Journal of Multidisciplinary Healthcare

Dovepress
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REVIEW

The Gut–Kidney Axis in Uric Acid Nephropathy: Microbiota, Metabolic Crosstalk, and Translational Prospects

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Abstract: Uric acid nephropathy (UAN) represents a critical and multifactorial renal disorder closely linked to hyperuricemia, inflammation, and gut microbiota dysregulation. Recent advances have revealed the pivotal role of the gut–kidney axis in modulating urate metabolism, immune activation, and oxidative stress. This review synthesizes emerging preclinical and clinical evidence to construct an integrative framework for understanding UAN, highlighting both crystal-dependent and crystal-independent mechanisms that drive tubular injury and fibrosis. Accumulating data underscore the reciprocal crosstalk between renal dysfunction and gut dysbiosis, mediated by microbial metabolites such as short-chain fatty acids (SCFAs), indoxyl sulfate, and p-cresol sulfate. We further evaluate therapeutic interventions targeting the gut–kidney axis—including probiotics, synbiotics, postbiotics, fecal microbiota transplantation (FMT), and engineered microbial therapies—which have shown promise in restoring microbial balance and improving urate handling. By integrating multi-omics profiling with systems biology, this review proposes a precision-medicine roadmap that leverages microbiome signatures and metabolic phenotyping for risk stratification and personalized intervention. Moreover, we emphasize the need for supportive regulatory frameworks and interdisciplinary collaboration to enable the clinical translation of microbiota-based strategies. Collectively, this work provides a strengthened conceptual foundation for microbiome-informed prevention and treatment of uric acid–related kidney disease.

Keywords: uric acid nephropathy, hyperuricemia, gut–kidney axis, microbiota, inflammation, oxidative stress, probiotics

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Introduction

Uric acid nephropathy (UAN) is an often overlooked but increasingly significant contributor to progressive kidney dysfunction, particularly under conditions of sustained hyperuricemia (HUA).[1] Epidemiological studies reveal a global upward trend in HUA, underscoring its growing significance as a public health concern. A recent global review estimates that HUA affects 2.6% to 36% of adults worldwide, with approximately 21% of adults in the United States affected.[2] Similarly, systematic analyses across East Asian countries, including Japan, China, and South Korea, report regional prevalence rates ranging from 10% to 15%.[3] In China, a nationwide survey found a HUA prevalence of 15.1% among adults, with rates markedly higher in men (21.2%) than in women (8.5%).[4]

Traditionally, the pathogenesis of UAN has been attributed to the intrarenal deposition of monosodium urate (MSU) crystals and the subsequent inflammatory response.[5] However, accumulating evidence suggests that mechanisms independent of crystal formation such as metabolic dysregulation, immune activation, and oxidative stress also play pivotal roles in the onset and progression of the disease.[6–8] Despite its increasing prevalence and pathogenic complexity, UAN remains diagnostically elusive and therapeutically challenging. Current management strategies primarily emphasize serum urate reduction, with limited focus on altering disease-driving mechanisms.

Recent advances in understanding uric acid metabolism have drawn attention to extra-renal pathways of urate clearance, particularly the intestinal route, which accounts for roughly one-third of total urate elimination.[9] This insight

Received: 16 October 2025
Accepted: 9 December 2025
Published: 18 December 2025

has shifted the focus toward the gastrointestinal tract as a key modulator of systemic uric acid levels. At the same time, the intestinal microbiota has gained recognition as a central regulator of host metabolic and immune homeostasis, with emerging evidence implicating it in both urate metabolism and renal inflammation.[10,11] Disruption of the gut microbial ecosystem, commonly referred to as dysbiosis, involves reduced microbial diversity and an imbalance between pro-inflammatory and beneficial bacterial populations. Such alterations have been linked to HUA and kidney injury via impaired urate degradation, compromised intestinal barrier function, and heightened systemic immune activation.[12,13]

This evolving understanding has led to the conceptualization of the "gut–kidney axis," a bidirectional communication pathway in which the composition and function of gut microbes influence kidney physiology, while renal injury, in turn, perturbs intestinal homeostasis.[14] In the context of UAN, this axis encompasses multifaceted interactions among microbial metabolism, intestinal barrier integrity, urate transport mechanisms, and immune signaling cascades, all of which contribute collectively to renal pathology.[15] This framework provides a compelling mechanistic rationale for exploring novel therapeutic avenues that move beyond traditional urate-lowering agents. These include interventions that specifically target the gut microbiota, dietary modifications, and the use of small-molecule compounds that modulate microbe- or host-derived metabolic signals.

This review synthesizes emerging evidence regarding the gut–kidney axis in UAN, with a particular emphasis on how intestinal microbiota regulate uric acid metabolism, renal inflammation, and systemic metabolic homeostasis. Given the current therapeutic landscape, in which urate-lowering agents remain the primary intervention but often provide inconsistent renoprotective benefits, we highlight the unmet clinical need and the therapeutic gap that motivates deeper exploration of gut-axis mechanisms. We examine the molecular pathways underlying gut–renal communication, evaluate the therapeutic potential of microbiota-based strategies, and discuss translational opportunities and challenges in advancing from mechanistic discovery to clinical application. By integrating mechanistic research with clinical evidence, this review aims to contribute to the development of microbiome-informed precision medicine approaches for the effective prevention and treatment of UAN. Renal injury mechanisms associated with hyperuricemia, including gut–kidney axis dysregulation and crystal-dependent and independent pathways, are shown in Figure 1.

UAN: Pathophysiological and Clinical Overview

Epidemiology and Clinical Burden

UAN is a kidney disorder caused by sustained elevations in serum uric acid levels. It is commonly observed in individuals with metabolic syndrome, gout, hypertension, and chronic kidney disease (CKD).[16] Despite affecting approximately 15.2% of adults worldwide, the renal manifestations of HUA are often overlooked or misclassified. This is largely due to nonspecific clinical presentations and the significant overlap with other kidney diseases.[3] UAN includes both acute forms, such as those seen in tumor lysis syndrome, and chronic progressive variants that contribute gradually to tubulointerstitial fibrosis and decline in renal function.[17]

Recent epidemiological studies have highlighted the increasing clinical relevance of UAN, particularly in East Asian and Western populations where high purine consumption, obesity, and diabetes are prevalent.[18,19] Despite renal biopsy being the gold standard for definitive diagnosis, it is rarely performed in routine clinical practice. This is due to its invasive nature and the often subtle or nonspecific clinical features of UAN.[20] As a result, many cases may go undiagnosed or be misattributed to other common forms of kidney disease such as hypertensive or diabetic nephropathy.

Mechanistic Insights: From Crystal Deposition to Systemic Dysregulation

The classical pathophysiological model of UAN focuses on the deposition of MSU crystals within the renal tubules and interstitial space. These crystals initiate a local inflammatory response involving macrophages, neutrophils, and pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). This process results in tubular injury, oxidative stress, and ultimately, progressive interstitial fibrosis.[21–23]

However, recent studies have broadened this understanding by identifying crystal-independent mechanisms that contribute significantly to disease progression. Elevated serum urate levels can induce mitochondrial oxidative stress in renal tubular epithelial cells, impair cellular processes such as autophagy and mitophagy, and trigger apoptosis even in the absence of crystal

