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Review

Gut microbiota: a potential therapeutic target for hyperuricemia and gout

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The prevalence of hyperuricemia (HUA) and gout has increased in recent decades. Current therapeutic approaches for HUA/gout are often limited by potential risks, necessitating the exploration of safer and more effective treatment options. Emerging evidence highlights the gut microbiota as a pivotal regulator of uric acid (UA) homeostasis. This review synthesizes current advances in microbiota-targeted interventions for HUA/gout, focusing on mechanistic insights and translational potential. We aim to provide a roadmap for optimizing microbiota-based therapies in HUA/gout management by bridging mechanistic discoveries with clinical translation. Gut microbiota can mitigate HUA/gout through several mechanisms, including regulating UA and purine metabolism, alleviating inflammation and modulating immune response, and enhancing the integrity of the intestinal barrier. Therapeutic strategies targeting gut microbiota include probiotics, prebiotics, traditional Chinese medicine, and fecal microbiota transplantation, which offer multi-target and multi-pathway benefits. While these microbiota-targeted therapies offer advantages over conventional drugs, several challenges remain. Future research should prioritize mechanistic elucidation, personalized microbiota modulation, and large-scale trials to optimize therapeutic paradigms for HUA/gout.

Key words: gut microbiota, hyperuricemia, gout, probiotics, prebiotics, traditional Chinese medicine, fecal microbiota transplantation

INTRODUCTION

Hyperuricemia (HUA) is a chronic condition characterized by increased serum uric acid (UA) levels as a result of purine metabolism disorder and/or UA metabolism dysfunction. HUA is the pathophysiological underpinning of gout, and it is an independent risk factor for chronic renal disease, diabetes mellitus, and cardiovascular disease, as well as an independent predictor of premature death [1]. Over the last 30 years, the number of gout patients globally has climbed from 22 million to 53 million, representing a 63.44% increase in incidence [2]. Gouty arthritis, both acute and chronic, has a negative impact on limb function and patients' quality of life. Therefore, it is necessary to prevent and standardize the treatment of HUA/gout.

According to the pathophysiological mechanism of HUA, the present urate-lowering therapies can be categorized as inhibiting UA production, promoting UA excretion, and increasing the degradation of UA. Although these drugs play an important role in clinical practice, they possess the potential to cause hepatic or renal damage, increased cardiovascular events, and severe hypersensitivity reactions, limiting their use in some individuals. As research progresses, new treatment targets continue to emerge.

The gut microbiota is the second genome of the human, is associated with many diseases, and has become an exciting area of research [3]. It maintains homeostasis and promotes health by protecting the intestinal-epithelial barrier, promoting immune system development, obtaining nutrients, and inhibiting the growth of pathogenic bacteria [4]. In recent years, numerous studies have revealed a link between gut microbiota and HUA/gout. A potential causal relationship may exist between the development of gout and specific gut microbiota [5]. The mechanism involves impacts on UA and purine metabolism, as well as anti-inflammatory and antioxidant properties [6]. HUA/gout can also alter the composition and metabolism of intestinal

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microorganisms and aggravate disorders of the intestinal microecology, creating a vicious cycle [7–9]. Therefore, gut microbiota may be a potential target for the treatment of HUA/gout. In this paper, we review the potential therapeutic strategies and possible mechanisms underlying gut microbiota in the treatment of HUA/gout.

POTENTIAL MECHANISMS OF GUT MICROBIOTA IN HUA/GOUT MANAGEMENT

Regulating UA metabolism

UA is the end product of purine metabolism, and Fig. 1 provides a clear and concise overview of the UA metabolism process in humans and the mechanisms through which the gut microbiota influences UA metabolism. An increasing number of studies have revealed that gut bacteria contribute to host purine metabolism homeostasis. Yamada *et al.* reported that *Lactobacillus gasseri* PA-3 reduces intestinal purine absorption [10]. Kasahara *et al.* identified some purine-degrading bacteria, including Bacillota, Fusobacteriota, and Pseudomonadota, that use purine as carbon and energy sources anaerobically. They also identified a cluster of genes associated with this function, which is widely distributed in the gut microbiota [11]. Some gut bacteria, such as *Lactobacillus*, are able to inhibit the activity of xanthine oxidase (XOD), reducing the conversion of purines into UA [12]. The excretion of UA *in vivo* depends mainly on a series of UA transporters in the renal tubules and intestinal epithelium, such as ATP-binding cassette subfamily G member 2 (ABCG2) and glucose transporter 9 (GLUT9). Hippuric acid, the key microbial effector mediating the UA-lowering effect of *Alistipes indistinctus*, upregulated the expression of ABCG2 by promoting the binding of peroxisome proliferator-activated receptor-γ (PPARγ) to the ABCG2 promoter region and facilitating the localization of ABCG2 in the intestinal brush membranes [13]. Metabolomics analysis indicates that dysbiosis of the gut microbiota can change the metabolic pathways of multiple amino acids, including tryptophan and phenylalanine, and indirectly regulate the expression of the solute carrier (SLC) family transporters, thereby affecting UA metabolism [14]. The gut microbiota can also alleviate intestinal inflammation and maintain the integrity of the intestinal barrier by producing specific metabolites, such as short-chain fatty acids (SCFAs), thereby ensuring the normal distribution and function of UA transporters [8, 15]. Unlike humans, some symbiotic bacteria in the human gut, such as *Pseudomonas aeruginosa*, can synthesize enzymes with UA-degrading activity, including urate oxidase (UOX), which catalyzes the conversion of urate into the more soluble compound allantoin [9, 16, 17]. Liu *et al.* found that some gut bacteria consumed UA anaerobically, converting it into either xanthine or lactate and SCFAs [6].

