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REVIEW ARTICLE

Gut microbiota and hyperuricemia: From mechanisms to therapeutic strategies

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Abstract

Hyperuricemia (HUA), a condition characterized by elevated levels of uric acid (UA) in the bloodstream, is intricately connected to an imbalance in the gut microbiota. UA, a byproduct of purine metabolism, serves as a crucial endogenous antioxidant. Recent research indicates that modifying the gut microbiome offers a promising avenue for managing HUA. This work delves into the complex relationship between HUA and changes in the gut microbiota, examining its impact on UA excretion, reabsorption, and the activity of enzymes involved in purine breakdown. Elucidating the precise mechanisms behind this connection is essential for developing effective treatments, and exploring various therapeutic approaches, including probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation, which target the gut microbiota to reduce UA levels. These treatments may exert their effects through diverse pathways, such as inhibiting key enzymes, regulating UA transporters, reducing oxidative stress and inflammation, and restoring the balance of the gut microbiome. Furthermore, maintaining a healthy gut barrier is a valuable complementary therapy. This review aims to provide insights into the potential of gut microbiota manipulation as a novel and promising strategy for managing HUA. While this approach holds great promise, it is important to consider the potential risks and challenges associated with gut microbiota manipulation, and further research and clinical trials are warranted to fully understand its efficacy and safety.

Keywords: Hyperuricemia; Intestinal flora; Uric acid metabolism; Probiotics; Nutritional interventions

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1. Introduction

The prevalence of hyperuricemia (HUA), characterized by elevated serum uric acid (UA) levels, has become a significant health concern, with implications for the development of gout, cardiovascular disease, and chronic kidney disease. HUA is multifactorial in origin, involving both genetic and environmental determinants. Genetic factors, such as polymorphisms in the solute carrier family 2 member 9 (SLC2A9) and glucose transporter-like protein-9 (GLUT9) genes, and reduced activity of the UA efflux transporter breast cancer resistance protein (BCRP)/ATP-binding cassette

subfamily G member 2 (ABCG2), play a substantial role in the pathogenesis of HUA, with approximately 90% of cases having a genetic component.[1-6] Concurrently, environmental contributors, including dietary patterns, lifestyle choices, age, and gender, significantly influence HUA development. Many studies have demonstrated that diet and dietary components have profound effects on the composition of the gut microbiota and are among the most important contributors to alterations in bacterial flora.[7-9]

The modern dietary trend toward increased consumption of sugars, fats, and purine-rich foods can perturb the gut microbiota composition, affecting nutrient metabolism, immune regulation, and inflammatory responses, ultimately contributing to metabolic disorders, including HUA. The prevalence of HUA varies by region and demographic, with higher rates in European and American countries and geographic differences observed within Chinese populations.[10-12]

Mounting scientific evidence and clinical data underscore a close link between the onset and progression of HUA and alterations in the intestinal microbiota's prevalence, distribution, and structural transformations. The gut microbiota is integral to regulating the host's metabolic functions and immune system. Dysbiosis, or disruption of the microbial equilibrium, can disturb multiple physiological metabolic pathways, including the UA metabolic cascade. The enzyme xanthine oxidase (XO), a key player in UA biosynthesis, is expressed in hepatocytes and exhibits peak expression in the duodenum and jejunum. In addition, certain gastrointestinal strains of *Escherichia coli* can secrete xanthine dehydrogenase (XOD), contributing to purine catabolism.[13-23]

The gastrointestinal tract plays a crucial role in maintaining UA homeostasis beyond the kidneys' primary role in urate excretion. Probiotics within the gut can degrade urate, and the consumption of *Lactobacillus gasseri* PA-3 has been associated with reduced serum UA (SUA) levels and stabilized gut microbiota by decreasing purine absorption. Disruption of the gut microbiota can affect the function of urate transporters on intestinal epithelial cells, influencing UA transport and elimination. Distinct differences in the abundance of intestinal flora between healthy individuals and those with HUA have been observed, with certain species such as *Prevotella*, *Akkermansia*, and *Barnesiella* being linked to HUA.[24-27]

HUA is a complex condition influenced by genetic and environmental factors, with diet and lifestyle habits playing significant roles. The balance between UA synthesis and excretion pathways is influenced by the gut microbiota, highlighting the importance of maintaining a healthy gut ecosystem in managing HUA. Further research is essential to fully understand the interplay between UA metabolism and the gut microbiota and to explore potential therapeutic interventions targeting gut microbiota dysbiosis in the context of HUA and its associated disorders.

2. The mechanism of gut microbiota affecting purine metabolism

The gut microbiota, a complex microbial community colonizing the intestines, is crucial for regulating UA metabolism. Dysregulation of the gut microbiota can disrupt UA homeostasis, leading to HUA – a condition characterized by elevated blood UA levels (Figure 1).

The adult gut microbiota primarily comprises *Firmicutes* (approximately 64%) and *Bacteroidetes* (approximately 28%), with a total abundance reaching around 10^{14} microorganisms. Bacteria within the gut microbiota have developed adaptive mechanisms for *de novo* biosynthesis and purine salvage, influencing UA metabolism. In addition, the gut microbiota can produce substrates that may enter the liver through the portal vein, leading to the production of new purine amino acids and UA.[28-31] Metabolites (cysteine, glutamine, phenylalanine, etc.) were significantly associated with UA change and incident HUA. Amino acid metabolism appears to play a critical role. Impairment of intestinal integrity and profound alterations in the profile of the solute carrier family resulted in dysregulation of amino acid transportation.[32-35]

Recent research suggests that the gut plays a pivotal role in the pathogenesis of HUA. Intestinal flora actively participates in purine metabolism and UA degradation. UA transporters located in intestinal epithelial cells facilitate the transport of UA from the bloodstream into the intestinal lumen. Key transporters involved in this process include ABCG2 and SLC2A9.[36-39] Elevated UA levels can induce inflammation through the toll-like receptors 4/NOD-like receptor protein 3 signaling pathway, adversely affecting intestinal epithelial cells. This inflammation leads to mitochondrial dysfunction and activation of the NF-κB signaling pathway, resulting in decreased expression of tight junction proteins and compromised integrity of the intestinal mucosal barrier. Consequently, the function of

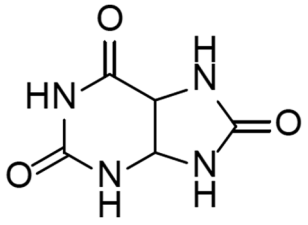


Figure 1. Structural formula of uric acid

UA transporters in intestinal epithelial cells is impaired, leading to disorders in intestinal UA excretion.[40,41]

The gut microbiota also participates in the oxidative metabolism of purine. Certain bacteria, such as *E. coli* and *Proteus*, can secrete XO, a key enzyme in purine oxidation. Studies have demonstrated that gut microbiota is involved in the catabolism of purine and UA through the secretion of active enzymes. An imbalance in the gut microbiota can lead to an increase in the abundance of microbiota associated with the XO gene, a decrease in the abundance of microbiota associated with the allantoinase gene, and an overall increase in intestinal UA levels. This imbalance is also closely associated with a decrease in short-chain fatty acids (SCFAs), which play a crucial role in maintaining gut health and regulating inflammation.[42-44]

Beyond direct involvement in purine metabolism, the gut microbiota can also regulate systemic metabolism through purinergic receptors in the gut and the release of extracellular adenosine triphosphate and nucleotide metabolites.

Research has revealed a significant increase in serum lipopolysaccharide (LPS) levels in gouty geese that is attributed to intestinal dysbiosis, leading to increased intestinal barrier permeability. The enhanced translocation of intestinal-derived LPS into the bloodstream may increase the risk of gout in geese.[45-48]

Further investigation is required to fully understand the complex interplay between the gut microbiota and UA metabolism. However, emerging evidence suggests that the gut microbiota plays a significant role in the pathogenesis of HUA. This knowledge opens new avenues for the development of targeted therapies for HUA, focusing on modulating the gut microbiota to restore UA homeostasis and mitigate the associated health risks (Figure 2).

3. Changes of gut microbiota in HUA

The intricate relationship between UA metabolism and gut microbiota involves a bidirectional interaction that can influence both the host's gut environment and UA levels. Liu *et al.*[49] conducted a screening process within the repository of human intestinal bacteria. By utilizing stable isotope tracing techniques, 46 species of UA-degrading bacteria were identified, spanning four phyla: *Actinobacteria*, *Firmicutes*, *Clostridia*, and *Proteobacteria*.

