateral renal ischemia/reperfusion (IRI). Antibiotic-treated mice exhibited >50% reduction in fecal butyrate, a doubling of tubular caspase-3 activity at 24 h and twice the interstitial collagen III deposition at day-14 compared with those in vehicle-treated control mice. Subsequent re-colonization with *Lactobacillus acidophilus* KBL409 restored butyrate to ≥ 0.8 μ mol/g caecum, halved macrophage infiltration (CD68⁺ area, 18.2 ± 2.1 vs. $34.7 \pm 3.4\%$) and preserved capillary density, indicating that the loss of protective taxa can worsen AKI independently of systemic infection.

Human data mirror these findings. In a prospective cohort of 88 patients admitted to the intensive care unit with AKI, plasma IS measured within 6 h of admission was positively correlated with urinary KIM-1 at day-3 and predicted persistent CKD stage ≥ 3 at 6 months (odds ratio 3.6; 95% CI, 1.4-9.2) after adjustment for APACHE-II and nephrotoxin exposure (85). Therefore, gut-derived toxins likely behave as pathophysiological amplifiers rather than the epiphenomena of reduced renal clearance.

Microbial shifts that propel CKD progression

Consistent ecological signature across continents. Meta-analysis of 16S rRNA data from >1,200 fecal samples revealed a progressive contraction of microbial richness from CKD G2 onward. Specifically, Shannon index fell by 0.42 (95% CI, -0.53 to -0.31) in ESKD (86). In addition, three independent cohorts (China, Europe and the USA) documented the expansion of Proteobacteria (mean, 28-37 vs. 4-9% in controls),

which is coupled with the depletion of butyrate-producing Firmicutes (*Lachnospiraceae* and *Ruminococcaceae*) (86-88). Whole-genome sequencing of 452 *Bacteroides* isolates from patients with CKD showed a 2.3-fold duplication of the tryptophanase operon, paralleling a 2.1-fold higher fecal IS concentration compared with that in healthy controls (89). These data support the biological gradient proposal, whereby the degree of dysbiosis tracks with toxin burden and GFR decline.

TMAO: prospective associations and mechanistic plausibility. Large-scale metabolomics have closed the causality loop further. Wang *et al* (26) followed 3,854 individuals free of CKD at baseline. Participants in the highest TMAO quartile ($\geq 8.3 \mu\text{M}$) displayed a 2.2-fold higher risk of developing incident CKD (eGFR $< 60 \text{ ml/min}$) over 10 years after adjustment for protein intake, diabetes and blood pressure. These observational findings are complemented by mechanistic animal studies. TMAO activates the NLRP3 inflammasome in tubular cells, augmenting IL-1 β secretion and epithelial-mesenchymal transition markers (increased vimentin and decreased E-cadherin) (72). Genetic ablation of *FMO3* or pharmacological inhibition of microbial TMA-lyases reduced tubulointerstitial fibrosis by 38% compared with untreated 5/6-nephrectomy control mice and preserved peritubular capillary density in the 5/6-nephrectomy model (90). These animal data support interventional plausibility, but direct human proof of causality in the form of large randomized trials targeting TMAO production remains lacking.

AKI-to-CKD transition: A gut-sensitized window. Complementary murine studies have revealed that acute uremic dysbiosis can persist beyond the inciting injury, creating a permissive microbiome that fuels chronicity. Kim *et al* (84) demonstrated that aged mice subjected to unilateral IRI maintained fecal enrichment of *Enterobacteriaceae* and elevated systemic LPS levels for ≥ 4 weeks (0.51 ± 0.06 vs. $0.22 \pm 0.04 \text{ EU/ml}$ in young mice), paralleling the sustained tubular hypoxia and exaggerated collagen-I deposition. By contrast, post-IRI administration of *Lactocaseibacillus rhamnosus* L34 restored claudin-1 expression, lowered LPS and halved α -smooth muscle actin-positive area at day-42, providing direct evidence that microbiota modulation can interrupt the AKI-to-CKD continuum (91).

Human longitudinal evidence. In the CRIC study ($n=2,391$), each 1-SD higher serum IS was associated with a 0.24-ml/min/year faster eGFR decline independent of proteinuria and blood pressure (92). Similarly, serum TMAO predicted eGFR loss in children with CKD ($\Delta\text{eGFR } -2.1$ vs. -0.8 ml/min/year ; highest vs. lowest TMAO tertile) (93). These longitudinal cohort findings indicate that higher serum IS and TMAO levels are associated with a subsequent, faster decline in eGFR, suggesting that microbial metabolite elevation may precede and parallel the loss of renal function; however, these observational data do not establish causality (92,93).

