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Lactic acid bacteria act as potent interventions in improving hyperuricemia: a review

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ABSTRACT

Hyperuricemia (HUA) is characterized by elevated levels of uric acid (UA) in the bloodstream, resulting from either excessive production or insufficient excretion of UA within the body. If left untreated, progressive or persistent HUA can lead to gout, causing significant harm to human health. Lactic acid bacteria (LAB), generally recognized as safe (GRAS) probiotics, have been shown to alleviate symptoms associated with gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease while supporting overall bodily functions and health. Recently, LAB has emerged as a potentially safe, cost-effective and efficient treatment for HUA. This comprehensive review aims to explore the current literature on the mechanisms through which LAB controls HUA. These mechanisms include suppressing purine metabolism, absorbing purine compounds, modulating microbiota to maintain host global purine homeostasis, reducing intestinal permeability, producing metabolites that alleviate HUA symptoms, promoting the expression of urate excretory proteins and inhibiting the expression of urate reabsorption proteins. The findings presented in this review provide a framework for further investigation into how probiotic LAB can alleviate HUA by influencing UA metabolism and elucidating their underlying action mechanisms.

1. Introduction

With the rapid economic development and concomitant changes in lifestyle and diet, hyperuricemia (HUA) has emerged as the fourth most prevalent health concern following hypertension, hyperglycemia, and high blood lipids[1]. Due to the absence of urate oxidase (UOX) in humans, nucleotides fail to undergo catalyzed into the more soluble end product allantoin and instead accumulate as uric acid (UA)[2-3]. Excessive production and impaired renal excretion of UA can result in elevated body UA levels, leading to HUA and deposition of sodium urate crystals in joints. This process triggers inflammatory responses that clinically manifest as gout[4]. The presence of HUA indeed serves as a harbinger for gout attacks. Statistics reveal that both the prevalence and incidence of gout seem to be rising across the globe[5], with the patient demographic shifting toward younger ages[6]. A cumulative number of 7.44 million cases of gout have been estimated around the world in 2017 (incidence, 0.097%), with a prevalence of 41.22 million cases (0.54%)[7]. From 2001 to 2017, the prevalence estimates of HUA steadily climbed from 8.5% to 18.4% in China[8]. Additionally, there were 1.28 million instances of gout-related disabilities which has been associated with a 39% increase in mortality from cardiovascular disease[4]. HUA poses a significant nationwide threat to public health and quality of life, resulting in a substantial societal burden. Consequently, there is an urgent imperative for the development of safe and efficient methodologies aimed at reducing UA levels and mitigating the prevalence of HUA and gout.

Gout has emerged as a prevalent and clinically significant disease that impacts public health, necessitating early preventative measures and treatment. Currently, pharmacological therapy is the

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primary approach for lowering UA, including xanthine oxidase inhibitors (e.g. allopurinol, febuxostat), UA transporter inhibitors (e.g. benzbromarone, probenecid, sulfinpyrazone), and uricase analogs (e.g. pegylated uricase)[9-10]. While medications can provide rapid relief from symptoms, they are frequently accompanied by adverse effects like gastrointestinal inflammation, rash, allergies, and nephrotoxicity[11]. Prolonged use can also lead to drug resistance, greatly limiting clinical application. Meanwhile, dietary therapy is also the conventional treatment for lowering urate. Restricting high-purine and high-fructose foods while adhering to a low-fat and low-sodium diet can moderately reduce UA production[12]. However, dietary restriction may not only cause nutritional deficiencies and decline in quality of life, but also have little effect on serum urate levels to suffice it for adequate gout management. Therefore, dietary restriction can be considered as adjunctive pharmacologic therapy to achieve the degree of urate-lowering needed to control gout disease activity[13]. Consequently, it is imperative to promptly develop innovative therapeutic strategies that can effectively mitigate UA levels without any untoward side effects.

It is well established that the gut serves as the primary site of UA degradation, with gut microbiota accounting for approximately 1/3 of daily UA metabolism in healthy individuals[14]. Studies have demonstrated that faecal microbiota transplantation can effectively decrease serum UA levels in gout patients and hyperuricemic rats by restoring the compromised intestinal barrier function[15]. Microbiota-based modulation has been emerging as a safe and innovative approach for alleviating and curing the pathogenesis of HUA, which necessitates to thoroughly investigate the mechanisms underlying the urate-lowering effects of gut probiotics[16].