Elevated UA can disrupt the gut microbiota, leading to dysbiosis, while alterations in the microbiota can further affect UA metabolism. This interaction impacts host health, as the gut microbiota plays a key role in UA

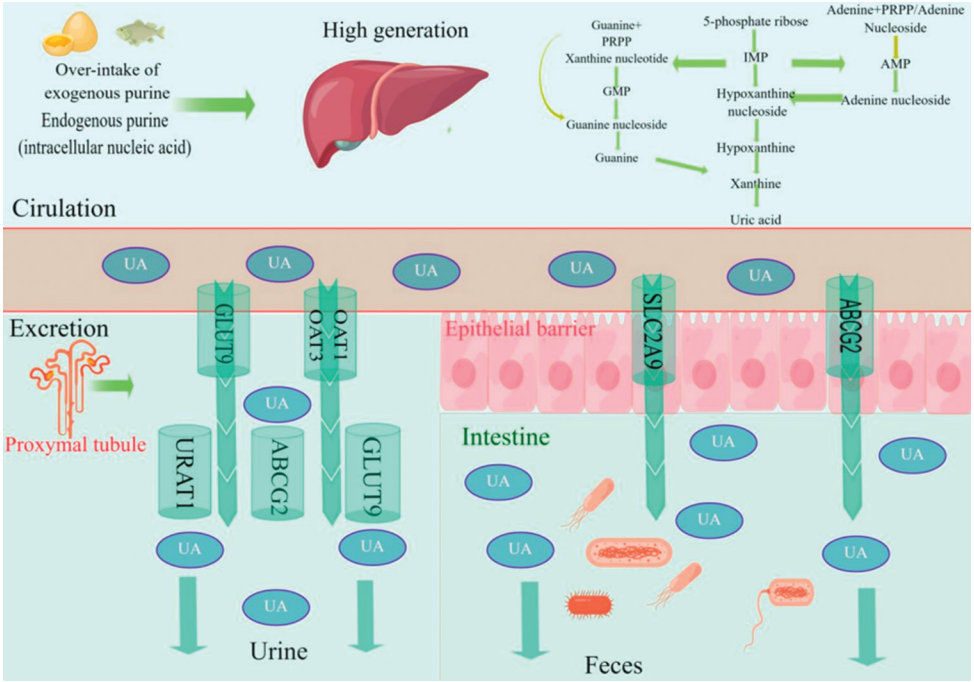


Figure 2. Schematic diagram of the metabolism of uric acid. Hyperuricemia is an imbalance in uric acid metabolism that includes increased uric acid production through endogenous or exogenous purine metabolism and decreased renal and extrarenal excretion of uric acid, or both. Intestinal flora can affect the metabolism of uric acid. The figure was created using Biorender.
Abbreviations: ABCG2: ATP-binding cassette, subfamily G, 2; AMP: Adenosine monophosphate; GLUT9: Glucose transporter 9; GMP: Guanine monophosphate; IMP: Inosine monophosphate; OAT1: Organic anion transporter 1; OAT3: Organic anion transporter 3; PRPP: Phosphor-ribosyl-pyrophosphate; UA: Uric acid; URAT1: Urate transporter 1.

elimination. UA is transported from the bloodstream into the intestine, where it is either directly excreted or decomposed by bacteria such as *E. coli*, *Lactobacillus*, and *Pseudomonas*. Microbiome analysis has revealed that gout patients have a distinct gut microbiota composition, with an increased abundance of genera, such as *Bacteroides* and *Proteobacteria*, and specific species, such as *Bacteroides caccae* and *Bacteroides xylanisolvens*. *Lactobacillus* DM9218 was found to improve the integrity of the intestinal barrier in high-fructose diet-fed mice. These findings highlight the gut microbiota as a potential therapeutic target for managing gout.[50-53]

Gout is associated with significant alterations in the gut microbiota, including changes in both composition and function. Metagenomic analysis revealed an increased abundance of *Prevotella*, *Fusobacterium*, and *Bacteroides* in gout patients, whereas *Enterobacteriaceae* and butyrate-producing species were reduced. *Lactiplantibacillus plantarum* X7022 demonstrated significant potential as a probiotic for managing HUA. Its ability to reduce UA levels, improve kidney health, colonize the gut, degrade purines, and modulate the gut microbiota makes it a promising candidate for further research and potential development as a therapeutic agent. HUA-induced dysbiosis affects key bacterial phyla, such as *Bacteroides*, *Firmicutes*, and *Proteobacteria*, with *Proteus* proliferation playing a crucial role in intestinal imbalance in gouty geese. Fecal microbiota transplantation (FMT) studies suggest that bacterial genera, such as *Vallitalea*, *Christensenella*, and *Insolitispirillum*, may contribute to HUA pathogenesis.[54-58]

In a recent study, Méndez-Salazar *et al.*[59] investigated the composition of gut microbiota in patients with gout and compared the differences between patients with tophi and those without tophi. The results indicated that after the deletion of the gut microbiota in patients with gout, the abundance of *Ruminococcus*, *Akkermansia*, *Bacteroides*, and *Phascolarctobacterium* appeared to be higher, whereas the abundance of other genera at the species level was reduced. These results suggest that there are significant differences in the composition of the gut microbiota between patients with tophi and those without tophi, which may have an impact on the development of the disease. The study aimed to assess the structured profile of the intestinal microbiome in these persistent groups and predict bacterial capacities that may affect urate metabolism. The research highlights potential links between intestinal microbiota composition and the pathophysiology of gout.[59]

4. Current status of treatment of HUA

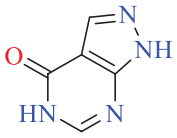
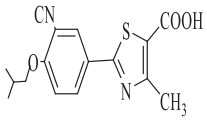
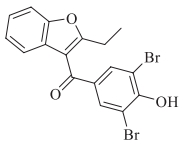
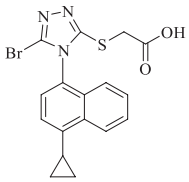
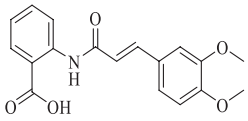
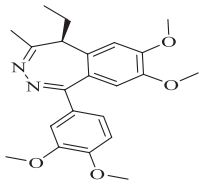
Within the routine treatment of intense gout, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly administered due to their effectiveness in easing pain and reducing inflammation. Nonetheless, it is critical to recognize that NSAIDs may modify the homeostasis of the intestinal microbiota, possibly increasing the abundance of Gram-negative microscopic organisms and concurrently reducing the abundance of Gram-positive microbes within the intestinal environment.[42,60,61] HUA management is a chronic and long-term commitment that demands persistent adherence to treatment strategies to maintain SUA levels below the therapeutic target of 360 μmol/L. This approach is pivotal in reducing the risks associated with elevated UA levels, which can precipitate both asymptomatic and symptomatic conditions, such as gout, kidney stones, and urate nephropathy. For asymptomatic HUA, preventive pharmacological treatment is generally not recommended due to the potential for adverse drug effects, as evidenced by the findings of the CARES trial.[63] Instead, lifestyle modifications, including regular physical activity, dietary adjustments to limit alcohol, purine-rich foods, and high-fat products, and promoting vegetable consumption, are the primary management strategies to maintain UA levels within a healthy range.

In contrast, symptomatic HUA, characterized by the presence of clinical symptoms, necessitates more aggressive treatment due to the significant risk of renal damage and the potential progression to end-stage renal disease. Pharmacotherapy is the cornerstone of clinical treatment for symptomatic HUA, offering rapid relief of symptoms and UA control. Current pharmacological options target various points in the pathogenesis of HUA, including enzyme inhibition, UA excretion enhancement, or dual inhibitory effects. However, the requirement for long-term or lifelong medication, coupled with the potential for serious side effects and the risk of UA rebound upon drug discontinuation, underscores the importance of exploring safer and more effective treatment alternatives. This pursuit may involve the development of novel pharmacological agents with improved safety profiles, as well as further investigation into non-pharmacological interventions, such as dietary supplements, probiotics, and other complementary therapies, which could provide alternative strategies for managing HUA and its associated complications (Table 1).[62-77]

5. Treatment of HUA based on gut microbiota

With the in-depth study of intestinal microbiota, increasing evidence indicates that the gut microbiota is not only associated with the pathogenesis of HUA but also serves as a promising drug target for treatment. The gut microbiota plays a crucial role in regulating host

Table 1. Conventional uric acid-lowering drugs

Structural formula	Medicine	Mechanism	Dose	Side effect	References
	Allopurinol	XOI	The conventional dose is 300 mg/d; the maximum dose is 600 mg/d	Rash combined with eosinophilia, leukocytosis, fever, hepatitis, and progressive renal failure	100,101
	Feibulista	XOI	The initial dose is 20 mg/d; the maximum dose is 40 mg/d	Headaches, abdominal pain, and diarrhea, as well as abnormal liver function; higher incidence of cardiovascular events than allopurinol	102,103
	Benzbromarone	Uric acid-excretory drugs	The initial dose is 25 mg/d; the commonly used dose is 50 mg/d	Abnormal liver function, gastrointestinal symptoms, skin allergies	104,105
	Lesinurad	Selective uric acid reabsorption inhibitor; URAT1 inhibitor	Must be taken in combination with one type of XOI (including allopurinol or febuxostat) at a recommended and maximum dose of 200 mg/d	Liver and kidney dysfunction (Phase III clinical trial; overall safe and well tolerated)	106,107
Unavailable	RLBN1001; KUX-1511	Both can simultaneously inhibit URAT1, promote uric acid excretion, and inhibit the function of xanthine oxidase to reduce uric acid production	At the research stage, but not listed	Renal injury in the research stage	104,108
	Tranilast	Urate-lowering action via inhibition of renal transporters URATl and GLUT9	100 mg, tid	The most notable side effect was headache	104
Unavailable (because this is not a discrete structure)	Pegloticase	Recombinant uricase in mammals can induce a sharp decrease in serum uric acid levels	Intravenous infusion once every 2 weeks; a total of 12 times; 8 mg each time	Infusion reactions, such as nausea, skin flushing, and difficulty breathing	109,110
	Levotofisopam	Unknown hypouricemic mechanism of action; it may work through uric acid excretion	Currently in Phase 2 clinical research phase; unknown dosage	Currently in Phase 2 clinical research phase; unknown side effects	111
Unavailable	Rasburicase (especially suitable for HUA caused by chemotherapy)	Uridase drugs promote uric acid catabolism and aid in its excretion from the kidneys	The adult dose is 0.2 mg/kg/day; 50 mL of 0.9% sodium chloride injection is added approximately 30 min before infusion	Common symptoms include fever, nausea, vomiting, rash, immunogenic infusion reactions, methemoglobinemia, hemolysis, and allergic reactions	112

Abbreviations: GLUT9: Glucose transporter 9; HUA: Hyperuricemia; URAT1: Urate transporter 1; XOI: Xanthine oxidase inhibitor.

metabolism, endocrine, and immune systems. Consequently, probiotics, prebiotics, nutrients, and FMT offer a relatively safe and effective approach to managing HUA (Table 2).