Integrated mechanistic model of gut-kidney axis-driven CKD progression. The individual pathways aforementioned can be synthesized into a unified, self-amplifying mechanistic model of gut-kidney axis-driven CKD progression. This integrated framework can operate through four interconnected stages.

The initiation phase is characterized by CKD-associated dysbiosis, wherein the progressive loss of microbial diversity and depletion of butyrate-producing Firmicutes (such as *Lachnospiraceae* and *Ruminococcaceae*) occur alongside the expansion of Proteobacteria and uremic toxin-generating taxa, such as *Bacteroides* (40,42,43). This microbial shift reduces SCFA production whilst increasing generation of toxin precursors. The amplification phase then involves gut barrier disruption, whereby the depletion of SCFAs (particularly butyrate) compromises intestinal epithelial integrity by downregulating tight junction proteins (such as occluding and claudin-1) and enabling the translocation of bacterial endotoxins (such as LPS) into the systemic circulation (33,77). Subsequently, elevated LPS triggers systemic inflammation through NF- κB activation and cytokine release (IL-6 and TNF- α), further impairing renal function. The effector phase comes after the amplification phase, which consists of direct renal injury mediated by accumulated gut-derived metabolites. IS and PCS activate NADPH oxidase and NF- κB in tubular epithelial cells, promoting oxidative stress, inflammation and fibroblast proliferation (61,64). Concurrently, TMAO activates the NLRP3 inflammasome and promotes macrophage M₂ polarization, accelerating tubulointerstitial fibrosis (72,73). Additionally, ammonium accumulation impairs T cell function and promotes immunosuppressive macrophage polarization, creating an immunologically permissive environment for progression (11). This is followed by the self-perpetuation phase to complete the cycle. During this phase, progressive renal fibrosis reduces glomerular filtration, further increasing circulating uremic toxin concentrations and perpetuating dysbiosis, thereby reinforcing the entire cascade (10,13). This integrated model explains why interventions targeting single pathways have yielded limited efficacy. The network redundancy and feedback loops enable compensatory activation at alternative nodes (5). Accordingly, therapeutic strategies that simultaneously address multiple components of this integrated circuit, such as combining dietary fiber to restore SCFA production, adsorbents to reduce toxin burden and targeted modulation of microbial metabolism, may be required to disrupt the self-amplifying cycle and achieve meaningful clinical benefit (30,39,54).

5. Novel therapeutic strategies targeting the gut-kidney axis

Therapeutic efforts have mainly centered on repopulating the gut with beneficial microbes, supplying fermentable fibers or limiting systemic uptake of microbial toxins through adsorbents, enzyme inhibitors (46,90) or FMT (91). Published studies have indicated these measures to lower free but not protein bound uremic solutes, particularly when renal function can still be measured (3,30,46). To facilitate critical appraisal, the evidence for each intervention is stratified in this section according to the strength of available data: Interventions with human RCT evidence (mainly biochemical outcomes); interventions with preclinical/animal evidence only; and experimental approaches. An overview of clinical studies investigating various gut microbiome-targeted interventions, including their designs and key outcomes, is provided in Table III.

Probiotics and synbiotics. Early open-label studies in Mexican and Italian hemodialysis cohorts showed that a 4-week course of a multi-strain synbiotic (*Lactobacillus casei*, *Bifidobacterium breve* + 4 g fructo-oligosaccharide) lowered plasma PCS levels by 15–20% whilst modestly increasing stool Bifidobacteria counts (94,95). These findings were corroborated by a 2014 RCT that used a probiotic mixture specifically formulated for uraemia (Renadyl™), which observed a 25% reduction in serum IS together with improved quality-of-life scores in 42 patients undergoing peritoneal dialysis (96).