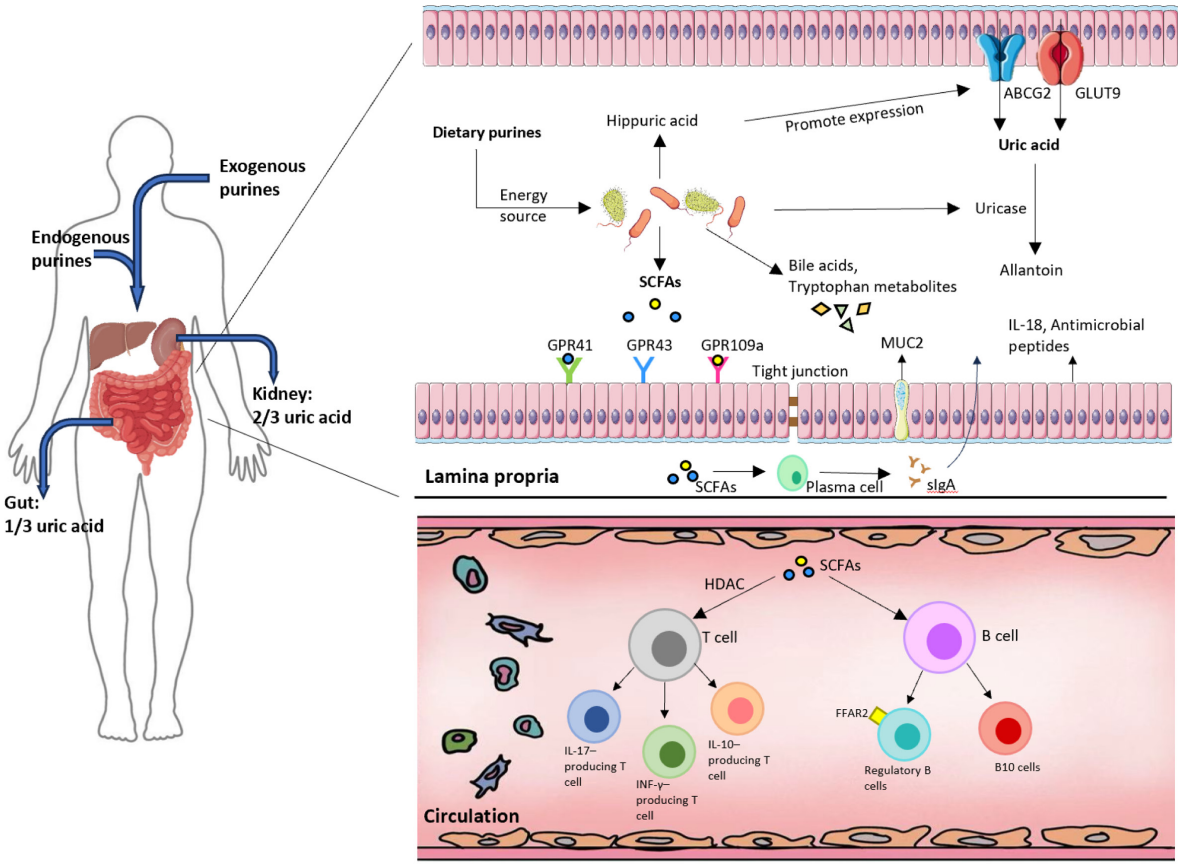

Fig. 1. The metabolism of uric acid (UA) and possible mechanisms of gut microbiota in the treatment of hyperuricemia (HUA)/gout. The gut microbiota improves HUA by regulating purine and UA metabolism. short-chain fatty acids (SCFAs), key anti-inflammatory metabolites produced by gut microbiota, regulate intestinal inflammation and modulate immune cell differentiation. Furthermore, SCFAs, bile acids, and tryptophan metabolites play a critical role in maintaining the integrity of the intestinal barrier. HDAC: histone deacetylase.

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Alleviating inflammation and regulating immune response

A variety of inflammatory cells and cytokines are involved in the development of gout. While persistent high levels of UA may not result in an acute attack of gouty arthritis, they can activate signaling pathways such as mitogen-activated protein kinase/nuclear factor kappa-B (MAPK/NF-κB) and protein kinase B/mammalian target of rapamycin (AKT/mTOR), leading to a chronic inflammatory state [18, 19]. Monosodium urate (MSU) crystals act on specific receptors of macrophages, such as purinergic 2X7 receptor (P2X7R), transient receptor potential vanilloid 4 (TRPV4), and toll-like receptor 2/4 (TLR2/4) and activate the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome. This is followed by the release of interleukin-1β (IL-1β) and interleukin-18 (IL-18), leading to an acute gout attack [7, 20]. SCFAs are metabolites produced by intestinal microbiota through fermentation of dietary fiber, including propionate, acetate, and butyrate, which exert important physiological effects such as providing energy to cells and repairing the intestinal barrier [21, 22]. They exert their effects primarily by inhibiting histone deacetylases (HDACs) and activating G protein-coupled receptors (GPRs), including GPR41, GPR43, and GPR109a [23, 24]. They activate the NF-κB pathway via TLR receptors on intestinal epithelial cells, modulating the production of pro-inflammatory cytokines such as interleukin-8 (IL-8) and tumor necrosis factor α (TNF-α) [25]. SCFAs also promote the expression of antimicrobial peptides in intestinal epithelial cells through the mTOR and signal transducer and activator of transcription (STAT3) pathways [26]. Additionally, they enhance the differentiation of regulatory T cells (Tregs) and boost interleukin-10 (IL-10) secretion [27, 28]. Park *et al.* demonstrated that SCFAs directly promote T cell differentiation into IL-17-, interferon-γ-, and/or IL-10-producing T cells in a cytokine-dependent manner. This effect is independent of GPR receptors and relies on the activity of HDAC [29]. SCFAs can also influence adaptive immunity [30]. In a rheumatoid arthritis model, SCFAs increase regulatory B cells (Bregs) and decrease pro-inflammatory B cell subsets via free fatty acid receptor 2 (FFAR2), thereby alleviating inflammation [31]. Acetate promotes the differentiation of B cells into IL-10-producing B10 cells both *in vitro* and *in vivo* [32]. Additionally, acetate stimulates intestinal B cells to secrete immunoglobulin A (IgA), which neutralizes pathogens and maintains gut microbiota homeostasis [33]. Lipopolysaccharide (LPS) is a component of the cell walls of gram-negative bacteria. Abnormal levels of LPS in the blood circulation induce the release of a large number of inflammatory factors, which is closely related to metabolic disorders such as obesity and insulin resistance [34–36]. In HUA/gout patients, gut dysbiosis increases serum LPS levels. Probiotics such as *Bifidobacterium* and *Lactobacillus* inhibit pathogen colonization and reduce gut endotoxin (e.g., LPS) release [37].

Protecting the integrity of the intestinal barrier

HUA and gout patients often exhibit intestinal barrier dysfunction, characterized by downregulation of tight junction proteins, such as Zonula occludens-1 (ZO-1) and occludin, and reduced mucus layer thickness [38, 39]. In these patients, inflammation-associated gut microbiota, such as *Alistipes* and *Parabacteroides*, are significantly increased. These bacteria activate the TLR/NF-κB pathway, promoting inflammation and disrupting tight junctions between intestinal epithelial cells. Meanwhile, major butyrate-producing genera (e.g., *Clostridium)* and protective bacteria (e.g., *Lactobacillus*) are depleted, leading to insufficient SCFAs and weakened energy support for intestinal epithelial cells [40]. A high UA level in the gut further raises intestinal permeability, facilitating the translocation of bacterial endotoxins (e.g., LPS) into the bloodstream, which exacerbates systemic inflammation [41]. Systemic inflammation contributes to the development of insulin resistance and impairs renal excretion of UA, thereby elevating serum UA levels.

Microbial metabolites serve as key regulators of intestinal barrier function. Macia *et al.* demonstrated that SCFAs signal through receptors GPR43 and GPR109A on colonic immune cells to promote the production of IL-18 via the NLRP3 inflammasome, which is essential for reducing intestinal permeability [42]. An *in vitro* study demonstrated that acetate enhances claudin-1 transcription and induces redistribution of ZO-1 and occludin in the cell membrane [43]. Butyrate reverses HUA-induced downregulation of MUC2 protein, protecting the intestinal mucus barrier [44]. Bile acids and the intestinal barrier exhibit bidirectional interaction. An impaired intestinal barrier can trigger disruptions in bile acid synthesis and cholestasis, while bile acids activate specific bile acid receptors or other downstream signaling pathways to modify the growth of gut microbiota, affect the expression of tight junction proteins, and regulate the local immune system in the intestinal mucosal lamina propria [45, 46]. Wang *et al*. observed altered tryptophan metabolism in probiotic-treated HUA mice, characterized by increased levels of its metabolites indoleacetic acid and indolepropionic acid, which were positively correlated with colonic Claudin-1 mRNA expression [47]. Indole and its derivatives derived from microbial tryptophan metabolism activate the aryl hydrocarbon receptor, leading to upregulation of tight junction proteins and stimulation of mucus secretion, thereby enhancing the physical barrier function [48]. Additionally, the gut microbiota can indirectly stabilize the intestinal barrier by modulating the inflammatory and immune responses through the mechanisms described in the previous section.

THERAPEUTIC APPROACHES TARGETING GUT MICROBIOTA

The intestinal microbiota of HUA/gout patients or animal models differ significantly from those of healthy subjects, with the differences manifesting as decreased microbial diversity, decreased abundances of probiotic and SCFA-producing bacteria such as *Bifidobacterium* and *Clostridium butyricum*, and increased abundances of potentially pathogenic bacteria such as *Prevotella* and *Fusobacterium* [49–53]. Dysbiosis of the gut microbiome elevates serum UA levels and promotes the progression of HUA/gout. Probiotics may be a potential therapeutic option for HUA/gout [8, 54, 55].