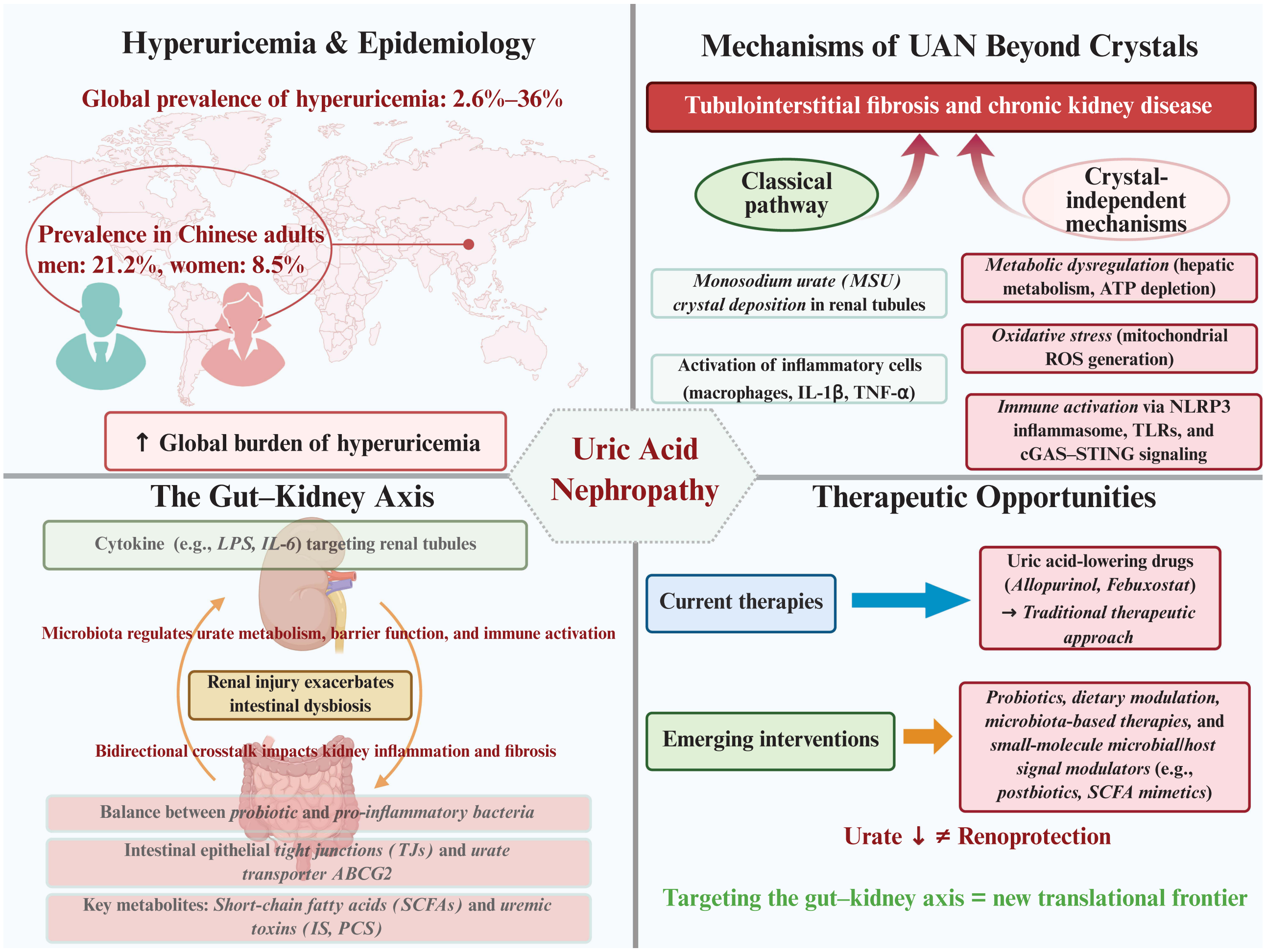

Figure 1 Hyperuricemia contributes to renal injury through gut–kidney axis dysregulation and both crystal-dependent and crystal-independent pathways. Beyond monosodium urate deposition, oxidative stress, metabolic imbalance, and immune activation drive tubulointerstitial fibrosis. While conventional urate-lowering agents provide limited renoprotection, microbiota-targeted therapies offer promising translational opportunities.

formation.[24] In addition, uric acid can activate several innate immune sensors, including the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, and toll-like receptors, thereby amplifying systemic inflammation.[25,26] Uric acid also disrupts vascular homeostasis by reducing endothelial nitric oxide bioavailability and stimulating vascular smooth muscle cell proliferation. These effects contribute to renal microvascular remodeling and promote hypoxia and fibrosis.[27]

Collectively, these findings indicate that uric acid is not merely an inert metabolic byproduct but a pathogenic factor capable of orchestrating metabolic, immune, and vascular dysfunctions that converge to drive chronic kidney damage.

Clinical Challenges and Therapeutic Gaps

UAN presents multiple diagnostic and therapeutic challenges in clinical practice. One of the primary difficulties lies in the absence of noninvasive and specific biomarkers for early detection. Although elevated serum urate is a necessary condition for UAN, it is neither sufficient nor definitive for diagnosis. Many individuals with HUA never develop renal impairment, while some patients with normal uric acid levels nonetheless develop urate-related kidney injury.[28] Current clinical guidelines emphasize that while HUA is prevalent in the general population, only a fraction of individuals go on to develop complications such as gout or nephropathy. Therefore, elevated serum urate should be viewed primarily as a modifiable risk factor rather than a diagnostic criterion for UAN.[29]

Therapeutically, management options for UAN remain limited. Most treatments focus on reducing urate levels using agents such as xanthine oxidase inhibitors, including allopurinol and febuxostat, or uricosuric drugs. Although these therapies are effective in lowering serum urate concentrations, their long-term impact on renal histopathological improvement and preservation of kidney function remains controversial. Retrospective studies comparing allopurinol and febuxostat in patients with CKD have so far yielded conflicting results. While febuxostat may offer slightly superior control of serum urate, no consistent renoprotective benefit has been demonstrated, and methodological limitations hinder definitive conclusions.[30,31] Similarly, randomized clinical trials conducted in asymptomatic hyperuricemic CKD patients have failed to show significant benefits of urate-lowering therapies on slowing renal function decline when added to standard care.[32] In addition, current treatment regimens lack targeted strategies that address the core pathogenic processes in UAN, such as inflammation, oxidative stress, and immune dysregulation. This underscores a pressing need for multi-targeted therapeutic approaches that go beyond simple urate reduction to address the complex biological mechanisms underlying disease progression.

Moreover, a significant gap remains between mechanistic research and clinical translation. Despite increasing awareness of uric acid's systemic effects, there is a paucity of interventions that directly modulate the upstream metabolic or immunological drivers, or the downstream consequences, of urate accumulation. Bridging this gap will require the development of innovative strategies that incorporate emerging insights from systems biology, particularly those centered on the gut–kidney axis and its role in modulating host–microbe interactions and renal pathophysiology. The high-risk populations, diagnostic challenges, pathogenic mechanisms, and translational gaps of uric acid nephropathy are shown in Figure 2.

Microbiota and Uric Acid Metabolism: Revisiting the Gut's Role

Intestinal Uric Acid Handling: A Nonrenal Excretory Pathway

While the kidneys account for the majority of uric acid excretion, approximately 30% to 40% is eliminated via the intestinal tract. This occurs primarily through active transport across the intestinal epithelium. It becomes particularly important in individuals with compromised renal function, where enhanced intestinal elimination serves as a compensatory mechanism to reduce systemic urate levels.[33]

The ATP-binding cassette transporter ABCG2, a key mediator of this process, is abundantly expressed on the apical surface of human intestinal epithelial cells. ABCG2 actively secretes urate into the intestinal lumen and thus plays a crucial role in extra-renal uric acid clearance.[34] Genome-wide association studies, along with follow-up functional analyses, have consistently demonstrated that loss-of-function variants in the ABCG2 gene, such as p.Q141K and p.Q126X, are associated with reduced transporter activity. These mutations lead to elevated serum urate concentrations and an increased risk of developing gout, highlighting the functional significance of ABCG2 in maintaining urate homeostasis.[35] Furthermore, recent experimental evidence supports a link between gut microbial metabolites and ABCG2 expression. In vitro studies have shown that short-chain fatty acids (SCFAs), which are produced by specific gut microbial taxa, can upregulate ABCG2 protein expression in intestinal epithelial cell models. Moreover, animal studies have demonstrated that probiotic supplementation enhances intestinal ABCG2 expression and promotes increased urate elimination.[36] Collectively, these findings establish a mechanistic connection between the gut microbiota and intestinal uric acid handling, supporting the notion that modulation of the microbiome may represent a viable strategy to optimize urate excretion and manage HUA.

Microbial Regulation of Uric Acid Metabolism

Purine Metabolism and Urate Generation

Intestinal microbes are increasingly recognized as key participants in host purine metabolism, with several commensal species contributing directly to uric acid production. Bacterial genera such as *Escherichia coli, Bacteroides*, and *Clostridium* harbor functional enzymes, such as xanthine dehydrogenase and various nucleotidases. These enzymes catalyze the degradation of both dietary and endogenous purines into urate. Under conditions of gut dysbiosis, enrichment of uricolytic microbial activity may emerge, which may contribute to increased intestinal and systemic urate levels.[37,38] This microbiota-derived contribution

