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Hyperuricemia: Gut-kidney axis connection, Mechanisms and applications for probiotic treatment, and future directions

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ABSTRACT: Hyperuricemia, a metabolic disorder marked by dysregulated uric acid (UA) metabolism, significantly contributes to the development of various chronic diseases. The homeostatic control of UA, affected by genetic background, environmental cues, and gut microbial activity, is essential for preventing dysregulated serum UA levels. Evidence indicates that high-purine diets cause gut dysbiosis and increase intestinal permeability, enabling translocation of harmful metabolites into systemic circulation. This can provoke renal inflammation and impair UA excretion, exacerbating hyperuricemia (HUA). The gut and kidneys interact bidirectionally through the gut-kidney axis, which is influenced by gut microbiota and their metabolites. Probiotics have demonstrated potential in restoring gut-kidney axis function and modulating UA metabolism by regulating the levels of short-chain fatty acids, bile acids, proline, and tryptophan derivatives. Nonetheless, comprehensive reviews on probiotic interventions for hyperuricemia remain scarce. This review explores the intricate interplay among gut-kidney axis, gut microbiota and metabolites, UA metabolism, and HUA. It further outlines the role of probiotics in regulating gut microbiota and UA metabolism. Finally, probiotic strategies including direct supplementation, functional foods, synbiotics, and delivery systems are summarized for the management of HUA. Despite this promise, challenges in strain selection, dosage standardization, and industrial scalability must be addressed. Future research should aim to improve the stability of probiotic formulations and develop personalized microbiota interventions based on individual variables.

Keywords: Hyperuricemia; Probiotics; Gut-kidney axis; Application

1. Introduction

Hyperuricemia (HUA), defined as elevated uric acid (UA) levels in serum (> 6.0 mg/dL in women, or > 7.0 mg/dL in men), is a common metabolic disorder characterized by either the overproduction or underexcretion of UA (Wu et al., 2023). The accumulation of UA can affect multiple systems and organs. In serum, UA primarily exists as sodium urate, and levels that exceed the saturation point result in the formation of monosodium urate crystals. The deposition of these crystals in the joints and other tissues triggers local inflammation, leading to intermittent pain (Lv et al., 2024). Besides, chronic HUA is associated with an increased risk of many diseases such as diabetes, hypertension, and renal diseases. The pathogenesis of HUA is multifactorial and involves intricate interactions, including abnormal UA metabolism, genetic predisposition,

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metabolic syndrome, unhealthy dietary patterns, and imbalanced gut microbiota (Mehmood et al., 2024).

The intricate interplay between the gut and kidneys has been elucidated, and understanding the mechanisms of substance exchange and signaling interactions along this axis is significant for investigating the pathogenesis of HUA. Dysbiosis of gut microbiota disrupts purine and UA metabolism and affects the production of short-chain fatty acids (SCFAs) and tryptophan-derived metabolites. Studies have shown that specific bacteria such as *Lactobacillus* and *Bifidobacterium* produce uricase, thereby degrading UA in the gut (Du et al., 2024). SCFAs produced by gut microbiota can modulate the expression of kidney UA transporters, thereby impacting UA reabsorption and secretion. Concurrently, some beneficial tryptophan-derived metabolites (including indole-3-acetic acid and indole-3-propionic acid) have been proved to potentially alleviate HUA by attenuating the inflammatory response and enhancing the function of colonic UA transport proteins (Q. Wang et al., 2024). Impaired gut barrier integrity leads to increased permeability, facilitating the translocation of harmful substances such as UA, bacteria and endotoxins into the systemic circulation. This process worsens HUA by boosting kidney reabsorption of UA through the upregulation of active transport mechanisms. The absorption of endotoxins further triggers systemic inflammation, activating the renin-angiotensin-aldosterone system and elevating the levels of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) (Kanugula et al., 2023). Moreover, gut-derived metabolites, including indoxyl sulfate (IS) and p-cresyl sulfate, exacerbate kidney dysfunction and contribute to the progression of chronic kidney disease (Koppe & Soulage, 2022). More importantly, these metabolites induce kidney inflammation and promote tubular damage, creating a feedback loop that not only impairs the kidneys' ability to handle UA but also exacerbates gut dysbiosis. Given this complex interplay, modulating the gut-kidney axis offers promising therapeutic avenues for HUA, particularly in regulating immune responses, restoring microbiota balance, and modulating metabolites.

Currently, treatment strategies for HUA focus on symptom relief and recurrence prevention. Clinical agents such as uricosuric medications and xanthine oxidase inhibitors are used to lower UA levels (Yuan et al., 2024). However, long-term use of these medications is often accompanied by side effects such as liver and kidney toxicity, hypersensitivity reactions, and gastrointestinal issues like diarrhea (Bi et al., 2024). Along with medication, lifestyle changes—such as reducing purine and fructose intake and increasing physical activity—are crucial for effectively managing HUA. Importantly, given the potential side effects and substantial economic burden associated with drug-based treatments, interventions focused on dietary improvements offer promising, safer, and more cost-effective alternatives for managing HUA.

Probiotics are active microorganisms that colonize the body and provide health benefits to the host (Cheng et al., 2025; You et al., 2025). Currently, they are being employed in the intervention of HUA in various forms, including oral liquids, capsules, and functional fermented foods rich in probiotics. Probiotics can modulate the gut-kidney axis by promoting microbial balance, enhancing intestinal epithelial barrier function, modulating UA metabolism, and suppressing inflammatory responses, thereby offering a potential therapeutic approach for managing HUA. For example, they can enhance UA metabolism and mitigate HUA-induced

kidney damage by modulating the NOD-like receptor protein 3/Caspase-1/Interleukin-1 β (NLRP3/Caspase-1/IL-1 β) inflammasome pathway (Zhao, Lu, et al., 2022). Some metabolites produced by probiotics, especially SCFAs, can influence host metabolism. Acetate, propionate, and butyrate are thought to facilitate UA excretion by serving as energy sources for intestinal cells, regulating the gut microbiota balance, reducing the absorption of UA precursors in the gut, and enhancing kidney excretion (James et al., 2023). Together, these mechanisms work synergistically to promote the elimination of UA. Therefore, probiotics have the potential to treat HUA through the gut-kidney axis and provide an effective way to ameliorate UA metabolism abnormalities and UA-induced inflammatory damage. However, a comprehensive understanding of the mechanisms involved remains limited, and the potential of probiotics as a therapeutic strategy has not been fully elucidated. While preliminary studies hint at the ability of probiotics to modulate gut microbial composition and improve metabolic disturbances, there is still a significant gap in systematic summaries and mechanistic insights. Therefore, this review aims to provide an in-depth analysis of the gut-kidney axis, the microbiota, and their metabolites in the regulation of UA metabolism, highlighting the potential of probiotics to treat HUA. Additionally, it assesses the pros and cons of various probiotic strategies for HUA intervention, emphasizing key factors such as bioavailability, cost-effectiveness, and safety. In summary, this review seeks to consolidate current knowledge and identify critical research gaps, thereby guiding the rational design of probiotic-based interventions for HUA with enhanced efficacy and translatability.

2. Predisposing factors and dangers of HUA

The pathogenesis of HUA is highly complex, involving the interaction of multiple factors (Figure 1). Research in the field of genome-wide association studies have identified some specific genes related to UA metabolism, such as SLC22A11, SLC22A12, SLC2A9, SLC22A4, and PDZK1 (Du et al., 2024). Abnormal expression of these genes may lead to the accumulation of UA, thereby increasing the risk of developing HUA. Besides, HUA has been shown to cluster in families, indicating a familial transmission pattern. Studies in South American ethnic groups have demonstrated heritability rates ranging from 39% to 45% (Du et al., 2024). However, genetic susceptibility alone cannot explain the changes in the incidence of HUA, where environmental exposures are considered another key driver of HUA onset. Numerous epidemiological studies have revealed that differences in lifestyle choices among individuals influence the onset of IBD, in which sedentary habits and medicine use are considered as representative risk factors. Behaviors characterized by reduced physical activity and energy expenditure are associated with obesity and chronic inflammation. These metabolic disturbances impair the function of kidney urate transporters, leading to decreased UA excretion (Copur et al., 2022). Excess UA crystals can deposit in the kidneys, causing renal damage, such as crystal-induced inflammation, tubulointerstitial fibrosis, and eventually leading to reduced glomerular filtration rate and kidney failure (L. Zhang et al., 2022).

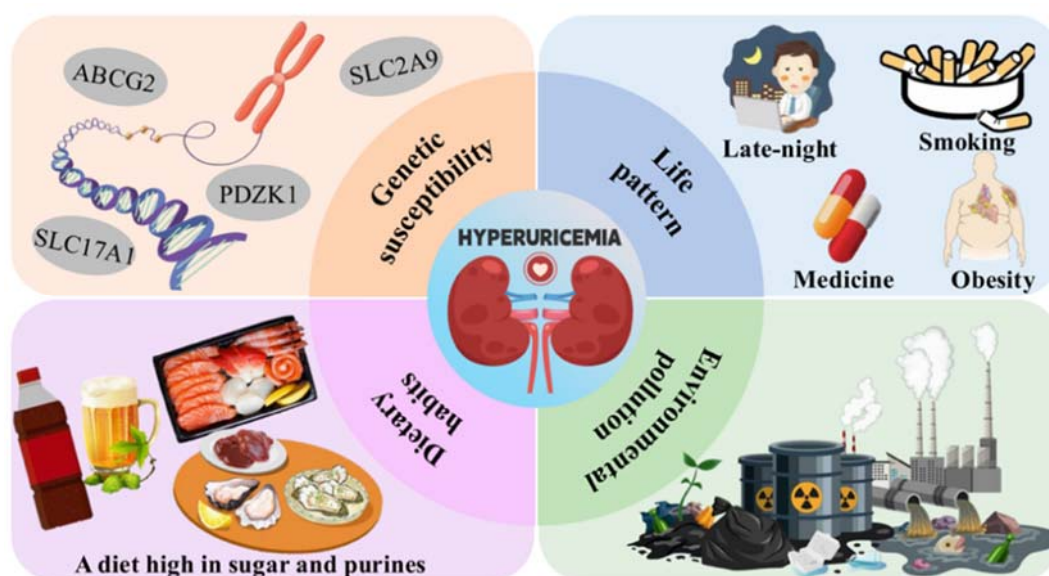


Figure 1. The multifactorial trigger diagram for HUA onset.