5.1. Probiotics

A probiotic is defined by the Food and Agriculture Organization and World Health Organization as live microorganisms that, when administered in adequate amounts, offer a health benefit to the host. Its functions include maintaining the stability and diversity of the human gut microbiota, regulating the expression of host genes, modulating immune responses, producing antibacterial substances, and releasing functional proteins. Due to its many health benefits, probiotics are considered a promising natural therapy. Strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* have a long history of safe and effective use as probiotics. Regular administration of *Lactobacillus salivarius* CECT 30632 (*L. salivarius* CECT 30632) can reduce the serum urate level, reduce the number of gout attacks, and can be used as a drug to control HUA and gout attacks. Probiotic LPN1 can prevent Ethylene glycol (EG)-induced hyperoxaluria by regulating the gut microbiota and enhancing intestinal barrier function. In a HUA rat model induced by oral potassium oxyacetate combined with a high purine diet, *Lactobacillus rhamnosus* 1155 (LR1155) and *Lactobacillus fermentans* 2644 (LF2644) inhibit the activity of XO, upregulate ABCG2, and reduce LPS and inflammatory indicators. Oral administration of LR1155 and LF2644 or a combination significantly reduced SUA levels after 4 weeks.[78] In a mouse model with hypoxanthine and intraperitoneal injection of potassium oxalate by oral gavage, *L. rhamnosus* R31, *L. rhamnosus* R28-1, and *Lactobacillus lucidus* L20M3 effectively reduced the concentration of UA in serum and urine, as well as the activity level of XOD in serum and liver tissue. They also promoted the production of SCFAs, reversed the rise of LPS, and alleviated liver and kidney injury.[78] *L. fermentans* F40-4 can remodel intestinal microbiota and inhibit inflammation to improve HUA, as it was reported to reduce SUA, blood urea nitrogen, creatinine, and XO levels by 40.84%, 11.61%, 57.66%, and 41.79%, respectively.[79] Oral administration of *Lactobacillus paracasei* X11 reportedly reduced SUA by 52.45% and inhibited renal pro-inflammatory cytokine IL-1β by 50.69%, as well as regulated the expression of adenosine deaminase (ADA), XOD, and various transporters (GLUT9, NPT1, and URAT1) to normal levels.[80] The study found that *L. gasseri* PA-3 can improve the UA level of patients with borderline HUA. For patients with HUA and gout, *Lactobacillus reuteri* TSR332 and *Lactobacillus fermentans* TSF331 strains are potential functional probiotics strains for controlling the development of HUA. Notably, the UA level in the treatment group of *Lactobacillus reuteri* TSR332 decreased more significantly compared to the placebo group, and no obvious side effects were observed in TSR332.[80] In a HUA mouse model induced by hypoxanthine and potassium oxybate, chlorogenic acid supplementation not only increased the production of SCFA in the feces of HUA mice but also increased the relative abundance of bacteria producing SCFA, including *Bacteroides*, *Prevoteaceae*

Table 2. Treatment of hyperuricemia based on intestinal flora

Treatment	Attribution	Mechanism	Shortcomings
Probiotic	Live microorganisms	Maintaining the stability and diversity of human gut microbiota, regulating host gene expression, regulating immune response, producing antibacterial substances, and releasing functional proteins	The research is still in its early stages, and there is still limited understanding of its relief mechanism; the safety and effectiveness of clinical use still need to be verified
Prebiotic	A selectively fermented ingredient	Changing bacterial composition and short-chain fatty acids	
FMT	Functional gut microbiota transferred from healthy human feces to the patient's gastrointestinal tract	Improve the structure of intestinal microbiota, increase the abundance of beneficial bacteria, inhibit the growth of pathogenic bacteria, and increase intestinal anti-inflammatory metabolites	Long-term follow-up should be conducted to monitor clinical efficacy and long-term adverse reactions
Nutrients	Essential substances for maintaining human physiological functions, including dairy products, tea with tea extracts, and vitamins	Inhibit xanthine oxidase, regulate uric acid transporter, inhibit oxidative stress, and reduce inflammation	The observation period is relatively short, and more research is needed to prove its impact pathways and targets; the dosage range and long-term safety recommendations still need to be improved

Abbreviation: FMT: Fecal microbiota transplantation.

UGC-001, and *Butyromonas*, which improved HUA and regulated intestinal homeostasis.

5.2. Prebiotics

Prebiotics exert beneficial effects on the host's intestinal health, primarily by altering bacterial composition and SCFAs, including resistance to irritation, improvement of the intestinal boundary, and changes in the gastrointestinal microbiota. Prebiotics were first defined in 1995 as substances that specifically promote the growth and/or migration of one or a limited number of bacteria in the colon, thereby exerting beneficial effects on the body to improve the health of the host. Based on this description, only a few compounds in the carbohydrate group are considered prebiotics, including beta-fructans (fructooligosaccharides and inulin), galacto-oligosaccharides, and lactulose. When prebiotics were first defined, they had very specific effects on the human intestinal microbiota, mainly manifested by increasing the populations of bifidobacteria and lactobacilli while reducing the cell numbers of *Bacteroidetes*, *Clostridium*, and *Fusobacteria*. At a meeting of the International Scientific Association of Probiotics and Prebiotics, the definition of the term "dietary prebiotic" was updated to "a specific senolytic ingredient that induces specific changes in the composition and/or activity of the gastrointestinal microbiota that are beneficial to host health." Bindels *et al*.[81,82] proposed a broader definition, in which prebiotics are defined as non-digestible compounds that balance the composition and/or activity of the intestinal microbiota through metabolism by intestinal microorganisms, thereby producing beneficial physiological effects on the body. At present, prebiotics are mainly composed of carbohydrates, but other substances, such as polyphenols and polyunsaturated fatty acids, may also play a role in prebiotics.[83]

Inulin is a type of fermentable dietary fiber. Within the HUA mouse established by knocking out the *Uox* (UA oxidase) gene, inulin supplements can reduce the expression and activity of liver XOD by increasing the intestinal microbial diversity and the expression of ABCG2 in the gut. It also promotes SCFAs-producing bacteria (e.g., *Akkermania* and *Ruminococcus*) and safely and effectively alleviates HUA. Fish meat oligopeptides (TMOP) can alleviate HUA and renal provocative phenotypes, repair intestinal epithelial obstruction, restore intestinal microbiota homeostasis, and increase the production of SCFAs. In HUA rats, mangiferin reduced serum urate levels and increased UA levels and UA excretion division (FEUA), which may be related to repressing the mRNA and protein expression of URAT1, OAT10, and GLUT9 within the kidney of hyperuricemic rats.[82-85]

At present, an increasing number of studies are investigating the role and mechanisms of probiotics and prebiotics in reducing UA. However, it is undeniable that research on the therapeutic effects of probiotics and prebiotics on HUA is still in its early stages, and the understanding of their underlying mechanisms remains limited. Therefore, their safety and effect on clinical applications require further verification. More research and transformation work on probiotics and prebiotics should be encouraged to facilitate their widespread use in treatment as soon as possible.

5.3. FMT

FMT has emerged as a promising technique with diverse applications. Initially, FMT entails transferring functional gut bacteria from healthy donors to patients, aiming to restore microbial balance and improve gut function, thereby offering a potential solution for HUA management. Xie *et al*.[86] demonstrated that the administration of washed microbiota transplantation substantially reduced SUA concentrations, alleviated the manifestations of gout, and restored the integrity of the intestinal barrier in individuals suffering from gout.

The efficacy of FMT is hypothesized to be contingent upon the reconstitution of a well-balanced microbial community within the gut, a process deemed essential for the therapeutic success of the procedure. However, the precise mechanisms underlying FMT remain partially obscured. In the context of HUA, the mechanism of action of FMT encompasses several pivotal elements. Initially, FMT promotes an increase in commensal bacteria while reducing pathogenic strains, thereby enhancing gut health and mitigating inflammation – a response of particular significance given the chronic inflammatory nature often associated with HUA. Furthermore, FMT may augment the functionality of UA transporters, such as ABCG2, within the intestinal tract, thereby facilitating the excretion of UA and reducing its serum concentration. Finally, FMT has the potential to regulate the immune system, inhibiting the secretion of pro-inflammatory cytokines and subsequently alleviating chronic inflammation linked to HUA.[87-93]

FMT holds promise for HUA management, with studies demonstrating reduced UA levels and improved symptoms in animal models and humans. For instance, whole-microbial transplantation, a modified form of FMT, has demonstrated the potential to reduce UA levels and improve gout symptoms.[87] In addition, goose carnosine, a naturally occurring compound, can restore gut microbiota balance, repair the intestinal barrier, and promote UA excretion, further supporting the role of FMT in HUA management.[94,95]

However, further research is warranted to identify specific bacterial strains and mechanisms responsible for FMT's efficacy in HUA management. Large-scale clinical trials are crucial to assess the long-term safety and efficacy of FMT and other gut microbiota-targeted therapies for HUA. Advancements in technology, such as precision FMT and personalized probiotic/prebiotic formulations, could further improve the effectiveness of gut microbiota-targeted HUA therapies.