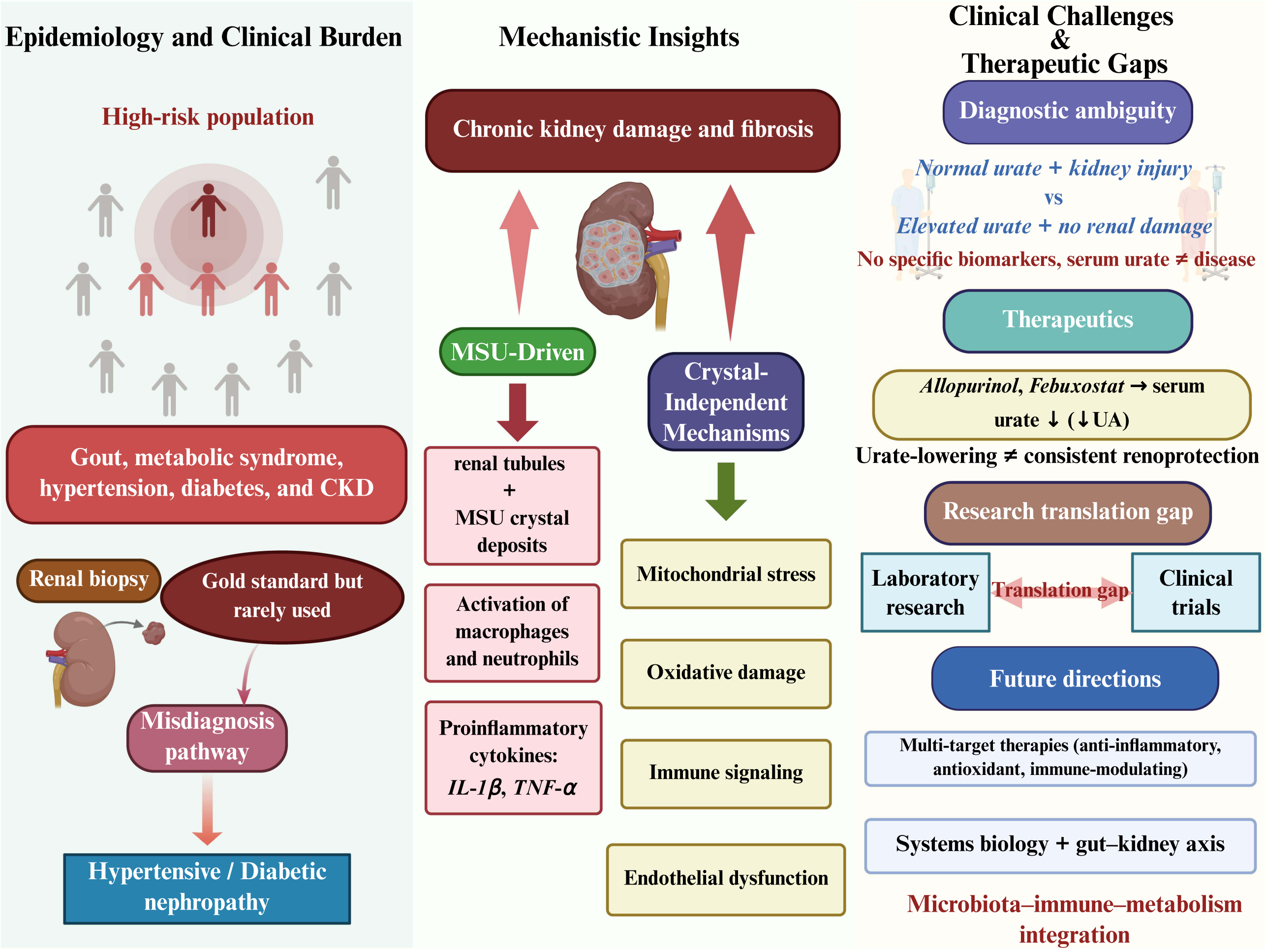

Figure 2 Uric acid nephropathy predominantly affects high-risk populations with gout, metabolic syndrome, hypertension, diabetes, and CKD. Although renal biopsy remains the diagnostic gold standard, it is rarely performed, often leading to misdiagnosis as hypertensive or diabetic nephropathy. Mechanistically, both MSU crystal deposition and crystal-independent processes contribute to kidney injury through macrophage activation, cytokine release (IL-1β, TNF-α), oxidative and mitochondrial stress, immune signaling, and endothelial dysfunction. Clinically, diagnostic ambiguity, lack of biomarkers, and limited efficacy of urate-lowering drugs highlight major translational gaps. Future strategies emphasize multi-target therapies and integration of microbiota–immune–metabolism networks to achieve better renoprotection.

to urate biosynthesis highlights an often-overlooked source of HUA and suggests that gut microbial composition may influence not only the clearance but also the generation of uric acid.

Urate Degradation and Microbial Uricase

Unlike humans, who lack a functional uricase enzyme due to evolutionary gene loss, certain intestinal microbes possess the enzymatic machinery necessary to degrade uric acid. Notably, *Lactobacillus plantarum* expresses ribonucleoside hydrolases (RihA, RihB, and RihC) that facilitate nucleoside catabolism. In hyperuricemic mouse models, administration of *L. plantarum* has been shown to significantly reduce serum urate concentrations.[39] Additionally, commensal or probiotic organisms such as *Akkermansia muciniphila* and *Bacillus subtilis* are capable of converting uric acid into more soluble and less toxic metabolites, such as allantoin.[40] Together, these microbial pathways represent a nonrenal mechanism for urate clearance and highlight the therapeutic potential of uricolytic bacteria or their enzymatic products in modulating systemic urate homeostasis.

Regulation by Microbial Metabolites

Microbial fermentation products, particularly SCFAs such as acetate, propionate, and butyrate, play critical roles in regulating host metabolic pathways, inflammatory responses, and the expression of epithelial transporters. Among these metabolites, butyrate has been shown to enhance intestinal barrier integrity by upregulating tight junction proteins such as

https://doi.org/10.2147/JMDH.S574758

claudin-1, occludin, and zonula occludens-1 (ZO-1). Improved barrier function reduces intestinal permeability and mitigates systemic inflammation associated with endotoxemia.[41] In preclinical models of CKD, supplementation with butyrate or SCFA-producing probiotics increases luminal SCFA concentrations, restores epithelial barrier function, and alleviates renal tubular injury and interstitial inflammation.[42] These findings underscore the therapeutic potential of microbial metabolites in maintaining gut–kidney homeostasis and highlight their relevance to the pathophysiology and treatment of UAN.

Dysbiosis and HUA: Clinical and Experimental Evidence

Depletion of SCFA-Producing Genera

Clinical and experimental studies have consistently demonstrated a marked reduction in key anti-inflammatory bacterial taxa among individuals with HUA and gout. Notably, *Faecalibacterium prausnitzii, Roseburia* spp., and various *Bifidobacterium* strains including *B. longum* and *B. pseudocatenulatum* are significantly underrepresented in these patient populations. These microbes are well recognized for their capacity to synthesize SCFAs, particularly butyrate, which plays a critical role in maintaining intestinal barrier integrity and regulating host immune responses.[38,43] The depletion of these beneficial bacteria may aggravate intestinal permeability, promote systemic inflammation, and impair urate homeostasis, thereby contributing to the initiation and progression of UAN.

Enrichment of Pro-Inflammatory Species

Elevated levels of pro-inflammatory microbial taxa have been consistently reported in individuals with HUA and gout. Notably, genera such as *Prevotella, Escherichia–Shigella*, and other members of the phylum *Proteobacteria* are frequently enriched in these patient cohorts. These bacteria are strongly associated with increased systemic inflammation and have been implicated in the upregulation of purine metabolism, potentially contributing to elevated serum urate concentrations.[44] Their overrepresentation underscores a microbiota-mediated mechanism that amplifies both metabolic and inflammatory pathways involved in the pathogenesis of UAN.

Functional Microbial Shifts

Metagenomic sequencing analyses have revealed distinct functional alterations in the gut microbiota of individuals with HUA. Notably, there is a reduction in the abundance of genes encoding uricase and enzymes responsible for SCFA biosynthesis, indicating impaired microbial capacity for urate degradation and anti-inflammatory metabolite production. Concurrently, an increased prevalence of genes involved in xanthine degradation suggests an upregulated purine catabolic pathway. Together, these shifts reflect a maladaptive microbial configuration marked by enhanced urate production and diminished clearance, potentially exacerbating HUA and contributing to the pathogenesis of UAN.[43]

Causal Validation via FMT

Fecal microbiota transplantation (FMT) from normouricemic to hyperuricemic rodent models has been shown to restore serum urate homeostasis and increase the abundance of beneficial bacterial taxa such as *Lactobacillus plantarum*. This species contributes to purine metabolism through the expression of nucleoside-degrading enzymes including RihA, RihB, and RihC, supporting a causal role for specific microbial strains in urate regulation.[39,45]

Further mechanistic evidence comes from strain-level interventions. For example, *L. plantarum* strain SQ001 harbors nucleoside hydrolases such as *iunH, rihA*, and *rihC*, which degrade purine precursors, thereby reducing urate production and promoting intestinal urate excretion.[39,40] In addition, bifidobacterial species such as *Bifidobacterium infantis* and *Bifidobacterium adolescentis* express purine nucleoside phosphorylase, facilitating the catabolism of hypoxanthine and inosine, thus lowering serum urate levels and mitigating systemic inflammation. Other strains, including *Lactobacillus casei*, enhance intestinal barrier function by upregulating tight junction proteins such as occludin and ZO-1, leading to reduced endotoxemia and renal inflammation.[46]

Collectively, these findings suggest that dysbiosis in HUA is not merely a taxonomic imbalance, but also a functional impairment marked by loss of urate-lowering microbial activity, expansion of pro-urate metabolic pathways, and compromised intestinal barrier integrity. Importantly, targeted microbial interventions can reverse these pathological features, underscoring the gut microbiome as a viable and modifiable target for the prevention and treatment of UAN.

Clinical Implications and Hypothesis Generation

Emerging insights call for a fundamental re-evaluation of HUA and UAN as systemic disorders driven by metabolic and microbial dysregulation, rather than conditions confined to the kidney. The gut microbiota functions not only as a contributing factor in disease pathogenesis but also as a modifiable therapeutic target. Interventions aimed at reshaping the intestinal microbiome such as the administration of probiotics, targeted dietary modifications, or pharmacological agents that modulate microbial metabolism have demonstrated the potential to enhance uric acid clearance and mitigate renal injury in experimental models of UAN.

These findings provide a conceptual foundation for ongoing investigations into gut–kidney interactions, wherein microbial composition, metabolite production, intestinal barrier integrity, and renal inflammatory signaling converge to drive disease progression and inform the development of innovative therapeutic strategies. The roles of gut microbiota in uric acid metabolism, intestinal barrier function, inflammation pathways, and microbiota-targeted therapeutic strategies are shown in Figure 3.