The liver serves as the primary site for UA production, metabolizing purines through various enzymatic processes. Elevated levels of UA can lead to significant metabolic disturbances in the liver, including hepatic steatosis, inflammation, and impaired liver function. Furthermore, insulin resistance associated with obesity and sedentary behavior disrupts normal lipid and glucose metabolism in the liver, exacerbating these metabolic disorders (Kuwabara, 2016). The chronic elevation of UA levels not only contributes to hepatic dysfunction but also creates a detrimental feedback loop, where impaired liver metabolism further increases UA production. Some medication including thiazide and loop diuretics can promote UA reabsorption by interfering with the renal sodium-urate cotransport mechanisms. Similarly, cyclosporine, commonly used in transplant patients, can induce HUA by reducing kidney blood flow and impairing urate handling (Nankivell et al., 2004). Additionally, influenced by geographical location differences, individuals exhibit significant variability in their living environments, affecting the incidence of HUA to varying degrees. The results of the National Health and Nutrition Examination Survey in the United States from 2001 to 2016 indicated that exposure to phenanthrene was positively associated with the prevalence of HUA in the population (C. Liu et al., 2024). Phthalate exposure lead to systemic immune inflammation, and elevated systemic immune inflammation can cause increased HUA risk (Niu et al., 2024). Moreover, microplastics and nuclear contamination may be involved in the development of HUA, although further investigation is warranted.

Unhealthy dietary habits are also key to the occurrence of HUA, including excessive intake of high-purine and high-fructose diets. UA originates from the breakdown of purines catalyzed by the oxidized and reduced forms of xanthine oxidoreductase and xanthine dehydrogenase (Du et al., 2024). Both endogenous purine metabolism and the intake of purine-rich diets (including meat, anchovies, sardines, soybeans, mushrooms and alcoholic beverages) contribute to UA production. Moreover, diet may alter the composition and functional characteristics of the individual's gut microbiota. Disturbances in gut microbiota caused by a western diet, characterized by high intake of carbohydrates and meat, along with low intake of dietary fiber, disrupt purine and UA metabolism, potentially increasing susceptibility to HUA (Danve et al., 2021). The

imbalanced gut microbiota can disrupt the gut barrier function, allowing harmful substances to translocate into the bloodstream, which may further burden the liver and kidneys.

Overall, HUA is influenced by a variety of factors, including genetics, diet, environment, and lifestyle, all of which significantly affect the health of the liver, kidneys, and gut. As illustrated in Figure 2, these organs interact in a bidirectional manner, with each organ's dysfunction potentially exacerbating the pathological processes in others. Despite the recognized importance of these organ interactions, current research has predominantly focused on the roles of the gut and kidneys in HUA, including the effects of gut microbiota dysbiosis on purine metabolism and UA homeostasis, as well as the renal and intestinal response to UA-induced inflammatory injury. In contrast, the specific mechanisms by which the liver contributes to HUA pathogenesis remain relatively understudied. This disparity in research focus underscores the need to synthesize existing knowledge on the gut-kidney axis in the context of HUA. In the following section, we summarize the current understanding of the intricate associations and functions of the gut and kidneys in HUA, aiming to illuminate the bidirectional communication and potential therapeutic targets within this organ-to-organ network.

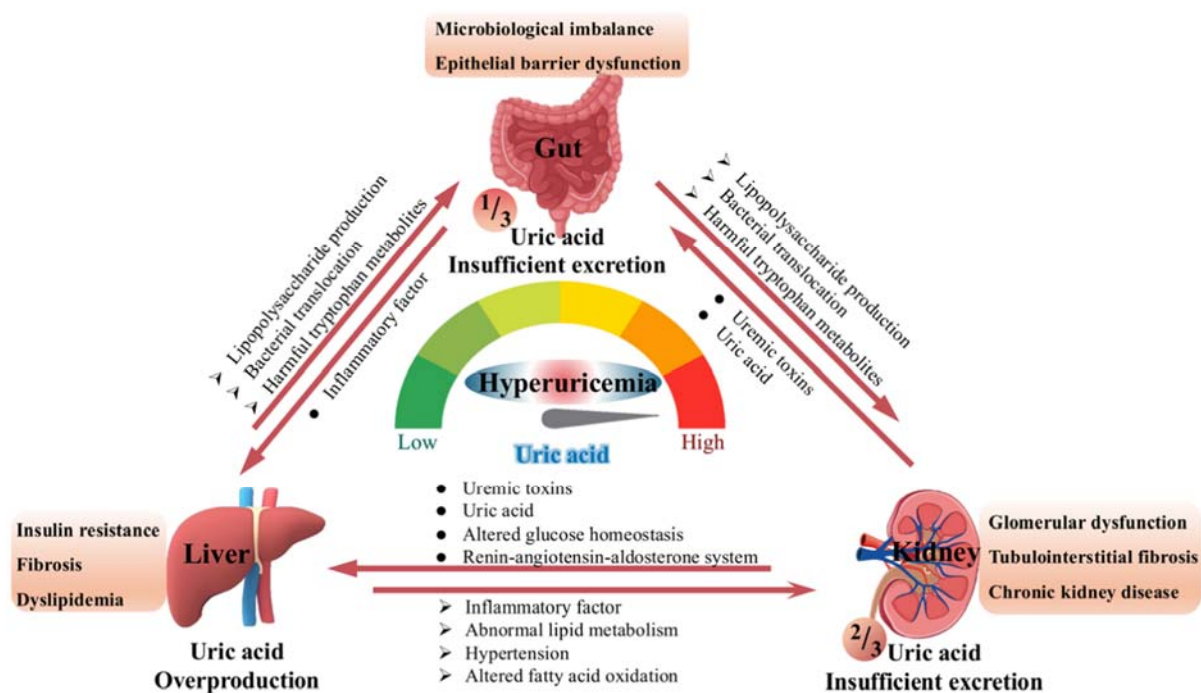


Figure 2. Gut-liver-kidney crosstalk in the pathophysiology of HUA.

3. Interaction between gut-kidney axis and HUA

The gut-kidney axis is a complex bidirectional network linking the gut and kidneys, involving gut barrier function, gut microbiota, immune system, and renal blood circulation pathways. The gut microbiota plays a crucial role in UA metabolism; when dysbiosis occurs, it may result in decreased UA excretion (Figure 3). Additionally, the damage to gut barrier allows inflammatory factors, harmful microbes, and their metabolites in the gut to enter the kidney through the systemic circulation, further inducing immune responses and UA metabolic disorders in the kidney (Figure 3).

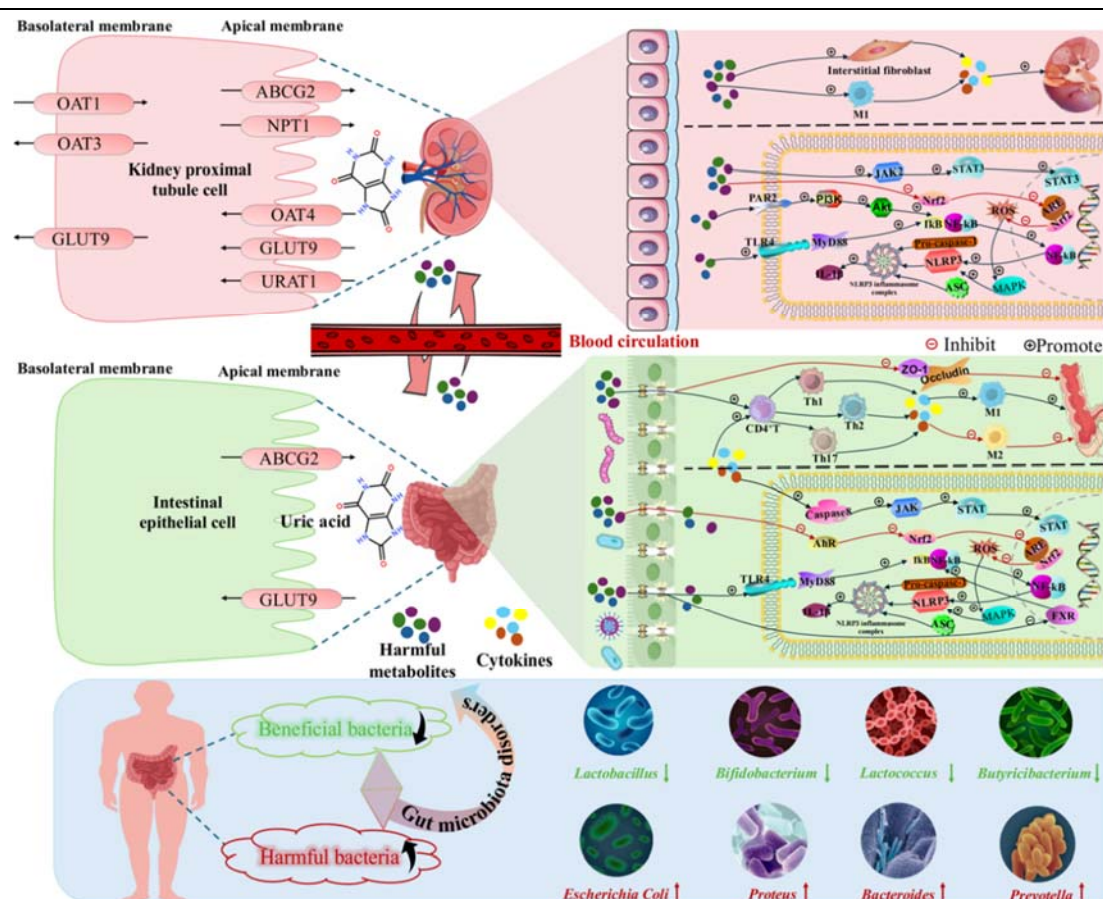


Figure 3. The pathogenesis of HUA and its impact on the gut-kidney axis.

