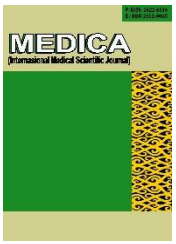
MEDICA

(International Medical Scientific Journal)
Vol.8, No.9, September 2026, pp. 867 – 885
ISSN 2622-660X (Online), ISSN 2622-6596 (Print)
https://doi.org/10.53770/medica.v8i9.1073



Modulation of the Gut–Kidney Axis Through Probiotics and Synbiotics in Chronic Kidney Disease: A Narrative Review

Agung Susanto[1]✉, Muhammad Ifham Hanif[2], Mentari Maratus Sholihah[2]

[1] Division of Nephrology and Hypertension, Department of Internal Medicine, Dr. Moewardi Hospital, Surakarta City, Central Java, Indonesia
[2] Department of Internal Medicine, Dr. Moewardi Hospital, Surakarta City, Central Java, Indonesia

Article Info

Article History:
Received:
16 May 2026
Revised:
13 June 2026
Accepted:
19 June 2026
Published:
22 September 2026

Keywords:
Gut–Kidney Axis
Probiotics
Synbiotics
Chronic Kidney Disease
Gut Microbiota

Citation:
Susanto, A., Hanif, M.I., & Sholihah, M.M. (2026). Modulation of the Gut–Kidney Axis Through Probiotics and Synbiotics in Chronic Kidney Disease: A Narrative Review. *MEDICA (International Medical Scientific Journal)*, 8(9), 867–885. https://doi.org/10.53770/medica.v8i9.1073

Abstract

Chronic kidney disease (CKD) is associated with increased cardiovascular morbidity and mortality, partly mediated through disruption of the gut–kidney axis. Gut microbiota dysbiosis contributes to the accumulation of uremic toxins, systemic inflammation, and oxidative stress, thereby accelerating CKD progression. This narrative review summarizes current evidence on the role of probiotics and synbiotics in modulating the gut–kidney axis in CKD. Literature was identified through searches of PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library up to April 2025, with emphasis on randomized controlled trials, systematic reviews, meta-analyses, and mechanistic studies. Current evidence indicates that probiotics and synbiotics may improve gut microbial balance, enhance short-chain fatty acid production, and reduce circulating uremic toxins and inflammatory markers. Additional approaches, including dietary interventions, fecal microbiota transplantation, and pharmacological modulation of the microbiome, have also shown potential benefits. However, despite favorable effects on surrogate biomarkers, evidence demonstrating significant improvements in kidney function and long-term clinical outcomes remains limited. Further well-designed randomized controlled trials with standardized formulations and clinically relevant endpoints are required to establish the therapeutic role of gut microbiota modulation as an adjunctive strategy in CKD management.

Corresponding Author:
✉ Agung Susanto
Division of Nephrology and Hypertension, Department of Internal Medicine, Dr. Moewardi Hospital, Surakarta City, Central Java, Indonesia
Email: agungsus08@staff.uns.ac.id

1. INTRODUCTION

Chronic kidney disease (CKD) is a global public health challenge, estimated to affect 9–14% of adults worldwide and expected to worsen alongside aging populations and the escalating prevalence of diabetes and hypertension (Hustrini et al., 2022; Stevens et al., 2024). Beyond the progressive loss of renal function, CKD confers substantial cardiovascular risk, with cardiovascular disease accounting for the majority of CKD-related mortality. A principal driver of this multisystem burden is persistent low-grade systemic inflammation, sustained by uremic toxin accumulation and dysregulated immune activation (Hustrini et al., 2022; Stevens et al., 2024; Williams et al., 2023).

In recent years, the gut–kidney axis has emerged as a pivotal pathophysiological framework in CKD one that encompasses the bidirectional interactions between the gut microbiota and renal function. Under conditions of progressive renal failure, gut microbiota dysbiosis characterized by depletion of health-promoting commensals and overgrowth of proteolytic, urease-containing bacteria leads to heightened production of gut-derived uremic toxins such as IS, pCS, and TMAO. These solutes, inadequately cleared by the failing kidney, accumulate in the circulation and exacerbate oxidative stress, endothelial dysfunction, renal fibrosis, and cardiovascular injury (Tzatzaki et al., 2024).

Concurrently, the uremic milieu disrupts intestinal barrier integrity, increasing mucosal permeability and facilitating the translocation of LPS and other pathogen-associated molecular patterns into the systemic circulation (Chen et al., 2019; Wakino et al., 2025). This endotoxemia activates innate immune pathways and sustains chronic inflammation, further accelerating CKD progression. The result is a self-reinforcing cycle: renal dysfunction promotes dysbiosis, and dysbiosis worsens renal dysfunction (Tsuji et al., 2024; Wakino et al., 2025).

Therapeutic strategies targeting the gut microbiota have consequently attracted considerable attention. Probiotics live microorganisms that confer health benefits when administered in adequate quantities and synbiotics, which pair probiotics with prebiotic substrates, have been investigated as means to restore microbial balance, enhance SCFA production, reduce uremic toxin generation, and attenuate systemic inflammation in CKD (Chen et al., 2019; Tsuji et al., 2024; Wakino et al., 2025). Complementary approaches, including dietary modification, prebiotic supplementation, FMT, targeted pharmacological agents, and defecation regulators, further extend this therapeutic paradigm (Tsuji et al., 2024; Wakino et al., 2025).

This narrative review provides a comprehensive synthesis of the gut–kidney axis in CKD, examining the mechanisms of dysbiosis, the pathophysiological roles of gut-derived uremic toxins and SCFAs, and the evidence for therapeutic interventions targeting this axis, with particular emphasis on probiotics and synbiotics. Although several reviews have discussed the relationship between gut microbiota dysbiosis and CKD progression, many have focused primarily on individual aspects of the gut–kidney axis, such as uremic toxin production, inflammatory pathways, or specific microbiota-targeted interventions. Furthermore, the rapidly expanding body of evidence regarding probiotics, synbiotics, short-chain fatty acids, fecal microbiota transplantation, and emerging microbiome-modulating therapies has not been comprehensively integrated in a single up-to-date narrative review. Therefore, a clear synthesis of current mechanistic insights and therapeutic evidence is needed to better understand the clinical relevance of gut microbiota modulation in CKD. This narrative review aims to address this gap by providing a comprehensive and updated overview of the gut–kidney axis, the role of microbial metabolites in CKD pathogenesis, and the current evidence supporting microbiota-based interventions, with particular emphasis on probiotics and synbiotics as potential adjunctive therapeutic strategies.

2. METHODS

This narrative review was designed to synthesize current evidence on the gut–kidney axis in chronic kidney disease (CKD) and evaluate therapeutic strategies targeting gut microbiota dysbiosis, with emphasis on probiotics and synbiotics. A narrative approach was selected to integrate mechanistic, preclinical, and clinical evidence into a cohesive conceptual framework addressing pathophysiology and therapeutic implications. A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library through April 2025, employing Medical Subject Headings (MeSH) terms and keywords across three domains: (1) CKD-related terms ("chronic kidney disease," "renal insufficiency," "end-stage renal disease," "glomerular filtration rate"); (2) gut–kidney axis mechanisms ("gut microbiota," "dysbiosis," "uremic toxins," "indoxyl sulfate," "p-cresyl sulfate," "TMAO," "short-chain fatty acids," "intestinal barrier," "endotoxemia"); and (3) interventions ("probiotics," "synbiotics," "prebiotics," "Lactobacillus," "Bifidobacterium," "fecal microbiota transplantation," "dietary intervention," "Mediterranean diet," "AST-120"). Boolean operators combined terms across domains, and reference lists of key systematic reviews and meta-analyses were manually screened for additional sources.