Probiotics

Probiotics are often used in the treatment of gastrointestinal diseases such as diarrhea and constipation [56]. Increasingly, probiotics such as *Lactobacillus* have been found to have urate-lowering effects [57–59]. Table 1 summarizes selected meaningful studies on the use of probiotics for treating HUA/gout. Li observed a 34.77 μmol/L decrease in serum UA after three months of treatment with a probiotic complex in patients with mild-to-

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Table 1. Studies of probiotics for the treatment of hyperuricemia (HUA)/gout

Probiotics	Dose	Study model	Therapeutic effects and mechanism	Refs.
Lactobacillus gasseri LG08; *Leuconostoc mesenteroides* LM58	0.5 mL of 1 × 10^9 CFU per day for 2 weeks	Rats model of HUA induced by oteracil potassium and adenine for 21 days	Chao1 index ↑; Firmicutes/Bacteroidetes ↓; *Bifidobacterium* ↑	[57]
Lactic acid bacteria strains (*Lactobacillus rhamnosus* strains, *Lactobacillus reuteri* strains)	10^9 CFU per day for 4 weeks	Mice model of HUA induced by 500 mg kg^{-1} hypoxanthine via oral gavage and 100 mg kg^{-1} PO via peritoneal injection for 2 weeks	Serum and hepatic XOD activity↓; Serum LPS ↓; IL-1β, IL-6 and TNF-α in liver ↓; SCFAs in caecum ↑; *Actinobacteria/Proteobacteria* ↑; *Ruminiclostridium* 5, *Ruminiclostridium* 9, Ruminococcaceae UCG 004 and Ruminococcaceae NK4A214 group ↑	[61]
Limosilactobacillus fermentum JL-3	10^8 CFU twice a day for 15 days	Mice model of HUA induced by basal diet plus 2% UA and 4% oteracil potassium for 15 days	Serum IL-1β ↓; XOD in liver ↓; *Bacteroidetes* ↓; *Firmicutes, Acidobacteria* ↑; *Alloprevotella, Oscillibacter* ↑; *Erysipelatoclostridium, Mucispirillum* ↓	[63]
Lacticaseibacillus paracasei JS-3	2 × 10^8 CFU per day for 2 weeks	French quails model of HUA induced by high-purine diet (20% yeast extract powder)	UA degradation in feces ↑; *Bifidobacterium*, *Bacteroides unclassified* Lachnospiraceae, and *norank Clostridia_UCG-014* ↑; *Macrococcus* and *Lactococcus* ↓; Serum SCFAs ↑	[62]
Lactobacillus rhamnosus GG	>1 × 10^{10} CFU/kg per day for 14 days	Geese model of HUA induced by crude protein 24.03% and calcium 3.04% for 28 days	Serum XOD, IL-1β, IFN-γ and TNF-α ↓; Intestinal and renal UA excretion ↑; and UA reabsorption ↓; *Lactobacillus*, family Lactobacillaceae, family Butyricicoccaceae, *Butyricicoccus* and family Ruminococcaceae ↑	[78]
Lactococcus cremoris D2022	0.3 mL 1.5 × 10^{10} CFU/mL for 14 days	Mice model of HUA induced by daily oral gavage of PO (250 mg/kg) and adenine (75 mg/kg) for 14 days	XOD in liver ↓; Renal ABCG2 ↑and GLUT9 ↓; FFAR2 in kidney ↑; Tight junction proteins (ZO-1, occludin and Claudin1) in the colon ↑; SCFA in gut↑	[79]
Lactobacillus aviarius CML180	0.2 mL (1 × 10^8 CFU/mL) daily for 4 weeks	Mice model of HUA induced by 100 mg/kg of adenine and 300 mg/kg of PO for 4 weeks	Hepatic XOD activity ↓; OAT3 in kidney ↓; Degrading purine nucleosides in intestine ↑	[80]
Lactobacillus paracasei GY-1 combine with colchicine	0.2 mL of GY-1 (1.0–1.2 × 10^9 CFU/mL) twice a day and 2.5 mg/kg colchicine once a day for 4 days	Mice model of acute gout induced by subcutaneously injecting 2 μL/g of MSU solution into the right hind paw	Serum IL-1β and TNF-α ↓; IL-10 ↑; Firmicutes/Bacteroidetes ↑; 4 *Alistipes* species and 6 Porphyromonadaceae species ↓; *Bacteroides sartorii*, *Enterococcus* sp. ↑	[66]
Alistipes indistinctus	5 × 10^8 CFU per day, or 10 mg/kg hippuric acid per day for 4 weeks	Mice model of HUA induced by HUA diet (2% UA and 4% Oxonic acid) for 4 weeks	ABCG2 expression in the jejunum ↑; Binding ability of PPARγ to ABCG2 promoter region ↑; Co-localization of PDZK1 and ABCG2 in the intestinal brush border ↑	[13]
Bifidobacterium quadruple viable	1.5 g orally 3 times a day for 2 weeks	300 gout patients	Serum IL-1β, TNF-α and IL-6 ↓; NO ↑; *Bifidobacterium*, *Lactobacillus* ↑; *Bacteroides*, *Escherichia coli* ↓	[64]
Live combined *Bifidobacterium*, *Lactobacillus* and *Enterococcus* capsules combined with febuxostat	420 mg of capsules 3 times a day and 40 mg/d of febuxostat slowly increased to 80 mg/d for 8 weeks	110 patients with intermittent gout	Serum XOD, IL-1β and IL-6 ↓; *Bifidobacterium*, *Lactobacillus*, *Enterococcus faecalis* and *Bacteroides* ↑; Enterobacteriaceae ↓	[67]
Rotabiotic symbiotic combined with allopurinol	Rotabiotic symbiotic and 300 mg/d of allopurinol with dose titration up to 100 mg every month for 3 months	130 female patients with gout in the remission phase	Serum CRP, IL-1β, IL-6, IL-8, IL-10 and TNF-α ↓; *Firmicutes*, *Candida* and *Bacteroides* spp. ↓; *Bifidobacterium* spp. ↑	[68]
Aqueous extract of *Cordyceps. militaris*	1.5 g/kg and 1.0 g/kg daily for 14 days	Mice model of HUA induced by 250 mg/kg OXO solution daily for 12 days	Serum XOD ↓; Regulate AMPK signal pathway; *Oscillibacter, Alistipes,* Prevotellaceae NK3B31, Lachnospiraceae NK4A136 ↓; *Bifidobacterium*, *Lactobacillus*, *Colidextribacter*, *Faecalibaculum*, and *Blautia* ↑; Improve metabolites in feces	[69]
Aqueous extract of *Phellinus igniarius*	200, 400, or 800 mg crude drug/kg for 14 days	Mice model of HUA induced by 300 mg/kg of PO and 50 mg/kg of adenine daily for 14 days	Hepatic XOD and ADA ↓; Renal ABCG2, OAT1, URAT1 expression ↑; Intestinal ABCG2 expression ↑	[70]

ADA: Adenosine deaminase; AMPK: Adenosine 5′-monophosphate (AMP)-activated protein kinase; CFU: Colony-Forming Units; CMC-NA: Carboxymethylcellulose sodium; CRP: C-reactive protein; IFN-γ: Interferon-γ; IL-6: Interleukin-6; NO: Nitric oxide; NPT1: Sodium dependent phosphate cotransporter 1; OAT1: Organic anion transporter 1; OAT3: Organic anion transporter 3; PDZK1: PDZ domain containing 1; PO: Potassium oxoxnate.

moderate asymptomatic HUA [60]. *Lactobacillus rhamnosus* R31 and *L. rhamnosus* R28-1 were demonstrated to inhibit serum and hepatic XOD activity, improve the gut microbiota structure, and increase intestinal levels of SCFAs [61]. *Limosilactobacillus fermentum* JL-3 and *Lacticaseibacillus paracasei* JS-3 were isolated from fermented food product "Jiangshui". Both strains exhibited UA-degrading capabilities, with JS-3 achieving up to 49% degradation of UA in fecal samples within 24 hr [62, 63]. In mice gavaged with live *Alistipes indistinctus,* intestinal UA excretion was markedly enhanced by over 2.5-fold, as evidenced by an almost 50% reduction in serum UA [13]. Huang *et al*. found that combining probiotics with conventional drugs more effectively reduced blood UA levels without increasing adverse reactions such as intestinal flatulence, diarrhea, and skin itching [64]. In mice with gout flares, administration of *Bifidobacterium longum* 51A significantly improved inflammatory markers and alleviated joint swelling and pain [65]. Zeng *et al.* reported that combining *Lactobacillus paracasei* GY-1 with colchicine enhanced therapeutic outcomes by reducing paw swelling, lowering IL-1β and TNF-α levels, elevating anti-inflammatory IL-10, and diminishing colchicine-related adverse effects [66]. Consistent results were observed by Wang *et al.* and Kondratiuk *et al.*, demonstrating that probiotics combined with conventional drugs reduced inflammatory activity and acute gout episodes [67, 68].