3.1 Gut microbiota: critical players in purine and UA metabolism

80% of total UA levels are derived from the endogenous accumulation of nucleic acids, adenine, and guanine, while the remaining portion comes from purine-rich foods. UA is transported to the intestinal tract and kidneys through the bloodstream and is then excreted through feces and urine (Zhao, Chen, et al., 2022). Gut microbiota can regulate serum uric acid (SUA) levels by participating in the purine and UA metabolism. *L. gasseri* was found to bind and internalize purine derivatives (adenosine, inosine, and guanosine 5'-monophosphate) in the gut by exogenous addition of various purine derivatives labeled with C¹⁴ (Yamada et al., 2018). Besides, *Limosilactobacillus fermentum* JL-3 and *L. rhamnosus* Fmb14 reduced purine absorption in the gut (Wu et al., 2021; Zhao, Chen, et al., 2022). Compared to healthy individuals, HUA patients exhibit a significant reduction in microbiota diversity, along with alterations in composition, such as an increased Firmicutes to Bacteroidetes ratio and a decreased abundance of *Lactobacillus* (X. Lin et al., 2024). *Proteus* and *Escherichia coli* can secrete xanthine oxidoreductase, an important rate-limiting enzyme in the synthesis of UA from hypoxanthine and xanthine, and their quantities are significantly increased in the gut of HUA patients (Crane et al., 2013). The abundance of *Prevotella*, *Dehalobacterium*, and *Ruminococcus* was found to be remarkably lower in the rat model of HUA (Y.-X. Xu et al., 2024). Similarly, the levels of *Lactobacillus* and *Pseudomonas* with the ability to synthesize UA degrading enzymes were markedly reduced (J. Wang et al., 2022). The phenotype of elevated UA was found to be transmissible via fecal microbial transplantation from HUA donors. Conversely, transplanting fecal microbiota from healthy individuals into HUA rats significantly reduced SUA levels. However, rat models have not successfully replicated UA metabolism as it

occurs in humans. Furthermore, the current human studies often employ a cross-sectional design and involve multiple comorbidities, which compromises biological validation and makes it difficult to draw causal inferences. Notably, fluctuations in SUA have been linked to gut microbiota in patients with diabetes mellitus or cardiovascular disease (W. Zhang et al., 2022; Zhang et al., 2024). Thus, these challenges underscore the need for more robust methodologies in studying the relationship between gut microbiota and SUA levels.

3.2 Gut barrier function: central nexus in immune activation and kidney inflammation

The gut barrier comprises various structural and functional components, which form coordinated and dynamic networks responding to the microenvironment. Thereinto, tight junction proteins, the gut microbiota, and immune cells work together directly or indirectly to maintain the integrity and function of the gut epithelial barrier. Once the integrity of the intestinal barrier is impaired, this collaborative dynamic is disrupted. Research has shown that in UA oxidase-knockout mice and individuals with HUA, there is a decrease in the expression of gut tight junction proteins such as zonula occludens-1 and occludin, leading to damage of the gut mucosal barrier (Wang & Ye, 2024; Zhou et al., 2024). This barrier injury directly triggers an immune cascade: lipopolysaccharides (LPS) activate macrophages via the TLR4/MyD88 pathway, inducing the release of pro-inflammatory cytokines such as IL-1 β and TNF- α . These cytokines further promote apoptosis of intestinal epithelial cells through the CASP8/JAK2-STAT1 signaling pathway. Notably, UA exacerbates processes associated with intestinal barrier damage and immune activation through a dual mechanism. On the one hand, UA crystals act as danger-associated molecular patterns (DAMPs), activating the NLRP3 inflammasome in macrophages and promoting IL-1 β release (Mei et al., 2022). On the other hand, UA binds to the urate transporter 1 (URAT1) receptor on macrophages, inhibiting their phagocytic activity and weakening their ability to clear pathogenic bacteria in the gut (Martínez-Reyes et al., 2020). The damage is not limited to the intestinal environment; leaked LPS, pro-inflammatory cytokines, and activated immune cells enter the systemic circulation via the portal vein, further triggering a systemic inflammatory response. In the kidneys, circulating IL-17 induces the recruitment of Th17 cells, promotes renal interstitial fibrosis, and suppresses the expression of the ATP-binding cassette subfamily G member 2 (ABCG2) (Lv et al., 2020). Simultaneously, LPS and UA crystals in the blood synergistically activate renal macrophage NLRP3 inflammasomes, leading to the release of IL-1 β and further tubular injury. Therefore, dysfunction of the gut barrier exacerbates the pathological progression of HUA through a cascade of "immune activation—systemic inflammation—renal damage."

3.3 Metabolic regulatory network of the gut-kidney axis: interactions between microbial metabolites and uric acid homeostasis regulation

Metabolites (including SCFAs, bile acids, proline, and tryptophan derivatives) produced by the gut microbiota are crucial in regulating the physiological functions of HUA patients. SCFAs, including butyrate, propionate, acetate, and isovalerate, are the end products of gut microbiota fermentation. They play a crucial role in regulating UA metabolism and maintaining renal homeostasis. Specifically, butyrate has been proven to promote intestinal UA excretion by upregulating ABCG2 expression and modulating purine metabolites

(Rongshuang et al., 2025). It is noteworthy that this regulatory process may be associated with the ligand-dependent transcription factor in the nuclear hormone receptor superfamily—peroxisome proliferator-activated receptor gamma (PPAR- γ). PPAR- γ is widely expressed in renal tissue, and its activation is known to modulate renal inflammatory responses (for instance, by inhibiting the NF- κ B pathway to reduce the release of pro-inflammatory cytokines such as IL-1 β and TNF- α) as well as the progression of fibrosis (Sharma & Patial, 2022). More importantly, it plays a crucial role in regulating renal excretory functions. Studies have demonstrated that in mouse models of hyperuricemic nephropathy, the PPAR- γ agonist rosiglitazone enhances the kidneys' ability to excrete UA by maintaining the expression levels of organic anion transporters (OATs), including OAT1 (SLC22A6) and OAT3 (SLC22A8), consequently leading to a reduction in SUA levels (Wang et al., 2020). Besides, metabolites produced by intestinal microbiota, such as acetate and propionate, have been shown to function as endogenous ligands for PPAR- γ or influence the PPAR- γ signaling pathway by activating G protein-coupled receptors. This multi-pathway regulation may ultimately ameliorate inflammatory damage and impaired excretory function in chronic kidney disease (Li et al., 2019; Olaniyi et al., 2023). Besides, SCFAs play a crucial role in regulating energy metabolism, immune cell function, gut mucosal barrier, and intestinal homeostasis. They have been shown to mitigate renal inflammation and injury by inhibiting the Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway (Xiong et al., 2024).

Bile acids (BAs), the end products of cholesterol metabolism, are crucial players in the gut-kidney axis. A community-based cohort study revealed BAs metabolites are closely associated with the abundance of gut microbiota (e.g., *Fusobacterium mortiferum* and *Blautia sp.* CAG-257), and alterations in both collectively mediate SUA levels in HUA patients (Zhuo et al., 2024). In the gut, BAs not only facilitate nutrient absorption and lipid metabolism but also profoundly shape the composition and function of the gut microbiota. This microbial landscape, in turn, influences the expression and activity of BAs receptors like farnesoid X receptor (FXR) and G protein-coupled receptor 5 (TGR5), which are abundant on immune cells and modulate intestinal immunity. Notably, BAs also directly affect xanthine oxidase (XOD), a key enzyme in UA synthesis, through nuclear receptor signaling. For example, Koyanagi et al. (2018) found that as the time-dependent accumulation of BAs, the recruitment of the co-transcriptional activator p300 to peroxisome proliferator-activated receptor- α (PPAR- α) was impaired, resulting in decreased expression of intestinal XOD. Conversely, dysregulation of BAs signaling (e.g., intestinal FXR deficiency or inhibition) disrupts this balance and contributes to HUA, with studies highlighting sex-specific differences in this pathological process (Bao et al., 2025). Mechanistically, intestinal FXR deficiency activates TNF- α signaling cascades. On the one hand, TNF- α directly upregulated intestinal XOD expression. On the other hand, activated TNF- α disrupted the phosphatase and tensin homolog (PTEN)/PI3K pathway, resulting in increased AKT phosphorylation—a modification that further enhances XOD enzymatic activity (Bao et al., 2025). This dual effect of FXR deficiency (elevated XOD expression and enhanced XOD activity) amplifies UA production, underscoring the critical role of intestinal BAs-FXR signaling in maintaining UA metabolic homeostasis. Beyond the gut, BAs are transported

via the systemic circulation to the kidneys, where they regulate multiple renal functions. For instance, they can inhibit the renin-angiotensin-aldosterone system through FXR activation, ensuring proper renal blood flow, glomerular filtration rate, and the excretion of UA (Guo et al., 2023). TGR5 is highly expressed in tubular cells as well as in glomerular cells, including podocytes and mesangial cells (Yang et al., 2016). BAs can activate receptors such as FXR and TGR5 to dampen inflammation, reduce oxidative stress, and protect kidney cells from damage in HUA models (P. Liu et al., 2024). All in all, the relationship between BAs and UA levels is complex. Existing studies point to several potential pathways, including the BAs-mediated regulation of XOD activity, interactions with the gut microbiota, and modulation of renal transport function. However, the precise underlying mechanisms are still not fully understood. Further research is essential to elucidate these interactions and their implications for HUA treatment.