Inclusion criteria encompassed peer-reviewed English-language articles including randomized controlled trials (RCTs), systematic reviews, meta-analyses, observational studies, and mechanistic investigations examining gut microbiota composition, gut-derived uremic toxins, or gut–kidney axis pathophysiology in CKD patients (stages 1–5, including dialysis-dependent populations), studies evaluating probiotics, synbiotics, prebiotics, or other gut-targeted therapies, and mechanistic studies elucidating roles of short-chain fatty acids, intestinal barrier dysfunction, or inflammation in renal pathophysiology. Exclusion criteria included non-English publications, studies on acute kidney injury without chronic sequelae, conference abstracts, non-peer-reviewed commentaries, and studies in non-CKD populations lacking clear mechanistic relevance. Study selection prioritized high-quality evidence, including large-scale RCTs, recent meta-analyses (Chen et al., 2023; Cooper et al., 2023; Liu et al., 2022), clinical practice guidelines (KDIGO 2024), and seminal mechanistic studies, while incorporating representative preclinical and observational data for mechanistic context.

Study screening and selection were performed in a stepwise manner. Following database searches, duplicate records were removed, and titles and abstracts were screened for relevance to the objectives of the review. Full-text articles were subsequently assessed against predefined inclusion and exclusion criteria. Priority was given to studies published within the last ten years, although earlier landmark studies were retained when considered essential for understanding the development of the field. To enhance methodological transparency and reduce selection bias, study selection focused on evidence with clear relevance to CKD pathophysiology, gut microbiota alterations, or microbiota-targeted interventions.

Because this study was conducted as a narrative review rather than a systematic review, formal risk-of-bias tools were not applied. Nevertheless, the methodological quality and clinical relevance of included studies were critically evaluated based on study design, sample size, methodological rigor, consistency of findings, and relevance to the review objectives. Greater weight was assigned to randomized controlled trials, systematic reviews, meta-analyses, clinical practice guidelines, and well-established mechanistic studies. Observational and preclinical studies were primarily used to provide biological context and support mechanistic interpretations

Data extraction focused on study design, CKD stage, intervention characteristics (formulations, dosing, duration), outcomes (microbiota composition, uremic toxin levels, inflammatory markers, renal function), and mechanistic insights. Evidence was synthesized thematically across six domains: CKD epidemiology and pathophysiology; gut–kidney axis mechanisms and dysbiosis; gut-derived uremic toxins; protective roles of short-chain fatty acids; therapeutic strategies; and clinical evidence for probiotics and synbiotics. Within each domain, findings were critically appraised for validity, consistency, and clinical applicability, with attention to reconciling discrepancies between mechanistic and clinical evidence, with quality prioritization favoring Cochrane reviews, KDIGO guidelines, and high-impact peer-reviewed publications while acknowledging inherent limitations of narrative methodology including potential selection bias and absence of quantitative synthesis.

Although this review followed a structured literature search and evidence selection strategy, it remains subject to the inherent limitations of narrative reviews, including the absence of formal quantitative synthesis and the potential for selection bias. To mitigate these limitations, transparent eligibility criteria, predefined thematic domains, and prioritization of high-quality evidence sources were applied throughout the review process.

3. RESULTS AND DISCUSSION

CKD is defined as structural or functional renal abnormalities persisting for three months or longer with implications for health, classified using the KDIGO CGA framework integrating Cause (C), GFR category (G1–G5), and albuminuria category (A1–A3). Diagnosis requires confirmation on at least two occasions separated by 90 days (Stevens et al., 2024).

CKD currently affects an estimated 673 million adults worldwide, with approximately 1.5 million CKD-related deaths recorded annually according to GBD 2021 data (Wang et al., 2025). Incidence has increased steadily since 1990, driven by the global rise in diabetes mellitus and hypertension, which together account for approximately half of all CKD-attributable disability-adjusted life years (DALYs) (Wang et al., 2025). Awareness remains critically low, with fewer than 10% of affected individuals aware of their diagnosis (Stevens et al., 2024). In Indonesia, the 2018 Riskesdas survey and 2023 SKI survey reported CKD prevalences of 0.5% and 0.18%, respectively, with CKD projected to rise from the twelfth to fifth leading cause of death by 2040 (Hustrini et al., 2022).

CKD progression is driven by interrelated mechanisms: intraglomerular hypertension and RAAS activation perpetuate glomerulosclerosis and fibrosis; hyperglycemia-driven formation of AGEs and ROS damages glomerular and tubular structures; and sustained NF-κB-mediated inflammatory signaling producing IL-6, TNF-α, and TGF-β promotes myofibroblast activation, nephron loss, and progressive fibrosis (Hustrini et al., 2022; Kadatane et al., 2023; Stevens et al., 2024; Tzatzaki et al., 2024). Cardiovascular disease, the principal cause of CKD-related mortality, is accelerated by dyslipidemia, endothelial dysfunction, and chronic low-grade inflammation sustained by uremic toxin accumulation (Stevens et al., 2024; Tzatzaki et al., 2024; Wang et al., 2025). Bidirectional cardiorenal interactions further amplify injury: uremic toxin burden, volume overload, and systemic inflammation drive left ventricular hypertrophy present in over 75% of advanced CKD patients—while reduced cardiac output worsens renal perfusion (Stevens et al., 2024; Tzatzaki et al., 2024; Williams et al., 2023). As GFR declines, progressive accumulation of nitrogenous uremic solutes inadequately cleared by the failing kidney compounds systemic oxidative stress and perpetuates immune dysregulation, establishing the biochemical substrate through which the gut–kidney axis

exerts its pathophysiological influence (Stevens et al., 2024; Tzatzaki et al., 2024; Wang et al., 2025).

The gut–kidney axis: physiology and dysbiosis in CKD

The human gastrointestinal tract harbors a vast and metabolically active microbial community, comprising an estimated 1013–1014 microorganisms dominated by the bacterial phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria (Czaja-Stolc et al., 2025; Loscalzo et al., 2022; Wakino et al., 2025). Keystone commensal genera including Lactobacillus, Bifidobacterium, Ruminococcus, Prevotella, and Faecalibacterium perform essential functions: fermentation of non-digestible dietary polysaccharides and resistant starch to produce SCFAs; synthesis of vitamins B and K; maintenance of intestinal epithelial barrier integrity; and bidirectional modulation of local and systemic immunity through interactions with gut-associated lymphoid tissue (GALT), regulatory T cells (Treg), and secretory immunoglobulin A (sIgA) (Czaja-Stolc et al., 2025; Loscalzo et al., 2022; Wakino et al., 2025).

The gut–kidney axis describes a bidirectional communication network through which the kidney and gastrointestinal microbiota exert reciprocal regulatory influence on one another. Renally excreted urea and uremic solutes diffuse into the gastrointestinal lumen, reshaping its intraluminal chemical environment and selectively favoring urease-expressing, proteolytic taxa over health-promoting commensals. Conversely, gut-derived metabolites, endotoxins, and microbial signals traverse the intestinal barrier to modulate renal function, immune activation, tubular injury, and fibrosis. This axis is now recognized not only as a mechanism of disease amplification in CKD, but as a therapeutically actionable target of growing clinical relevance (Tsuji et al., 2024; Wakino et al., 2025). (Figure 1).