In summary, FMT and other gut microbiota-targeted strategies offer promising avenues for HUA management, potentially providing safer and more effective alternatives to traditional treatments.

5.4. Nutrients

Nutrients are essential substances for maintaining human physiological functions. Studies have demonstrated that beneficial microbes, such as *Bifidobacteria* and *Lactobacilli*, within the gut microbiota can help lower UA levels through various mechanisms. First, they can synthesize basic supplements, such as folic acid and Vitamin B, which are vital for maintaining overall health. In addition, they can inhibit XO, an enzyme responsible for converting purines into UA, thereby reducing UA production. Moreover, they can regulate UA transporters in the gut, facilitating its excretion and preventing its accumulation in the blood. Therefore, nutrient supplementation may be a safe and viable approach for the prevention and treatment of HUA.[95-97]

5.4.1. Protein diets

The Third National Wellbeing and Nourishment Study revealed people who consumed milk once or more per day had lower SUA levels compared to those who did not drink milk (multivariate contrast: −0.25 [95% CI: −0.40, −0.09]; $p < 0.001$). In a short-term randomized controlled trial of 16 male volunteers, the ingestion of all types of milk resulted in a decrease in serum urate concentrations by approximately 10% ($p < 0.0001$). The mechanism by which protein diets can lower SUA levels may involve glycomacropeptide and G600 milk fat extract, both of which inhibit IL-1β gene and protein expression. From a urate-lowering and possibly anti-inflammatory perspective, protein diets may offer protection against gout.[97,98]

5.4.2. Tea and tea extracts

Tea, a healthy beverage with numerous benefits, has displayed the potential to alleviate HUA through various mechanisms. Studies have demonstrated that tea and its extracts can reduce SUA levels by inhibiting XO, regulating urate-specific proteins, and modulating the gut microbiota. In addition, tea has exhibited some kidney-protective effects.[99,100]

In a HUA mouse model induced by continuous potassium oxonate administration, black brick tea with high levels of theaflavins displayed superior efficacy in reducing SUA levels compared to traditional black tea. Green tea polyphenols have been found to lower UA levels by inhibiting UA generation and stimulating UA excretion. Due to the distinct processing methods, green tea and black tea extracts demonstrate varying degrees of effectiveness in reducing HUA. Particularly, black tea extracts tend to be more effective than green tea extracts in reducing SUA levels, displaying a significant dose-dependent effect. A meta-analysis of long-term randomized controlled trials revealed that tea or tea extracts can lower SUA levels in asymptomatic HUA patients by regulating XO excretion and urate-specific proteins.[101-103]

Despite the promising applications and development prospects of tea and its functional components in lowering UA, challenges remain. The research on the mechanism, pathway, and target of tea's urate-lowering effect is not yet comprehensive enough. Further studies are needed to determine whether tea can be utilized for the treatment of HUA.

5.4.3. Vitamins

Vitamins are essential organic compounds required for the maintenance of normal physiological function within the body. They can be classified into two categories: Fat-soluble and water-soluble vitamins. These vitamins play a significant and imperative part in human growth, metabolism, and development. Increasing evidence suggests that vitamins have a substantial impact on intestinal microbiota composition. They can either enhance or maintain the diversity and abundance of the intestinal microbiota, regulate the intestinal immune response or barrier function, and play a crucial part in maintaining intestinal homeostasis and the balance between the host and gut microbiota.[104-106]

Combining probiotics with vitamins can enhance the beneficial effects of probiotics. By improving gut microbial populations, vitamins can increase mucus secretion, which helps to prevent the breakdown of tight junction proteins and maintain the integrity of the gut barrier.[106]

In addition, vitamins can reduce the concentration of LPS, which are harmful bacterial components that can trigger inflammation and compromise gut barrier function.[107] Several key vitamins are essential for maintaining a healthy intestinal barrier and optimal immune homeostasis. The incorporation of these vitamins into diets and using probiotics can help maintain a healthy

gut microbiota and gut barrier function, which is essential for overall health and well-being (Table 3).

The human gut harbors certain bacteria capable of synthesizing Vitamin B12, highlighting the gut microbiota as a potential source of Vitamin B. Prospective cohort studies have demonstrated that the intake and serum concentrations of folic acid, Vitamin B6, and Vitamin B12 are inversely associated with the risk of metabolic syndrome in young individuals of both black and white ethnicities in the United States.[108] Using multivariate logistic regression analysis, studies have reported that increasing folic acid and Vitamin B12 intake may reduce the risk of HUA in men.[109] Folic acid, also known as Vitamin B9, is a potent competitive inhibitor of XO, an enzyme involved in UA metabolism. Comparisons have demonstrated that folic acid and its coenzyme derivative, tetrahydrofolate, are approximately twice as effective as allopurinol, a commonly used urate-lowering medication, in inhibiting XO activity.[110] The Chinese Primary Prevention Trial of Stroke (CSPPT) indicated that compared with enalapril alone, enalapril-folic acid therapy significantly reduced SUA concentration in hypertensive adults.[111] The urate-lowering effects of folic acid may be attributed to its ability to reduce homocysteine levels. In a retrospective cross-sectional analysis, serum homocysteine levels were positively correlated with SUA levels, displaying a significant association between hyperhomocysteinemia and HUA.[112]

Vitamin C has been demonstrated to have antioxidant and anti-inflammatory properties. A logistic regression analysis revealed an inverse relationship between Vitamin C intake and the risk of HUA in both men and women. However, a meta-analysis demonstrated no significant difference in effect between high and low doses of Vitamin C supplementation. Further clinical trials with longer supplementation periods and varying doses are warranted to determine the optimal dosage for preventing HUA.[113-117]

In addition, high-dose Vitamin D supplementation has been found to modify the intestinal microbiome composition. In pre-adolescent females, 9 weeks of supplementation with 50,000 IU of cholecalciferol per week resulted in a decrease in *Bacteroides* and *Lactobacillus* abundance and an increase in *Firmicutes* and *Bifidobacteria*. The relationship between Vitamin D and UA levels is complex and bidirectional. Vitamin D deficiency is approximately 1.5 times more common in individuals with HUA compared to those with normal Vitamin D levels. According to the National Wellbeing and Nourishment Examination Study,[115] serum 25-hydroxyvitamin D levels may be negatively correlated with HUA in the general American adult population. A two-sample bidirectional Mendelian randomization investigation demonstrated

Table 3. The role of vitamins in diets

Type	Attribution	Function	Mechanisms affecting hyperuricemia
Vitamin B (B6/ B12/folic acid)	Water-soluble vitamins	Improves immunity, maintains the nervous system, and is a cofactor used by hundreds of enzymes that perform energy metabolism, DNA, and protein synthesis; folic acid is involved in purine and thymine synthesis, as well as in the synthesis of heme	Inhibiting uric acid biosynthesis and stimulating uric acid excretion by regulating gut microbiota; folic acid can reduce homocysteine and reduce the catabolism of purine nucleotides
Vitamin C	Water-soluble vitamin	It can eliminate free radicals and ascorbic acid (donor electrons in various enzymatic and non-enzyme catalysis) in the body; it is a powerful antioxidant; preventing arteriosclerosis can promote intestinal absorption of iron and prevent anemia; participates in collagen synthesis	Improves renal function; increases glomerular filtration rate; reduces serum urate concentration; competitively inhibits the reabsorption of serum urate
Vitamin D	Fat-soluble vitamins	Maintain serum calcium and phosphorus levels, and resist rickets; activating Vitamin D has potential renal protective effects, which can slow down the progression of chronic kidney disease and reduce inflammatory biomarkers; low doses of active Vitamin D analogs can prevent aortic calcification and lower blood pressure	It can affect uric acid transport in the proximal tubule of the kidney by affecting the parathyroid hormone and reducing uric acid salt excretion; improves intestinal permeability and restores tight intestinal connections to protect intestinal epithelial barrier function, thereby reducing inflammation
Vitamin E	Fat-soluble vitamins	Enhance anticoagulant and vasodilator effects, and promote plasma membrane repair; as a free radical scavenger molecule, it can inhibit lipid peroxidation	Interferes with bacterial biofilm and prevents the formation of biofilm *in vitro*, preventing oxidative stress; inhibition of xanthine oxidase to reduce uric acid production

that each additional mg/dL of UA was associated with a 74.25 nmol/L decrease in serum 25-hydroxyvitamin D levels, with results remaining consistent in sensitivity analysis.[118,119]

Dietary Vitamin E intake has also been reported to be inversely related to HUA in American adults, especially in men and individuals aged 60 years or older.[121] Vitamin E acts as a scavenger of hydroxyl, peroxy, and superoxide radicals, protecting the body from the harmful effects of free radicals. It can also inhibit XO activity, thereby lowering UA levels. Furthermore, studies have demonstrated that Vitamin E can interfere with bacterial biofilms and prevent biofilm formation *in vitro*. Moreover, Vitamin E application has been demonstrated to reduce the ability of *Staphylococcus aureus* and *Staphylococcus epidermidis* to colonize surfaces.[120-123]

While the potential benefits of vitamin supplementation in HUA management are promising, further research is warranted to clarify the precise mechanisms, optimal dosages, and long-term safety profiles. Larger-scale clinical trials with longer durations of observation are essential to establish the efficacy and safety of vitamin supplementation as a potential therapeutic approach for HUA.