The Gut–Kidney Axis in UAN: Mechanisms and Crosstalk

The gut–kidney axis constitutes a dynamic, bidirectional communication network that connects the gastrointestinal tract and the renal system through immune, metabolic, and neurohumoral pathways. In UAN, this axis plays a central role in mediating the impact of gut dysbiosis and microbiota-derived metabolites on renal pathology, while kidney dysfunction reciprocally contributes to intestinal barrier impairment, microbial imbalance, and altered metabolite composition. This

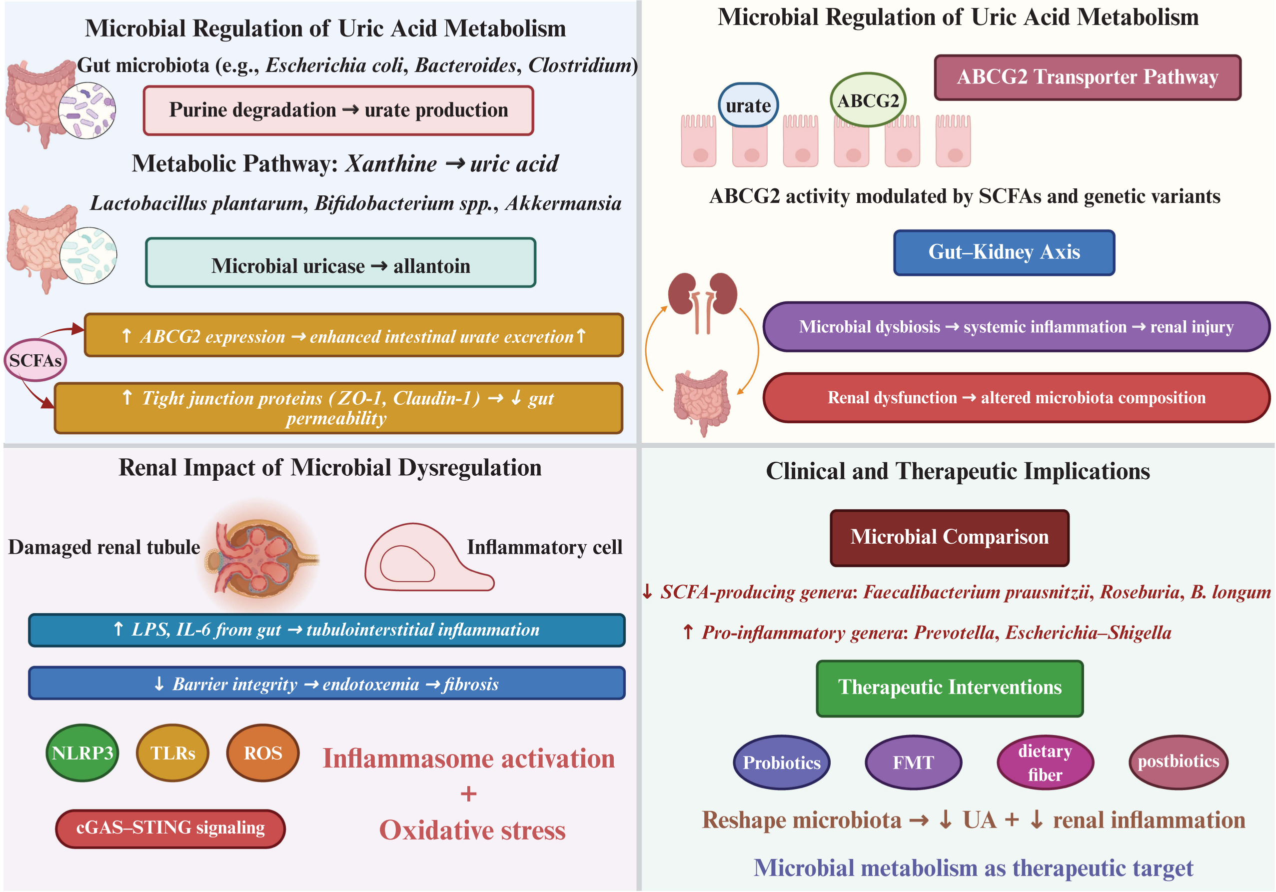

Figure 3 Gut microbiota influence uric acid metabolism through purine degradation and uricase-mediated allantoin production. SCFAs enhance intestinal urate excretion via ABCG2 and strengthen epithelial tight junctions. Dysbiosis induces systemic inflammation and renal injury through LPS, IL-6, NLRP3, TLRs, ROS, and cGAS–STING pathways, while kidney dysfunction further disrupts microbial balance. Reduced SCFA-producing and increased pro-inflammatory genera worsen hyperuricemia. Microbiota-targeted therapies—probiotics, FMT, dietary fiber, and postbiotics—may restore microbial balance, lower urate levels, and alleviate renal inflammation.

https://doi.org/10.2147/JMDH.S574758

reciprocal interaction establishes a self-reinforcing loop that amplifies systemic inflammation and metabolic stress.[47] In this section, we delineate the mechanistic underpinnings of gut–renal crosstalk and assess its functional relevance in the onset and progression of UAN.

Intestinal Barrier Dysfunction and Endotoxemia

A central consequence of gut dysbiosis in UAN is the impairment of intestinal barrier integrity. Under hyperuricemic conditions, elevated serum urate levels downregulate the expression of key tight junction proteins, including occludin and claudin-1, within the intestinal epithelium. This disruption results in increased intestinal permeability, a phenomenon commonly referred to as "leaky gut".[38]

The compromised epithelial barrier facilitates the translocation of bacterial components, particularly lipopolysaccharide (LPS), into the systemic circulation. Circulating LPS engages Toll-like receptor 4 (TLR4) and activates the nuclear factor kappa B (NF-κB) signaling cascade in renal tubular and immune cells, thereby inducing the production of proinflammatory cytokines such as interleukin-6 (IL-6), TNF-α, and IL-1β. This inflammatory milieu also promotes the activation of the NLRP3 inflammasome, further amplifying renal inflammation and accelerating tubulointerstitial fibrosis.[48]

In experimental hyperuricemic mouse models, restoration of intestinal barrier integrity via butyrate supplementation or probiotic administration has been shown to reduce circulating LPS levels, attenuate renal macrophage infiltration, and improve renal function as reflected by decreased serum creatinine concentrations. These findings provide compelling evidence for a causative link between intestinal barrier dysfunction and renal inflammatory injury in the pathogenesis of UAN.[49]

Microbial Metabolites as Immune-Modulatory Signals

SCFAs

SCFAs, primarily produced through the microbial fermentation of dietary fibers by commensal taxa such as *Faecalibacterium prausnitzii* and *Roseburia* spp., serve as key mediators of host–microbe interactions. Among them, butyrate and propionate have been extensively studied for their immunomodulatory and renoprotective properties. SCFAs exert their biological effects in part via activation of G protein–coupled receptors, specifically GPR41 and GPR43, which are expressed on various immune and renal epithelial cells. Experimental studies using human renal cortical epithelial cells have demonstrated that SCFAs suppress TNF-α-induced expression of monocyte chemoattractant protein-1. This anti-inflammatory effect is mediated through GPR41/GPR43 signaling and is associated with the downregulation of the p38 mitogen-activated protein kinase and c-Jun N-terminal kinase pathways. These findings underscore the role of SCFAs as endogenous immunoregulatory metabolites that attenuate renal inflammation and fibrosis, thereby contributing to kidney protection in the context of UAN.[50]

Tryptophan Metabolites

Tryptophan-derived metabolites produced by commensal gut bacteria, including indole and indole-3-acetic acid, play a critical role in maintaining renal immune homeostasis. These metabolites serve as endogenous ligands for the aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor that modulates immune cell differentiation, suppresses NF-κB signaling, and regulates intracellular reactive oxygen species (ROS) levels within renal tubular epithelial cells. Through these mechanisms, AHR activation exerts anti-inflammatory and antioxidant effects, thereby mitigating renal injury. However, under dysbiotic conditions, microbial metabolism of tryptophan shifts toward the increased production of uremic toxins such as *p*-cresol sulfate and indoxyl sulfate. These toxins accumulate systemically, impair mitochondrial bioenergetics, induce oxidative stress, and aggravate tubulointerstitial injury, as demonstrated in models of CKD. The dualistic nature of tryptophan metabolism generating both protective and harmful metabolites underscores the importance of microbial composition in determining renal outcomes.[51]

Uremic Toxins

Uremic toxins such as *p*-cresol sulfate and indoxyl sulfate are byproducts of gut microbial metabolism of aromatic amino acids, notably tyrosine and tryptophan. These compounds accumulate systemically in patients with UAN and CKD, particularly in the context of impaired renal excretory capacity. Functioning as endogenous nephrotoxins, they induce oxidative stress, disrupt mitochondrial bioenergetics, and activate profibrotic signaling cascades within renal tubular and interstitial cells. These effects promote extracellular matrix accumulation and drive the progression of tubulointerstitial fibrosis.[52]

The pathogenic accumulation of these microbial metabolites underscores the critical role of maintaining a balanced gut metabolic profile. In a eubiotic state, the gut microbiota predominantly generates anti-inflammatory and antioxidative metabolites that reinforce immune homeostasis and epithelial integrity. Conversely, dysbiosis skews microbial activity toward the production of pro-oxidative and pro-inflammatory compounds, thereby exacerbating renal inflammation and tissue damage in UAN. Restoring the balance between protective and harmful microbial metabolites thus represents a promising therapeutic strategy for preserving renal structure and function.