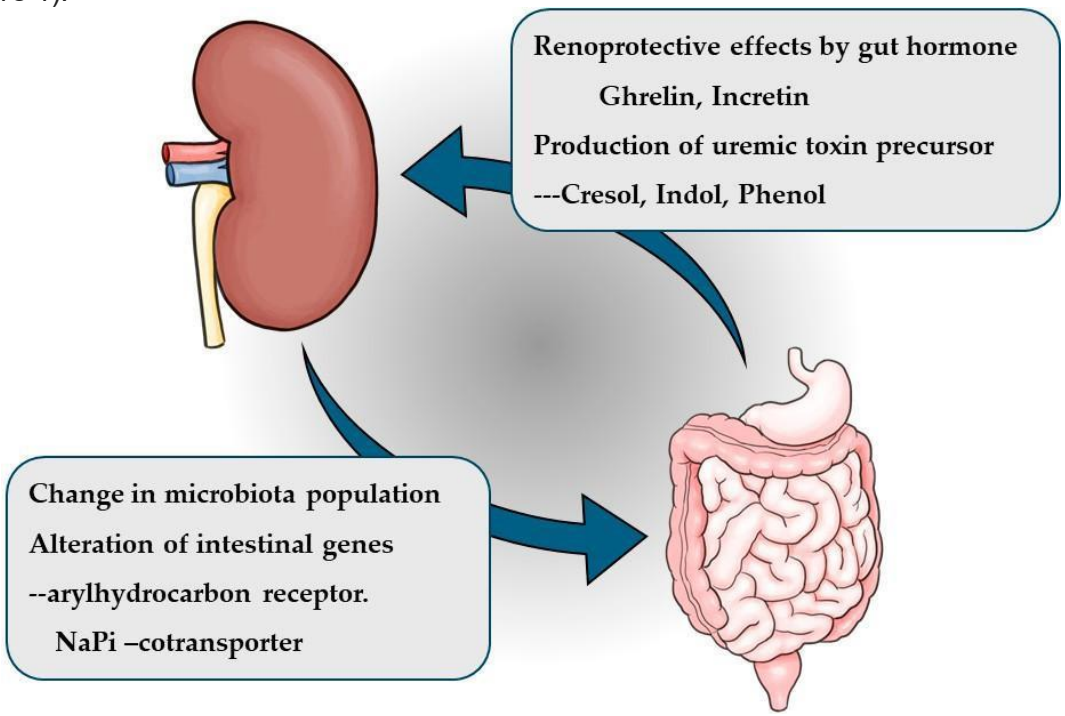


Figure 1. Bidirectional schematic of the gut–kidney axis, illustrating interactions between gut microbiota dysbiosis, uremic toxin production, intestinal barrier disruption, and systemic inflammation in CKD. Adapted from Wakino et al. (2025).

Gut microbiota dysbiosis in CKD encompasses both compositional and functional perturbations. Protective anaerobic genera including Lactobacillus, Bifidobacterium, Prevotella, Roseburia, and Faecalibacterium prausnitzii are consistently depleted, while potentially pathogenic taxa such as Proteobacteria, Enterococcus, Bacteroides, and Clostridium are overrepresented (Li et al., 2024; Młynarska et al., 2024; Tsuji et al., 2024). Multiple mechanisms underlie this dysbiosis. Elevated circulating urea diffuses into the gastrointestinal lumen, where bacterial urease enzymes hydrolyze it to ammonia, raising intraluminal pH and selectively favoring urease-expressing organisms (Kadatane et al., 2023; Tsuji et al., 2024). Uremic metabolic acidosis, restricted dietary fiber intake (often recommended to limit potassium), widespread use of oral iron supplements and phosphate binders, and reduced intestinal motility with prolonged colonic transit further perturb microbial ecology (Jackson et al., 2024; Kadatane et al., 2023). These changes collectively diminish SCFA production, impair intestinal barrier integrity, and amplify generation of gut-derived uremic toxins (Cahyadi et al., 2023; Chen et al., 2019; Wakino et al., 2025).

The functional consequence of this dysbiosis increased intestinal mucosal permeability ("leaky gut") facilitates translocation of LPS and other pathogen-associated molecular patterns (PAMPs) into the systemic circulation, activating innate immune pathways and sustaining chronic inflammation and oxidative stress (Chen et al., 2019; Kadatane et al., 2023; Wakino et al., 2025).

Intestinal epithelial barrier disruption in CKD patients is evidenced by reduced expression of tight junction proteins ZO-1, occludin, and claudin-1, and by measurably elevated circulating endotoxin levels relative to healthy controls (Tsuji et al., 2024; Wakino et al., 2025). DNA from Klebsiella spp., Proteus spp., Escherichia spp., and related genera has been detected in the bloodstream of approximately 20% of ESRD patients, underscoring the clinical significance of this barrier failure (Hsu et al., 2022; Krukowski et al., 2023). These interacting perturbations create a vicious cycle in which renal dysfunction amplifies dysbiosis, and dysbiosis worsens renal injury (Tsuji et al., 2024; Wakino et al., 2025).

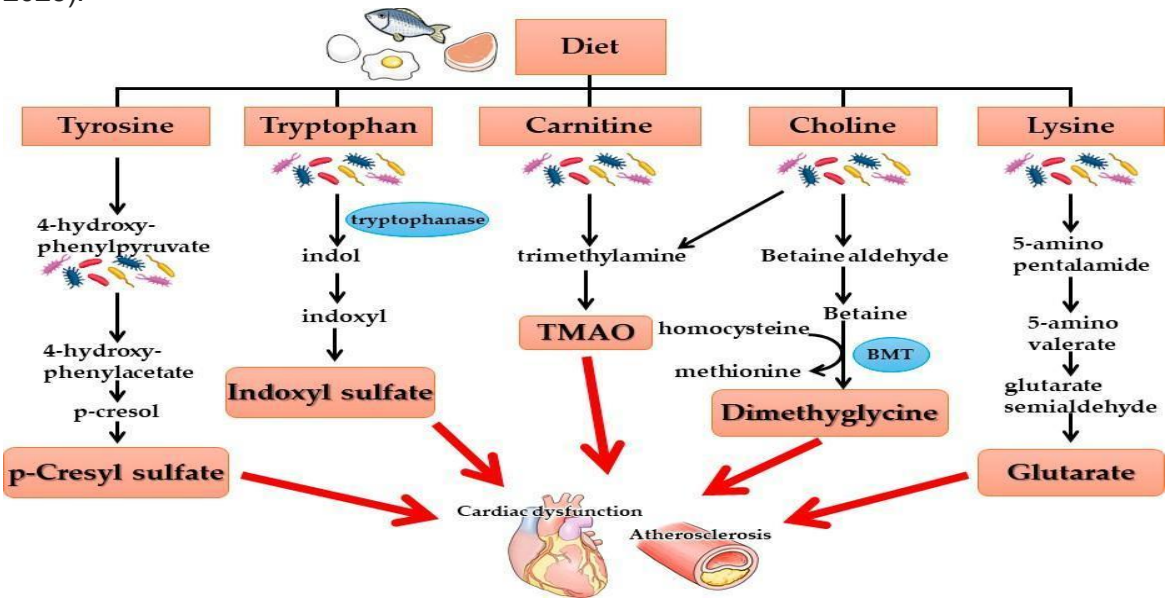


Figure 2. Principal gut-derived uremic toxins, including IS, pCS, and TMAO and their metabolic origins from bacterial fermentation of dietary amino acids and other substrates. Adapted from Wakino et al. (2025).

Gut microbiota–derived uremic toxins

Gut-derived uremic toxins are a chemically diverse group of compounds generated through bacterial fermentation of dietary proteins and amino acids. In CKD, their accumulation is driven by two converging factors: increased gut microbial production due to dysbiosis, and reduced renal clearance due to declining GFR. The majority of these compounds circulate predominantly bound to plasma proteins particularly albumin which limits their removal by conventional hemodialysis and contributes to their progressive accumulation (Tsuji et al., 2024; Wakino et al., 2025). The three most extensively studied and clinically significant toxins are IS, pCS, and TMAO.

Indoxyl Sulfate (IS)

IS is synthesized via a two-step microbial-hepatic pathway: intestinal bacteria principally Bacteroides and related taxa metabolize dietary tryptophan to indole, which is absorbed into the portal circulation and sulfated by hepatic sulfotransferases to form IS (Cahyadi et al., 2023; Kadatane et al., 2023; Wakino et al., 2025). Circulating IS binds tightly to albumin, limiting its removal by conventional hemodialysis, and accumulates progressively as tubular secretory capacity declines with falling GFR. IS induces oxidative stress in renal tubular cells by stimulating ROS generation and upregulating pro-fibrotic mediators (TGF-β, CTGF), thereby promoting tubular cell apoptosis and interstitial fibrosis processes that directly contribute to nephron loss and CKD progression (Chen et al., 2019; Kadatane et al., 2023; Tsuji et al., 2024). In addition, IS exerts significant cardiovascular toxicity: circulating IS impairs endothelial function, promotes atherogenesis, and has been independently associated with elevated IL-6 levels and heightened cardiovascular mortality risk in CKD patients (Haller, 2018; Wakino et al., 2025).

p-Cresyl Sulfate (pCS)

Like IS, pCS circulates predominantly albumin-bound and accumulates progressively with declining GFR properties that render it poorly dialyzable and clinically significant across all CKD stages. pCS originates from intestinal bacterial metabolism of the aromatic amino acids tyrosine and phenylalanine, yielding p-cresol, which undergoes hepatic sulfation to its final form (De Mauri et al., 2022; Inoshita et al., 2023). pCS promotes renal tubular oxidative stress and inflammation, induces endothelial dysfunction, and drives atherogenesis. Elevated pCS levels correlate independently with all-cause and cardiovascular mortality in CKD populations (De Mauri et al., 2022; Krukowski et al., 2023; Piccoli et al., 2023). Notably, both IS and pCS contribute to vascular calcification through mechanisms involving oxidative stress, NF-κB activation, and osteogenic differentiation of vascular smooth muscle cells further amplifying cardiovascular risk in CKD (Matsui et al., 2023; Piccoli et al., 2023).