6. Discussion

Genetic mutations in the uricase gene that increase human susceptibility to HUA lead to elevated UA levels. In mice with uricase deficiency, the removal of the microbiota results in a profound state of HUA.[49] In addition, clinical observations have correlated the administration of antibiotics that target anaerobic bacteria in humans with a heightened risk of developing gout. These findings underscore the therapeutic potential of microbiome-targeted interventions for the treatment of HUA.

The increasing prevalence of HUA necessitates the development of safe and effective treatment strategies. Current HUA treatments provide rapid symptom relief but come with risks, including allergic reactions and systemic damage. The intestine emerges as a critical alternative route for UA elimination. Elevated UA levels can compromise the intestinal barrier, induce oxidative stress, exacerbate inflammation, and dysregulate UA metabolism. Understanding the gut microbiota's role in UA metabolism is crucial for HUA diagnosis and treatment.[124-126]

In the context of cancer, research suggests that UA-derived nucleotides within the intestinal environment can promote the growth of colorectal cancer cells, subsequently enhancing the tumor's resistance to both chemotherapy and radiation treatments.[127] This comprehensive work underscores the complex interplay between HUA and the intestinal environment. The mechanisms through which the intestinal microbiota can lower UA levels primarily involve inhibiting key proteins involved in UA regulation, modulating the expression of UA transporters, and restoring the integrity of the intestinal barrier. These actions collectively contribute to the reduction of UA, providing a foundation for exploring the potential of the intestinal microbiota in alleviating HUA and supporting the development of novel therapeutic approaches. Manipulating the intestinal microbiota – through probiotics, prebiotics, targeted nutrients, and FMT – represents a safe, cost-effective, and promising strategy for preventing elevated SUA levels, with significant implications for both clinical practice and public health.

However, the intestinal microbiota operates within a complex and dynamic microenvironment influenced by numerous factors. Precisely controlling UA metabolism through the synergistic action of multiple mechanisms poses a considerable challenge. While the current research landscape is abundant with animal studies, clinical trial data remains limited. Larger and more rigorous clinical investigations are necessary to bridge the knowledge gap regarding the role of the intestinal microbiota in metabolic diseases, including HUA, and to elucidate their specific mechanisms. In addition, clinical studies are needed to verify the practicality and safety of therapies based on intestinal microbiota regulation for HUA. In the pursuit of therapeutic efficacy, it is essential not only to focus on the immediate effects of interventions but also to consider potential adverse reactions and long-term outcomes. Translating basic theoretical insights into clinical practice represents a key direction for future research endeavors.[58,61,128,129]

7. Conclusion

The complex relationship between the gut and HUA highlights the intricate role of the gut as both a digestive and detoxifying organ. In this context, the gut microbiota develops into a complex environment with significant impacts on metabolic patterns. The interplay between the gut microbiota and the UA metabolic system suggests a bidirectional relationship, where the uncoordinated nature of the gut microbiota may contribute to the development of HUA. This understanding highlights the potential of manipulating the gut microbiota as a novel and promising therapeutic approach for managing HUA. This approach may open new avenues for the development of innovative drugs, providing an exciting perspective to treating this metabolic disorder.

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Conflict of interest

The authors declare that there are no competing interests.

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References

1. Crane JK. Role of host xanthine oxidase in infection due to enteropathogenic and Shiga-toxigenic *Escherichia coli*. *Gut Microbes*. 2013;4(5):388-391.

   doi: 10.4161/gmic.25584

2. Kurosaki M, Li Calzi M, Scanziani E, Garattini E, Terao M. Tissue-and cell-specific expression of mouse xanthine oxidoreductase gene *in vivo*: Regulation by bacterial lipopolysaccharide. *Biochem J*. 1995;306(Pt 1):225-234.

   doi: 10.1042/bj3060225

3. Yamada N, Iwamoto C, Kano H, *et al*. Evaluation of purine utilization by *Lactobacillus gasseri* strains with potential to decrease the absorption of food-derived purines in the human intestine. *Nucleosides Nucleotides Nucleic Acids*. 2016;35:670-676.

   doi: 10.1080/15257770.2015.1125000

4. Martínez-Nava GA, Méndez-Salazar EO, Vázquez-Mellado J, *et al*. The impact of short-chain fatty acid-producing bacteria of the gut microbiota in hyperuricemia and gout diagnosis. *Clin Rheumatol*. 2023;42:203-214.

   doi: 10.1007/s10067-022-06392-9

5. Wei J, Zhang Y, Dalbeth N, *et al*. Association between gut microbiota and elevated serum urate in two independent cohorts. *Arthritis Rheumatol*. 2022;74:682-691.

   doi: 10.1002/art.42009

6. Borghi C, Agabiti-Rosei E, Johnson RJ, *et al*. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. *Eur J Intern Med*. 2020;80:1-11.

   doi: 10.1016/j.ejim.2020.07.006

7. Beam A, Clinger E, Hao L. Effect of diet and dietary components on the composition of the gut microbiota. *Nutrients*. 2021;13(8):2795.

   doi: 10.3390/nu13082795

8. Soldán M, Argalášová Ľ, Hadvinová L, Galileo B, Babjaková J. The effect of dietary types on gut microbiota composition and development of non-communicable diseases: A narrative review. *Nutrients*. 2024;16(18):3134.

   doi: 10.3390/nu16183134

9. Randeni N, Bordiga M, Xu B. A comprehensive review of the triangular relationship among diet-gut microbiota-inflammation. *Int J Mol Sci*. 2024;25(17):9366.

   doi: 10.3390/ijms25179366

10. Johnson RJ, Bakris GL, Borghi C, *et al*. Hyperuricemia, acute and chronic kidney disease, hypertension, and cardiovascular disease: Report of a scientific workshop organized by the national kidney foundation. *Am J Kidney Dis*. 2018;71:851-865.

    doi: 10.1053/j.ajkd.2017.12.009

11. Wu X, You C. The biomarkers discovery of hyperuricemia and gout: Proteomics and metabolomics. *PeerJ*. 2023;11:e14554.

    doi: 10.7717/peerj.14554

12. Wan H, Zhang K, Wang Y, *et al*. The associations between gonadal hormones and serum uric acid levels in men and postmenopausal women with diabetes. *Front Endocrinol* (*Lausanne*). 2020;11:55.

    doi: 10.3389/fendo.2020.00055

13. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: The national health and nutrition examination survey, 2007-2016. *Arthritis Rheumatol*. 2019;71(6):991-999.

    doi: 10.1002/art.40807

14. Li L, Zhang Y, Zeng C. Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. *Am J Transl Res*. 2020;12(7):3167-3181.

15. Trifirò G, Morabito P, Cavagna L, *et al*. Epidemiology of gout and hyperuricaemia in Italy during the years 2005-2009: A nationwide population-based study. *Ann Rheum Dis*. 2013;72(5):694-700.

    doi: 10.1136/annrheumdis-2011-201254

16. Cai Z, Xu X, Wu X, Zhou C, Li D. Hyperuricemia and the metabolic syndrome in Hangzhou. *Asia Pac J Clin Nutr*. 2009;18(1):81-87.

17. Nan H, Qiao Q, Dong Y, *et al.* The prevalence of hyperuricemia in a population of the coastal city of Qingdao, China. *J Rheumatol.* 2006;33(7):1346-1350.