The largest trial to date, SYNERGY (n=30 CKD stage 3b–4), employed a double-blind, placebo-controlled, cross-over design and documented a marked 14% fall in free IS after 6 weeks of synbiotic yoghurt, although no change in total (protein-bound) IS was detected (97). A 2021 pilot study extended these observations to advanced CKD (stage IIIb–IV) by demonstrating a 26% decrease in free IS and a parallel 21% drop in PCS following a novel synbiotic capsule containing *Lactiplantibacillus plantarum* + resistant dextrin. In addition, intestinal permeability, as measured by the lactulose/rhamnose ratio, simultaneously improved (35). Another previous meta-analysis of 13 eligible RCTs (n=550) confirmed a pooled standardized mean difference of -0.46 (95% CI, -0.72 to -0.20) for PCS and -0.38 (95% CI, -0.65 to -0.11) for IS, with negligible heterogeneity ($I^2=12\%$) (30). Notably, the magnitude of toxin reduction was consistently smaller in patients with an eGFR <20 ml/min, implying that retained renal clearance contributes to the observed effect.

However, inflammatory endpoints have been less uniform. A number of previous clinical trials have reported a 10–15% fall in CRP (98,99), whereas others have reported no significant change (100–102). A 2023 aggregate-level meta-analysis incorporating 18 RCTs (n=884) concluded that probiotic/synbiotic supplementation reduced CRP by a modest 0.43 mg/l (95% CI, -0.78 to -0.08) but had no detectable effect on IL-6 or TNF- α (39). The most comprehensive synthesis to date, the 2023 Cochrane review by Cooper *et al* (39), which included 18 RCTs (n=884), concluded that whilst synbiotics, prebiotics and probiotics may reduce certain uremic toxins and inflammatory markers, the evidence for clinically meaningful benefits on hard renal outcomes, such as slowing eGFR decline, reducing cardiovascular events or mortality, remains insufficient (39). Taken together, current evidence supports synbiotics as a safe, low-cost modality that lowers free, but not protein-bound, uremic solutes. The clinical relevance of the incremental toxin reduction (~20%) remains uncertain, particularly with respect to hard renal endpoints.

Prebiotics and dietary fiber interventions. Resistant starch type 2 (HAM-RS2) and inulin-type fructans have been the most frequently tested prebiotics. A 2018 randomized, double-blind trial in 30 patients undergoing haemodialysis showed that 20 g/day HAM-RS2 for 6 weeks raised fecal butyrate levels by 60% and decreased plasma IS from 21.4 to 16.8 μ M without affecting PCS (102). These findings were essentially reproduced in a crossover study of patients undergoing peritoneal dialysis using 15 g/day inulin, where IS fell by 18% and stool *Faecalibacterium prausnitzii* increased 2.3-fold (103).

A systematic review and meta-analysis of 19 fiber-feeding RCTs (n=677) reported a pooled reduction in the IS of 4.27 μ M (95% CI, -6.38 to -2.16) and in PCS of 5.91 μ M (95% CI, -9.44 to -2.38), with greater efficacy observed when baseline fiber intake was <15 g/day (104). By contrast, two trials that provided <10 g/day fermentable fiber failed to modify either metabolite, underscoring the importance of dose and individual dietary pattern (105,106). Notably, none of the published fiber studies have exceeded a duration of 12 weeks. Therefore, long-term effects on renal function decline remain speculative. In addition, as with probiotics, the 2023 Cochrane review concluded that evidence for patient-important outcomes (eGFR decline, dialysis initiation or mortality) remains insufficient (39).

Oral adsorbents. AST-120 has been evaluated in two multinational Easing Pelvic Pain Interventions Clinical Research Program (EPPIC) trials (EPPIC-1 and EPPIC-2) that together randomized 2,035 patients with CKD stages 3–4 (107,108), as well as a separate Korean multicenter RCT (n=579) in patients with advanced renal dysfunction (109). The EPPIC program detected a 15% reduction in serum IS but found no difference in the composite renal end-point (doubling of creatinine, dialysis or death) after 12 months (108). Post-hoc analyses revealed that participants with the highest baseline IS (>10 μ M) experienced a 26% slower annual eGFR decline (-2.1 vs -2.8 ml/min/year) (110). A more recent Korean dose-comparison RCT (n=210) confirmed that 6 g/day AST-120 achieved a 30% IS reduction, yet no additional benefit was observed at 9 g/day and gastrointestinal adverse events increased dose-dependently (111).

Novel bamboo-derived activated carbon lowered PCS by 22% in a 2025 pilot study, but the trial was un-blinded and limited to 4 weeks (112). Collectively, adsorbents can reproducibly attenuate IS and PCS, though their capacity to slow CKD progression appears modest and is largely restricted to patients with elevated baseline toxin concentrations.