Trimethylamine-N-Oxide (TMAO)

TMAO is generated through a hepatic-microbial metabolic circuit: gut bacteria convert dietary choline, carnitine, and lecithin abundant in red meat, eggs, and dairy products to trimethylamine (TMA), which is subsequently oxidized by hepatic flavin monooxygenase 3 (FMO3) to TMAO. High plasma TMAO concentrations are strongly associated with increased cardiovascular risk, mediated through promotion of macrophage foam cell formation, platelet hyperreactivity, and vascular pro-inflammatory signaling. TMAO also potentiates renal inflammatory injury by activating NF-κB-dependent inflammatory pathways. Because CKD patients frequently harbor expanded communities of TMA-producing bacteria alongside reduced renal clearance of TMAO, this toxin accumulates to particularly high levels in this population (Li et al., 2022; Otani et al., 2023; Ranganathan & Anteyi, 2022).

Short-chain fatty acids: central protective mediators of the gut–kidney axis

SCFAs produced through saccharolytic fermentation of dietary fiber by commensal bacteria represent the principal endogenous protective axis within the gut–kidney relationship. Acetate, propionate, and butyrate exert complementary renoprotective and intestinal-protective effects at multiple levels (Czaja-Stolc et al., 2025; Ebrahim et al., 2022; Ranganathan & Anteyi, 2022).

At the intestinal epithelial level, butyrate functioning both as a nutrient for colonocytes and as an HDAC inhibitor upregulates expression of tight junction proteins (occludin, claudin, ZO-1), reducing paracellular permeability, limiting endotoxin translocation, and preserving mucosal homeostasis (Chen et al., 2023; Wakino et al., 2025; Yu et al., 2020). SCFAs concurrently stimulate Treg differentiation via HDAC inhibition and GPR41/43/109a activation, suppressing mucosal and systemic pro-inflammatory signaling including NF-κB-dependent transcription of IL-6 and TNF-α (Floch et al., 2017; Matsui et al., 2023; Otani et al., 2023; Yu et al., 2020).

At the renal level, SCFAs activate GPR41 and GPR43 on tubular and interstitial cells, attenuating oxidative stress and fibrogenic signaling (Matsui et al., 2023; Otani et al., 2023). A seminal experimental study by Li et al. demonstrated that Faecalibacterium prausnitzii attenuates CKD progression in mice through a butyrate-mediated renal GPR43 signaling axis, identifying this specific microbial metabolite pathway as a candidate therapeutic target (Li et al., 2022). SCFAs also stimulate glucagon-like peptide-1 (GLP-1) secretion from intestinal L-cells, enhancing glucose metabolism regulation and exerting systemic anti-inflammatory effects (Wakino et al., 2025; Williams et al., 2023).

In CKD, this protective SCFA axis is undermined by dysbiosis-driven loss of saccharolytic species and iatrogenic dietary fiber restriction, rendering restoration of SCFA production a central objective of gut–kidney axis therapy (Matsui et al., 2023; Piccoli et al., 2023).

The depletion of SCFA-producing commensals and impaired barrier integrity in CKD facilitates the translocation of LPS and other pathogen-associated molecular patterns (PAMPs) into the systemic circulation. LPS engages Toll-like receptor 4 (TLR4) on monocytes, macrophages, and endothelial cells, triggering NF-κB-mediated release of IL-6, TNF-α, and related cytokines that promote glomerulosclerosis, tubular injury, and vascular damage (Chen et al., 2019; Kadatane et al., 2023; Wakino et al., 2025). Endotoxin reaching the kidney directly activates tubular and glomerular TLRs, initiating leukocyte infiltration and reactive oxygen species (ROS) generation. Oxidative stress amplified by circulating IS, pCS, and TMAO damages mitochondrial function, induces lipid peroxidation, and accelerates tubular apoptosis and fibrosis (Chen et al., 2019; Kadatane et al., 2023; Tsuji et al., 2024; Wakino et al., 2025). Concurrently, reduced dietary fiber intake due to iatrogenic potassium restriction or low plant-food consumption further depletes the fermentation substrate for saccharolytic bacteria, worsening the SCFA deficit, amplifying barrier permeability, and compounding uremic toxin generation (Koppe & Soulage, 2022; Młynarska et al., 2024; Ranganathan & Anteyi, 2022). Together, these overlapping mechanisms create a self-reinforcing cycle in which the inflamed renal microenvironment further perturbs gut ecology, and gut-derived insults accelerate renal injury (Tsuji et al., 2024; Wakino et al., 2025).

Additional metabolic contributors further potentiate this inflammatory milieu. Advanced glycation end-products (AGEs), accumulating in CKD through reduced renal clearance and high-temperature dietary intake, bind receptor for AGE (RAGE) to activate pro-inflammatory and oxidative stress pathways, directly compromising intestinal barrier integrity and amplifying LPS translocation into the systemic circulation (De Mauri et al., 2022; Koppe & Soulage, 2022; Lázaro et al., 2024; Ranganathan & Anteyi, 2022; T. Wang

et al., 2023). Conversely, β-hydroxybutyrate the principal ketone body produced during carbohydrate restriction functions as an endogenous HDAC inhibitor with anti-inflammatory properties mechanistically analogous to butyrate, and ketogenic dietary patterns may enrich SCFA-producing microbial taxa; however, the long-term safety of sustained ketogenic diets in CKD warrants careful consideration given the risk of exacerbating metabolic acidosis (D'Alessandro et al., 2023; Liu et al., 2022).

Therapeutic strategies targeting the gut–kidney axis

The growing understanding of gut–kidney axis pathophysiology has catalyzed the development of multiple therapeutic strategies aimed at restoring microbial homeostasis, reducing uremic toxin burden, and attenuating systemic inflammation in CKD (Tsuji et al., 2024; Wakino et al., 2025). These approaches summarized in Figure 3 and Table 1 range from dietary and microbiota-based interventions to pharmacological agents and defecation modulators, and are increasingly considered as adjuncts to standard CKD care.

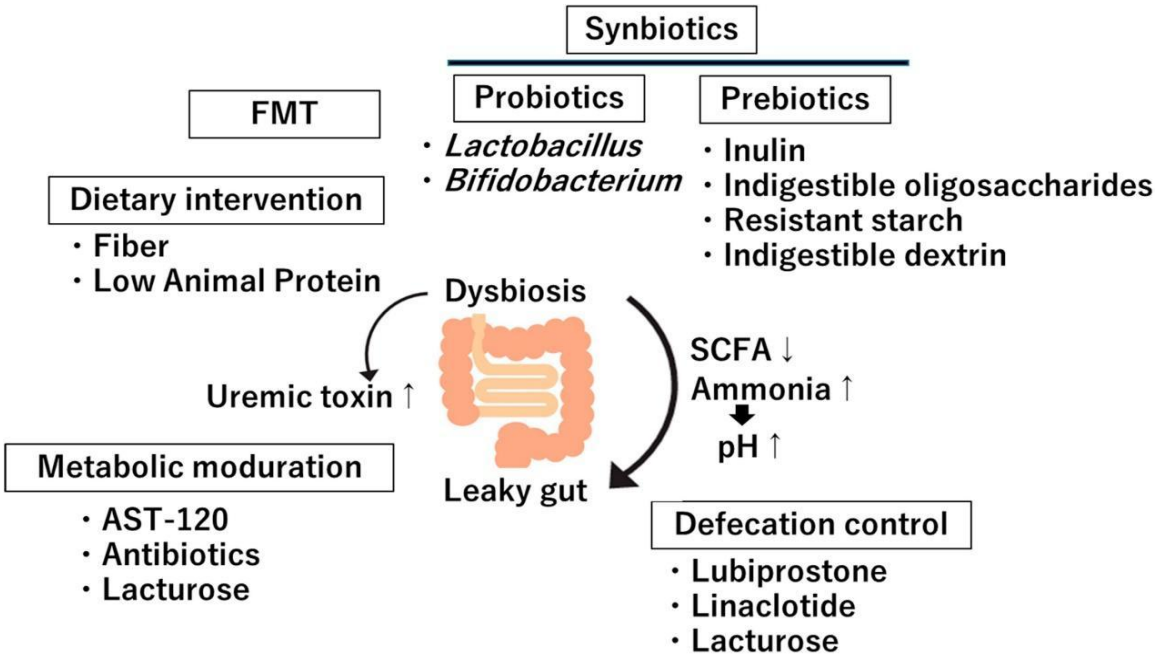


Figure 3. Overview of therapeutic strategies targeting the gut–kidney axis in CKD, organized by mechanism of action and intervention type. Adapted from Tsuji et al. (2024).