Some fungi constitute a treasure trove of medicinal resources, possessing substantial research significance. An extract of *Cordyceps militaris* exhibited good urate-lowering activity in both *in vivo* and *in vitro* experiments. It reshaped the homeostasis of intestinal microbiota in the HUA mouse, enhanced the abundance of Firmicutes/Bacteroidetes, and modified metabolites and metabolic pathways associated with changes in HUA [69]. *Phellinus igniarius* is a parasitic fungus which contains abundant bioactive components such as polysaccharides, flavonoids, and triterpenoids. Wang *et al.* reported that it ameliorated HUA by inhibiting the activity and expression of XOD, improving the expression of ABCG2 in the colon and kidney, and regulating mitochondrial function to improve HUA-related renal injury [70].

Probiotics engineered for HUA/gout management has emerged through strategic genetic modifications. The relevant research primarily aims to achieve two goals: enhancement of the microbial capacity for UA degradation and optimization of the gastrointestinal tract colonization efficiency. Initial approaches developed an engineered bacteria that expresses UOX, which significantly reduced serum UA levels in rat models [71]. Zhao *et al*. addressed the oxygen-dependent nature of UOX by implementing oxygen-recycling systems in *Escherichia coli* Nissle 1917 (EcN) which integrate bacterial hemoglobin Vhb from *Vitreoscilla sp.* and the catalase KatG from *E. coli*, maintaining enzymatic activity under hypoxic conditions and achieving a >50% serum urate reduction in mice [72]. He *et al*. enhanced therapeutic outcomes through periplasmic UOX localization in EcN, which improved enzyme stability and gut microbiota modulation in rats with UA induced by a high purine diet [73]. To overcome persistent limitations in urate-lowering efficiency, Zou *et al*. developed a precursor-targeting strategy by overexpressing the xanthine transporter XanQ in EcN, amplifying xanthine uptake 8.6-fold to block urate biosynthesis. This innovation achieved physiological serum urate normalization with renal protection in murine models [74], marking a paradigm shift from simple enzyme expression to integrated metabolic pathway interventions.

Regarding the complexity of purine metabolism, Tong *et al.* engineered EcN with an anaerobic purine degradation pathway from *Clostridium*, enabling xanthine as sole carbon source under anaerobic conditions. This metabolic bypass strategy reduces exogenous urate formation without relying on the oxygen-dependent UOX pathway [75]. This preemptive interception strategy may be suitable for patients with different dietary habits. In parallel, Gong *et al.* modified the type zero secretion system (T0SS) of engineered EcN to utilize its outer membrane vesicles as carriers of therapeutic proteins. This strategy significantly enhanced the stability of orally administered UOX and promoted its systemic delivery. Compared with engineered probiotics designed to secrete UOX directly into the gut, this T0SS-based approach demonstrated superior therapeutic efficacy [76]. Gencer *et al.* engineered EcN with dual-functionality: a UA bioreporter and degradation modules. This self-regulating system demonstrated a 40.35% apical urate reduction in *in vitro* models through real-time detection and response mechanisms [77].

Prebiotics

The probiotics and prebiotics (2023) guidelines of the World Gastroenterology Organisation state that the commonly known prebiotics are oligofructose, inulin, galactooligosaccharides, lactulose, and breast milk oligosaccharides (human milk oligosaccharides or HMOs) [81]. The International Scientific Association for Probiotics and Prebiotics defines prebiotics as substrates that are selectively utilized by host microorganisms and confer a health benefit [82]. This definition broadens the traditional concept of prebiotics by extending substrate types from carbohydrates to non-carbohydrate compounds (e.g., polyphenols and conjugated fatty acids). Its scope encompasses not only the gastrointestinal tract but also other microbiota-colonized sites, such as the vagina and skin. In this review, we address a wider range of prebiotics. Table 2 summarizes the potential benefits of different prebiotics in the management of HUA and gout.

Inulin is a soluble polysaccharide compound, which is more abundant in chicory, ginger, and garlic [83]. In a HUA mouse model generated by UOX gene knockout, seven weeks of inulin supplementation reduced serum UA levels by 30% compared with the model group, though levels remained elevated compared with normal controls. Inulin also enhanced intestinal barrier integrity by upregulating occludin and ZO-1 expression and increased the expression of ABCG2 without significantly affecting GLUT9 or sodium-dependent phosphate cotransporter 5 (NPT5). Furthermore, inulin restored the gut microbial diversity and enriched SCFA-producing bacteria, including *Akkermansia* and *Ruminococcus* [84]. Bian *et al.* reported that chicory ameliorates HUA through the modulation of intestinal microbiota, although the specific role of inulin was not further clarified [85]. Similarly, polysaccharides derived from *Alpinia oxyphylla* fruit significantly reduced serum UA levels in a dose-dependent manner in HUA mice, with a dose of 200 mg/kg achieving efficacy comparable to benzbromarone. Notably, treatment restored the gut microbiota composition by reversing the decline in *Prevotella* and *Ruminococcus* while enhancing the abundances of genera such as *Bacteroides*, *Parabacteroides*, *Helicobacter*, and *Flexispira* [86]. *Sphacelotheca reiliana* polysaccharides were also found to alleviate HUA by modulating the microbial structures of

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Table 2. Summary of the potential benefits of prebiotics for the treatment of hyperuricemia (HUA)/gout