Lactic acid bacteria (LAB), serving as gut probiotics in the intestinal tract, exhibit immense potential and distinctive advantages for modulating UA levels within the microbiome. LAB are ubiquitously present in the intestinal mucosa of mammals and healthy and functional food formulations. Moreover, LAB are generally recognized as safe (GRAS) probiotics that play critical roles in antioxidant activity, modulation of bowel disorders, mitigation of inflammation, and regulation of hypertension and hyperlipidemia[17-18]. They have been utilized as food-grade microbes for creating high-value-added products such as bacteriocins, extracellular polysaccharides, and nicotinamide mononucleotide[19]. In recent years, LAB have also been explored for tailored applications including targeted drug delivery, live vaccines, and modulation of the gut microbiota. Notably, LAB with purine-lowering capabilities have recently garnered substantial interest. These purine-lowering LAB are reported to catabolize purine nucleotides by removing the phosphate and ribose moieties, yielding relatively insoluble purine bases that decrease absorption in the small intestine and thereby attenuating UA production[20]. For instance, *Lactobacillus fermentum* 9-4 isolated from Chinese traditional fermented foods with Zhuang ethnic characteristics exhibited rapid nucleotide catabolism abilities[21]. Genomic analysis revealed that this strain harbored a more complete pathway for nucleotide metabolism compared to previously documented strains[22]. These findings indicate promising potential for LAB in alleviating HUA.

However, the published mechanisms of purine degradation and UA reduction by LAB are usually descriptive, lacking a comprehensive and critical comparative analysis. Undoubtedly, a critical review on mechanisms underlying the HUA alleviation by LAB is beneficial for developing novel therapies. This review should include their roles in inhibiting UA synthesis, promoting UA conversion, enabling UA elimination *via* transporters, and reducing inflammation through modulating intestinal permeability. In an attempt to conduct such a review here, a thorough analysis of purine metabolism, HUA, gout, and related metabolic syndromes was introduced, the current knowledge on mechanisms of LAB-mediated purine metabolism was comparatively summarized, and a framework for further investigating the involvement of LAB in UA metabolism was prospected as well.

2. Pathogenesis of hyperuricemia and gout

HUA is clinically defined as elevated serum UA levels in the blood to a certain threshold. The upper limit of normal serum urate concentration is generally 420 μmol/L (7 mg/dL) in adult males and 360 μmol/L (6 mg/dL) in females[23]. Gout, an arthritic disorder primarily characterized by recurrent acute inflammatory arthritis flares, can be attributed to prolonged HUA leading to crystallization and deposition of urate in joints. This process triggers the inflammatory pain associated with gout flares; however, it should be noted that not all individuals with HUA patients develop gout[24].

HUA is attributed to a multitude of factors, encompassing inborn errors associated with purine metabolism, such as aberrant enzymatic activity or deficiency within the purine metabolic pathway, which encompasses ribulose phosphate pyrophosphate synthase. Furthermore, this condition is exacerbated by suboptimal dietary habits characterized by high intake of purine-rich foods, protein, or fructose[25-26], as illustrated in Fig. 1.

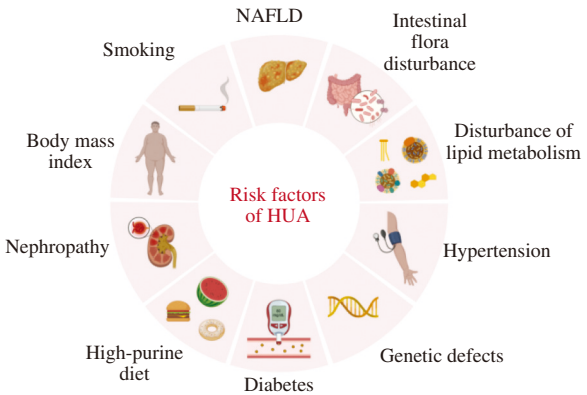

Fig. 1 Risk factors for the development of HUA. NAFLD, nonalcoholic fatty liver disease.

Regardless of the etiology, the underlying pathology of HUA involves obstruction of the purine pathway. As depicted in Fig. 2, purines are synthesized endogenously through nucleic acid catabolism and also obtained from dietary intake, subsequently undergoing degradation into UA *via* a cascade of enzymatic reactions. The primary contributor to HUA is diet intake, as demonstrated by Fig. 2, where a high-purine and fructose-rich diet leads to a significant increase in UA production. Fructose undergoes metabolism by fructokinase, resulting in the generation of adenosine monophosphate (AMP)[27-29]. Obese individuals exhibit enhanced purine metabolism and increased synthesis of highly active metabolic enzymes[30]. Epidemiological evidence suggests a robust association between elevated UA levels