Table 1. Summary of therapeutic strategies targeting the gut–kidney axis in CKD, with mechanisms and principal outcomes.

Therapy	Intervention	Outcome
Dietary Interventions	High-fiber diet	Increases SCFA-producing bacteria
	Low red/processed meat intake	Reduces uremic toxins
	Plant-based diet	Reduces uremic toxins
Probiotics	*Lactobacillus, Bifidobacterium*	Reduces toxin levels; improves gut barrier integrity; reduces inflammatory markers

Prebiotics	Inulin, fructo-oligosaccharides, resistant starch, non-digestible dextrin, galacto-oligosaccharides	Increases beneficial bacteria; increases SCFA production
FMT	FMTT	Improves gut barrier integrity; reduces proinflammatory metabolites
Metabolic Modulation	AST-120	Reduces indoxyl sulfate
	Vancomycin	Reduces indoxyl sulfate and p-cresyl sulfate
	SGLT-2 inhibitors	Reduces gut-derived uremic toxins
Defecation Modulation	Lubiprostone	Reduces gut-derived uremic toxins
	Lactulose	Reduces indoxyl sulfate

SCFA, short-chain fatty acids; FMT, fecal microbiota transplantation; AST-120, spherical activated carbon; SGLT-2, sodium-glucose cotransporter-2; TMAO, trimethylamine N-oxide. Adapted from Tsuji et al. (2024).

Probiotics and synbiotics

Probiotics are live microorganisms that confer health benefits when administered in adequate amounts; commonly employed strains in CKD research include Lactobacillus acidophilus, L. rhamnosus, L. casei, Bifidobacterium longum, B. bifidum, B. breve, Streptococcus thermophilus, and the yeast Saccharomyces boulardii. Synbiotics pair a probiotic with a prebiotic substrate such as inulin, FOS, or GOS to synergistically enhance microbial colonization efficiency, augment SCFA production, and reduce uremic toxin burden beyond what either component achieves alone (Chen et al., 2023; Tsuji et al., 2024; Wakino et al., 2025).

Clinical evidence for these interventions in CKD is growing but requires critical appraisal. A 2023 meta-analysis by Chen et al. of RCTs in dialysis patients reported significant reductions in serum IS, pCS, CRP, and IL-6 with probiotic or synbiotic supplementation, alongside improvements in albumin and gastrointestinal outcomes (Chen et al., 2023). A Cochrane systematic review by Cooper et al. (2023), the most comprehensive appraisal to date, confirmed reductions in uremic toxins and inflammatory markers but found insufficient evidence for clinically meaningful improvements in GFR or hard renal endpoints—such as progression to ESKD or cardiovascular events (Cooper et al., 2023). De Mauri et al. demonstrated that a synbiotic-supplemented low-protein diet significantly reduced IS and pCS levels and improved inflammatory parameters in patients with advanced CKD (stages 4–5) (De Mauri et al., 2022). A meta-analysis by Liu et al.

encompassing 32 RCTs similarly identified beneficial effects on uremic toxins and inflammatory markers, with synbiotics demonstrating superior efficacy compared to probiotics alone (Liu et al., 2022).

To facilitate comparison of the available clinical evidence, key studies evaluating probiotics and synbiotics in CKD are summarized in Table 2. The table highlights study design, patient population, intervention characteristics, and principal outcomes reported across major randomized controlled trials, systematic reviews, and meta-analyses.

Table 2. Key clinical evidence on probiotics and synbiotics in chronic kidney disease.

Study	Design	Population	Intervention	Duration	Main Findings	Strength of Evidence
Liu et al., 2022	Meta-analysis (32 RCTs)	CKD patients (various stages)	Probiotics and synbiotics	Variable	Reduced IS, pCS, CRP, and inflammatory markers; synbiotics showed greater efficacy than probiotics alone	High
Chen et al., 2023	Meta-analysis of RCTs	Dialysis patients	Probiotics and synbiotics	Variable	Significant reductions in IS, pCS, IL-6, and CRP; improved albumin levels and gastrointestinal symptoms	High
Cooper et al., 2023	Cochrane Systematic Review	CKD and dialysis patients	Probiotics, prebiotics, synbiotics	Variable	Improvements in surrogate biomarkers but insufficient evidence for improvement in eGFR, ESKD progressi	Very High

					on, or mortality	
De Mauri et al., 2022	Randomized Clinical Trial	CKD stages 4–5	Synbiotic-supplemented low-protein diet	Several months	Reduced IS and pCS levels and improved inflammatory parameters	Moderate
Ebrahim et al., 2022	Randomized Clinical Trial	CKD stages 3–5	Beta-glucan prebiotic supplementation	Several weeks	Improved gut microbiota composition and reduced inflammatory markers	Moderate
Arteaga-Muller et al., 2024	Pilot Clinical Study	CKD patients	Fecal microbiota transplantation	Short-term	Improved inflammatory markers and modest kidney function improvement	Low–Moderate

As shown in Table 2, most studies consistently report beneficial effects of probiotics and synbiotics on gut microbiota composition, uremic toxin concentrations, and inflammatory biomarkers. The strongest evidence derives from systematic reviews and meta-analyses, which demonstrate reductions in indoxyl sulfate, p-cresyl sulfate, C-reactive protein, and interleukin-6. However, evidence supporting improvements in hard clinical outcomes, including decline in kidney function, progression to end-stage kidney disease, cardiovascular events, and mortality, remains limited and inconsistent. These findings suggest that microbiota-targeted interventions may serve as promising adjunctive therapies, although further large-scale and long-term randomized controlled trials are required to establish their clinical effectiveness.

Despite these encouraging findings, several limitations constrain clinical translation: trials are predominantly short-term, enroll small samples, employ heterogeneous microbial formulations, and rely on surrogate endpoints. Optimal strain selection, dosing regimens, duration of supplementation, and CKD-stage-specific applications remain to be established through well-designed, adequately powered long-term RCTs (Cooper et al., 2023).

Overall, current evidence consistently supports the beneficial effects of probiotics and synbiotics on gut microbiota composition, uremic toxin concentrations, and inflammatory biomarkers in CKD patients. The strongest evidence originates from

systematic reviews and meta-analyses demonstrating improvements in surrogate biochemical outcomes. However, the consistency of findings regarding renal function preservation, cardiovascular outcomes, hospitalization, and mortality remains limited due to heterogeneity in study populations, microbial formulations, treatment duration, and outcome measures. Consequently, while microbiota-targeted interventions appear promising as adjunctive therapies, their impact on hard clinical endpoints remains insufficiently established

Prebiotics

Prebiotics are non-digestible dietary compounds that selectively promote the growth and metabolic activity of health-promoting gut bacteria, principally SCFA-producing *Lactobacillus, Bifidobacterium, and F. prausnitzii* species. Key prebiotic categories include non-starch polysaccharides (inulin, pectin), resistant oligosaccharides (FOS, GOS, XOS), and resistant starches, all fermentable substrates that drive colonic SCFA production (Tsuji et al., 2024; Wakino et al., 2025).