Prebiotics	Dose	Study model	Therapeutic effects and mechanism	Refs.
Quercetin	200 mg/kg for 7 weeks	Broilers model of HUA induced by yeast (10 g/kg) and adenine (100 mg/kg) for 49 days	Hepatic and serum XOD activity ↓; *Lactobacillus aviarius* CML180 ↑	[80]
Flavonoid extract from saffron	340 mg/kg, 170 mg/kg, 85 mg/kg daily for 2 weeks	Rats model of HUA induced by 10 mL/kg of PO (150 mg/mL) daily for 3 weeks	Serum and hepatic XOD and MDA ↓; Renal URAT1, GLUT9 ↓; ABCG2 in kidney and ileum↑; Significant regulation of 28 differential bacteria, such as *Roseburia*, *Paludicola*	[101, 102]
Strictinin	Strictinin of 400 mg/kg, 700 mg/kg and 1,000 mg/kg were orally administered for 7 days	Mice model of HUA induced by saline containing PO of 400 mg/kg for 7 days	Liver XOD activity ↓; *Clostridium thermosuccinogenes, Marvinbryantia formatexigens,* and *Ruminococcus lactaris* ↑; *Clostridium aldenense, Clostridium cellulovorans, Clostridium lavalense, Clostridium saccharolyticum, Clostridium symbiosum, Ruminococcus gauvreauii, Roseburia faecis,* and *Ruminococcus gnavus* ↓	[94]
Epigallocatechin gallate	50 mg/kg by oral gavage for 7 days	Mice model of HUA induced by CMC-NA-supplemented PO 250 mg/kg by oral gavage for 7 days	OAT1 and OCT1 in kidney ↑; URAT1 and GLUT9 in kidney ↓; *Actinobacteriota, Bacteroidota* ↑; Significant change in genera *Lactobacillus, Faecalibaculum, Bifidobacterium*, and norank Muribaculaceae	[113]
Ferulic acid	0.05% and 0.1% ferulic acid (50 mg and 100 mg per 100 g diet) for 20 weeks	Rats model of HUA induced by high-fructose/fat diet (18.9 kJ/g, 18% fructose and 20% lard) for 20 weeks	URAT1 and GLUT9 in kidney ↓; ABCG2, OAT3, OCT1, OCT2, and OCTN2 in kidney ↑; *Abcg2* mRNA level in intestine ↑; *Slc2a9* and *Slc22a13* in intestine ↓; Firmicutes/Bacteroidetes ↓; *Ruminococcus*, Lachnospiraceae UCG-006, norank Muribaculaceae, *Lactobacillus,* and *Alistipes* ↑; *Blautia, Bacteroides, Roseburia,* and *Fusicatenibacter* ↓	[92]
Chlorogenic acid	30 mg/kg and 60 mg/kg were orally administered for 19 days	Mice model of HUA induced by hypoxanthine (300 mg/kg) and PO (300 mg/kg) for 19 days	Serum XOD activity ↓; Renal ABCG2 and OAT1, Ileal ABCG2 ↑; TLR4/MyD88/NF-κB signaling pathway in kidney ↓; Serum LPS ↓; SCFAs ↑; ZO-1 and Occluding ↑; *Bacteroides, Alistipes*, and *Butyricimonas* ↑; *Muribaculum*, *Faecalibaculum*, and *Aeromonas* ↓	[89]
Punicalagin	100, 200 and 300 mg/kg/d of punicalagin were administered once a daily for 2 weeks	Mice model of HUA induced by 200 mg/kg adenine and 300 mg/kg PO daily for two weeks	Renal URAT1 and GLUT9 ↓; ABCG2 and OAT1 ↑; Intestinal ABCG2 and GLUT9 ↑; IL-1β, IL-6, and TNF-α in kidney ↓; MAPK/NF-κB activation in kidney and gut↓; Proinflammatory bacteria *Parabacteroides*, *Oscillibacter*, *Desulfovibrio*, and *Tuzzerella* ↓; SCFA-generating bacteria Prevotellaceae UCG-001 and Muribaculaceae ↑	[91]
Combination of *Artemisia selengensis* Turcz leaves polysaccharides (APS) and dicaffeoylquinic acids (diCQAs)	High-dose: 300 mg/kg·d of APS and 50 mg/kg·d of diCQAs for 12 days Low-dose: 100 mg/kg·d of APS and 50 mg/kg·d of diCQAs for 12 days	Mice model of HUA induced by hypoxanthine (500 mg/kg) and PO (100 mg/kg) for 12 days	XOD activity and MDA in liver ↓; *Bacteroides*, *Verrucomicrobia* ↓; *Proteobacteria* ↑; *Alloprevotella*, *Bacillus* ↓; *Lactobacillus*, *Desulfovibrio* ↑; Acetic acid in feces ↑	[93]
Nuciferine	25 mg/kg	Rats model of HUA induced by PO (250 mg/kg)	Restoring *Lactobacillus*, *Escherichia−Shigella*, *Enterococcus*, and *Bacteroides*	[114]
Inulin	9.5 g/kg/day of inulin by oral gavage for 7 weeks	Uox-knockout mice model for HUA	Hepatic XOD activity and XOD mRNA level ↓; TNF-α, IL-6, and IL-1β in blood and ilem ↓; Serum LPS ↓; ABCG2 expression in intestine ↑; Occludin and ZO-1 in intestine ↑; *Akkermansia*, *Ruminococcus*, *Parasutterella* and *Bifidobacterium* ↑; Fecal acetate, propionate and butyrate ↑	[84]
Chicory	16.7 g/kg, 13.3 g/kg, and 6.6 g/kg chicory inulin water solution by intragastric administration for 60 days	French quails model of HUA induced by formulation with added yeast extract powder twice a day for 60 days	Serum LPS, DAO, d-LAC, TNF-α and IL-6 ↓; Occludin, Claudin-1 protein expression ↑; Proteobacteria ↓; Actinobacteria ↑; Prevotellaceae, *Bifidobacterium*, *Megasphaera* ↑	[85]
Polysaccharide from green alga *Ulva lactuca*	300 mg/kg was administered for 2 weeks	Mice model of HUA induced by hypoxanthine (300 mg/kg) and oteracil potassium (250 mg/kg) for 4 weeks	Serum and hepatic XOD activities ↓; Renal GLUT9 and URAT1 ↓; ABCG2 ↑; *Dubosiella*, *Lactobacillus*, *Mucispirillum*, *Parasutterella*, and *Bifidobacterium* ↑; *Staphylococcus*, *Escherichia−Shigella*, *Alloprevotella*, Lachnospiraceae NK4A136_group, and *Ruminococcus* ↓	[115]

APS: *Artemisia selengensis* Turcz leaves polysaccharides; DAO: Diamine oxidase; diCQAs: Dicaffeoylquinic acids; d-LAC: d-lactate; MDA: Malondialdehyde; MYD88: Myeloid differentiation primary response 88; OCT 1: Organic cation transporters 1; OCT 2: Organic cation transporters 2; OCTN2: Organic cation/carnitine transporter.

Table 2. Continued

Prebiotics	Dose	Study model	Therapeutic effects and mechanism	Refs.
Polysaccharide from green alga *Enteromorpha prolifera*	300 mg/kg was administered for 2 weeks	Mice model of HUA induced by hypoxanthine (300 mg/kg) and oteracil potassium (250 mg/kg) for 4 weeks	Serum and hepatic XOD activity ↓; Expression of ABCG2, OAT1, and NPT1 ↑; Expression of URAT1↓; Firmicutes/Bacteroidetes ↓; *Alistipes* and *Parasutterella* ↑	[116]
Polysaccharides from *Alpinia oxyphylla*	100 mg/kg, 200 mg/kg were orally administered for 21 days	Mice model of HUA induced by 50 mg/kg PO and 250 mg/kg adenine by gavage once a day for 21 days	Liver XOD activity ↓; Renal expressions of URAT1 and GLUT9 ↓; ABCG2 ↑; Renal IL-1β, TNF-α and IL-6 ↓; *Bacteroidetes* ↑; *Firmicutes* and *Proteobacteria* ↓; *Prevotella* and *Ruminococcus* ↑; *Bacteroides*, *Parabacteroides*, *Helicobacter* and *Flexispira* ↓	[86]
Sporisorium reiliana polysaccharides	50 mg/kg/day, 100 mg/kg/day for 8 weeks	Mice model of HUA induced by 13% fructose solution for 8 weeks	Restore the transcription of XOD in liver; IL-1β, IL-6 ↓; *Bacteroidetes* and *Proteobacteria* ↓; Expression of genes involved in purine metabolism ↓	[87]
Apostichopus japonicus Oligopeptide	50 mg/kg/d by gavage for 8 weeks	Mice model of HUA induced by 200 mg kg^{-1} d^{-1} hypoxanthine, 30 mg kg^{-1} d^{-1} yeast extract, and 250 mg kg^{-1} d^{-1} PO by gavage for 8 weeks	Hepatic XOD and ADA activities and expression ↓; Renal GLUT9 and URAT1 ↓; ABCG2↑; Modulate NLRP3 inflammasome and NF-κB-related signaling pathways; ZO-1, occludin, and claudin-1 ↑; SCFAs in feces↑; Restore Coriobacteriaceae, Ruminococcaceae, Bacteroidaceae, and Helicobacteraceae	[103]
Marine Fish Protein Peptide	100 mg/kg, 200 mg/kg and 400 mg/kg marine fish protein peptide by gavage daily for 21 days	Rats model of HUA induced by 2.0 g/kg of PO once a day for 4 weeks	Serum DAO and d-LAC levels ↓; *Lactobacillus*, *Blautia*, *Colidextribacter*, and *Intestinimonas* ↑ Genes related to the intestinal barrier (Ildr2, Ccr7, and Nr4a3) ↑;	[104]
Whey Protein Peptide Pro-Glu-Trp	60 mg/kg, 30 mg/kg by oral gavage for 21 days	Rats model of HUA induced by 500 mg/kg PO and 500 mg/kg hypoxanthine by gavage for 28 days	XOD activities in the serum, jejunum, and ileum ↓; ABCG2 and GLUT9 in intestine ↑; *Muribaculaceae*, *Lactobacillus*, *Eubacterium*, and Prevotellaceae_UCG-001 ↑; Lachnospiraceae NK4A136_group, *Bacteroides*, *Roseburia*, and *Alloprevotella* ↓; Acetic acid, butyric acid, and valeric acid ↑; Occludin and ZO-1 ↑	[117]
Folic Acid	2.5 mg/kg, 5 mg/kg folic acid once a day for 10 weeks	Mice model of HUA induced by 1 g/kg yeast extract powder, 100 mg/kg adenine and 250 mg/kg PO once a day for 10 weeks	TNFα, IL-1β, and IL-6 in the intestine ↓; LPS in kidney ↓; Reverse expression levels of TLR4, MyD88; Restore spleen Th17/Treg cell ratio; Claudin-1, Occludin and ZO-1 ↑; Acetic acid and propionic acid ↑	[118]
	84 μg/kg folic acid per day for 8 weeks	Rats model of HUA induced by diet consisting of a mixture of AIN-93 M feed and yeast at a 4:1 ratio	*Actinobacteria* ↑; *Lactobacillus*, *Bacteroides*, *Collinsella*, and *Blautia* ↑; *Clostridium*, *Romboutsia*, nonrank Lachnospiraceae, and *Ruminococcus* ↓	[119]
Total saponins of Dioscoreae Nipponicae Rhizoma	400 mg/kg, 200 mg/kg, 40 mg/kg daily for 14 days	Rats model of HUA induced by 250 mg/kg PO and 10% yeast extract by gavage per day for 14 days	Firmicutes/Bacteroidetes, *Proteobacteria*↑; *Parabacteroides*, *Bacteroides* ↓; *Lactobacillus*, Ruminococcaceae_*Ruminococcus*, ↑; Restore amino acid metabolism and energy metabolism	[120]
	480 mg/kg daily for 20 days	Rats model of HUA induced by 250 mg/kg 5% PO and 10% yeast extract by gavage per day for 35 days	*Firmicutes*, *Lactobacillus*, *Clostridium*, *Ruminococcus* ↑; *Prevotella*, *Bacteroides*, *Marvinbryantia* ↓; Propionic acid and butyric acid in feces ↑	[121]
Rare ginsenosides	50, 100, and 200 mg/kg/d rare ginsenosides by oral administration for 35 days	Mice model of HUA induced by intraperitoneal injection of PO and oral administration of 10% fructose for 35 days	Serum and hepatic XOD activities ↓; Restore the richness of the intestinal flora; Firmicutes/Bacteroidetes ↓; *Lactobacillus* ↑	[122]
Sulforaphane	10 mg/kg of glucoraphanin by gavage daily for 6 weeks	Rats model of HUA induced by 20% yeast and 4% PO daily for 6 weeks	Serum ADA activity ↓; Renal GLUT9 and URAT1 ↓; ABCG2 ↑; Firmicutes/Bacteroidetes ↑; *Lactobacillus, Parabacteroides, Eubacterium, and Lachnoclostridium*; ↑; *Bacteroides*, *Parasutterella*, and *Alistipes* ↓	[123]