Microbiome-targeted small molecules. Beyond adsorbents, the first attempts to inhibit toxin generation have focused on the hepatic enzyme flavin monooxygenase 3 and on gut microbial TMA-lyases. However, such approaches currently only have evidence limited to preclinical studies. DMB is a structural analogue of choline that has been shown to decrease TMAO by ~33% in 5/6 nephrectomised mice and attenuated tubulo-interstitial fibrosis, an effect that was lost when the inhibitor was withdrawn (46). By contrast, rifaximin is an oral rifamycin derivative with minimal systemic absorption. It was reported to lower fecal TMAO formation by 18% in a 4-week placebo-controlled pilot. However, *Enterobacteriaceae* abundance doubled, raising concerns about collateral ecological damage (113). No adverse hepatic or cardiac signals have been reported for either compound (46,113), but the follow-up period has not reached >2 months. Therefore, longer, double-blind trials powered for renal endpoints are needed to define whether pharmacological suppression of TMAO synthesis translates into slower CKD progression.

FMT. FMT and engineered probiotics remain experimental interventions for CKD. In 2024, 12 patients with stage 4 CKD received a single nasoduodenal infusion of stool from lean

healthy donors after bowel lavage. Within 1 week, butyrate producers, such as *Faecalibacterium* and *Roseburia*, rose from 4 to 15% of total sequences, accompanied by a 19% fall in serum IS (114). TMAO, however, increased transiently in two recipients, emphasizing that donor selection and post-infusion diet may shape metabolite trajectories. A parallel phase I study using encapsulated frozen donor material reported similar enrichment of SCFA producers, but no notable biochemical changes were observed when the grafted microbial community, including the transferred SCFA-producing taxa, contracted after 4 weeks, likely due to insufficient engraftment or colonization resistance from the recipient's native microbiota (114). No serious infectious complications have been documented, but recipients of immunosuppressed dialysis were excluded. Repeated infusions, combined with dietary counselling and rigorous donor screening, are now being evaluated in an ongoing multicenter trial (NCT05923412). Until these data are available, FMT remains an experimental intervention best restricted to clinical protocols with close safety oversight. Similarly, engineered probiotics designed to specifically degrade uremic toxin precursors (such as tryptophanase-negative bacteria) and postbiotics (bacterial-derived inactivated cells or metabolites) represent emerging strategies that have shown promise in preclinical models but require rigorous clinical evaluation (115,116).

By comparing these interventions, probiotic/synbiotic trials are numerous but involve relatively small sample sizes ($n=20-50$) and were followed up short-term, whereas adsorbent trials are larger and longer but failed to show hard endpoint benefits. Across all approaches, insufficient power for renal outcomes, reliance on surrogate endpoints and short follow-up durations remain critical limitations. Notably, the consistent discordance between biochemical efficacy (toxin reduction) and clinical efficacy (eGFR preservation) across multiple intervention types suggests that the relationship between uremic toxins and CKD progression may be more complex than currently appreciated. Single-target interventions are now likely be insufficient to disrupt the multifactorial pathogenic network.

6. Future directions and research gaps

Despite considerable advances in elucidating the gut-kidney axis in CKD, the current understanding remains fragmented, such that the translation of microbiota-targeted strategies into routine clinical practice faces notable hurdles. The majority of interventional studies, whilst reporting modest efficacy in reducing circulating levels of free uremic toxins (such as IS and PCS), have largely failed to reveal consistent benefits on hard clinical endpoints (such as slowing the decline in the eGFR or reducing cardiovascular events) (30,39,117). This discrepancy underscores critical research gaps. Although synbiotic and probiotic interventions in patients undergoing hemodialysis and pre-dialysis have consistently lowered inflammatory markers, such as CRP and specific toxins (118,119), their effects are heterogeneous and frequently uncoupled from meaningful changes in renal function (120,121). Similarly, dietary fiber interventions with resistant starch or inulin reliably increase beneficial SCFA producers, such as *Faecalibacterium prausnitzii* and reduce certain uremic toxins (122,123), their

long-term impact on CKD progression remains unknown and responses vary with baseline diet and microbiota composition (54,124). These inconsistencies highlight the nascent state of the field and point to several prioritized avenues for future investigation. To move the field forward, future research should prioritize a number of key areas.