In CKD, prebiotic supplementation consistently increases *Bifidobacterium and F. prausnitzii* abundance, augments SCFA production, and reduces uremic toxin levels. Ebrahim et al. (2022) demonstrated in an RCT that beta-glucan supplementation significantly improved gut microbiota profiles and modestly reduced inflammatory markers in CKD stages 3–5 (Ebrahim et al., 2022). Inulin-type prebiotics and resistant starches similarly increase fecal SCFA concentrations and reduce IS and pCS levels (Koppe & Soulage, 2022; Ranganathan & Anteyi, 2022).

Dietary interventions

Diet is the primary determinant of gut microbiota composition and function, making dietary modification a foundational strategy in gut–kidney axis therapy (Tsuji et al., 2024; Wakino et al., 2025). High-fiber, plant-based diets enrich SCFA-producing taxa, reduce proteolytic fermentation of dietary proteins, and diminish the substrate available for uremic toxin synthesis. Conversely, diets high in red or processed meat provide abundant tryptophan, tyrosine, phenylalanine, and choline, promoting IS, pCS, and TMAO generation (Koppe & Soulage, 2022; Ranganathan & Anteyi, 2022; Tsuji et al., 2024; Wakino et al., 2025).

Plant-based diets and the Mediterranean dietary pattern are particularly beneficial in this context, providing ample prebiotic fiber, polyphenols, and unsaturated fatty acids while restricting dietary AGE content and animal protein (D'Alessandro et al., 2023; Kwon et al., 2024; Podadera-Herreros et al., 2024; Wang et al., 2023; Zarantonello & Brunori, 2023). A secondary analysis of the CORDIOPREV RCT demonstrated that Mediterranean diet adherence was associated with preserved kidney function in patients with coronary artery disease, type 2 diabetes, and obesity (Podadera-Herreros et al., 2024). A pilot crossover RCT by Kwon et al. confirmed the safety and clinical feasibility of a CKD-adapted Mediterranean diet and reported improvements in gut microbiota diversity and inflammatory parameters (Kwon et al., 2024). Observational data further support associations between plant-based dietary patterns and lower uremic toxin levels in CKD populations (Wang et al., 2023; Zarantonello & Brunori, 2023).

Practical implementation of these dietary strategies must account for CKD-specific nutritional constraints, including the need to limit potassium-rich plant foods in patients with hyperkalemia. The CKD-modified Mediterranean diet (MedRen) addresses these concerns by tailoring fiber and macronutrient targets to renal function stage (D'Alessandro et al., 2023). Protein diets supplemented with essential amino acid ketoacid analogs

reduce the protein-derived generation of IS, pCS, and ammonia while preserving nutritional adequacy (Bellizzi et al., 2022; Otani et al., 2023).

Fecal Microbiota Transplantation (FMT)

FMT involves the transfer of fecal material from a healthy donor into the recipient's gastrointestinal tract to reconstitute a balanced microbial community. While well-established for recurrent Clostridioides difficile infection, its application in CKD remains investigational (Tsuji et al., 2024; Wakino et al., 2025). Preclinical studies demonstrate that FMT in CKD animal models reduces renal inflammation, normalizes circulating uremic toxin levels, and restores intestinal barrier integrity (Arteaga-Muller et al., 2024). A clinical pilot study by Arteaga-Muller et al. (2024) reported modest improvements in kidney function and inflammatory markers in CKD patients undergoing FMT, although the sample size was insufficient to draw definitive conclusions (Arteaga-Muller et al., 2024).

The principal barriers to broader FMT application in CKD include risks of pathogen transmission, unpredictable immunological responses, absence of standardized protocols, and limited long-term safety evidence particularly relevant in the immunosuppressed uremic patient (Tsuji et al., 2024; Wakino et al., 2025). Nonetheless, FMT represents a potentially transformative approach in the modulation of the gut–kidney axis, warranting further rigorous investigation.

Pharmacological modulation

Pharmacological agents targeting gut-derived uremic toxins complement microbiota-based strategies through direct intraluminal adsorption or systemic drug effects on microbial composition. The oral carbon adsorbent AST-120 (spherical activated charcoal) adsorbs indole and IS precursors within the intestinal lumen, reducing systemic IS accumulation. In CKD animal models, AST-120 restored Lactobacillus abundance, normalized tight junction protein expression (occludin, ZO-1, claudin-1), and significantly reduced serum IS and pro-inflammatory cytokines (Hsu et al., 2022). Sevelamer, a phosphate-binding resin, has been shown to reduce circulating p-cresol concentrations in CKD patients as a secondary benefit beyond its primary phosphate-binding function (Tsuji et al., 2024; Wakino et al., 2025). Translating these preclinical findings to clinical outcomes has proven difficult: the large EPPIC trial failed to demonstrate a significant effect of AST-120 on GFR decline, whereas a Japanese multicenter RCT enrolling 465 participants over three years did report significantly attenuated eGFR decline, suggesting that adherence and patient population characteristics critically influence outcomes (Tsuji et al., 2024; Wakino et al., 2025). Oral vancomycin has demonstrated reductions in IS and pCS in ESRD patients, though antimicrobial resistance concerns limit its clinical utility (Tsuji et al., 2024; Wakino et al., 2025).

Several pharmacological agents routinely used in CKD management also exert secondary gut microbiota effects that may partially mediate their established renoprotective and cardioprotective benefits. SGLT2 inhibitors particularly canagliflozin increase luminal glucose delivery to the distal colon through partial inhibition of intestinal SGLT1, enriching saccharolytic bacteria including Lactobacillus species, restoring tight junction protein expression, and reducing serum IS and hippuric acid levels in experimental models (Matsui et al., 2023). These microbiota-mediated effects raise the hypothesis that a component of SGLT2 inhibitor efficacy operates via the gut–kidney axis a mechanism warranting prospective investigation in human trials. Other pharmacological classes with documented microbiota-modifying properties relevant to CKD including metformin, statins, and proton pump inhibitors represent an important area for future

investigation regarding both potential therapeutic synergies and adverse compositional effects (Tsuji et al., 2024; Wakino et al., 2025).

Defecation modulation

Constipation, highly prevalent in CKD due to diminished mesenteric blood flow, polypharmacy, iatrogenic dietary fiber restriction, and dysbiosis-related motility impairment, independently predicts CKD progression and ESKD by prolonging colonic transit, amplifying proteolytic fermentation, and increasing uremic toxin precursor retention (Wakino et al., 2025). Several agents targeting colonic motility confer gut–kidney axis benefits: lubiprostone, a selective chloride channel activator, reduced circulating uremic toxin levels and restored Lactobacillus and Prevotella abundance alongside intestinal barrier function in CKD animal models; linaclotide similarly attenuated TMAO levels and renal fibrosis in rodent models; and lactulose, beyond its laxative action, functions as a prebiotic substrate acidifying the colonic lumen to trap ammonia as non-absorbable ammonium ion and reducing serum urea and creatinine levels effects confirmed in clinical trial data (Tsuji et al., 2024; Wakino et al., 2025). These converging mechanisms position defecation modulation as an accessible and underutilized component of the therapeutic armamentarium targeting the gut–kidney axis in CKD.

4. CONCLUSION

The gut–kidney axis represents a critical pathophysiological mechanism in chronic kidney disease, wherein gut microbiota dysbiosis perpetuates disease progression through generation of protein-bound uremic toxins, disruption of intestinal barrier integrity, and amplification of systemic inflammation. Depletion of short-chain fatty acid-producing commensals particularly Lactobacillus, Bifidobacterium, and Faecalibacterium prausnitzii alongside expansion of proteolytic bacteria drives accumulation of indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide, which exacerbate oxidative stress, endothelial dysfunction, and cardiovascular injury. Probiotics and synbiotics consistently demonstrate efficacy in restoring microbial equilibrium, augmenting short-chain fatty acid production, and reducing uremic toxin burden and inflammatory markers, with synbiotics exhibiting superior effects through synergistic probiotic-prebiotic interactions. However, evidence supporting clinically meaningful improvements in kidney function or disease progression remains limited, constrained by trial heterogeneity, short follow-up periods, and reliance on surrogate endpoints.