Recent studies have identified proline metabolism as a critical key node for distinguishing HUA patients from healthy individuals (Shen et al., 2021). Additionally, proline has demonstrated a protective role in renal tissues by mitigating oxidative stress (Song et al., 2022). One investigation further revealed that stimulation with nucleosides significantly elevates proline levels in the extracellular products of *Lactobacillus rhamnosus* GG (Fu et al., 2024). *In vitro/vivo* experiments indicate that proline can attenuate intestinal nucleoside transport and UA reabsorption, while concurrently down-regulating hepatic purine synthesis. These findings suggest that proline may serve as a potential therapeutic target for managing HUA. Tryptophan is metabolized via three major pathways, modulated directly or indirectly by gut microbiota, to produce kynurenine, serotonin, and indole derivatives. Its increased metabolism facilitates the regulation of gut-kidney axis homeostasis, thereby alleviating HUA. Firstly, the influence of the gut microbiota on host tryptophan metabolism in kynurenine pathway is associated with the immune system. Kynurenic acid, cinnabarinic acid, and xanthurenic acid produced by kynurenine pathway function as direct ligands of aryl hydrocarbon receptor (AhR), stimulating AhR-dependent gene expression, and simultaneously modulate intestinal homeostasis (Gao et al., 2018). Secondly, approximately 1-2% of ingested tryptophan is converted to serotonin by enterochromaffin cells, which plays an important role in gut motility and immune regulation. Serotonin is not an AhR ligand, but it can bind with AhR ligands, as a cytochrome P4501 (CYP1) enzymes substrate, to prevent ligand inactivation. Finally, the indole pathway, such as indole-3-acetic acid (IAA), indole-3-aldehyde (I3A), indole-3-lactic acid (ILA), and indole-3-propionic acid (IPA), which are primarily metabolized by symbiotic bacteria in the gut. For instance, tryptophan could be metabolized to I3A by *Lactobacillus spp.*, to ILA by *Bifidobacterium spp.*, to IAA by *Bacteroides spp.* and *Clostridium spp.*, and IPA by *Peptostreptococcus spp.* (Liu et al., 2021). It has been demonstrated that IPA and IAA may inhibit the inflammatory response associated with gut NLRP3/gasdermin D pyroptosis, while also increasing ABCG2 expression to promote UA excretion in the gut (Q. Wang et al., 2024). Overall, beneficial metabolites can alleviate HUA by maintaining the balance of gut microbiota, ameliorating disturbances in UA metabolism, and reducing inflammation.

3.4 Dysfunction of the gut-kidney axis: a driving force exacerbating HUA

The gut-kidney axis dysregulation refers to the disruption of normal bidirectional communication

between the gut and kidneys—an interplay where dysfunction in either organ propagates pathological changes in the other. This dysregulation is typically associated with gut microbiota imbalances, gut barrier dysfunction, and altered signaling between the two organs.

Gut dysbiosis, by altering gut UA metabolism and disrupting immune homeostasis, synergistically initiates complex immunometabolism disturbances in HUA patients. Besides, damage to mucosal integrity and permeability results from gut dysbiosis, and the increased translocation of gut-derived LPS to the kidney via blood circulation can promote Toll-like receptor 4/myeloid differentiation primary response protein 88/nuclear factor kappa-B (TLR4/MYD88/NF- κ B) inflammatory cascade response in HUA, forming LPS/TLR4 axis, which subsequently impaired the excretion of UA in the kidney (Bian et al., 2020). More importantly, disruption of intestinal immune homeostasis, characterized by Treg cell dysfunction, Th17 cell overactivation, and decreased immunoglobulin A (IgA) secretion, results in sustained and amplified inflammatory responses (Monteiro & Berthelot, 2021). These pathological changes are reflected in serum markers, with studies showing significant elevations in blood urea nitrogen (BUN) and creatinine (CRE) in rat models of HUA (J. Xu et al., 2024). Compromised intestinal barrier integrity also permits the translocation of peptidoglycans and bacterial DNA into the systemic circulation, leading to the activation of NOD-like receptors, particularly the NLRP3 inflammasome. MSU crystals, acting as endogenous danger-associated molecular patterns, directly stimulate the NLRP3 inflammasome, resulting in the release of IL-1 β and IL-18 (Chen et al., 2025). These inflammatory mediators induce renal tubular cell damage, thereby impacting the expression and activity of crucial urate transporters, including URAT1, organic anion transporter 1 (OAT1), OAT3, and ABCG2. In addition, they are activators of the JNK2/signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathway, which plays a crucial role in kidney inflammation and fibrosis (Lin et al., 2021). More in-depth studies suggest that inflammatory factors may regulate the expression of UA transporter proteins through epigenetic modifications (e.g., DNA methylation and histone acetylation), leading to decreased renal excretion of UA. Elevated levels of UA can stimulate inflammatory cells to release cytokines such as IL-1 β and TNF- α , which can inhibit the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signaling pathway through various mechanisms, thereby exacerbating kidney injury in HUA patients (Y.-j. Chen et al., 2024).

In addition to the immune response, metabolites produced by gut microbiota play a significant role in gut-kidney axis. Uremic toxins, including IS and p-cresol, harm the kidneys through direct toxicity or activation of the AhR pathway (Xie et al., 2024). AhR is a transcription factor expressed in cells, and its signal transduction is tightly regulated by CYP1 in a feedback loop, controlling ligand availability and activating the AhR pathway. As AhR ligands, these toxins trigger the AhR/CYP1 pathway, leading to increased inflammation and oxidative stress. Besides, trimethylamine N-oxide (TMAO), a key uremic toxin produced by gut microbiota-mediated choline metabolism, acts as a signaling molecule to suppress the Nrf2/glutathione peroxidase 4 (Nrf2/GPX4) axis, thereby inducing ferroptosis (Xie et al., 2024). This ferroptosis in kidney tissue contributes to inflammation and fibrosis, ultimately accelerating the progression of hyperuricemia.

Critically, renal dysfunction and uremia directly alter gut microbiota composition and impair intestinal barrier integrity, creating a pathological feedback loop. Impaired renal excretion leads to systemic accumulation of uremic toxins (e.g., IS, p-cresol, TMAO) that are not fully cleared by the kidneys in HUA patients. The presence of elevated uremic toxins such as IS and p-cresol not only contributes to kidney damage but also alters gut microbial composition, promoting dysbiosis. This dysbiosis manifests as a reduced diversity of gut microbiota and a decrease in beneficial bacterial species. For example, through an analysis of the gut microbiota in 103 patients with chronic kidney disease stages 1 to 5 and 46 healthy controls, Kim et al. (2020) found that, compared to healthy individuals, the relative abundance of *Alistipes* and *Oscillibacter* increased with the severity of chronic kidney disease. Lv et al. (2023) suggested that *Ruminiclostridium*, *Bacteroides*, *Bilophila*, *Burkholderiaceae* and *Parasutterella* were the key bacteria that play vital roles in the progression of HUA and compromised intestinal barrier. Uremia-induced systemic metabolic disturbances also compromise intestinal barrier function. Renal impairment disrupts systemic acid-base balance, leading to metabolic acidosis—a key driver of intestinal epithelial cell injury (Kim, 2021). Acidosis alters the expression of tight junction proteins (e.g., occludin, zonula occludens-1) in the gut mucosa, increasing paracellular permeability. Uremic toxins such as IS can suppress intestinal immune responses by increasing the expression of cyclooxygenase-2, nitrotyrosine, and Bcl-2-associated X protein (Rapa et al., 2021). Additionally, recent studies have found IS can induce intestinal barrier injury, as the intervention of intestinal epithelial cells with IS suppressed the transepithelial electrical resistance and the expression of tight junction-related genes (Li et al., 2025). It is suggested that impairment of mitophagy, mediated by the interferon regulatory factor 1-dynamin-related protein 1 axis, contributes significantly to IS-induced intestinal barrier damage (Huang et al., 2020). This impaired barrier permits increased translocation of gut-derived toxins and bacteria into the circulation, amplifying renal inflammation and UA excretion dysfunction, thus perpetuating the gut-kidney axis pathology.

Overall, gut-kidney axis dysfunction is a complex pathological process involving multifaceted interactions between the gut microbiota, the immune system, and various metabolites. Disruption of this axis creates a self-reinforcing loop: gut dysbiosis drives renal injury and impaired UA excretion, while renal dysfunction reciprocally exacerbates gut dysbiosis and barrier impairment. Recognizing the significance of these mechanisms is crucial for providing novel avenues for HUA treatment, encompassing precise modulation of gut microbiota, targeting inflammatory pathways, and the manipulation of specific metabolites.

4. Mechanisms of probiotics in treating HUA through the gut-kidney axis

Probiotics are increasingly recognized for their safety and potential health benefits, as these beneficial microorganisms help regulate gut microbiota and UA metabolism. Mechanistically, they prevent UA disorders through the following aspects: (i) modulating the production and excretion of UA, (ii) inhibiting the inflammation of kidney and gut, (iii) enhancing gut microbial diversity and its production of beneficial metabolites, and (iv) additional mechanisms that include the regulation of lipid metabolism and liver function. Table 1 summarizes the probiotics studied for HUA treatment, including their strains, proposed mechanisms,

and observed outcomes, highlighting the potential of probiotics as a therapeutic approach for HUA.