Mitochondrial Dysfunction and Oxidative Stress: A Converging Pathway

Accumulating evidence suggests that microbial metabolites, systemic inflammation, and uric acid overload converge upon mitochondrial dysfunction as a central downstream pathway driving renal injury in UAN. In renal tubular epithelial cells, excessive production of ROS, impaired mitophagy, and leakage of mitochondrial DNA collectively trigger innate immune responses via activation of cGAS–STING and the NLRP3 inflammasome. These pathways promote sustained inflammation, cellular injury, and apoptosis, ultimately contributing to progressive kidney damage.[53,54]

Among microbiota-derived metabolites, SCFAs—notably butyrate—exert protective effects on renal mitochondria by promoting mitochondrial biogenesis, maintaining redox homeostasis, and mitigating urate-induced cytotoxicity. In experimental models of CKD, butyrate supplementation has been shown to inhibit NLRP3-driven pyroptosis and attenuate tubulointerstitial fibrosis, underscoring its role in preserving mitochondrial integrity. In contrast, harmful microbial products such as LPS and uremic toxins like indoxyl sulfate exacerbate mitochondrial fragmentation, impair ATP production, disrupt mitochondrial dynamics, and activate pro-apoptotic cascades within renal tissues.[55]

These deleterious effects reinforce the notion that the gut microbiome profoundly influences renal mitochondrial health. Mitochondrial stress—arising in part from gut dysbiosis—may represent a common pathological nexus linking metabolic derangement, immune activation, and fibrotic remodeling in UAN.

The Bidirectional Nature of the Gut–Kidney Axis

Increasing evidence has firmly established the gut–kidney axis as a bidirectional communication pathway, particularly relevant in the context of UAN and CKD. As renal function declines, the systemic accumulation of uric acid and nitrogenous waste alters the intestinal microenvironment, inducing a pathological state termed uremic dysbiosis.[56] This condition is characterized by impaired epithelial renewal, disruption of tight junction architecture, reduced production of beneficial SCFAs, and a shift toward a pro-inflammatory microbial profile.

Both clinical and preclinical studies consistently report increased intestinal permeability in CKD, evidenced by elevated ethylenediaminetetraacetic acid excretion and histopathological findings showing downregulation of tight junction proteins such as claudin-1 and occludin.[57] This compromised barrier permits the translocation of endotoxins and microbial products into systemic circulation. Elevated serum LPS levels are frequently observed in uremic patients and strongly correlate with systemic inflammatory markers, including IL-6, TNF-α, and C-reactive protein (CRP), underscoring the role of gut barrier disruption in renal inflammation.[58]

Furthermore, commonly prescribed medications in CKD—such as phosphate binders, oral antibiotics, and iron supplements—can further disrupt microbial diversity and SCFA biosynthesis. These agents may inadvertently impair intestinal barrier integrity and exacerbate the systemic accumulation of uremic toxins.[59]

Collectively, these findings support the existence of a self-perpetuating pathogenic cycle in which renal dysfunction promotes intestinal barrier breakdown and dysbiosis, while gut-derived pro-inflammatory and metabolic signals accelerate kidney injury and fibrotic progression. This reciprocal relationship is particularly relevant in UAN, where elevated uric acid levels interface with microbial pathways to sustain renal inflammation. Recognizing the bidirectional dynamics of the gut–kidney axis underscores the therapeutic value of integrative strategies aimed at restoring microbial homeostasis, enhancing epithelial integrity, and attenuating renal immune activation. Such approaches hold promise for interrupting the vicious cycle of gut–renal dysfunction in UAN.

Integrated Mechanistic Model of the Gut–Kidney Axis in UAN

Cumulative mechanistic and clinical evidence supports an integrated model in which the gut–kidney axis functions as a central mediator in the development and progression of UAN. This model encompasses interconnected pathways involving metabolic stress, microbial dysbiosis, immune activation, and mitochondrial dysfunction, forming a self-perpetuating pathological cascade.

The cascade is initiated by sustained HUA and excessive dietary purine intake, which alter the composition of the gut microbiota and compromise intestinal epithelial integrity. Dysbiosis—particularly the depletion of SCFA-producing bacteria and downregulation of tight junction proteins such as occludin and claudin-1—leads to increased intestinal permeability. This “leaky gut” condition facilitates the translocation of microbial products into systemic circulation.[60,61]

Among these translocated molecules, LPS is particularly pathogenic. LPS activates TLR4, triggering downstream NF-κB signaling in renal tissues. This cascade results in elevated expression of key pro-inflammatory cytokines, including IL-6, TNF-α, and IL-1β, thereby sustaining renal inflammation.[62,63]

Simultaneously, damage-associated molecular patterns of mitochondrial origin—such as ROS and leaked mitochondrial DNA—stimulate intracellular danger sensors. Notably, both the NLRP3 inflammasome and the cGAS–STING pathway are activated by these stress signals and microbial components. This amplifies innate immune responses and promotes renal tissue injury.[64]

Mitochondrial dysfunction represents a critical convergence point in this pathogenic network. Elevated urate levels and microbial toxins impair mitophagy, disrupt mitochondrial biogenesis, and lead to excessive ROS accumulation and ATP depletion. These events exacerbate oxidative stress, further activate immune signaling, and drive tubulointerstitial fibrosis, thereby accelerating CKD progression.[63]

Collectively, this integrated model positions the gut–kidney axis not as a secondary effect but as an active and central contributor to UAN pathophysiology. It provides a mechanistic foundation for the development of multimodal therapeutic strategies aimed at restoring microbial balance, enhancing intestinal barrier integrity, modulating renal immune activation, and preserving mitochondrial function. These therapeutic avenues are further discussed in the following section. The effects of gut microbial imbalance on intestinal barrier disruption, inflammatory signaling, uremic toxin production, and the gut–kidney inflammatory loop contributing to chronic renal fibrosis are shown in Figure 4.

Therapeutic Targeting of the Gut–Kidney Axis in UAN

A growing body of evidence implicates the gut–kidney axis as a central contributor to the pathogenesis and progression of UAN. This axis mediates disease through a complex network involving microbial dysbiosis, immune activation, and metabolic disturbances. Targeting the gut–kidney axis therapeutically offers significant potential to overcome the limitations of conventional urate-lowering therapies, which often fail to address the upstream drivers of renal injury. Interventions that restore gut and renal homeostasis may enable more comprehensive disease control by correcting intestinal barrier dysfunction, suppressing pro-inflammatory signaling pathways, and mitigating mitochondrial damage in renal tissues.[63,65,66] As understanding of this integrative network advances, various novel strategies are being explored. These include microbiota-based interventions such as probiotics, prebiotics, synbiotics, and FMT, as well as agents that modulate microbial metabolites or host metabolic pathways.

The following sections examine these therapeutic modalities in detail, focusing on their mechanisms of action, supporting preclinical and clinical evidence, and potential for integration into personalized management strategies for UAN.

Probiotic and Synbiotic Therapy

Probiotic and synbiotic interventions have demonstrated promising renoprotective effects in models of HUA and early-stage kidney disease, suggesting their potential utility in the management of UAN. In a hyperuricemic rat model, oral administration of *Lacticaseibacillus rhamnosus* LR1155 and *Lactobacillus fermentum* 2644 for four weeks significantly