Future research should prioritize adequately powered randomized controlled trials employing standardized probiotic and synbiotic formulations, clearly defined microbial strains, optimized dosing regimens, and extended follow-up periods. Particular emphasis should be placed on evaluating clinically meaningful outcomes, including preservation of glomerular filtration rate, delayed progression to end-stage kidney disease, reduced cardiovascular events, hospitalization rates, quality of life, and mortality. Greater consistency in study design and outcome reporting will facilitate comparison across studies and strengthen the evidence base for clinical decision-making.

From a clinical perspective, modulation of the gut–kidney axis represents a promising adjunctive approach within a comprehensive CKD management strategy. High-fiber, plant-based dietary patterns adapted to CKD-specific nutritional requirements, together with individualized probiotic or synbiotic supplementation, may contribute to reducing systemic inflammation and uremic toxin burden. However, these interventions should currently be viewed as complementary rather than replacement therapies, as robust evidence demonstrating long-term renal and cardiovascular benefits remains insufficient. Integration of microbiota-targeted therapies into routine clinical practice will

require confirmation of efficacy, safety, cost-effectiveness, and patient acceptability through large-scale multicenter clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Agung Susanto contributed to the conceptualization and design of this narrative review, literature search, study selection, critical appraisal of relevant studies, interpretation and synthesis of the available evidence, and preparation of the initial manuscript draft. Muhammad Ifham Hanif contributed to the literature search, study selection, interpretation of the findings, methodological and scientific supervision, and critical revision of the manuscript for important intellectual content. Mentari Maratus Sholihah contributed to the literature search, critical appraisal of relevant studies, interpretation and synthesis of the available evidence, and critical revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript for publication and agreed to be accountable for all aspects of the work.

ACKNOWLEDGEMENT

The authors would like to express their sincere gratitude to Dr. Moewardi Hospital and the Department of Internal Medicine for their institutional support. The authors also thank all colleagues who provided valuable input and support during the development and preparation of this manuscript.

FUNDING

This research received no external funding.

DECLARATION OF ARTIFICIAL INTELLIGENCE USE

No generative artificial intelligence (AI) was used to generate the scientific content, data, analysis, interpretation, or conclusions of this manuscript. The authors take full responsibility for the content of the manuscript.

REFERENCES

Arteaga-Muller, G. Y., Flores-Treviño, S., Bocanegra-Ibarias, P., Robles-Espino, D., Garza-González, E., Fabela-Valdez, G. C., & Camacho-Ortiz, A. (2024). Changes in the progression of chronic kidney disease in patients undergoing fecal microbiota transplantation. *Nutrients,* 16(8), 1109. https://doi.org/10.3390/nu16081109

Bellizzi, V., Garofalo, C., Ferrara, C., & Calella, P. (2022). Ketoanalogue supplementation in patients with non-dialysis diabetic kidney disease: a systematic review and meta-analysis. *Nutrients,* 14(3), 441. https://doi.org/10.3390/nu14030441

Cahyadi, A., Yuwono, A., Subagio, S. W., & Iryaningrum, M. R. (2023). Gut dysbiosis and the role of probiotics in chronic kidney disease. *Journal of the Medical Sciences (Berkala Ilmu Kedokteran),* 55(3). https://doi.org/10.19106/JMedSci005503202309

Chen, C., Wang, J., Li, J., Zhang, W., & Ou, S. (2023). Probiotics, prebiotics, and synbiotics for patients on dialysis: a systematic review and meta-analysis of randomized controlled trials. *Journal of Renal Nutrition,* 33(1), 126–139. https://doi.org/10.1053/j.jrn.2022.04.001

Chen, Y.-Y., Chen, D.-Q., Chen, L., Liu, J.-R., Vaziri, N. D., Guo, Y., & Zhao, Y.-Y. (2019). Microbiome–metabolome reveals the contribution of gut–kidney axis on kidney

disease. *Journal of Translational Medicine*, 17(1), 5. https://doi.org/10.1186/s12967-018-1756-4

Cooper, T. E., Khalid, R., Chan, S., Craig, J. C., Hawley, C. M., Howell, M., Johnson, D. W., Jaure, A., Teixeira-Pinto, A., & Wong, G. (2023). Synbiotics, prebiotics and probiotics for people with chronic kidney disease. *Cochrane Database of Systematic Reviews*, 2023(10). https://doi.org/10.1002/14651858.CD013631.pub2

Czaja-Stolc, S., Potrykus, M., Ruszkowski, J., Styburski, D., Dębska-Ślizień, A., & Małgorzewicz, S. (2025). The associations between nutrition and circulating gut microbiota-derived uremic toxins in patients undergoing kidney replacement therapy: An observational, cross-sectional study. *Clinical Nutrition ESPEN*, 65, 105–114. https://doi.org/10.1016/j.clnesp.2024.11.022

D'Alessandro, C., Giannese, D., Panichi, V., & Cupisti, A. (2023). Mediterranean dietary pattern adjusted for CKD patients: *The MedRen diet*. *Nutrients,* 15(5), 1256. https://doi.org/10.3390/nu15051256

De Mauri, A., Carrera, D., Bagnati, M., Rolla, R., Vidali, M., Chiarinotti, D., Pane, M., Amoruso, A., & Del Piano, M. (2022). Probiotics-supplemented low-protein diet for microbiota modulation in patients with advanced chronic kidney disease (ProLowCKD): Results from a placebo-controlled randomized trial. *Nutrients,* 14(8), 1637. https://doi.org/10.3390/nu14081637

Ebrahim, Z., Proost, S., Tito, R., Raes, J., Glorieux, G., Moosa, M., & Blaauw, R. (2022). The effect of ß-glucan prebiotic on kidney function, uremic toxins and gut microbiome in stage 3 to 5 chronic kidney disease (CKD) predialysis participants: a randomized controlled trial. *Nutrients,* 14(4), 805. https://doi.org/10.3390/nu14040805

Floch, M. H., Ringel, Y., & Walker, W. A. (Eds.). (2017). *The microbiota in gastrointestinal pathophysiology: Implications for human health, prebiotics, probiotics, and dysbiosis.* Elsevier.

Haller, D. (2018). *The gut microbiome in health and disease*. Springer.

Hsu, C.-K., Su, S.-C., Chang, L.-C., Yang, K.-J., Lee, C.-C., Hsu, H.-J., Chen, Y.-T., Sun, C.-Y., & Wu, I.-W. (2022). Oral absorbent AST-120 is associated with compositional and functional adaptations of gut microbiota and modification of serum short and medium-chain fatty acids in advanced CKD patients. *Biomedicines*, 10(9), 2234. https://doi.org/10.3390/biomedicines10092234

Hustrini, N. M., Susalit, E., & Rotmans, J. I. (2022). Prevalence and risk factors for chronic kidney disease in Indonesia: an analysis of the National Basic Health Survey 2018. *Journal of Global Health,* 12, 04074. https://doi.org/10.7189/jogh.12.04074

Inoshita, H., Asaoka, D., Matsuno, K., Yanagisawa, N., Suzuki, Y., & Miyauchi, K. (2023). Cross-sectional study on the association between dietary patterns and sarcopenia in elderly patients with chronic kidney disease receiving conservative treatment. *Nutrients*, 15(23), 4994. https://doi.org/10.3390/nu15234994

Jackson, R., Yao, T., Bulut, N., Cantu-Jungles, T. M., & Hamaker, B. R. (2024). Protein combined with certain dietary fibers increases butyrate production in gut microbiota fermentation. *Food & Function,* 15(6), 3186–3198. https://doi.org/10.1039/D3FO04187E

Kadatane, S. P., Satariano, M., Massey, M., Mongan, K., & Raina, R. (2023). The role of inflammation in CKD. *Cells,* 12(12), 1581. https://doi.org/10.3390/cells12121581

Koppe, L., & Soulage, C. O. (2022). The impact of dietary nutrient intake on gut microbiota in the progression and complications of chronic kidney disease. *Kidney International,* 102(4), 728–739. https://doi.org/10.1016/j.kint.2022.06.025

Krukowski, H., Valkenburg, S., Madella, A.-M., Garssen, J., Van Bergenhenegouwen, J., Overbeek, S. A., Huys, G. R. B., Raes, J., & Glorieux, G. (2023). Gut microbiome

studies in CKD: Opportunities, pitfalls and therapeutic potential. *Nature Reviews Nephrology,* 19(2), 87–101. https://doi.org/10.1038/s41581-022-00647-z