18. Zhang Q, Gong H, Lin C, *et al.* The prevalence of gout and hyperuricemia in middle-aged and elderly people in Tibet Autonomous Region, China: A preliminary study. *Medicine* (*Baltimore*). 2020;99:e18542.

doi: 10.1097/MD.0000000000018542

19. Wang J, Chen Y, Chen S, *et al.* Prevalence and risk factors of hyperuricaemia in non-obese Chinese: A single-centre cross-sectional study. *BMJ Open.* 2022;12(6):e048574.

doi: 10.1136/bmjopen-2020-048574

20. Li S, Sanna S, Maschio A, *et al.* The GLUT9 gene is associated with serum uric acid levels in Sardinia and Chianti cohorts. *PLoS Genet*. 2007;3(11):e194.

doi: 10.1371/journal.pgen.0030194

21. Hosomi A, Nakanishi T, Fujita T, Tamai I. Extra-renal elimination of uric acid via intestinal efflux transporter BCRP/ABCG2. *PLoS One.* 2012;7(2):e30456.

doi: 10.1371/journal.pone.0030456

22. Hyndman D, Liu S, Miner JN. Urate handling in the human body. *Curr Rheumatol Rep.* 2016;18(6):34.

doi: 10.1007/s11926-016-0587-7

23. Emmerson BT. Effect of oral fructose on urate production. *Ann Rheum Dis*. 1974;33:276-280.

doi: 10.1136/ard.33.3.276

24. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout [published correction appears in *Lancet*. 2021;397(10287):1808.

doi: 10.1016/S0140-6736(21)01010-2.]. *Lancet*. 2021;397 (10287):1843-1855.

doi: 10.1016/S0140-6736(21)00569-9

25. Zhang WZ. Why does hyperuricemia not necessarily induce gout? *Biomolecules*. 2021;11(2):280.

doi: 10.3390/biom11020280

26. Ramazzina I, Costa R, Cendron L, *et al.* An aminotransferase branch point connects purine catabolism to amino acid recycling. *Nat Chem Biol*. 2010;6(11):801-806.

doi: 10.1038/nchembio.445

27. Pan L, Han P, Ma S, *et al.* Abnormal metabolism of gut microbiota reveals the possible molecular mechanism of nephropathy induced by hyperuricemia. *Acta Pharm Sin B*. 2020;10(2):249-261.

doi: 10.1016/j.apsb.2019.10.007

28. Milani C, Duranti S, Bottacini F, *et al.* The first microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut microbiota. *Microbiol Mol Biol Rev*. 2017;81(4):e00036-17.

doi: 10.1128/MMBR.00036-17

29. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*. 2016;14:e1002533.

doi: 10.1371/journal.pbio.1002533

30. Méndez-Salazar EO, Martínez-Nava GA. Uric acid extrarenal excretion: The gut microbiome as an evident yet understated factor in gout development. *Rheumatol Int*. 2022;42(3):403-412.

doi: 10.1007/s00296-021-05007-x

31. Pascart T, Lioté F. Gout: State of the art after a decade of developments. *Rheumatology* (*Oxford*). 2019;58(1):27-44.

doi: 10.1093/rheumatology/key002

32. Song S, Lou Y, Mao Y, *et al.* Alteration of gut microbiome and correlated amino acid metabolism contribute to hyperuricemia and Th17-driven inflammation in Uox-KO mice. *Front Immunol.* 2022;13:804306.

doi: 10.3389/fimmu.2022.804306

33. Zhang H, Hua R, Zhang B, Zhang X, Yang H, Zhou X. Serine alleviates dextran sulfate sodium-induced colitis and regulates the gut microbiota in mice. *Front Microbiol.* 2018;9:3062.

doi: 10.3389/fmicb.2018.03062

34. Mahbub MH, Yamaguchi N, Takahashi H, *et al.* Association of plasma free amino acids with hyperuricemia in relation to diabetes mellitus, dyslipidemia, hypertension and metabolic syndrome. *Sci Rep.* 2017;7(1):17616.

doi: 10.1038/s41598-017-17710-6

35. Wang F, Sun L, Zong G, *et al.* Associations of amino acid and acylcarnitine profiles with incident hyperuricemia in middle-aged and older Chinese individuals. *Arthritis Care Res* (*Hoboken*). 2020;72(9):1305-1314.

doi: 10.1002/acr.24013

36. Ma C, Yang X, Lv Q, *et al.* Soluble uric acid induces inflammation via TLR4/NLRP3 pathway in intestinal epithelial cells. *Iran J Basic Med Sci*. 2020;23(6):744-750.

doi: 10.22038/ijbms.2020.44948.10482

37. Halimulati M, Wang R, Aihemaitijiang S, *et al.* Anti-hyperuricemic effect of anserine based on the gut-kidney axis: Integrated analysis of metagenomics and metabolomics. *Nutrients*. 2023;15(4):969.

doi: 10.3390/nu15040969

38. Espírito Santo C, Caseiro C, Martins MJ, Monteiro R, Brandão I. Gut microbiota, in the halfway between nutrition and lung function. *Nutrients*. 2021;13(5):1716.

doi: 10.3390/nu13051716

39. Li M, Liu B, Li R, Yang P, Leng P, Huang Y. Exploration of the link between gut microbiota and purinergic signalling.

Purinergic Signal. 2023;19:315-327.

doi: 10.1007/s11302-022-09891-1

40. Shao T, Shao L, Li H, Xie Z, He Z, Wen C. Combined signature of the fecal microbiome and metabolome in patients with gout. *Front Microbiol*. 2017;8:268.

doi: 10.3389/fmicb.2017.00268

41. Guo Z, Zhang J, Wang Z, *et al.* Intestinal microbiota distinguish gout patients from healthy humans. *Sci Rep.* 2016;6:20602.

doi: 10.1038/srep20602

42. Chu Y, Sun S, Huang Y, *et al*. Metagenomic analysis revealed the potential role of gut microbiome in gout. *NPJ Biofilms Microbiomes.* 2021;7(1):66.

doi: 10.1038/s41522-021-00235-2

43. He L, Tang W, Huang L, *et al*. Rational design of a genome-based insulated system in *Escherichia coli* facilitates heterologous uricase expression for hyperuricemia treatment. *Bioeng Transl Med.* 2022;8(2):e10449.

doi: 10.1002/btm2.10449

44. Liu X, Lv Q, Ren H, *et al.* The altered gut microbiota of high-purine-induced hyperuricemia rats and its correlation with hyperuricemia. *PeerJ*. 2020;8:e8664.

doi: 10.7717/peerj.8664

45. Sapankaew T, Thadanipon K, Ruenroengbun N, *et al.* Efficacy and safety of urate-lowering agents in asymptomatic hyperuricemia: Systematic review and network meta-analysis of randomized controlled trials. *BMC Nephrol.* 2022;23(1):223.

doi: 10.1186/s12882-022-02850-3

46. Wang J, Chen Y, Zhong H, *et al*. The gut microbiota as a target to control hyperuricemia pathogenesis: Potential mechanisms and therapeutic strategies. *Crit Rev Food Sci Nutr*. 2022;62(14):3979-3989.

doi: 10.1080/10408398.2021.1874287

47. Dong L, Dong F, Guo P, *et al*. Gut microbiota as a new target for hyperuricemia: A perspective from natural plant products. *Phytomedicine*. 2025;138:156402.

doi: 10.1016/j.phymed.2025.156402

48. Ananthakrishnan AN, Luo C, Yajnik V, *et al.* Gut microbiome function predicts response to anti-integrin biologic therapy in inflammatory bowel diseases. *Cell Host Microbe.* 2017;21(5):603-610.e3.

doi: 10.1016/j.chom.2017.04.010

49. Liu Y, Jarman JB, Low YS, *et al.* A widely distributed gene cluster compensates for uricase loss in hominids [published correction appears in *Cell*. 2023;186(20):4472-4473.

doi: 10.1016/j.cell.2023.08.036]. *Cell.* 2023;186(16):3400-3413.e20.

doi: 10.1016/j.cell.2023.06.010

50. Marco ML, Sanders ME, Gänzle M, *et al*. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on fermented foods. *Nat Rev Gastroenterol Hepatol.* 2021;18(3):196-208.

doi: 10.1038/s41575-020-00390-5

51. Dimidi E, Christodoulides S, Scott SM, Whelan K. Mechanisms of action of probiotics and the gastrointestinal microbiota on gut motility and constipation. *Adv Nutr*. 2017;8(3):484-494.

doi: 10.3945/an.116.014407

52. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic [published correction appears in *Nat Rev Gastroenterol Hepatol*. 2019;16(10):642.

doi: 10.1038/s41575-019-0199-6]. *Nat Rev Gastroenterol Hepatol.* 2019;16(10):605-616.

doi: 10.1038/s41575-019-0173-3

53. Wang H, Mei L, Deng Y, *et al. Lactobacillus brevis* DM9218 ameliorates fructose-induced hyperuricemia through inosine degradation and manipulation of intestinal dysbiosis. *Nutrition*. 2019;62:63-73.

doi: 10.1016/j.nut.2018.11.018

54. Rodríguez JM, Garranzo M, Segura J, *et al*. A randomized pilot trial assessing the reduction of gout episodes in hyperuricemic patients by oral administration of *Ligilactobacillus salivarius* CECT 30632, a strain with the ability to degrade purines. *Front Microbiol*. 2023;14:1111652.

doi: 10.3389/fmicb.2023.1111652

55. Wei Z, Cui Y, Tian L, *et al*. Probiotic *Lactiplantibacillus plantarum* N-1 could prevent ethylene glycol-induced kidney stones by regulating gut microbiota and enhancing intestinal barrier function. *FASEB J*. 2021;35(11):e21937.

doi: 10.1096/fj.202100887RR

56. Li Y, Zhu J, Lin G, *et al.* Probiotic effects of *Lacticaseibacillus rhamnosus* 1155 and *Limosilactobacillus fermentum* 2644 on hyperuricemic rats. *Front Nutr*. 2022;9:993951.

doi: 10.3389/fnut.2022.993951

57. Ni C, Li X, Wang L, *et al*. Lactic acid bacteria strains relieve hyperuricaemia by suppressing xanthine oxidase activity via a short-chain fatty acid-dependent mechanism. *Food Funct*. 2021;12(15):7054-7067.

doi: 10.1039/d1fo00198a

58. Zou Y, Ro KS, Jiang C, *et al.* The anti-hyperuricemic and gut microbiota regulatory effects of a novel purine assimilatory strain, *Lactiplantibacillus plantarum* X7022 [published correction appears in *Eur J Nutr.* 2024;63(5):1997.