APS: *Artemisia selengensis* Turcz leaves polysaccharides; DAO: Diamine oxidase; diCQAs: Dicaffeoylquinic acids; d-LAC: d-lactate; MDA: Malondialdehyde; MYD88: Myeloid differentiation primary response 88; OCT 1: Organic cation transporters 1; OCT 2: Organic cation transporters 2; OCTN2: Organic cation/carnitine transporter.

HUA mice, and a correlation was found between the intestinal microbiota and serum metabolites, as well as glucose, purine, and amino acid metabolic pathways [87].

Chlorogenic acid, a phenolic acid abundant in vegetables and fruits, has been demonstrated to lower serum UA, protect renal function, and attenuate inflammation [88]. In HUA mice, it increased the abundances of SCFA-producing bacteria such as *Bacteroides*, *Prevotella* UGC-001, and *Butyricimonas* while restoring microbial purine and glutamate metabolism. Additionally, chlorogenic acid enhanced gut barrier integrity by upregulating the tight junction proteins ZO-1 and occludin [89]. It also ameliorates renal fibrosis in hyperuricemic nephropathy by reducing trimethylamine N-oxide (TMAO) production through gut microbiota modulation, thereby inhibiting TMAO-mediated oxidative stress and inflammatory responses [90]. Han *et al.* first reported that punicalagin could dose-dependently decrease UA levels in HUA mice by promoting urinary and intestinal UA excretion via inhibition of the MAPK/NF-κB pathway and restoring the composition and function of gut microbiota [91]. Ferulic acid regulates the expression of the UA transporters in the intestine and kidney, thereby reducing UA levels in blood. It also remodels the composition of the intestinal microbiota, increases probiotics such as *Lactobacillus*, and decreases pathogens such as *Bacteroides* [92]. Lian *et al*. found that the combination of dicaffeoylquinic acids and polysaccharides, obtained from *Artemisia selengensis Turcz leaves*, could significantly reduce the XOD activities in the jejunum, restore the balance of *Bacteroidetes* and *Firmicutes*, and increase the abundance of *Desulfovibrio* and levels of SCFA [93]. Strictinin, a major polyphenol in Pu'er tea, has been suggested to alleviate HUA by modulating gut microbiota toward a healthier composition, which may confer protection against inflammation-related pathologies [94].

Flavonoids are widely found in plants in nature and have antioxidant, anti-inflammatory, antitumor, and cardiovascular protective effects [95]. In recent years, several studies have reported that some flavonoids have UA-lowering effects [96–100]. Li *et al.* showed that quercetin alleviated HUA in a chicken model by increasing intestinal *Lactobacillus aviarius* CML180 abundance. Further genetic analysis showed that *L. aviarius* CML180 contains nhy69, a nucleoside hydrolase gene that exhibits strong purine nucleoside hydrolyzing activity at a mesophilic temperature and under neutral potential of hydrogen (pH) conditions, thereby reducing UA production [80]. Chen *et al.* demonstrated that a flavonoid extract from saffron significantly modulated gut microbiota by restoring microbial diversity and normalizing the abundance of 30 taxa, including *Roseburia*, *Clostridium*, and *Gastranaerophilales*. Notably, the treatment effectively lowered serum and intestinal UA levels, downregulated the urate transporters 1 (URAT1) and GLUT9, and upregulated ABCG2 expression. Correlation analysis showed that the abundances of differential bacteria were highly correlated with the levels of serum metabolites, indicating that the gut microbiota was closely related to host metabolism [101, 102].

Lu *et al*. reported that *Apostichopus japonicus* oligopeptide could exert an anti-hyperuricemic effect in a gut microbe-dependent manner [103]. Fan *et al.* studied two novel hexapeptides derived from *Apostichopus japonicus*, GPAGPR and GPSGRP, both of which were able to ameliorate intestinal microbiota disruption caused by a high-purine diet and restore the abundance of 15 genera, including *Lactobacillus*. In addition, this study identified changes in the renal microRNA (miRNA) profiles among groups, which showed a high correlation with genera related to the metabolism of SCFA, bile acids, and tryptophan, but the underlying mechanisms need to be further explored [7]. Marine fish protein peptide has been reported to upregulate the expression of genes associated with the intestinal barrier, including *Ildr2, Ccr7,* and *Nr4a3* [104].

Rhein is thought to attenuate the inflammatory response in gouty arthritis by inhibiting formation of the NLRP3 inflammasome [105]. Xing *et al.* studied the effect of rhein-praseodymium complex (Rh-Pr) on intestinal UA excretion in rats with renal injury. Rh-Pr could upregulate the expression of ABCG2 and downregulate the expression of GLUT9 in the intestine, reducing the burden on the kidney [106]. Several studies on HUA mice have shown that berberine can decrease XOD activity, regulate the expression of urate transporters, lower blood urea nitrogen and creatinine levels, and inhibit the activation of inflammatory signaling pathways [107–109]. Its mechanism may be closely related to the intestinal microbiota [110]. Shan *et al.* and Zhang *et al.* found that berberine was able to increase the abundances of bacteria conducive to UA metabolism, such as *Coprococcus*, *Bacteroides*, and *Akkermansia* [111, 112].

Traditional Chinese medicine (TCM)

In recent years, TCM has become an active area of research in the treatment of HUA/gout. Beyond their traditional antipyretic and detoxifying properties, emerging evidence suggests that the anti-hyperuricemic effects of certain TCMs are mediated through modulation of the gut microbiota, as summarized in Table 3 [124–126]. Simiao decoction and modified Baihu decoction are among the classic formulae used to HAU/gout via the oral route; Shuangbai powder is among those used for external application. They are also combined with acupuncture to help the medicine work faster [127].