Kwon, Y.-J., Joo, Y. S., Yun, H.-R., Lim, L. R., Yang, J., Lee, H. S., Kim, H.-M., Lee, H., Lee, J. E., & Lee, J.-W. (2024). Safety and impact of the Mediterranean diet in patients with chronic kidney disease: a pilot randomized crossover trial. *Frontiers in Nutrition,* 11, 1463502. https://doi.org/10.3389/fnut.2024.1463502

Lázaro, Á., Vila-Donat, P., & Manyes, L. (2024). Emerging mycotoxins and preventive strategies related to gut microbiota changes: probiotics, prebiotics, and postbiotics – a systematic review. *Food & Function,* 15(18), 8998–9023. https://doi.org/10.1039/D4FO01705F

Li, H.-B., Xu, M.-L., Xu, X.-D., Tang, Y.-Y., Jiang, H.-L., Li, L., Xia, W.-J., Cui, N., Bai, J., Dai, Z.-M., Han, B., Li, Y., Peng, B., Dong, Y.-Y., Aryal, S., Manandhar, I., Eladawi, M. A., Shukla, R., Kang, Y.-M., … Yang, T. (2022). Faecalibacterium prausnitzii Attenuates CKD via butyrate-renal GPR43 Axis. *Circulation Research,* 131(9). https://doi.org/10.1161/CIRCRESAHA.122.320184

Li, J., Shen, Y., Yan, K., Wang, S., Jiao, J., Chi, H., Zhong, J., Dong, Y., & Wang, P. (2024). The compositional and functional imbalance of the gut microbiota in CKD linked to disease patterns. *Journal of Translational Medicine,* 22(1), 773. https://doi.org/10.1186/s12967-024-05578-w

Liu, J., Zhong, J., Yang, H., Wang, D., Zhang, Y., Yang, Y., Xing, G., & Kon, V. (2022). Biotic supplements in patients with chronic kidney disease: meta-analysis of randomized controlled trials. *Journal of Renal Nutrition*, 32(1), 10–21. https://doi.org/10.1053/j.jrn.2021.08.005

Loscalzo, J., Fauci, A. S., Kasper, D. L., Hauser, S. L., Longo, D. L., & Jameson, J. L. (Eds.). (2022). *Harrison's principles of internal medicine (21st edition*). McGraw Hill.

Matsui, A., Yoshifuji, A., Irie, J., Tajima, T., Uchiyama, K., Itoh, T., Wakino, S., & Itoh, H. (2023). Canagliflozin protects the cardiovascular system through effects on the gut environment in non-diabetic nephrectomized rats. *Clinical and Experimental Nephrology,* 27(4), 295–308. https://doi.org/10.1007/s10157-022-02312-y

Młynarska, E., Budny, E., Saar, M., Wojtanowska, E., Jankowska, J., Marciszuk, S., Mazur, M., Rysz, J., & Franczyk, B. (2024). Does the composition of gut microbiota affect chronic kidney disease? molecular mechanisms contributed to decreasing glomerular filtration rate. *International Journal of Molecular Sciences*, 25(19), 10429. https://doi.org/10.3390/ijms251910429

Otani, H., Okada, T., Saika, Y., Sakagashira, M., Oda, H., Ito, Y., Yasuda, T., Kanno, T., Shimazui, M., Yamao, S., Kanazawa, Y., Shimode, M., Otani, M., Ueda, S., Nakao, T., & Yoshimura, A. (2023). Effect of nonsupplemented low-protein diet on the initiation of renal replacement therapy in stage 4 and 5 chronic kidney disease: a retrospective multicenter cohort study in Japan. *Journal of Renal Nutrition*, 33(5), 649–656. https://doi.org/10.1053/j.jrn.2023.05.001

Piccoli, G. B., Cederholm, T., Avesani, C. M., Bakker, S. J. L., Bellizzi, V., Cuerda, C., Cupisti, A., Sabatino, A., Schneider, S., Torreggiani, M., Fouque, D., Carrero, J. J., & Barazzoni, R. (2023). Nutritional status and the risk of malnutrition in older adults with chronic kidney disease – implications for low protein intake and nutritional care: A critical review endorsed by ERN-ERA and ESPEN. *Clinical Nutrition*, 42(4), 443–457. https://doi.org/10.1016/j.clnu.2023.01.018

Podadera-Herreros, A., Arenas-de Larriva, A. P., Gutierrez-Mariscal, F. M., Alcala-Diaz, J. F., Ojeda-Rodriguez, A., Rodriguez-Cantalejo, F., Cardelo, M. P., Rodriguez-Cano, D., Torres-Peña, J. D., Luque, R. M., Ordovas, J. M., Perez-Martinez, P., Delgado-Lista, J., Lopez-Miranda, J., & Yubero-Serrano, E. M. (2024). Mediterranean diet as a

strategy for preserving kidney function in patients with coronary heart disease with type 2 diabetes and obesity: A secondary analysis of CORDIOPREV randomized controlled trial. *Nutrition & Diabetes,* 14(1), 27. https://doi.org/10.1038/s41387-024-00285-3

Ranganathan, N., & Anteyi, E. (2022). The role of dietary fiber and gut microbiome modulation in progression of chronic kidney disease. *Toxins,* 14(3), 183. https://doi.org/10.3390/toxins14030183

Stevens, P. E., Ahmed, S. B., Carrero, J. J., Foster, B., Francis, A., Hall, R. K., Herrington, W. G., Hill, G., Inker, L. A., Kazancıoğlu, R., Lamb, E., Lin, P., Madero, M., McIntyre, N., Morrow, K., Roberts, G., Sabanayagam, D., Schaeffner, E., Shlipak, M., … Levin, A. (2024). KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International*, 105(4), S117–S314. https://doi.org/10.1016/j.kint.2023.10.018

Tsuji, K., Uchida, N., Nakanoh, H., Fukushima, K., Haraguchi, S., Kitamura, S., & Wada, J. (2024). The gut–kidney axis in chronic kidney diseases. *Diagnostics*, 15(1), 21. https://doi.org/10.3390/diagnostics15010021

Tzatzaki, E., Didagelos, M., Karlafti, E., Melexopoulou, C., Tsavdaris, D., Ziakas, A., Marinaki, S., & Karvounis, H. (2024). Cardiac involvement in chronic kidney disease: epidemiology, pathophysiology, and complications. *Heart Views*, 25(4), 249–254. https://doi.org/10.4103/heartviews.heartviews_118_24

Wakino, S., Hasegawa, K., Tamaki, M., Minato, M., & Inagaki, T. (2025). Kidney-gut axis in chronic kidney disease: therapeutic perspectives from microbiota modulation and nutrition. *Nutrients,* 17(12), 1961. https://doi.org/10.3390/nu17121961

Wang, L., He, Y., Han, C., Zhu, P., Zhou, Y., Tang, R., & He, W. (2025). Global burden of chronic kidney disease and risk factors, 1990–2021: an update from the global burden of disease study 2021. *Frontiers in Public Health*, 13, 1542329. https://doi.org/10.3389/fpubh.2025.1542329

Wang, T., Masedunskas, A., Willett, W. C., & Fontana, L. (2023). Vegetarian and vegan diets: Benefits and drawbacks. *European Heart Journal,* 44(36), 3423–3439. https://doi.org/10.1093/eurheartj/ehad436

Williams, M. J., White, S. C., Joseph, Z., & Hruska, K. A. (2023). Updates in the chronic kidney disease-mineral bone disorder show the role of osteocytic proteins, a potential mechanism of the bone—Vascular paradox, a therapeutic target, and a biomarker. *Frontiers in Physiology*, 14, 1120308. https://doi.org/10.3389/fphys.2023.1120308

Yu, A. S. L., Chertow, G. M., Luyckx, V. A., Marsden, P. A., Skorecki, K., & Taal, M. W. (Eds.). (2020). *Brenner & Rector's the kidney (Eleventh edition).* Elsevier.

Zarantonello, D., & Brunori, G. (2023). The role of plant-based diets in preventing and mitigating chronic kidney disease: more light than shadows. *Journal of Clinical Medicine,* 12(19), 6137. https://doi.org/10.3390/jcm12196137