doi: 10.1007/s00394-024-03382-2]. *Eur J Nutr.*

2024;63(3):697-711.

doi: 10.1007/s00394-023-03291-w

59. Méndez-Salazar EO, Vázquez-Mellado J, Casimiro-Soriguer CS, *et al*. Taxonomic variations in the gut microbiome of gout patients with and without tophi might have a functional impact on urate metabolism. *Mol Med*. 2021;27(1):50.

doi: 10.1186/s10020-021-00311-5

60. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol*. 2020;180:114147.

doi: 10.1016/j.bcp.2020.114147

61. Singh AK, Durairajan SSK, Iyaswamy A, Williams LL. Elucidating the role of gut microbiota dysbiosis in hyperuricemia and gout: Insights and therapeutic strategies. *World J Gastroenterol*. 2024;30(40):4404-4410.

doi: 10.3748/wjg.v30.i40.4404

62. Cao J, Wang T, Liu Y, *et al*. *Lactobacillus fermentum* F40-4 ameliorates hyperuricemia by modulating the gut microbiota and alleviating inflammation in mice [published correction appears in *Food Funct*. 2024;15(4):2328.

doi: 10.1039/d4fo90016b]. *Food Funct*. 2023;14(7):3259-3268.

doi: 10.1039/d2fo03701g

63. Cao J, Liu Q, Hao H, et al. *Lactobacillus paracasei* X11 ameliorates hyperuricemia and modulates gut microbiota in mice [retracted in: *Front Immunol*. 2024;15:1517021.

doi: 10.3389/fimmu.2024.1517021]. *Front Immunol*. 2022;13:940228.

doi: 10.3389/fimmu.2022.940228

64. Hamada T, Hisatome I, Wakimizu T, *et al*. *Lactobacillus gasseri* PA-3 reduces serum uric acid levels in patients with marginal hyperuricemia. *Nucleosides Nucleotides Nucleic Acids*. 2022;41(4):361-369.

doi: 10.1080/15257770.2022.2039702

65. Yamanaka H, Taniguchi A, Tsuboi H, Kano H, Asami Y. Hypouricaemic effects of yoghurt containing *Lactobacillus gasseri* PA-3 in patients with hyperuricaemia and/or gout: A randomised, double-blind, placebo-controlled study. *Mod Rheumatol*. 2019;29(1):146-150.

doi: 10.1080/14397595.2018.1442183

66. Kuo YW, Hsieh SH, Chen JF, *et al*. *Lactobacillus reuteri* TSR332 and *Lactobacillus fermentum* TSF331 stabilize serum uric acid levels and prevent hyperuricemia in rats. *PeerJ*. 2021;9:e11209.

doi: 10.7717/peerj.11209

67. Stamp LK, Chapman PT. Allopurinol hypersensitivity: Pathogenesis and prevention. *Best Pract Res Clin Rheumatol*. 2020;34(4):101501.

doi: 10.1016/j.berh.2020.101501

68. Jordan A, Gresser U. Side effects and interactions of the xanthine oxidase inhibitor febuxostat. *Pharmaceuticals* (*Basel*). 2018;11(2):51.

doi: 10.3390/ph11020051

69. White WB, Saag KG, Becker MA, *et al*. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;378(13):1200-1210.

doi: 10.1056/NEJMoa1710895

70. Kawenoki-Minc E, Brzozowska-Jurkowska AM. Zastosowanie benzbromaronu w leczeniu chorych na dne [Benzbromarone in the treatment of gout]. *Reumatologia*. 1980;18(1):61-67.

71. Shen Z, Rowlings C, Kerr B, *et al*. Pharmacokinetics, pharmacodynamics, and safety of lesinurad, a selective uric acid reabsorption inhibitor, in healthy adult males. *Drug Des Dev Ther*. 2015;9:3423-3434.

doi: 10.2147/DDDT.S85193

72. Pérez-Ruiz F, Jansen T, Tausche AK, Juárez-Campo M, Gurunath RK, Richette P. Efficacy and safety of lesinurad for the treatment of hyperuricemia in gout. *Drugs Context*. 2019;8:212581.

doi: 10.7573/dic.212581

73. Shi X, Zhao T, da Silva-Júnior EF, *et al*. Novel urate transporter 1 (URAT1) inhibitors: A review of recent patent literature (2020-present). *Expert Opin Ther Pat*. 2022;32(12):1175-1184.

doi: 10.1080/13543776.2022.2165911

74. Schlesinger N, Lipsky PE. Pegloticase treatment of chronic refractory gout: Update on efficacy and safety. *Semin Arthritis Rheum*. 2020;50(3S):S31-S38.

doi: 10.1016/j.semarthrit.2020.04.011

75. Sundy JS, Baraf HS, Yood RA, *et al*. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: Two randomized controlled trials. *JAMA*. 2011;306(7):711-720.

doi: 10.1001/jama.2011.1169

76. Stamp LK, Merriman TR, Singh JA. Expert opinion on emerging urate-lowering therapies. *Expert Opin Emerg Drugs*. 2018;23(3):201-209.

doi: 10.1080/14728214.2018.1527899

77. Zhou X, Zhang B, Zhao X, *et al*. Chlorogenic acid supplementation ameliorates hyperuricemia, relieves renal inflammation, and modulates intestinal homeostasis. *Food Funct*. 2021;12(12):5637-5649.

doi: 10.1039/d0fo03199b

78. Gao J, Azad MAK, Han H, Wan D, Li T. Impact of prebiotics on enteric diseases and oxidative stress. *Curr Pharm Des*.

2020;26(22):2630-2641.

doi: 10.2174/1381612826666200211121916

79. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J Nutr.* 1995;125(6):1401-1412.

doi: 10.1093/jn/125.6.1401

80. Bindels LB, Delzenne NM, Cani PD, Walter J. Towards a more comprehensive concept for prebiotics. *Nat Rev Gastroenterol Hepatol*. 2015;12(5):303-310.

doi: 10.1038/nrgastro.2015.47

81. Guo Y, Yu Y, Li H, *et al*. Inulin supplementation ameliorates hyperuricemia and modulates gut microbiota in Uox-knockout mice. *Eur J Nutr*. 2021;60(4):2217-2230.

doi: 10.1007/s00394-020-02414-x

82. Yang H, Gao L, Niu Y, *et al.* Mangiferin inhibits renal urate reabsorption by modulating urate transporters in experimental hyperuricemia. *Biol Pharm Bull*. 2015;38(10):1591-1598.

doi: 10.1248/bpb.b15-00402

83. Han J, Wang X, Tang S, *et al*. Protective effects of tuna meat oligopeptides (TMOP) supplementation on hyperuricemia and associated renal inflammation mediated by gut microbiota. *FASEB J*. 2020;34(4):5061-5076.

doi: 10.1096/fj.201902597RR

84. Xie WR, Yang XY, Deng ZH, *et al*. Effects of washed microbiota transplantation on serum uric acid levels, symptoms, and intestinal barrier function in patients with acute and recurrent gout: A pilot study. *Dig Dis*. 2022;40(5):684-690.

doi: 10.1159/000521273

85. Leshem A, Horesh N, Elinav E. Fecal microbial transplantation and its potential application in cardiometabolic syndrome. *Front Immunol.* 2019;10:1341.

doi: 10.3389/fimmu.2019.01341

86. Kelly CR, Khoruts A, Staley C, *et al*. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* Infection: A randomized trial. *Ann Intern Med*. 2016;165(9):609-616.

doi: 10.7326/M16-0271

87. Ademe M. Benefits of fecal microbiota transplantation: A comprehensive review. *J Infect Dev Ctries.* 2020;14(10):1074-1080.

doi: 10.3855/jidc.12780

88. Zhang L, Ma X, Liu P, *et al*. Treatment and mechanism of fecal microbiota transplantation in mice with experimentally induced ulcerative colitis. *Exp Biol Med* (*Maywood*). 2021;246(13):1563-1575.

doi: 10.1177/15353702211006044

89. Ooijevaar RE, Terveer EM, Verspaget HW, Kuijper EJ, Keller JJ. Clinical application and potential of fecal microbiota transplantation. *Annu Rev Med*. 2019;70:335-351.

doi: 10.1146/annurev-med-111717-122956

90. Kelly CR, Ihunnah C, Fischer M, *et al*. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol*. 2014;109(7):1065-1071.

doi: 10.1038/ajg.2014.133

91. Lu C, Tang S, Han J, *et al*. *Apostichopus japonicus* oligopeptide induced heterogeneity in the gastrointestinal tract microbiota and alleviated hyperuricemia in a microbiota-dependent manner. *Mol Nutr Food Res*. 2021;65(14):e2100147.

doi: 10.1002/mnfr.202100147

92. Han J, Wang Z, Lu C, *et al*. The gut microbiota mediates the protective effects of anserine supplementation on hyperuricaemia and associated renal inflammation. *Food Funct*. 2021;12:9030-9042.

doi: 10.1039/d1fo01884a

93. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: The Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 2005;52(1):283-289.

doi: 10.1002/art.20761

94. Dalbeth N, Wong S, Gamble GD, *et al*. Acute effect of milk on serum urate concentrations: A randomised controlled crossover trial. *Ann Rheum Dis.* 2010;69(9):1677-1682.