4.1 Degradation and absorption of purines in the gut

Purines in the body exist as nucleotides, nucleosides, and bases. In the absence of uricase, they are ultimately excreted after being converted from nucleotides to nucleosides, then to bases, and subsequently to xanthine, which is oxidized to UA by xanthine oxidase. Probiotics can reduce UA production through the assimilation of purine substances, thereby alleviating HUA. However, different strains exhibit significant variations in their ability to utilize different forms of purines (nucleotides, nucleosides, nucleobases). For example, *L. gasseri* PA-3 has been shown to incorporate hypoxanthine, inosine, and inosine 5'-monophosphate (Yamada et al., 2017), while *Levilactobacillus brevis* PDD-5 and *Lactocaseibacillus rhamnosus* Fmb14 compete with intestinal epithelial cells for dietary purine nucleosides, limiting host absorption of these UA precursors (J. Xu et al., 2024; Yamada et al., 2017; Zhao et al., 2023). The result also showed that *L. brevis* PDD-5 exhibited significantly higher uptake capacities for inosine and guanosine, reaching approximately 68.9% and 95.8%, respectively, compared to *L. rhamnosus* Fmb14. Notably, certain strains such as *L. gasseri* PA-3 and *L. brevis* GRX821 can bind both purine mononucleotides and nucleosides (Kano et al., 2020; H. Wang et al., 2024)—a dual capability that enhances their efficiency in reducing host purine uptake, as nucleotides represent a significant fraction of dietary purines.

Host absorption of nucleobases is inherently lower than that of nucleosides, as evidenced by mice fed a nucleobase-rich diet exhibiting lower SUA levels compared to those fed nucleosides (M. Li et al., 2023). This physiological trait (differential absorption of purines) highlights the relevance of probiotic nucleoside hydrolase activity. Specific bacteria, particularly *Lactobacillus*, *Escherichia coli*, *Clostridium*, and *Acetobacter*, were known to produce nucleoside hydrolases (Shaposhnikov et al., 2023). It was shown that *L. brevis* DM9218, *L. reuteri* TSR332, and *L. aviarius* CML180 produce nucleoside hydrolases, which can convert nucleosides to nucleobases (Kuo et al., 2021; D. Li et al., 2023; Wang et al., 2019). Further, *L. plantarum* encodes three ribonucleoside hydrolases (RihA, RihB, RihC) that catalyze nucleoside degradation into hypoxanthine and guanine (M. Li et al., 2023). Critically, these strains lack enzymes to convert hypoxanthine/guanine to xanthine and UA, effectively blocking the downstream UA synthesis pathway. Overall, the differences in purine-utilizing capabilities among probiotic strains explain the variations observed in the effectiveness of different probiotic interventions in alleviating HUA.

Table 1. Some probiotics reported for HUA treatment

Probiotics	Models and dosage	Inflammation reaction	Kidney function	UA synthesis and excretion	Gut microbiota and its metabolites	Reference
<i>L. rhamnosus</i> UA260	Male C57BL/6 mice (1×10^9 cfu/d)	↓IL-1 β ↓LPS ↓NLRP3/Caspase-1/GSDMD signaling pathway	N/A	Gut: ↑ABCG2	↑ <i>Lactobacillus</i> ↑ <i>Coprococcus</i> ↑Indole-3-propionic acid ↑Indole-3-acetic acid	(Q. Wang et al., 2024)
<i>L. rhamnosus</i> NCUH0610 12	Male KM mice (1×10^9 cfu/mL)	↓TNF- α ↓IL-1 β	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↓OAT1 ↓GLUT9 ↓URAT1 Gut: ↑ABCG2	↑Firmicutes ↓Bacteroidetes ↑Acetate ↑Propionate ↑Butyrate ↑Succinic acid	(X. Zhao et al., 2024)
<i>L. rhamnosus</i> GG	Male goslings (1×10^{10} cfu/mL)	↓IL-1 β ↓TNF- α	↓BUN ↓CRE	Serum: ↓UA Kidney: ↓URAT1 ↑ABCG2 ↓GLUT9	↑Lactobacillaceae ↑ <i>Lactobacillus</i> ↑ <i>Butyricicoccus</i> ↑Ruminococcaceae	(Fu et al., 2024)
<i>L. rhamnosus</i> Fmb14	Male Kunming mice (1×10^9 cfu/mL)	↓IL-1 β ↑IL-10 ↓NF- κ B signaling pathway	↓BUN ↓CRE	Liver: ↓XOD Kidney: ↓URAT1 ↑ABCG2	↑ <i>Bacteroides</i> ↑ <i>Ruminococcus</i> ↑Isobutyric acid ↑Isovaleric acid	(Zhao, Chen, et al., 2022)
<i>L. rhamnosus</i> 2016SWU.0 5.0601	Male Kunming mice (1×10^8 cfu/kg)	N/A	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↑ABCG2 ↓URAT1 ↓GLUT9	↑ <i>Enterorhabdus</i> ↑Lachnospiraceae ↑ <i>Akkermansia</i> ↑ <i>Monoglobus</i> ↑Taurohyocholate ↑Caffeyl alcohol	(Y. Chen et al., 2024)
<i>L. reuteri</i> RE225	Male ICR mice (1×10^9 cfu/mL)	↓TLR4/MyD88/NF- κ B signaling pathway	↓CRE	Serum: ↓UA ↓XOD	↑ <i>Lactobacillus</i> ↑ <i>Ruminococcus</i> ↑ <i>Alistipes</i>	(Qin et al., 2025)
<i>L. plantarum</i> X7022	Male ICR mice (1×10^{10} cfu/mL)	↓IL-1 β ↓TNF- α	↓BUN ↓CRE	Liver: ↓XOD Kidney: ↑OAT1 ↓GLUT9	↑Lactobacillaceae ↓Helicobacteraceae ↑fecal propionate ↑butyrate	(Zou et al., 2024)
<i>L. plantarum</i> MC14	Male KM mice (1×10^9 cfu/mL)	↓IL-1 β ↓TNF- α ↓IL-6 ↓PI3K/AKT/mTOR signaling pathway	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↑OAT1 ↑ABCG2	↑Desulfobacterota ↑ <i>Alloprevotella</i> ↑ <i>Candidatus_Arthromitus</i>	(Xiong et al., 2024)
<i>L. plantarum</i> DY1	Male Kunming mice (1×10^9 cfu/mL)	↓IL-1 β ↓TNF- α	↓CRE	Serum: ↓UA ↓XOD Liver: ↓XOD ↓ADA	↓ <i>Bacteroides</i> ↑ <i>Enterorhabdus</i> ↓Indoleacetaldehyde ↓3-(3-indolyl)-2-oxopropanoic acid	(Zhu et al., 2024)
<i>L. plantarum</i>	Male Kunming mice (1×10^8 cfu/mL)	N/A	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↑ABCG2 ↓GLUT9 ↑NPT1 Gut: ↑ABCG2	↓ <i>Lactobacillus johnsonii</i> ↓ <i>Lactobacillus reuteri</i> ↑ <i>Lactobacillus murinus</i> ↑Propionate	(M. Li et al., 2023)

<i>L. plantarum</i> LLY-606	C57BL/6J male mice (1×10 ⁹ cfu/mL)	↓IL-1β ↓TNF-α ↓IL-6 ↓TLR4/MyD88/NF-κB signaling pathway	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↓OAT4 ↓GLUT9 ↓URAT1 ↑OAT1 ↑ABCG2	↑ <i>Akkermansia muciniphila</i> ↑ <i>Lactobacillus plantarum</i> ↑Acetate ↑Butyrate ↑Propionate	(Shi et al., 2023)
<i>L. pentosus</i> P2020	Male Kunming mice (1×10 ⁹ cfu/0.3 mL)	↓TNF-α ↓IL-6 ↓TLR4/MyD88/NF-κB signaling pathway	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD ADA Kidney: ↓ABCG2 ↓GLUT6 ↑OAT3	↑Firmicutes ↓Bacteroidetes ↑ <i>Prevotella</i> ↓ <i>Clostridium XlVa</i>	(Wang et al., 2023)
<i>L. fermentum</i> F40-4	Male Balb/c mice (1×10 ⁹ cfu/mL)	↓IL-1β ↓TNF-α	↓BUN ↓CRE	Serum: ↓UA ↓XOD ↑NPT1	↑Firmicutes ↓Bacteroidetes ↑Akkermansiaceae	(Cao et al., 2023)
<i>L. brevis</i> PDD-5	Male SD rats (1×10 ⁸ - 1×10 ¹⁰ cfu/mL)	↓TNF-α ↓IL-1β ↓IL-6 ↓NLRP3/ASC/Caspase-1 signaling pathway	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↓URAT1 ↓GLUT9 ↑OAT1	N/A	(J. Xu et al., 2024)
<i>L. aviarius</i> CML180	Male Kunming mice (1×10 ⁸ cfu/mL)	↓IL-1β	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↑OAT3 ↑OCTN2	N/A	(D. Li et al., 2023)
<i>L. acidophilus</i> F02	Male KM mice (1×10 ⁹ cfu/mL)	↓TNF-α ↓IL-1β ↓IL-12 ↓iNOS ↓LPS ↓NLRP3/ASC/Caspase-1 signaling pathway	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD ADA	↑ <i>Alloprevotella</i> ↑ <i>Bacteroides</i> ↑ <i>Lactobacillus</i> ↑ <i>Prevotella</i> ↑ <i>Ruminococcus</i> ↑ <i>Enterorhabdus</i>	(Meng et al., 2023)
<i>Heyndrickxi</i> <i>a coagulans</i> TBC169	Male SD rats (6×10 ⁸ cfu/mL)	N/A	N/A	Serum: ↓UA ↓XOD Gut: ↑ABCG2	↓ <i>Helicobacter</i> ↓ <i>Staphylococcus</i>	(Duan et al., 2025)
<i>Enterococcus faecalis</i> W5	Male C57BL/6J mice (2×10 ⁹ cfu/mL)	N/A	↓BUN ↓CRE	Kidney: ↓XOD Gut: ↓GLUT9 ↑ABCG2	↑Isovaleric acid ↑Caproic acid	(X. Liu et al., 2024)
<i>Akkermansia muciniphila</i>	Male ICR mice (1×10 ⁹ cfu/mL)	↓IL-1β ↓TNF-α ↓IL-6 ↓Caspase 1	↓BUN ↓CRE	Serum: ↓UA Liver: ↓XOD Kidney: ↓GLUT9 ↓URAT1 ↑ABCG2	↑ <i>Ruminococcus</i> ↑ <i>Oscillospira</i> ↑Valeric acid ↑Butyrate ↑Propionate	(L. Zhang et al., 2022)