Simiao decoction is a common TCM formula for the treatment of gouty arthritis [128]. Lin *et al.* demonstrated that Simiao decoction alleviated gouty symptoms—including foot swelling and low pain threshold—in a mouse model of gouty arthritis while also lowering serum UA levels without inducing hepatic or renal toxicity. Further analysis suggested that the therapeutic effects may be mediated by regulating the intestinal ecosystem to alleviate inflammation. Compared with the model group, Simiao decoction altered the gut microbiota composition, notably decreasing the abundance of Prevotellaceae NK3B31 and Ruminococcaceae UCG-014. Meanwhile, Simiao decoction also reduced intestinal levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, an effect not observed in a febuxostat group [129]. Qu-zhuo-tong-bi decoction has been shown to significantly reduce the serum UA level and inhibit XOD activity [130]. A subsequent study revealed that these effects are mediated through gut microbiota modulation, characterized by an increase in the abundances of *Bifidobacterium* and *Collinsella* and a decrease in the abundances of *Desulfovibrio* and *Gemella* [131]. Furthermore, Wen *et al.* demonstrated that this decoction promotes butyrate-producing bacteria and upregulates intestinal ABCG2 expression to alleviate gouty arthritis [132]. Wang *et al.* found that modified Baihu decoction was able to control the acute inflammation of gout by increasing the abundances of probiotics such as *Bifidobacterium* and decreasing the abundance

of Erysipelotrichaceae [133]. Another study showed that Liji decoction combined with acupoint application can significantly alleviate the joint swelling and pain of gouty arthritis, increase the abundances of *Lactobacillus* and *Bifidobacterium*, and reduce the abundances of Enterobacteriaceae and *Enterococcus* [134].

Fecal microbiota transplantation (FMT)

FMT is a therapeutic method for treating diseases by reconstituting the intestinal microbiota [135]. Washed microbiota transplantation (WMT) is a new transplantation pathway based on automatic purification systems in the generation of bacterial

Table 3. Studies of traditional Chinese medicine (TCM) and fecal microbiota transplantation (FMT) for the treatment of hyperuricemia (HUA)/gout

TCM/ FMT	Dose	Study model	Therapeutic effects and Mechanism	Refs.
Simiao decoction	4.0 g/kg, 8.0 g/kg and 16.0 g/kg per day for 28 days	Mice model of gouty arthritis induced by 10% yeast extract and MSU crystals for 7 days	XOD and ADA activity ↓; TNF-α, IL-6, IL-1β and sIgA in colon ↓; NLRP3, ASC, and Caspase-1 in colon ↓; *Prevotella*, *Escherichia-Shigella*, *Klebsiella*, *Megamonas*, *Enterococcus*, and *Phascolarctobacterium* ↓	[129]
Quzhuo Tongbi Prescription	9 g/kg, 18 g/kg and 36 g/kg of Quzhuo Tongbi Prescription per day for 8 weeks	Rats model of abnormal UA metabolism induced by high-fat diet, 10% yeast extract and 2% PO for 8 weeks	Alpha diversity of gut microbiota ↑; *Collinsella*, *Proteus* ↑; *Gemella*, *Anaerostipes* and *Desulfovibrio* ↓	[131]
	18.0 g/kg/day of Quzhuo-tong-bi decoction for 6 weeks	Mice model of gouty arthritis induced by 10% yeast extract and MSU crystals every 10 days	NLRP3, IL-1β, and TNF-α in intestine ↓; ABCG2 and GPR43 in intestine ↑; ZO-1 and Occludin in colon ↑; Lachnospiraceae_A2 ↓; *Muribaculum* and *Butyricicoccus* ↑; Fecal acetate, propionate, and butyrate ↑	[132]
Modified Baihu decoction	5.84 g/kg/d and 35 g/kg/d of Modified Baihu decoction by gavage daily for 21 days	Mice model of acute gouty arthritis induced by high-fat meal and honeywater (200 g/L) for 21 days, and injection with MSU (0.1 mL/rat, 50 mg/mL) in the right ankle joint	Expression of TNF-α, IL-1β, NLRP3, ASC and Caspase-1 proteins in the synovial tissue ↓; Lachnospiraceae, Muribaculaceae and Bifidobacteriacea ↓; Lactobacillaceae, Ruminococcaceae, Prevotellaceae and Peptostreptococcaceae ↑	[133]
Liji Decoction combined with acupoint application	600 mL/d of Liji Decoction and 2 hr of acupoint application daily for 7 days	110 acute gouty arthritis patients with syndrome of [accumulated] dampness-heat	Serum TNF-α, IL-8, CRP and PGE2 ↓; *Enterobacter* and *Enterococcus* ↓; *Bifidobacterium* and *Lactobacillus* ↑	[134]
Tongfengning	19.11 g/(kg·d) of Tongfengning liquid by gavage for 21 days	Mice model of HUA of spleen deficiency with exuberance of dampness syndrome induced by high-fat and high-sugar diet combined with excessive exercise, and hypoxanthine combined with PO for 42 days	ADA and XOD in intestine ↓; Intestinal expression of ABCG2 ↑, GLUT9 ↓; Firmicutes/Bacteroidetes ↓; *Lactobacillus* and uncultured *Bacteroides* ↑; *Paracoides*, *Klebsiella* and *Enterococcus* ↓; Acetic acid in intestinal lavage fluid ↓; Butyric acid in intestinal lavage fluid ↑	[141]
Dendrobium officinalis six nostrum	13.2 g/kg, 6.6 g/kg and 3.3 g/kg of dendrobium officinalis six nostrum every afternoon for 8 weeks	Rats model of HUA induced by 10 mL/kg of lipid emulsion every morning for 8 weeks	Renal URAT1 protein levels ↓; Renal ABCG2 protein level ↑; Expression of intestinal GLUT9 ↓; ABCG2↑; Activation of the LPS/TLR4/NF-κB signaling pathway ↓	[128]
Fresh fecal microbiota suspension from healthy donors	200 mL per dose, 1–3 courses (3 doses/course, administered every other day)	Acute and recurrent gout patients	Serum UA ↓; Frequency and duration time of acute gout flares ↓; DAO, endotoxin ↓	[137]
Bacterial solution from healthy multi-donor feces	200 mL once daily; 3 days per course; repeated monthly for 4 courses	HUA patients and normal UA people	Serum UA at 3 months after the first WMT ↓	[138]
Fecal solution from HUA mice treated with anserine	200 μL per day for 8 weeks	Mice model of HUA induced by purine-rich solution (containing 200 mg kg^{-1} d^{-1} hypoxanthine, 200 mg kg^{-1} d^{-1} potassium oxalate and 30 mg kg^{-1} d^{-1} yeast extract) for 7 weeks	Serum UA, creatinine, ADA and XOD ↓; GLUT9 and URAT1 ↓, ABCG2 ↑ in kidney; IL-1β and IL-6 ↓, IL-10 and TGF-β ↑; *Porphyromonas* ↓, *Lactobacillus* and *Bacteroides* ↑; Propionic, isobutyric and butyric acid ↑; ZO-1, Occludin and Claudin-1 ↑	[139]
Fecal solution from HUA mice treated with TMOP	100 μL per day for 5 weeks	Mice model of HUA induced by purine-rich solution (containing 200 mg kg^{-1} d^{-1} hypoxanthine and 30 mg kg^{-1} d^{-1} yeast extract) and 250 mg kg^{-1} d^{-1} potassium oxonate for 8 weeks	Serum UA ↓, urine UA ↑; TGF-α, IL-1β and IL-6 ↓; NLRP3 inflammasome complex and TLR4/NF–κB signaling pathway ↓; Firmicutes ↓, Bacteroidetes and Proteobacteria ↑; Acetic, propionic and n-butyric acids in intestine ↑; Occludin and Claudin-1 ↑	[140]

ASC: Apoptosis-associated speck-like protein containing a CARD; PGE2: Prostaglandin E2; sIgA: Secretory immunoglobulin A; TGF-β: Transforming growth factor β.

solutions, which reduces adverse events caused by traditional transplantation and greatly improves the treatment efficacy [136]. Xie *et al.* found that the levels of blood UA and endotoxin, as well as the frequency and duration of acute gout attacks, decreased in gout patients after WMT treatment the reason for which may be related to the improvement of damaged intestinal barriers [137]. A retrospective study [138] found that serum UA levels decreased in approximately 78% of patients with HUA at 3 months after the first WMT treatment and that the UA levels of about 30% patients returned to normal. Furthermore, no significant change in UA was observed in the control group, and no serious adverse effects were found. Anserine, a water-soluble dipeptide, mitigates HUA by suppressing UA synthesis and enhancing its excretion, while also inhibiting the NLRP3 inflammasome and TLR4/NF-κB signaling pathways. Han *et al.* further demonstrated that the anti-hyperuricemic effects of anserine are mediated through the gut microbiome; fecal microbiota transplantation from anserine-treated mice conferred significant UA-lowering benefits to recipient HUA mice [139]. Similarly, tuna meat oligopeptides (TMOPs) were found to alleviate HUA and renal inflammation partially mediated by intestinal microbiota, and their anti-hyperuricemic effects were transmissible by transplanting the fecal microbiota from TMOP-treated mice [140].