and obesity[31]. From an excretory perspective, it can be observed that obese individuals have reduced renal excretion capacity, leading to lower urinary excretion of UA but higher blood levels. Both environmental factors and genetic factors contribute to the regulation of HUA. The latter importantly contribute to the development of HUA and gout. Genetic mutations in UA transporter protein genes occur in patients with HUA and can be hereditarily transmitted[32]. There is also an association between alcoholism and HUA. Consumption of beer results in an increased lactic acid metabolism that hinders UA excretion and increases urate crystallisation, ultimately causing gout. Certain conditions such as epilepsy can lead to significant ATP decomposition while strenuous exercise may result in elevated blood UA levels. In addition, several drugs including diuretics (chlorthalidone, hydrochlorothiazide, etc.), aspirin, and immunosuppressive drugs (Ciclosporin, Tacrolimus, etc.) can induce HUA[33].

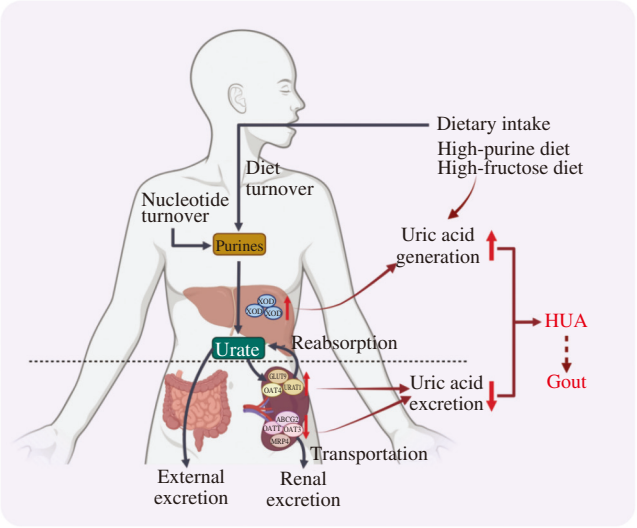

Fig. 2 Schematic representation of the pathophysiological model of HUA.

Disturbances in UA metabolism are linked with the development of gout. Elevations in serum UA concentrations result from increased UA production (due to a high-purine diet or enhanced xanthine oxidase (XOD) activity) or decreased excretion (due to enhanced UA reabsorption in the kidneys and abnormal transport and excretion). Consequently, HUA occurs along with urate deposition in joints, ultimately leading to the manifestation of gout.

The prevention and management of HUA and gout should commence by addressing the aforementioned risk factors associated with HUA. These factors can be primarily divided into 2 groups: inhibiting UA production and promoting UA conversion and elimination. Effective control of HUA can be achieved through a combination of medication and lifestyle modifications. While genetic factors do play an important role, it is essential to reduce the intake of high-purine foods, avoid alcohol abuse, and maintain a healthy body weight. Lifestyle adjustments serve as preventive measures that can delay the onset of HUA and gout. Conversely, pharmacotherapy yields immediate results but often comes with inevitable notorious adverse effects such as gastrointestinal discomfort and renal impairment. Therefore, proactive exploration of safer and more effective therapies for reducing UA levels without side effects remains essential.

3. Physiological and metabolic basis of HUA and gout

Purine metabolism is a vital physiological process in organisms. Purines are composed of fused pyrimidine and imidazole rings, forming planar bicyclic compounds. Endogenous purines include purine nucleotides such as inosine monophosphate (IMP), AMP, and guanosine 5′-monophos-phate (GMP), along with purine nucleosides, including adenosine, inosine, xanthosine, and guanosine, as well as purine bases, like adenine, hypoxanthine, xanthine, and guanine, all of which contain the purine backbone structure. Apart from serving as the fundamental building blocks for nucleic acids, purines regulate energy homeostasis, ensure cell survival, and promote cell division by providing energy and cofactors[34]. As demonstrated in Fig. 3, the metabolic pathway of purines involves a multistep reaction that can be categorized into *de novo* synthesis and salvage pathways. Notably, cells preferentially utilize the recycling salvage pathway over *de novo* biosynthesis due to its lower energetic cost[35].