4.2 Enhancement of UA elimination

UA excretion in the human body primarily occurs through the kidneys (approximately 70%) and the gut (about 30%), which is essential for maintaining SUA levels. The regulation of UA excretion involves various transport proteins, including urate reabsorption proteins such as GLUT9, OAT10, OAT4, and URAT1, as well as urate secretion transporters like OAT1, OAT3, multidrug resistance proteins MRP2 and MRP4, nicotinate phosphoribosyl transferase 1 (NPT1), and ABCG2. Recent studies have highlighted the role of probiotics in influencing UA excretion. On the one hand, they can enhance the expression of urate secretion transporters

while inhibiting reabsorption proteins. On the other hand, they may directly degrade UA or convert it into more soluble derivatives, such as allantoin, thereby facilitating its excretion. *Lactiplantibacillus pentosus* P2020 promoted UA excretion by regulating the levels of UA transporters (ABCG2 and OAT1), thus reducing UA content (Wang et al., 2023). HUA-induced reduction in gene expression levels of OAT1 and OAT3, along with the elevation of URAT1 and Glucose transporter 9 (GLUT9) in mice, was significantly reversed by the intervention of *L. paracasei* MJM60396 (Lee et al., 2022). Conjugated linoleic acid, a specific metabolite produced by *L. plantarum* X7023, has been reported to reduce SUA levels by regulating the transcription of GLUT9 and URAT1 (Ro et al., 2024). Besides, it was shown that *L. rhamnosus* UA260, *L. fermentum* Fmb14 and *L. plantarum* LLY-606 similarly enhance ABCG2 expression to alleviate HUA symptoms (Shi et al., 2023; Q. Wang et al., 2024; Zhao, Chen, et al., 2022). Interestingly, the results revealed that *L. fermentum* Fmb14 exhibited more pronounced anti-hyperuricemic effects, which may be attributed to its stronger bile salt hydrolase activity or enhanced colonization capacity. The adhesion rate of Fmb14 reached 55.6% after co-culturing with Caco-2 cells for 3 h, and it demonstrated excellent tolerance to bile salts (Zhao, Chen, et al., 2022). Taken together, these animal study findings highlight a potential association between probiotics (and their metabolites) and urate transporter modulation, suggesting such microbial interventions may help regulate UA excretion and mitigate HUA-related phenotypes. However, the specific mechanistic pathways through which probiotics or their bioactive metabolites regulate urate transporters remain poorly defined. This critical knowledge gap warrants further investigation to deepen understanding of the gut microbiota-urate metabolism axis and provide a robust theoretical basis for targeted probiotic-based HUA management.

Certain probiotics can directly break down UA through the production of uricase, an enzyme that converts UA into allantoin, a more soluble compound that can be excreted from the body. El-Dein et al. concluded that *L. plantarum* strains KU985438 and KU985439 are viable candidates for uricase production based on their uricase production in simulated gastrointestinal systems (El-Dein et al., 2023). Subsequently, the significant decrease in UA and inflammatory cytokine levels in the HUA rat model confirmed their potential for fermenting functional yogurt that exhibited hypouricemic and anti-inflammatory properties. *L. brevis* SF121, *L. plantarum* Mut-7 and *L. plantarum* Dad-13 could produce uricase while remaining active in the respective environments (Handayani et al., 2017, 2018; Yasiri & Seubsasana, 2020). Currently, various techniques were available to assess uricase activity, ranging from qualitative methods that observed UA consumption on solid media to quantitative approaches that measured H₂O₂ production or UA degradation using spectrophotometry and chromatography (Huang & Wu, 2004; Pugin et al., 2022; Pustake et al., 2019). While spectrophotometric and fluorescent methods hold promise for the development of high-throughput screening assays due to the efficiency, their non-specific nature may introduce analytical artifacts, particularly in complex media. Overall, further studies are essential to efficiently screen for uricase-producing probiotic strains and accurately investigate uricase activity *in vitro/vivo*.

4.3 Modulation of gut microbiota homeostasis

The interplay between gut microbiota, mucosal barrier integrity, and metabolites is crucial for

understanding the pathophysiology in HUA. Dysbiosis, characterized by reduced microbial diversity, leads to decreased SCFAs production and increased harmful tryptophan metabolites (Wang & Ye, 2024). When SCFAs levels are low due to dysbiosis, the gut mucosal barrier may become compromised, resulting in increased intestinal permeability. This heightened permeability allows inflammatory mediators and gut-derived uremic toxins to enter systemic circulation, exacerbating inflammation and promoting further UA accumulation (Zhou et al., 2024). Consequently, therapeutic interventions aimed at restoring gut microbiota balance in HUA patients may enhance SCFAs synthesis, regulate tryptophan metabolism, reinforce mucosal barrier function, and subsequently mitigate systemic inflammation.

Recent evidence emphasizes the potential of probiotic interventions in restoring gut microbiota balance. Cao et al. (2023) reported a correlation between HUA and disrupted gut microbiota balance, while their findings also indicated an association between *L. fermentum* F40-4 administration and favorable shifts in the gut microbiota—specifically, increased relative abundances of *Lactobacillus* and *Akkermansia*. Besides, Bi et al. (2024) found that administration of *L. paracasei* 259 to rats with HUA could increase the abundances of Bacteroidetes and Firmicutes to levels approaching normal and significantly elevate abundances of *Bifidobacterium* and *Lactobacillus*. *L. rhamnosus* UA260 and YU28 affected tryptophan metabolism by modulating the gut microbiota structure in HUA mice (i.e., increased IAA and IPA levels), thereby reducing gut inflammation, repairing damage to the gut barrier, and increasing the ABCG2 expression (Q. Wang et al., 2024). *In vitro* experiments revealed that *L. rhamnosus*-stimulated Caco-2 cells produce heat shock proteins and soluble proteins p40, p57, and p75, which are mediated by the MAPK pathway (Tao et al., 2006). This stimulation may help repair the damage caused by UA to the tight junctions and barrier function of the Caco-2 cell monolayer, potentially altering UA permeability and reducing inflammatory damage. Interestingly, it was found that *L. gasseri* LG08 and *Leuconostoc mesenteroides* LM58 significantly prevented the occurrence and development of HUA in healthy rats by repairing the antioxidant system and intestinal barrier; however, their intervention effects were not significant once HUA had formed (Liang et al., 2023). Li et al. showed that the decreased abundance of *L. johnsonii* and the increased concentration of eight metabolites, including propionate, may be the gut-modulated pathway used by *L. plantarum* to decrease SUA in HUA mice (M. Li et al., 2023). The abundance of *Clostridium*, *Lactobacillaceae* and *Ruminococcus* was decreased in urate oxidase knockout-induced HUA mice (Xu et al., 2019). Further research revealed that *L. Plantarum* TCI227 not only increased the abundance of *Lactobacillaceae* and *Ruminococcus* but also increased the concentrations of acetic acid, butyric acid, and valeric acid in potassium oxonate-induced HUA rats, improving gut barrier dysfunction and facilitating UA metabolism. Zhao et al. compared the differences in anti-HUA effects of three *L. rhamnosus* strains (Fmb14, Fmb4, and Fmb6). Interestingly, while adhesion assays using Caco-2 cells indicated no significant differences in adhesion among the three strains, *in vivo* experiments revealed that Fmb14 exhibited a more pronounced ability to reduce SUA levels compared to Fmb4 and Fmb6 (Zhao, Chen, et al., 2022). This enhanced effect may be attributed to *L. rhamnosus* Fmb14's superior SCFAs production capabilities and gut microbiota regulation. *L. rhamnosus* 1155 enhanced gut barrier function by up-regulating

the gene expression of tight junction protein Occludin and mucin 2 in HUA rats, while *L. fermentum* 2644 ameliorated HUA-induced dysbiosis of the gut microbiota (Y. Li et al., 2022). Overall, these findings suggest that therapeutic strategies targeting gut microbiota through probiotic interventions present promising avenues for managing HUA.

4.4 Inhibition of inflammation reaction

Elevated UA functions as a damage-associated molecular pattern, promoting inflammation. UA crystals activate the NLRP3 inflammasome upon phagocytosis, inducing the release of pro-inflammatory cytokines (e.g., IL-1 β) through TLR4/NF- κ B signaling. Notably, XOD is closely linked to inflammation, as it produces UA and reactive oxygen species (ROS) during purine metabolism, which can initiate inflammatory responses in HUA models. The XOD gene has several binding sites on its promoter for inflammatory factors including interferon-gamma (IFN- γ), NF- κ B, and TNF- α (Xu et al., 1996). Critically, inflammatory cytokines can trans-activate the XOD promoter via factors like NF- κ B, establishing a vicious cycle that amplifies both UA production and the inflammatory response. Previous studies have reported that probiotics have shown promising results in reducing inflammation-induced damage caused by HUA and effectively blocking the majority of inflammatory signaling cascades. Meng et al. (2023) found that *L. acidophilus* F02 effectively alleviated the symptoms of HUA mice, i.e., ameliorating kidney injury by inhibiting NLRP3 inflammasome and inflammatory cytokine levels. Xiong et al. (2024) proved that *L. plantarum* MC14 alleviated renal inflammation and fibrosis in HUA mice by inhibiting the excessive activation of the PI3K/AKT/mTOR pathway. Besides, it was shown that *Akkermansia muciniphila* could inhibit XOD activity of HUA rats, thereby suppressing the expression of IL-1 β and TNF- α in the kidneys (L. Zhang et al., 2022). Gut microbiota dysbiosis leads to elevated levels of LPS, which stimulates the secretion of inflammatory cytokines such as IFN- γ and IL-1 β . This process further enhances the XOD activity, resulting in increased synthesis of UA. An upregulation of XOD gene expression in rat kidney by hypoxia, LPS, and IL-1 β treatment contributed to the development of acute kidney injury (Hassoun et al., 1998). *L. fermentum* JL-3 and *L. brevis* DM9218 were shown to reduce the concentrations of LPS and IL-1 β in the kidneys of the HUA mice (Wang et al., 2019; Wu et al., 2021). Exogenous purines alone did not influence XOD levels in hepatocytes, but they prompted immune cells to release IFN- γ , which subsequently enhanced XOD expression in hepatocytes (H. Wang et al., 2022). Therefore, probiotics may mediate the immune system to regulate inflammatory cytokines and inhibit XOD activity to reduce the conversion of purines to UA.