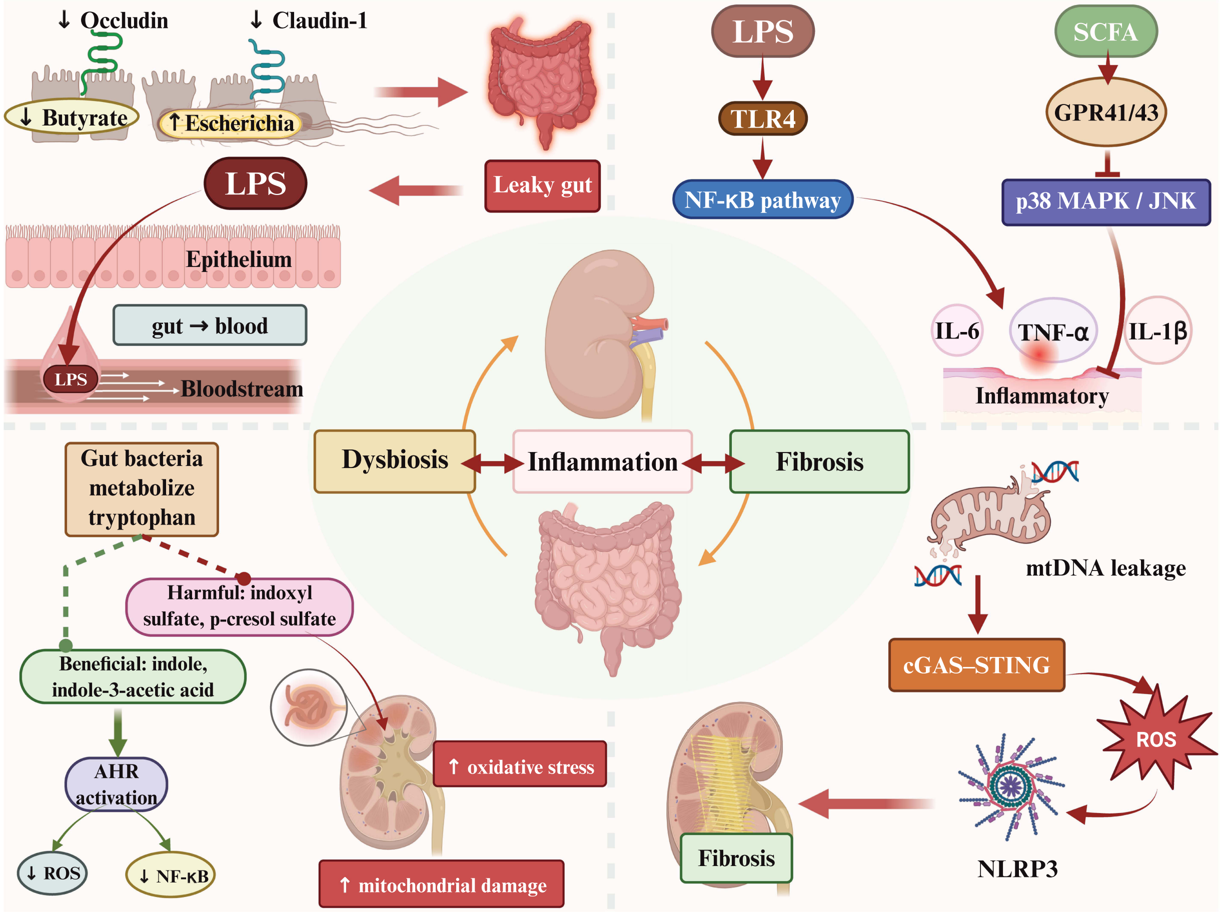

Figure 4 Gut microbial imbalance disrupts epithelial tight junctions (occludin, claudin-1), increasing permeability and LPS translocation into circulation. LPS activates TLR4 and the NF-κB pathway, inducing inflammatory cytokines (IL-6, TNF-α, IL-1β). Meanwhile, SCFAs modulate inflammation via GPR41/43 and p38 MAPK/JNK signaling. Dysregulated tryptophan metabolism generates uremic toxins (indoxyl sulfate, p-cresol sulfate) that promote oxidative stress, mitochondrial damage, and fibrosis through AHR, ROS, cGAS–STING, and NLRP3 activation. These mechanisms form a gut–kidney inflammatory loop driving chronic renal fibrosis.

reduced serum urate levels. This was accompanied by enhanced intestinal urate excretion via upregulation of the urate transporter ABCG2, restoration of intestinal barrier integrity through increased expression of occludin and mucin-2, reductions in circulating LPS and interleukin-1β levels, and favorable modulation of the gut microbiota, including increased abundance of *Roseburia* and *Bifidobacterium* species.[46,67]

Clinical data also support the safety and feasibility of synbiotic therapy. In a randomized, double-blind crossover trial involving patients with CKD, six weeks of synbiotic supplementation led to reduced serum levels of p-cresyl sulfate, a representative uremic toxin, and increased fecal abundance of beneficial genera such as *Bifidobacterium* and *Blautia*. However, the reduction in indoxyl sulfate levels did not reach statistical significance.[68]

Additional preclinical studies reinforce the therapeutic potential of probiotics. In oxonic acid–induced hyperuricemic rats, probiotic treatment prevented hypertension onset, alleviated renal histopathological damage, enhanced urinary urate excretion, and reduced renal urate accumulation. Notably, these renoprotective effects occurred despite minimal changes in overall fecal microbiota composition, suggesting that functional modulation of microbial activity may be more critical than taxonomic restoration.[69]

Collectively, these findings suggest that well-formulated probiotic or synbiotic regimens may attenuate renal inflammation, preserve renal function, and serve as effective adjuncts to conventional urate-lowering therapies in the management of UAN.

https://doi.org/10.2147/JMDH.S574758

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) has garnered growing interest as a therapeutic approach for restoring gut microbial homeostasis in diseases marked by dysbiosis, including CKD and UAN. Preclinical studies have demonstrated that transplantation of fecal material from normouricemic donors into hyperuricemic or UAN model animals effectively normalizes serum urate levels. FMT has also been shown to restore the expression of intestinal tight junction proteins, suppress IL-1β production and NLRP3 inflammasome activation in renal tissues, improve tubular epithelial morphology, and reduce interstitial fibrosis in murine models of UAN.[70]

Emerging clinical data suggest that FMT is both feasible and safe in patients with HUA and early-stage CKD. Preliminary studies have reported that FMT may reduce serum urate concentrations and lower urinary biomarkers of tubular injury, such as neutrophil gelatinase–associated lipocalin and kidney injury molecule-1.[71]

Despite its therapeutic potential, the clinical application of FMT in UAN remains constrained by several important limitations. First, donor heterogeneity introduces substantial variability in microbial composition and functional capacity, making treatment responses unpredictable across patients.[72] Second, FMT carries the risk of acute adverse events, including infection transmission and immune-mediated complications, which raises safety concerns in vulnerable populations.[73] Third, dosing remains poorly standardized, with uncertainties regarding the optimal microbial load, frequency, and delivery route needed to achieve durable engraftment.[74] In addition, dietary patterns and concomitant medications—such as antibiotics, probiotics, or urate-lowering agents—act as uncontrolled confounding factors that can alter microbial dynamics and attenuate therapeutic effects. Finally, many patients exhibit only transient clinical or microbiological improvements, reflecting the challenges of achieving long-term colonization and sustained functional benefits. These limitations underscore the need for more controlled microbial therapeutics, standardized donor selection criteria, and improved delivery systems before FMT can be widely adopted for UAN management.

Overcoming these challenges will require rigorous mechanistic investigations, harmonized clinical trial designs, and the development of defined microbial consortia or next-generation microbial therapeutics that replicate the beneficial effects of FMT while mitigating associated risks.

Dietary and Lifestyle Modulation

Diet plays a critical role in shaping gut microbiota composition and regulating uric acid metabolism, offering a noninvasive and cost-effective approach to managing UAN. High-fiber diets, combined with reduced intake of purine-rich foods and fructose-containing beverages, have been shown to shift the gut microbiota toward a more anti-inflammatory profile.[75] Notably, Mediterranean and plant-based dietary patterns—rich in polyphenols, omega-3 fatty acids, and complex carbohydrates—are associated with increased abundance of beneficial genera such as *Bifidobacterium* and enhanced production of SCFAs. These metabolic effects improve intestinal barrier integrity and attenuate systemic inflammation, both of which are highly relevant to UAN pathophysiology.[76]

In addition, specific dietary components exhibit prebiotic properties. For instance, resistant starch, quercetin, and polyphenols found in green tea have been reported to modulate gut microbial composition and indirectly lower serum urate levels by promoting uricolytic bacterial pathways and reducing intestinal permeability. Given their safety, scalability, and ease of implementation, dietary interventions represent a promising long-term strategy for the prevention and management of UAN. When incorporated into broader lifestyle and metabolic care plans, such strategies may delay disease onset and reduce dependence on pharmacological therapy.[77]

Pharmacological Modulation of Microbial and Host Pathways

Beyond probiotics and dietary strategies, pharmacological agents that modulate microbial metabolism or host–microbe signaling are emerging as innovative therapies for UAN. These small-molecule compounds offer targeted means to influence the gut–kidney axis and address the multifactorial mechanisms driving disease progression.

One promising approach involves the use of SCFA analogs or agonists of G protein-coupled receptors (GPRs) such as GPR43 and GPR41. These compounds mimic the effects of endogenous SCFAs by activating anti-inflammatory signaling pathways in renal and immune cells. GPR43 and GPR41 activation has been shown to suppress kidney inflammation and confer renoprotective effects in experimental models of renal injury.[50,78]

Another strategy focuses on modulating the AHR pathway using natural or synthetic ligands, including indole derivatives and tryptophan metabolites. AHR activation helps suppress oxidative stress, maintain mitochondrial integrity, and promote immune tolerance within renal tissues, suggesting therapeutic relevance in UAN.[79,80]

In addition, inhibition of the NLRP3 inflammasome represents a critical target in the context of microbial-induced renal inflammation. Compounds such as MCC950 and plant-derived agents like curcumin have shown efficacy in attenuating NLRP3 activation, thereby reducing interleukin-1β production and limiting tubulointerstitial fibrosis.[81–83]

Collectively, these pharmacological strategies offer a multifaceted therapeutic framework that complements conventional urate-lowering treatments. By targeting inflammation, oxidative damage, and host–microbe crosstalk, they hold promise for preventing disease progression and improving clinical outcomes in patients with UAN.

Integration with Existing Therapies: A Combined Approach

Given the complex and multifactorial nature of UAN, monotherapy is unlikely to achieve optimal disease control. Instead, a comprehensive treatment strategy that combines microbiota-targeted interventions with conventional pharmacological agents may offer more effective and durable outcomes. Current standard therapies for UAN include xanthine oxidase inhibitors such as allopurinol and febuxostat, uricosuric agents such as benzbromarone, and anti-inflammatory drugs like colchicine or corticosteroids for the management of acute gout flares.[84–86]

Microbiota modulation—via probiotics, synbiotics, dietary adjustments, or microbial metabolite-based therapies—may augment the therapeutic efficacy of these conventional agents by reducing systemic and renal inflammation, preserving epithelial barrier function, and improving overall treatment tolerability. Importantly, by addressing upstream drivers of renal injury, microbiome-targeted strategies may allow for lower doses of urate-lowering drugs, thereby minimizing the risk of treatment-related adverse effects such as hypersensitivity reactions, hepatic dysfunction, and gastrointestinal intolerance.[87–89]

Looking forward, the future management of UAN may increasingly rely on precision medicine approaches that incorporate microbial profiling, metabolomic signatures, and host genetic data. These multidimensional insights can inform the development of individualized therapeutic regimens targeting both metabolic dysregulation and immune dysfunction inherent to UAN pathophysiology. Such an integrative framework holds considerable promise for improving long-term outcomes by addressing not only serum urate levels but also the systemic mechanisms underlying disease progression. The therapeutic strategies for modulating gut microbiota to improve urate control, including probiotics, FMT, dietary interventions, pharmacological modulators, and combination regimens with urate-lowering drugs, are shown in Figure 5.