doi: 10.1136/ard.2009.124230

95. Dalbeth N, Gracey E, Pool B, *et al*. Identification of dairy fractions with anti-inflammatory properties in models of acute gout. *Ann Rheum Dis*. 2010;69:766-769.

doi: 10.1136/ard.2009.113290

96. MacFarlane LA, Kim SC. Gout: A review of nonmodifiable and modifiable risk factors. *Rheum Dis Clin North Am*. 2014;40(4):581-604.

doi: 10.1016/j.rdc.2014.07.002

97. Wu D, Chen R, Li Q, *et al*. Tea (*Camellia sinensis*) Ameliorates hyperuricemia via uric acid metabolic pathways and gut microbiota. *Nutrients*. 2022;14:2666.

doi: 10.3390/nu14132666

98. Yuan D, Lin L, Peng Y, *et al*. Effects of black tea and black brick tea with fungal growth on lowering uric acid levels in hyperuricemic mice. *J Food Biochem*. 2022;46(7):e14140.

doi: 10.1111/jfbc.14140

99. Chen G, Tan ML, Li KK, Leung PC, Ko CH. Green tea polyphenols decreases uric acid level through xanthine oxidase and renal urate transporters in hyperuricemic mice. *J Ethnopharmacol*. 2015;175:14-20.

doi: 10.1016/j.jep.2015.08.043

100. Zhu C, Tai LL, Wan XC, Li DX, Zhao YQ, Xu Y. Comparative effects of green and black tea extracts on lowering serum uric acid in hyperuricemic mice. *Pharm Biol.* 2017;55(1):2123-2128.

doi: 10.1080/13880209.2017.1377736

101. Peluso I, Teichner A, Manafikhi H, Palmery M. *Camellia sinensis* in asymptomatic hyperuricemia: A meta-analysis of tea or tea extract effects on uric acid levels. *Crit Rev Food Sci Nutr*. 2017;57(2):391-398.

doi: 10.1080/10408398.2014.889653

102. Lee C, Lau E, Chusilp S, *et al*. Protective effects of vitamin D against injury in intestinal epithelium. *Pediatr Surg Int.* 2019;35(12):1395-1401.

doi: 10.1007/s00383-019-04586-y

103. Stacchiotti V, Rezzi S, Eggersdorfer M, Galli F. Metabolic and functional interplay between gut microbiota and fat-soluble vitamins. *Crit Rev Food Sci Nutr.* 2021;61(19):3211-3232.

doi: 10.1080/10408398.2020.1793728

104. Yang Q, Liang Q, Balakrishnan B, Belobrajdic DP, Feng QJ, Zhang W. Role of dietary nutrients in the modulation of gut microbiota: A narrative review. *Nutrients*. 2020;12(2):381.

doi: 10.3390/nu12020381

105. Peterson CT, Rodionov DA, Osterman AL, Peterson SN. B vitamins and their role in immune regulation and cancer. *Nutrients*. 2020;12(11):3380.

doi: 10.3390/nu12113380

106. Zhu J, Chen C, Lu L, *et al*. Vitamin B6, and vitamin B12 status in association with metabolic syndrome incidence. *JAMA Netw Open.* 2023;6(1):e2250621.

doi: 10.1001/jamanetworkopen.2022.50621

107. Lewis AS, Murphy L, McCalla C, Fleary M, Purcell S. Inhibition of mammalian xanthine oxidase by folate compounds and amethopterin. *J Biol Chem*. 1984;259(1):12-15.

108. Qin X, Li Y, He M, *et al*. Folic acid therapy reduces serum uric acid in hypertensive patients: A substudy of the China Stroke Primary Prevention Trial (CSPPT). *Am J Clin Nutr*. 2017;105(4):882-889.

doi: 10.3945/ajcn.116.143131

109. Slot O. Homocysteine, a marker of cardiovascular disease risk, is markedly elevated in patients with gout. *Ann Rheum Dis.* 2013;72(3):457.

doi: 10.1136/annrheumdis-2012-202023

110. Cohen E, Levi A, Vecht-Lifshitz SE, Goldberg E, Garty M, Krause I. Assessment of a possible link between hyperhomocysteinemia and hyperuricemia. *J Investig Med*. 2015;63(3):534-538.

doi: 10.1097/JIM.0000000000000152

111. Granger M, Eck P. Dietary vitamin C in human health. *Adv Food Nutr Res*. 2018;83:281-310.

doi: 10.1016/bs.afnr.2017.11.006

112. Sun Y, Sun J, Wang J, Gao T, Zhang H, Ma A. Association between vitamin C intake and risk of hyperuricemia in US adults. *Asia Pac J Clin Nutr.* 2018;27(6):1271-1276.

doi: 10.6133/apjcn.201811_27(6).0014

113. Csupor D, Lantos T, Hegyi P, *et al. Vitex agnus-castus* in premenstrual syndrome: A meta-analysis of double-blind randomised controlled trials. *Complement Ther Med.* 2019;47:102190.

doi: 10.1016/j.ctim.2019.08.024

114. Brzezińska O, Styrzyński F, Makowska J, Walczak K. Role of vitamin C in prophylaxis and treatment of gout-a literature review. *Nutrients*. 2021;13(2):701.

doi: 10.3390/nu13020701

115. Pham VT, Dold S, Rehman A, Bird JK, Steinert RE. Vitamins, the gut microbiome and gastrointestinal health in humans. *Nutr Res.* 2021;95:35-53.

doi: 10.1016/j.nutres.2021.09.001

116. Han Y, Han K, Zhang Y, Zeng X. Correction to: Serum 25-hydroxyvitamin D might be negatively associated with hyperuricemia in U.S. adults: An analysis of the National Health and Nutrition Examination Survey 2007-2014. *J Endocrinol Invest.* 2022;45(4):907.

doi: 10.1007/s40618-021-01734-x

117. Han Y, Zhang Y, Zeng X. Assessment of causal associations between uric acid and 25-hydroxyvitamin D levels. *Front Endocrinol* (*Lausanne*). 2022;13:1024675.

doi: 10.3389/fendo.2022.1024675

118. Zhang L, Shi X, Yu J, Zhang P, Ma P, Sun Y. Dietary vitamin E intake was inversely associated with hyperuricemia in US adults: NHANES 2009-2014. *Ann Nutr Metab.* 2020;76(5):354-360.

doi: 10.1159/000509628

119. Ghaffari T, Nouri M, Saei AA, Rashidi MR. Aldehyde and xanthine oxidase activities in tissues of streptozotocin-induced diabetic rats: Effects of vitamin E and selenium supplementation. *Biol Trace Elem Res.* 2012;147(1-3):217-225.

doi: 10.1007/s12011-011-9291-7

120. Mohd Fahami NA, Ibrahim IA, Kamisah Y, Mohd Ismail N. Palm vitamin E reduces catecholamines, xanthine oxidase activity and gastric lesions in rats exposed to water-immersion restraint stress. *BMC Gastroenterol.* 2012;12:54.

doi: 10.1186/1471-230X-12-54

121. Vos MB, Colvin R, Belt P, *et al.* Correlation of vitamin E, uric acid, and diet composition with histologic features of pediatric NAFLD. *J Pediatr Gastroenterol Nutr.*

2012;54(1):90-96.

doi: 10.1097/MPG.0b013e318229da1a

122. Vergalito F, Pietrangelo L, Petronio Petronio G, *et al.* Vitamin E for prevention of biofilm-caused healthcare-associated infections. *Open Med* (*Wars*). 2019;15:14-21.

doi: 10.1515/med-2020-0004

123. Khanna D, Fitzgerald JD, Khanna PP, *et al.* 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res* (*Hoboken*). 2012;64(10):1431-1446.

doi: 10.1002/acr.21772

124. Pascart T, Richette P. Investigational drugs for hyperuricemia, an update on recent developments. *Expert Opin Investig Drugs*. 2018;27(5):437-444.

doi: 10.1080/13543784.2018.1471133

125. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome [published correction appears in *N Engl J Med*. 2018;379(11):1094]. *N Engl J Med*. 2011;364(19): 1844-1854.

doi: 10.1056/NEJMra0904569

126. Teng H, Wang Y, Sui X, *et al*. Gut microbiota-mediated nucleotide synthesis attenuates the response to neoadjuvant chemoradiotherapy in rectal cancer. *Cancer Cell*. 2023;41(1):124-138.e6.

doi: 10.1016/j.ccell.2022.11.013

127. Wang L, Ye J. Commentary: Gut microbiota reduce the risk of hyperuricemia and gout in the human body. *Acta Pharm Sin B*. 2024;14(1):433-435.

doi: 10.1016/j.apsb.2023.11.013

128. Wan Y, Wong OWH, Tun HM, *et al*. Fecal microbial marker panel for aiding diagnosis of autism spectrum disorders. *Gut Microbes*. 2024;16(1):2418984.

doi: 10.1080/19490976.2024.2418984

129. Wang Q, Liang J, Zou Q, *et al*. Tryptophan metabolism-regulating probiotics alleviate hyperuricemia by protecting the gut barrier integrity and enhancing colonic uric acid excretion. *J Agric Food Chem*. 2024;72(48):26746-26761.

doi: 10.1021/acs.jafc.4c07716