4.5 Modulation of lipid metabolism and liver function

The elevated levels of UA are intricately linked to lipid metabolism disorders and liver impairment, with underlying mechanisms encompassing fat accumulation and inflammatory responses. On the one hand, aberrant XOD activity not only disturbs UA biosynthesis but also triggers the activation of the NLRP3 inflammasome, ultimately culminating in hepatocyte damage (Yu et al., 2025). Liang et al. (2024) demonstrated that fatty acid oxidation enhanced oxygen consumption in cells, leading to the activation of hypoxia-inducible factor 1 alpha in liver cells. This activation upregulated 5'-nucleotides II and XOD, thereby

promoting the production of intracellular UA. On the other hand, high UA levels cause a reduction in lipoprotein lipase activity, thereby disrupting lipid metabolism. Elevated UA heightens the production of ROS and activates the c-Jun N-terminal kinase/activator protein-1 signaling pathway, which promotes the expression of genes related to fatty acid synthesis (Yu et al., 2025). URAT1 exerts an essential role in UA metabolism and is expressed not only in renal tubules but also in adipocytes. It was shown that its expression in adipocytes facilitated the entry of UA into adipose tissue, thereby disrupting normal adipose tissue function (Zhang et al., 2021). Lipid metabolism dysregulation initiates a cascade of detrimental effects on the gut-kidney axis, exacerbating the progression of HUA. This disruption impacts BAs homeostasis and enterohepatic circulation, leading to alterations in gut microbiota and the release of endotoxins. Once these endotoxins enter the bloodstream, they trigger inflammatory responses characterized by the release of pro-inflammatory cytokines. This cascade ultimately impairs UA metabolic homeostasis, compromising UA excretion.

Probiotic have shown promising potential in mitigating lipid metabolism disorders and liver function damage caused by HUA. *L. rhamnosus* Fmb14 and *L. acidophilus* F02 intervention were found to effectively attenuate liver injury in purine-induced HUA mice by inhibiting NLRP3/Caspase-1/gasdermin-D-mediated pyroptosis (Meng et al., 2023; H. Zhao et al., 2024). Besides, a clinical study involving subjects with elevated levels of aspartate aminotransferase, alanine aminotransferase, and UA demonstrated that the administration of multi-strain probiotic capsules improved liver function and UA management (J.-H. Lin et al., 2024). Beyond liver protection, probiotics directly modulate lipid metabolism through specific metabolites and microbial interactions (Y. Wang et al., 2024). For example, Taurohyocholate, a metabolite produced by the cytochrome CYP3A4-catalyzed metabolism of taurochenodeoxycholic acid, has been shown to modulate excessive hepatic lipid accumulation in grouper through increasing the relative abundance of bile salt hydrolase-producing microorganisms and enhancing BAs reabsorption (Xu et al., 2022). Interestingly, Chen et al. found that *L. rhamnosus* 2016SWU.05.0601 significantly increased the abundance of the metabolite taurohyocholate by modulating the gut microbiota in HUA mice (Y. Chen et al., 2024). This modulation subsequently lowers XOD activities and up-regulates the expression of URAT1 and ABCG2 in the kidney, ultimately reducing systemic UA levels. Other probiotic strains (e.g., *Lactobacillus kefir* DH5 and *Lactobacillus plantarum* Q16) have been reported to reduce adipose tissue accumulation by upregulating the expression of PPAR- α , fatty acid-binding protein 4 and carnitine palmitoyltransferase-1 (Kim et al., 2017; Tang et al., 2022). Similarly, dietary supplementation with *Lactobacillus plantarum* HAC01 was shown to downregulate de novo lipogenesis-related genes including fatty acid synthase and stearyl-CoA desaturase, resulting in the reduction of the mesenteric adipose depot (Park et al., 2017). Overall, probiotics have shown promising potential in mitigating lipid metabolism disorders and liver function damage caused by HUA. However, research on the specific mechanisms underlying probiotics-mediated regulation of HUA-related lipid metabolism disorders remains limited, requiring further in-depth investigation.

5. Strategies for treating HUA through probiotics

Building on the extensive discussion of how probiotics modulate the gut-kidney axis, this section further explores future intervention strategies for the management of HUA. As shown in Figure 4, these strategies encompass direct probiotic supplementation, the development of functional probiotic products, the synergistic application of synbiotics, and the design of novel probiotic delivery systems. By employing diverse intervention approaches, we aim to provide valuable insights into the innovative use of probiotics in addressing metabolic diseases.

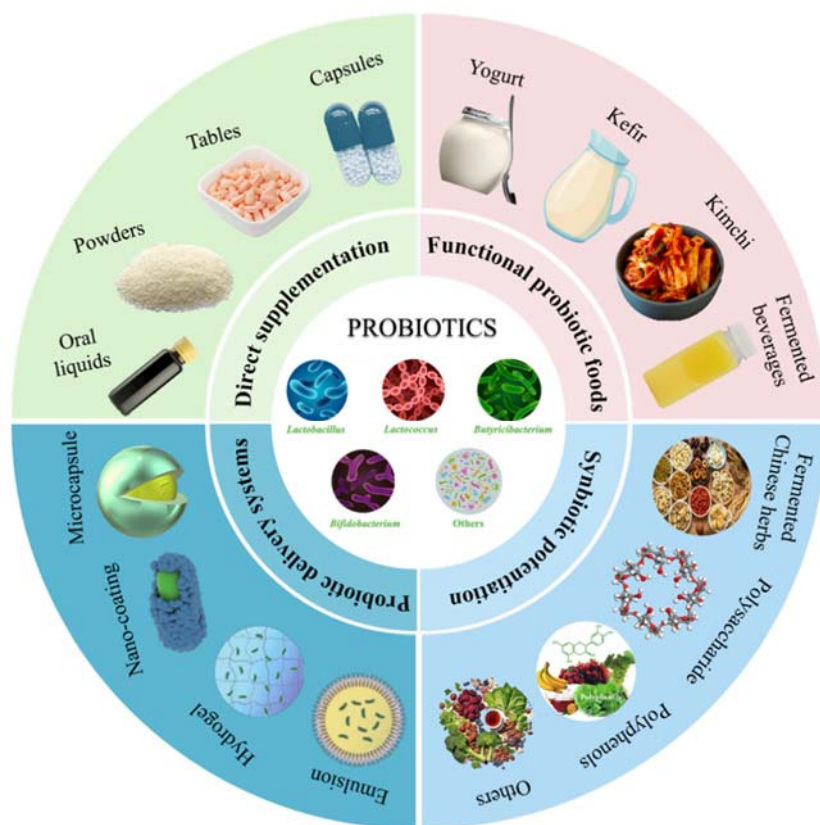


Figure 4. Various strategies for using probiotics in the treatment of HUA.

5.1 Direct supplementation of probiotics treats HUA

The application forms of probiotic preparations for the HUA intervention are diverse, including capsules, tablets, powders, and oral liquids. Their effectiveness in animal models as well as clinical applications have been confirmed. *L. casei* Zhang (1×10^9 CFU/g), *L. paracasei* (1×10^7 CFU/g), and *Faecalibacterium prausnitzii* (2×10^8 CFU/g) capsule formulations have been reported to restore gut microbiota diversity and mucosal barrier integrity, and to reduce the expression of pro-fibrotic markers (type I collagen and fibronectin) in kidney-injured mice (Huang et al., 2021; H.-B. Li et al., 2022; Zhu et al., 2021). In a randomized, double-blind, crossover, placebo-controlled study, the administration of probiotic formulations in gel capsules containing *L. acidophilus* KB31, *Bifidobacterium longum* KB35, and *S. thermophilus* KB27 in patients with kidney disease led to a reduction in serum levels of urea nitrogen and UA (Ranganathan et al., 2009). A key limitation of this study, however, is its small sample size, which may have obscured potential changes in other biochemical or hematologic parameters that could be detected in larger cohorts. Besides, four weeks treatment with the *Probinul-neutro*® powder was found to significantly reduce plasma p-cresol and serum creatinine

levels in patients with chronic renal failure (Guida et al., 2014), though this study similarly suffered from a small sample size and short observation period. Despite these promising findings, the broad implementation of probiotic formulations for managing HUA faces several significant challenges. In practice, most clinical studies with probiotics typically utilize a dosage range of 10^7 to 10^{10} CFU, which seems to be an efficacious, safe and economical dose range (Forssten et al., 2020). However, when it comes to animal studies, the intervention doses tend to be significantly higher than this range. This discrepancy raises important questions about the translation of animal study results to human applications. Besides, there are significant differences in the efficacy of different formulations and strains, and their potential mechanisms of action remain unclear. Individual differences in gut microbiota composition and metabolic profiles introduce substantial variability, complicating the predictability of treatment outcomes. Additionally, certain probiotic strains may contain proteins or components that can trigger an immune response in sensitive individuals. The inconsistent quality of probiotic products, along with a lack of standardized quality control measures, undermines the reliable application of probiotics in HUA management.