Clinical Translation and Research Outlook

From Mechanisms to Biomarkers: The Need for Precision Stratification

Although substantial progress has been made in elucidating the mechanistic role of the gut–kidney axis in UAN, clinical translation remains hindered by the lack of reliable, noninvasive biomarkers to identify at-risk individuals and monitor treatment response.[84] Bridging this translational gap will require precision stratification strategies grounded in microbiome research and systems biology.

One promising avenue involves profiling the intestinal microbiota through 16S rRNA gene sequencing or shotgun metagenomic analysis. These approaches can identify dysbiotic signatures associated with HUA and renal injury, offering both diagnostic and prognostic potential.[75,90] In parallel, metabolomic profiling provides quantitative insights into gut-derived metabolites—including SCFAs, indole derivatives, and LPS—through measurements in blood, urine, or fecal samples. These data reflect functional host–microbiome interactions that are often disrupted in UAN.[91]

Integrating multiple omics layers—microbiome, transcriptomics, and metabolomics—can yield composite indices that more comprehensively capture dysfunction of the gut–renal axis than single biomarkers alone.[92] Such integrative biomarkers may support patient stratification based on microbial or metabolic phenotypes and guide personalized interventions, including tailored probiotic formulations, individualized dietary plans, or microbiota-modulating pharmacotherapies.

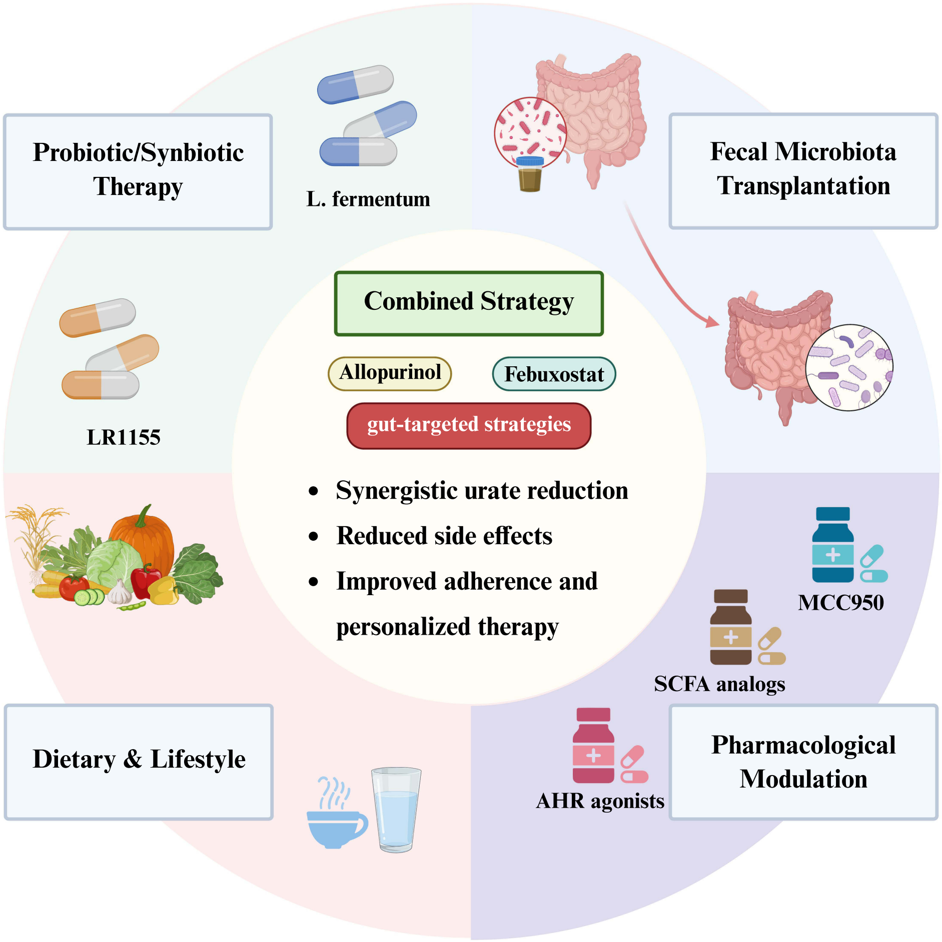

Figure 5 Multiple complementary approaches are proposed to modulate gut microbiota and improve urate control. Strategies include probiotic/synbiotic therapy (Lactobacillus fermentum, LR1155), FMT, dietary and lifestyle interventions, and pharmacological modulation using SCFA analogs, AHR agonists, or NLRP3 inhibitors (MCC950). Combined regimens with traditional urate-lowering drugs (allopurinol, febuxostat) enhance efficacy, reduce side effects, and promote personalized, gut-targeted renoprotective therapy.

To enhance both the predictive value and clinical applicability of omics-based tools, machine learning algorithms are increasingly applied to integrate high-dimensional biological datasets with conventional clinical indicators. In CKD, multi-omics integration via platforms such as genomics, transcriptomics, proteomics, and metabolomics has facilitated the identification of novel biomarkers, molecular subtypes, and patient-specific therapeutic targets.[93,94] A recent study published in *JCI Insight* (2025) demonstrated that dual-omics frameworks—using models such as MOFA (Multi-Omics Factor Analysis) and DIABLO (Data Integration Analysis for Biomarker discovery using Latent variable approaches for Omics studies)—can uncover molecular signatures predictive of CKD progression, thereby enabling more refined patient classification and targeted therapy planning.[92] In diabetic kidney disease, machine learning–driven integration of gut microbial and host metabolite profiles has further revealed key immune-metabolic interactions contributing to renal injury.[95] Collectively, these advancements support the development of a precision medicine framework for UAN, one that unites microbiome-informed risk profiling, mechanistic insights, and personalized treatment strategies.

Clinical Trial Design: Barriers and Opportunities

The successful translation of gut-targeted strategies into effective therapies for UAN hinges on the implementation of rigorously designed clinical trials. However, several persistent challenges continue to hinder progress. A major obstacle lies in the considerable heterogeneity among patients, encompassing interindividual differences in baseline gut microbiota composition, renal function, comorbidities, medication use, and dietary habits. This variability complicates the identification of reproducible therapeutic effects across diverse cohorts.[96]

Another critical limitation is the lack of standardized clinical endpoints for assessing microbiota restoration or modulation of the gut–renal axis. In the absence of uniform criteria, it remains difficult to compare results across studies or to determine the clinical relevance of microbiota-related changes.[97] Furthermore, the inherently multifactorial nature of dietary and microbiota-based interventions poses significant challenges for the design of double-blind, placebo-controlled trials, which remain the gold standard for evidence generation.[96]

Despite these barriers, early-phase clinical studies have yielded encouraging findings. For instance, the SYNERGY II trial in patients with moderate to severe CKD demonstrated that synbiotic supplementation significantly reduced uremic toxins such as indoxyl sulfate and improved markers of intestinal barrier function.[98] Meta-analyses have similarly reported that probiotic and synbiotic interventions are associated with reductions in blood urea nitrogen and CRP, suggesting potential benefits for both renal function and systemic inflammation.[99] More recently, observational studies have shown that “washed” FMT is safe and may improve estimated glomerular filtration rate and renal outcomes in patients with CKD.[100]

Looking ahead, clinical trials in UAN should adopt adaptive trial designs, incorporate longitudinal multi-omics profiling, and evaluate combination therapies that integrate microbiota-targeted interventions with standard pharmacologic treatments. These strategies will enhance the translational relevance of trial outcomes and support the development of personalized, mechanism-based therapies for UAN.

From Population to Personalization: Toward Microbiome-Guided Therapy

The considerable interindividual variability in gut microbiota composition presents both a challenge and an opportunity for advancing personalized medicine in UAN. Unlike conventional therapeutic approaches that rely on standardized protocols, microbiota-centered interventions offer the potential for dynamic personalization tailored to each patient’s unique microbial configuration, metabolic profile, and genetic background. A narrative review on epigenetics and precision medicine has underscored the critical role of microbiome heterogeneity in shaping disease susceptibility and therapeutic responses, thereby reinforcing the feasibility of individualized treatment strategies in renal disorders.[101] Similarly, a comprehensive review of the gut–kidney axis in CKD advocates for integrating individual microbial profiles with systems biology–based frameworks and adaptive therapeutic models to realize the promise of microbiome-informed precision medicine.[102] In parallel, the emerging field of pharmacomicrobiomics highlights how gut microbiota variability can significantly influence drug metabolism, bioavailability, and therapeutic efficacy. These insights underscore the need to incorporate baseline microbial signatures into personalized treatment algorithms to enhance both efficacy and safety.[103]

Several innovative strategies are being explored to operationalize microbiota-guided therapy. One approach involves microbial signature–matched interventions, wherein patients are assigned specific probiotic or synbiotic formulations based on their baseline microbiota profiles to optimize clinical outcomes.[104] Another strategy employs host–microbe interaction modeling through systems biology platforms to simulate the downstream effects of microbial perturbations on key host pathways, including urate metabolism, oxidative stress, and renal inflammation.[105] Additionally, artificial intelligence–driven frameworks are being developed to predict individual therapeutic responses, refine microbial strain selection, and generate personalized dietary recommendations by integrating multi-omics datasets with clinical metadata.[103]

Translating these concepts into clinical practice will require several foundational developments. These include the establishment of large-scale, longitudinal cohorts with standardized microbiome and metabolome profiling, integration of omics data with electronic health records, and the creation of user-friendly, clinician-oriented decision-support tools. Collectively, these efforts are essential for building a precision medicine paradigm in UAN—one that reflects the intricate interplay between gut microbial ecology and renal pathophysiology.