Other approaches

In addition to medications, dietary therapy is gradually becoming an adjunctive treatment for gout/HUA. Wu *et al.* investigated the intervention effects of six kinds of tea in HUA mice, and their results showed an enhancement of ABCG2 expression in the intestines as well as an improvement of intestinal microbiota composition [142]. Some natural plants also have UA lowering effects. Kidney tea markedly reduced the serum level of UA in HUA mice and showed hepatoprotective effects compared with allopurinol, the reasons for which may be related to improvements in the structure of the intestinal microbiota, especially increased abundances of *Roseburia* and *Enterorhabdus* and decreased abundances of *Ileibacterium* and UBA1819 [143]. In another study, supplementation with β-carotin and green tea powder improved the gut microbiota profile and alleviated systemic inflammation in mice with gout. The relative abundances of Muribaculaceae, Ruminococcaceae UCG-014, and Lachnospiraceae NK4A136 group decreased in the gouty arthritis group and correlated negatively with serum IL-1β, IL-6, and TNF-α. It also significantly reduced inflammatory cell numbers in foot joints and relieved joint swelling and pain [144].

THERAPEUTIC APPROACHES FOR HUA/GOUT: ADVANTAGES AND LIMITATIONS

The conventional pharmacological agents for HUA/gout in clinical practice fall into two primary categories. The first category comprises rapid symptom-relief medications, including colchicine and non-steroidal anti-inflammatory drugs. While these agents provide rapid pain alleviation during acute gout attacks, most carry significant adverse effects [145]. The second category consists of urate-lowering therapy agents such as allopurinol, febuxostat, and benzbromarone. Although these drugs demonstrate clear urate-lowering efficacy, they each have a single mechanism of action. Notably, allopurinol carries a 0.1–0.4% incidence of severe hypersensitivity reactions strongly correlated with the HLA-B*5801 allele, particularly in Asian populations (RR=3.03, 95% CI 1.72–5.34) [146, 147]. Additionally, febuxostat has been associated with increased mortality risk in gout patients with cardiovascular comorbidities [148], while benzbromarone elevates UA concentrations in renal tubules and ureters, thereby increasing risks of urolithiasis [149].

In contrast, microbiota-based therapies, such as probiotics and prebiotics, offer multi-target and multi-pathway benefits. They can modulate UA metabolism through multiple pathways while ameliorating systemic inflammation, regulating immune responses, and restoring intestinal barrier integrity [150]. These therapies may synergistically enhance urate-lowering and anti-inflammatory effects when combined with conventional medications without substantially increasing adverse events. However, critical limitations persist: Different strains of the same probiotic species may carry distinct functional genes, impacting their ability to regulate UA metabolism. The sustained colonization of exogenous bacteria may be influenced by gut microbiota competition, host immune clearance, diet, and lifestyle, with no current method to predict it effectively [151]. Fortunately, scientists have recently developed various strategies to address this challenge, such as engineering bacteria to depend on specific nutrients to enhance colonization or modifying native gut strains with high colonization capacity. These approaches have shown great potential for treating other diseases [152–154]. Safety concerns remain, as interactions between exogenous probiotics and the gut microbiota are poorly understood and may pose risks such as bacteremia, gene transfer, and immune rejection [155, 156]. Additionally, these therapies act slowly, typically requiring 8–12 weeks, which is unsuitable for acute gout treatment. Cai *et al.* demonstrated in a rat model that the therapeutic efficacy of engineered bacteria gradually diminished within two weeks post-treatment cessation, necessitating the development of a periodic dosing regimen [71]. Furthermore, current evidence primarily derives from animal studies and small-scale human trials, lacking robust validation through large randomized controlled studies.

TCM demonstrates unique advantages in modulating gut microbiota, with growing evidence supporting its integration with Western medicine for gout/HUA management [157]. Representative formulations like Simiao Powder enhance beneficial gut bacteria (e.g., *Akkermansia)*, suppress the TLR4/NF-κB pathway, and upregulate intestinal urate excretion proteins such as ABCG2 [158]. However, their slow onset necessitates combination with Western medications during gout attacks and potential long-term administration for sustained urate reduction. Furthermore, the complex compositions of TCM compounds challenge mechanistic interpretation, while the standardization of syndrome differentiation-based personalized treatment remains problematic for widespread clinical adoption [159].

FMT, an emerging therapeutic approach, has demonstrated potential in small-scale human studies for remodeling purine metabolism, regulating UA levels, and alleviating symptoms [137, 138, 160]. However, clinical implementation faces several challenges, including donor screening, standardization of transplantation methods, and long-term safety concerns. The risk of bacteremia is increased in patients with dysbiosis or immunosuppression undergoing FMT. DeFilipp *et al.* reported two cases of extended-spectrum β-lactamase-producing *Escherichia coli* bacteremia following FMT in two clinical trials

[161]. Moreover, while the short-term efficacy of FMT appears promising, sustained therapeutic effects remain unverified and may depend on host genetic background and baseline microbial architectures.

Currently, traditional medications remain the foundation of HUA/gout treatment, but the therapeutic paradigms are shifting from a single focus on lowering urate to a multi-target intervention that integrates metabolism, microbiota, and immunity. A promising strategy is the combination of pharmacotherapy and microbiota modulation, tailored to different disease stages and individual patient needs. For instance, acute flare management could combine low-dose anti-inflammatory agents with probiotics to simultaneously enhance UA degradation.

CONCLUSION AND PERSPECTIVES

Increasing evidence suggests a close relationship between gut microbiota and HUA/gout. We herein reviewed the possible mechanisms and potential therapeutic strategies mediated by intestinal microbiota in order to provide new insights for the management of HUA/gout. Targeted interventions including probiotics, prebiotics, and TCM achieve therapeutic effects via multiple pathways, including improving urate metabolism, modulating inflammatory and immune response, and protecting intestinal barrier integrity. Emerging studies demonstrate their viability through enhanced safety and sustained efficacy compared with conventional pharmacotherapies. However, current evidence predominantly derives from animal models, necessitating verification through large-scale cohorts. Given the high-dimensional complexity of human gut microbiota, enterotype classification offers a feasible approach to categorize microbial communities, thereby enhancing correlation analyses between microbial profiles and disease pathogenesis while informing targeted therapies. Nevertheless, the application of this methodology remains absent in HUA/gout research, representing a critical knowledge gap requiring urgent investigation. As microbiome research has advanced, some evidence has highlighted the critical role of gut virome and fungal communities in HUA/gout. Huang *et al.* reported that gout patients displayed a diminished viral richness and altered viral family composition, characterized by reduced *Siphoviridae* and *Myoviridae* abundances alongside elevated *Quimbyviridae* and *Retroviridae* levels. Notably, gut viral signatures exhibit superior diagnostic performance for gout compared with bacterial-derived models, demonstrating enhanced predictive potential in clinical applications [162]. The gut microbiota is a huge biological database. Future research efforts could focus on the integration of metagenomics, genomics, epigenomics, transcriptomics, proteomics, and metabolomics to help identify the potential molecular targets and active biomarkers involved in HUA/gout, as well as guide precision disease treatments and prognosis.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conceptualization. The first draft of the manuscript was written by JT, and all authors commented on previous versions of the manuscript. YL performed the literature search. NW prepared the figures and tables. Supervision and program administration were performed by JL, YZ, NT, and QL. Our funding was obtained by QL. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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