5.2 Functional probiotic foods improve HUA

Functional probiotic foods hold considerable promise in the management and prevention of HUA by presenting a multifaceted strategy for UA regulation and overall metabolic health. Items such as yogurt, kefir, kimchi, and various fermented beverages are abundant in live beneficial microorganisms that promote gut health and optimize metabolic processes, thereby aiding in the effective regulation of UA levels. For example, in a study where HUA patients discontinued urate-lowering medications for 12 weeks, daily consumption of yogurt containing *Lactobacillus gasseri* PA-3 (8.5×10^7 CFU/g)—100 grams twice daily (morning and evening, before meals) from weeks 4 to 12 was associated with reduced SUA levels (Yamanaka et al., 2019). However, key limitations of this work include a small sample size ($n=25$), an 8-week intervention period that is relatively short, and inadequate control of dietary purine intake. Besides, a dealcoholized apple juice intervention sequentially fermented with urate-lowering probiotics significantly reduced UA levels and improved gut microbiota disorders in HUA mice (Li et al., 2024). Improvement in antioxidant status and inflammatory mediator levels in gouty rats demonstrated the potential of yogurt supplemented with *L. plantarum* KU985438 to be used as dietary supplements for alleviating HUA and inflammation (El-Dein et al., 2023). Moreover, the use of fermented soy vinegar showed promising effects in inhibiting XOD activity and improving oxidative stress markers, further establishing the multifaceted benefits of probiotics in HUA management (Pyo et al., 2018). Overall, these studies underscore the need for further investigation into the integration of probiotic-rich foods into dietary regimens for effective HUA prevention and management.

5.3 Synbiotics-superimposed effect on the treatment of HUA

The combined application of probiotics and a diverse range of functional substances, through a multi-target synergistic action mechanism, has the potential to demonstrate remarkable enhanced effects in alleviating HUA. Previous studies have demonstrated that polyphenols (e.g. chlorogenic acid and caffeic acid), polysaccharides (e.g. inulin and fucoidan) and other phytochemicals, are effective in reversing UA excretory

dysfunction, repairing the gut epithelial barrier, reducing inflammation, and improving gut microbiota dysbiosis (Guo et al., 2021; Meng et al., 2014; Sun et al., 2023; Wan et al., 2019). A randomized, double-blind, controlled study demonstrated that bioactive peptides (chicken protein peptides and marine fish oligopeptide powder) combined with probiotics effectively lower SUA levels in patients aged 55 years and older without hypertension (Dan et al., 2025). A 5-week intervention with dietary supplements containing *L. acidophilus* KB27 (5.0 B CFU/day), *L. rhamnosus* KB79 (5.0 B CFU/day), xylooligosaccharides (50.0 mg/day), and curcumin (25.0 mg/day) significantly lowered SUA levels and alleviated HUA-induced renal changes and hypertension in rats. Prebiotics, as selective substrates, may enhance the effectiveness of probiotic intervention in HUA by promoting the proliferation, metabolic activity, and gut colonization ability of probiotics. The inclusion of inulin and fructooligosaccharides in the diet induced an increase in fecal bifidobacteria and, to a lesser extent, lactobacilli in the colon (Parhi et al., 2024). Besides, herbal and probiotic combinations have more active responses and produce new substances to enhance beneficial responses in animals. Fermentation with *L. plantarum* not only enhances the antioxidant capacity of *Flos sophorae*, but also significantly improves its anti-HUA activity by down-regulating the mRNA expression of ADA and GLUT9, and up-regulating the mRNA expression of ABCG2 (Cui et al., 2025). Honeysuckle fermented by *L. rhamnosus* L08 and *L. plantarum* NCU1546 significantly enhanced the release of their active ingredients, as well as their XOD inhibitory activity (Song et al., 2024; Yin et al., 2025). Overall, herbal-fermented probiotics or herbal combinations of probiotic supplements demonstrate significant potential in treating hyperuricemia by enhancing UA metabolism. These options provide a cost-effective, eco-friendly, and non-toxic alternative to traditional treatments for HUA.

5.4 Innovative probiotic delivery systems optimize HUA treatment

The effectiveness of probiotics for HUA treatment is affected by numerous factors, especially their activity and survival in the gastrointestinal tract. With targeted release strategies, delivery systems such as microcapsules, nanoparticles, and hydrogels can significantly enhance the survival and colonization of probiotics in the gut, thereby improving their *in vivo* bioavailability. Microencapsulation significantly enhances the survival of probiotics, as demonstrated by the improved viability of *Enterococcus faecium* through chitosan-alginate microcapsules (Golnari et al., 2024). The advantage of microfluidics over spray-drying, freeze-drying, and extrusion (for microcapsules) is its ability to accurately control droplet formation through microchannels, thereby producing microcapsules with smaller diameters and a uniform size distribution. Nanocellulose/alginate microcapsules prepared with microfluidics improved gut adhesion and gastrointestinal survival of *L. paracasei*, with the release of probiotics above 7 log CFU/g after being digestion for 6 h (K. Wang et al., 2022). Calcium carbonate microparticles produced by co-precipitation increased the survivability of *L. plantarum* TISTR 543 under gastric conditions (Khoothiam et al., 2025). Besides, probiotic microspheres encapsulated with whey proteins had a more significant inhibition of intrarenal UA accumulation in oxalic acid-induced HUA rats compared to unencapsulated *L. acidophilus* KB27 and *L. rhamnosus* KB79 (Garcia-Arroyo et al., 2018). Alginate/hydroxypropyl methylcellulose and alginate/ methylcellulose hydrogels

improved *L. plantarum* LAB12 viability against simulated gastrointestinal system conditions and high temperatures (Fareez et al., 2018). Nanocoating, a simple and fast preparation process, can improve the bioavailability of encapsulated probiotics by increasing the surface area ratio. Encapsulation of *L. plantarum* using a nanocoating comprising polydopamine co-deposited with poly-L-lysine exhibited enhanced intestinal adhesion, allowing it to colonize the gut more effectively, and UA levels were reduced by 31.63% (Zhu et al., 2024). Furthermore, the personalized design of the delivery system can be tailored to the unique characteristics of each patient's gut microbiome, allowing for more precise enhancements in efficacy and improvements in patient adherence to treatment. Overall, enhancing both gut adhesion and survival of probiotics in the gastrointestinal tract through innovative delivery systems is expected to significantly enhance their effectiveness in HUA intervening.

6. Conclusions, future prospects and challenges

This review elucidates the potential interplay between the gut and kidneys in the context of HUA. It also summarizes the mechanisms through which probiotics exert beneficial effects on UA metabolism and kidney function. The gut-kidney axis is a complex biochemical pathway that connects the gut and kidneys, facilitating bidirectional communication through various metabolites, signaling molecules, and cytokines. In the development of HUA, dysbiosis may disrupt the gut barrier, alter the gut microbiota composition, and impair UA transport processes, leading to renal dysfunction. Probiotics play a significant role in enhancing gut health, restoring microbial balance, and regulating UA levels through several mechanisms. These include the degradation and absorption of purines in the gastrointestinal tract, modulation of UA transporter expression in both the gut and kidneys, enhancement of beneficial microbiota metabolites, and reduction of inflammation reaction through the regulation of key signaling pathways. Thus, probiotics may serve as valuable dietary supplements for improving UA levels and mitigating complications associated with HUA. However, the regulation of UA metabolism by probiotics still faces numerous challenges, there are some areas where further research is required:

- (I) While current studies affirm the role of probiotics in UA metabolism, there remains a significant gap in understanding the underlying molecular mechanisms, particularly regarding urate transporter regulation. Future research should focus on elucidating the specific signaling pathways and transcription factors involved, which will provide insights into how probiotics and their metabolites influence transporter function and contribute to metabolic homeostasis.
- (II) Most research on probiotics has primarily relied on *in vitro* and animal studies, revealing a critical lack of large-scale, long-term clinical trials to validate their safety and efficacy in managing HUA. Additionally, the potential adverse effects and long-term risks associated with high-dose probiotic use remain insufficiently explored, underscoring the need for thorough safety evaluations before clinical implementation.
- (III) Many animal studies employ probiotic doses significantly higher than those typically feasible or safe for human consumption. While such doses are useful for establishing proof-of-concept and elucidating mechanistic pathways, they represent a key translational challenge. Future studies should aim to optimize

dosing regimens that are physiologically relevant to humans.

(IV) The bioavailability of probiotics significantly impacts their therapeutic efficacy, determined by their viability, gut colonization ability, resistance to gastric acid and bile salts, and individual gut microbiota composition. Future research should aim to enhance probiotic bioavailability through targeted delivery carriers or co-administration with other compounds, thereby increasing their effectiveness.

(V) Existing probiotic strategies for HUA management insufficiently account for host variables (including age, sex, genetics, and microbiome), contributing to response disparities. A paradigm shifts toward biomarker-driven patient stratification—utilizing machine learning analysis of UA-related metabolic networks—is urgently needed to achieve personalized microbiota modulation.

(VI) Probiotic product heterogeneity—spanning pharmaceutical preparations (including capsules, tablets, powders, and oral liquids) to functional foods (such as yogurt, kimchi, and beverages)—introduces significant batch-to-batch variations in UA-lowering capacity. To address these challenges, it is essential to implement stringent quality control measures and standardized production protocols, guaranteeing the stability and viability of probiotic strains to optimize therapeutic outcomes.

Author contribution

Wei Wang: Writing-original draft, Methodology, Software, Validation, Visualization. Yan Cui: Writing-original draft, Methodology, Software. Wantang Ji: Methodology, Software. Mingxue Sun: Methodology, Software. Qianxi Zhao: Methodology, Software. Huimin Liu: Conceptualization, Supervision, Writing-review & editing. Mingzhu Zheng: Conceptualization, Supervision, Writing-review & editing. Yu Wang: Conceptualization, Supervision, Writing-review & editing. Bo Nan: Conceptualization, Supervision, Writing-review & editing. Xia Li: Conceptualization, Supervision, Writing-review & editing. Yuhua Wang: Conceptualization, Formal analysis, Supervision, Project administration, funding acquisition, Writing-review & editing. Jingsheng Liu: Conceptualization, Supervision, Writing-review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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