Expanding the Therapeutic Landscape: Future Targets

As understanding of the gut–kidney axis continues to evolve, a new generation of therapeutic targets is being identified. Molecular sensors such as GPR43,[106] AHR,[107] and STING[108] have gained attention as key regulatory nodes in the interplay between microbial metabolites, immune signaling, and renal injury. Targeting these receptors may enable precise modulation of inflammatory and metabolic pathways central to the pathogenesis of UAN.

In parallel, advances in synthetic biology and microbial engineering are enabling the development of next-generation probiotics with enhanced functional specificity.[109] These engineered microbial strains can be tailored to secrete urate-degrading enzymes, anti-inflammatory compounds, or SCFAs directly within the intestinal environment, thereby delivering targeted therapeutic effects.[110,111] Additionally, postbiotics—defined as non-viable microbial components or metabolites with biological activity—represent an emerging class of interventions. Compared to live microorganisms, postbiotics offer advantages in terms of safety, storage stability, and regulatory compliance, particularly in vulnerable populations such as immunocompromised individuals.[112]

Furthermore, increasing attention is being directed toward renal-to-gut feedback mechanisms. Kidney-derived factors, including ROS, uremic toxins, and pro-inflammatory cytokines, can impair intestinal epithelial renewal, disrupt microbial niches, and reinforce dysbiosis. Chronic uremia has been shown to compromise the integrity of the intestinal barrier, facilitating the translocation of microbial products such as indoxyl sulfate and p-cresyl sulfate into the circulation. These metabolites not only exert nephrotoxic effects but also promote systemic inflammation and oxidative stress, thereby exacerbating intestinal dysfunction.[113] In patients with CKD, elevated levels of gut-derived uremic toxins are associated with impaired barrier function and increased systemic inflammation due to enhanced efflux of endotoxins, ROS, and inflammatory mediators.[114]

Investigation into these retrograde signaling pathways is essential for understanding the full spectrum of gut–renal communication. It may also reveal additional intervention points to interrupt the vicious cycle of microbial imbalance, barrier disruption, and renal injury characteristic of UAN.

Strategic Vision: A Roadmap for Integration

Translating gut–kidney axis–oriented strategies into clinical practice for UAN necessitates a coordinated and forward-thinking roadmap. This roadmap should be anchored by several strategic pillars. First, rigorous validation of mechanistic insights in preclinical models is essential. This should involve the application of multi-omics technologies such as metagenomics, metabolomics, and transcriptomics, combined with functional assays to ensure relevance to human disease.

Second, early-phase clinical trials must be implemented to evaluate safety, feasibility, and biomarker-based surrogate endpoints. These studies will be critical in guiding the design of subsequent larger-scale trials and refining patient selection criteria.

Third, the development of scalable and accessible interventions is a priority. This includes probiotics, synbiotics, and postbiotics, which must be adaptable to diverse patient populations that vary in genetic background, microbial ecology, and dietary habits.

Equally important is the establishment of supportive regulatory and policy frameworks to facilitate the safe and timely clinical adoption of microbiota-directed therapies. This will require collaborative engagement across disciplines, bringing together nephrologists, microbiologists, immunologists, nutrition scientists, and computational biologists.

Through such integrated and interdisciplinary efforts, the therapeutic potential of targeting the gut–kidney axis can be fully realized. This approach may ultimately lead to a transformative shift in how UAN is prevented, diagnosed, and managed in clinical settings. The key stages for advancing gut–kidney axis research toward clinical translation, including mechanistic insights, biomarker integration, personalized microbiome-guided strategies, and precision therapeutic development, are shown in Figure 6.

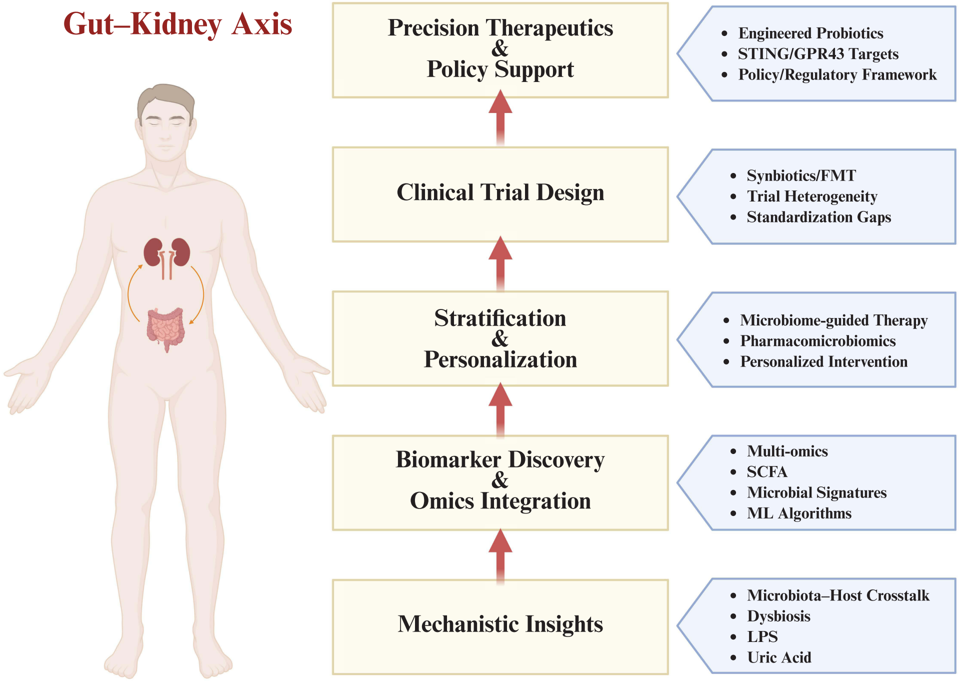

Figure 6 This schematic outlines key stages for advancing gut–kidney axis research toward clinical translation. Mechanistic insights from microbiota–host crosstalk and multi-omics analyses enable biomarker discovery and integration. These findings support stratification and personalization through microbiome-guided and pharmacomicrobiomic strategies. Rigorous clinical trial design and precision therapeutics, including engineered probiotics and STING/GPR43 targeting, require policy and regulatory support to achieve standardized, personalized interventions for kidney disease.

Conclusion

UAN is emerging as a significant clinical and public health concern, particularly amid the global rise in HUA, obesity, and metabolic syndrome. Conventional perspectives that focus solely on urate crystallization and renal excretion have proven insufficient to explain the variable clinical presentations and the suboptimal outcomes of current therapies. Accumulating evidence now highlights the gut–kidney axis as a central integrative framework that connects intestinal microbiota, urate metabolism, immune signaling, and renal pathology.

This review has summarized how gut microbial dysbiosis, compromised intestinal barrier function, and imbalances in microbial metabolites contribute to both the onset and progression of UAN. It has further examined how elevated uric acid levels disrupt gut microbial ecosystems and systemic immunity, establishing a self-amplifying cycle of metabolic disturbance and chronic inflammation that culminates in kidney injury. Importantly, we discussed the emerging therapeutic potential of interventions that target this axis, including probiotics, synbiotics, FMT, dietary modification, and small-molecule modulators, which offer mechanistic advantages beyond traditional urate-lowering strategies.

Despite these promising developments, the clinical translation of microbiota-based approaches faces several barriers. These include high interindividual variability in gut microbiota composition, the absence of validated noninvasive biomarkers, and the lack of standardized clinical protocols for assessing gut–renal interactions. Nonetheless, ongoing advances in multi-omics profiling, computational modeling, and precision therapeutics are gradually overcoming these challenges.

Looking ahead, the integration of gut-targeted interventions into the clinical management of UAN offers a promising avenue for improving disease prevention, early diagnosis, and treatment outcomes. A systems biology approach that considers the interconnected roles of the gut, kidney, and immune system will be essential to shift the therapeutic focus from urate level control to comprehensive mechanism-based intervention.

By embracing the gut–kidney axis as both a conceptual model and a therapeutic platform, researchers and clinicians may uncover innovative strategies not only for UAN but also for other chronic diseases shaped by microbiota–metabolism–inflammation interactions. Moving forward, several actionable priorities will be essential for advancing

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the field. These include establishing standardized and clinically meaningful microbiome and metabolomic biomarkers to improve patient stratification, fostering interdisciplinary collaborations to accelerate translational research and clinical trial implementation, and harmonizing study designs with integrated multi-omics endpoints to more rigorously evaluate gut-targeted therapies. Collectively, these steps will help consolidate the gut–kidney axis as a foundation for next-generation precision medicine in UAN and beyond.

Acknowledgments

The figures in this article were created using BioRender. The authors sincerely thank the platform for its support in the professional scientific illustration.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Heilongjiang University of Chinese Medicine Graduate Student Innovation Research Project (Project No. 2025yjscx008).

Disclosure

The authors report no conflicts of interest in this work.

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