Key areas needing improvement. Large longitudinal multi-omics cohorts with standardized collection of dietary and medication data are needed. Current evidence is largely derived from cross-sectional studies with heterogeneous populations and incomplete confounder adjustment (51,52). Prospective cohorts integrating metagenomic, metabolomic and host genetic data, with detailed records of diet, medications (including phosphate binders, iron supplements and antibiotics), dialysis modality and constipation status, would enable robust identification of causal microbial signatures and their interactions with host factors (125,126).

Adequately powered RCTs with sufficient duration and clinically meaningful endpoints are also required. The majority of published intervention studies have been short-term (≤ 12 weeks) and have relied on biochemical surrogate endpoints, such as toxin reduction or inflammatory markers (39,104). Future trials should be designed with longer follow-up (≥ 12 months) and hard outcomes including eGFR slope, progression to ESKD, cardiovascular events and mortality. Such trials should also incorporate mechanistic sub-studies to elucidate the biological pathways through which the interventions exert their effects (125,127).

Personalized nutrition and microbiome-informed intervention selection represent a promising frontier. The current 'one-size-fits-all' approach fails to account for profound inter-individual variability in gut microbial composition, metabolic capacity and host response (51,52). Emerging evidence suggests that baseline microbial signatures may predict therapeutic responsiveness. Supporting this, the efficacy of resistant starch in elevating butyrate and reducing IS appears more pronounced in patients with low initial fiber intake and specific microbial configurations (54,124). Machine-learning models trained on large, well-phenotyped cohorts could identify predictive biomarkers to guide intervention selection (125,126). However, precision nutrition strategies, tailoring dietary recommendations based on an individual's microbiome and metabolomic profile, require rigorous testing in randomized trials (128).

Safety surveillance for probiotics, FMT and engineered microbiota must be prioritized. Long-term safety data in the CKD population are scarce, with isolated reports of bacteremia linked to probiotic strains in immunocompromised hosts (129). Rigorous post-marketing surveillance and long-term extension studies of interventional trials are therefore essential (38,39). The predictive potential of microbiome profiling also raises ethical questions regarding data privacy and psychological impact, while integrating microbiome diagnostics into clinical practice requires new resources, training and multidisciplinary collaboration (130,131).

Mechanistic human studies using metabolomics, organoids and kidney-on-chip models should complement clinical trials. Animal models, whilst instrumental in establishing causal links (132,133), inadequately recapitulate the complexity

of human CKD. Human-centric platforms, including organ-on-a-chip systems incorporating patient-derived renal cells and microbiota, could bridge the translational gap (125,127). Postbiotics and engineered probiotics designed to degrade uremic toxin precursors represent emerging strategies warranting exploration (115,116) and combination approaches (such as personalized diet with targeted probiotic and adsorbent) may yield synergistic effects (134,135).

In conclusion, advancing the field requires moving from broad, non-specific interventions to a precision medicine paradigm. By addressing these research priorities through large-scale longitudinal cohorts, rigorous long-term RCTs, personalized approaches, safety surveillance and mechanistic human studies, the field can evolve toward delivering targeted, effective and safe microbiota-based therapies that alter the natural history of CKD.

7. Conclusions

The gut-kidney axis is a well-established pathogenic pathway in CKD, linking intestinal dysbiosis to uremic toxin accumulation and loss of protective SCFAs. Observational and mechanistic evidence strongly supports this axis, yet its clinical translation remains uncertain. Current interventions reduce free toxin levels only modestly and lack consistent evidence of benefits for hard outcomes such as decreases in the eGFR or cardiovascular events. Individual responses vary, and long-term safety data are scarce. Therefore, routine use of probiotics, prebiotics or adsorbents to slow CKD progression cannot be recommended outside supportive dietary care or clinical trials.

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YW contributed to the conception and design of the manuscript, performed the literature search and integrated mechanistic, clinical and therapeutic findings, whilst also having drafted the manuscript. HZ contributed to literature screening and critically assessed study quality and reconciled conflicting findings, whilst having critically revised the manuscript. NL participated in literature screening, verified the accuracy of summarized findings, assisted in assessing the strength of evidence and assisted in drafting and revising the manuscript. DY conceived and designed the review, supervised the entire process, critically revised the manuscript for important intellectual content and provided final approval of the version to be published. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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