Additionally, several key enzymes play vital roles in the purine metabolic pathway, often serving as critical markers indicative of the status of purine metabolism. Among them, UOX and XOD are particularly crucial. UOX is the specific enzyme responsible for converting UA to allantoin, thereby preventing UA accumulation. Unfortunately, during primate evolution, including in humans, a CGA-to-TGA nonsense mutation occurred in the arginine codon within the exonic region, rendering uricase a pseudogene and abolishing its enzymatic activity. Consequently, this led to UA becoming the final product of purine metabolism in humans and other primates[36]. On the other hand, XOD is the last enzyme in the

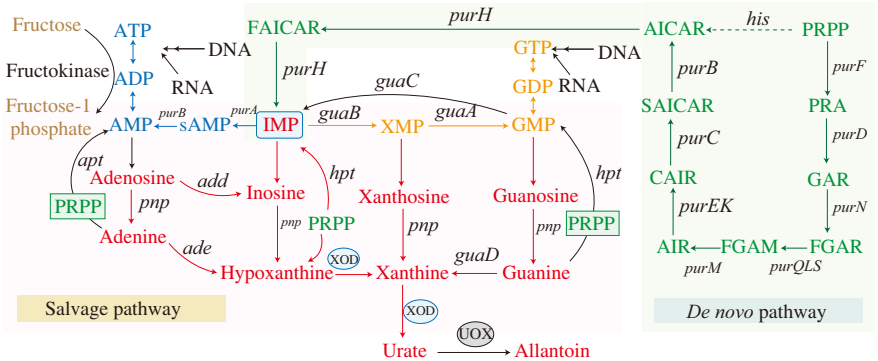

Fig. 3 *De novo* and salvage pathway for purine synthesis.

purine metabolism and catalyzes the conversion from hypoxanthine to xanthine and xanthine to UA across all organisms. Mutations or aberrant expression of the *XOD* gene can perturb UA metabolism, contributing to the pathogenesis of HUA. Hence, XOD commonly serves as an important therapeutic target for the treatment of HUA and gout in clinical settings.

Ribose phosphate pyrophosphate (PRPP) serves as a substrate for purine *de novo* synthesis (green background) and produces IMP at the end of the *de novo* pathway in a 10-step reaction catalyzed by 6 enzymes with different functional domains. The salvage pathway (pink background) is catalyzed by 2 main enzymes, hypoxanthine-guanine phosphoribosyltransferase (HPRT) and adenosine phosphoribosyltransferase (APRT). In this metabolic pathway, the synthesis of nucleotides requires PRPP as an essential co-substrate. Adenosine can undergo conversion to inosine under the catalytic influence of adenosine deaminase (ADA) enzyme. Purine nucleoside phosphorylase (PNP) catalyzes the production of adenine, xanthine, guanine, and hypoxanthine from adenosine, xanthosine, guanosine, and inosine, respectively. Subsequently, ADA, XOD, and guanine deaminase (GDA) convert these compounds into UA. The end product, UA, undergoes additional oxidation by UOX, a protein expressed in the majority of organisms, but lacking in humans and certain primate species.

4. Mechanisms by which LAB modulate HUA

LAB is widely recognized for its health-promoting effects, including antioxidant properties, immune enhancement, cancer prevention, and improvement of intestinal barrier function. Various mechanisms have been proposed to explain these beneficial effects, including the inhibition of harmful bacteria growth, maintenance of a balanced intestinal flora, and secretion of antimicrobials that resist pathogenic bacteria[37-40]. Several studies have also revealed the potential of LAB in alleviating symptoms related to HUA and its applications in general populations, along with proposed mechanisms of action. As depicted in Fig. 4, although yet to be fully elucidated, a universally accepted mechanism that explains the alleviation of HUA by LAB may encompass the following aspects: firstly, degradation of nucleosides into purines, which are absorbed at a slower rate in the body than nucleosides and nucleotides, thus reducing the absorption of purines to lower the generation of UA. Secondly, UA is metabolized into smaller molecules such as allantoin to decrease the absorption of UA from the intestinal tract. Thirdly, key enzymes involved in purine metabolism are inhibited to reduce the production of UA. Fourthly, the reabsorption of UA transporter protein is inhibited and the excretion of UA transporter protein is up-regulated to increase the excretion of UA. Finally, LAB and their metabolites can restore the intestinal flora to regulate UA levels.

LAB activate PNP, which catalyzes the conversion of nucleosides into purine bases that are poorly absorbable by the small intestine. They also inhibit the hepatic xanthine oxidase activity, decreasing UA production, and promoting UA oxidase activity. This leads to the production of allantoin from UA. LAB upregulate the expression of renal UA excretory proteins, inhibit UA reabsorption proteins and promote UA excretion. LAB can adhere to the intestinal mucus layer, promote mucin secretion and have an antagonistic effect on pathogenic bacteria and toxins adhesion. Moreover, they can effectively regulate the proportion of intestinal probiotics. LAB can additionally break down dietary fiber in the intestines, creating short-chain fatty acids which impede inflammatory factors and alleviate the inflammatory response in gout patients.

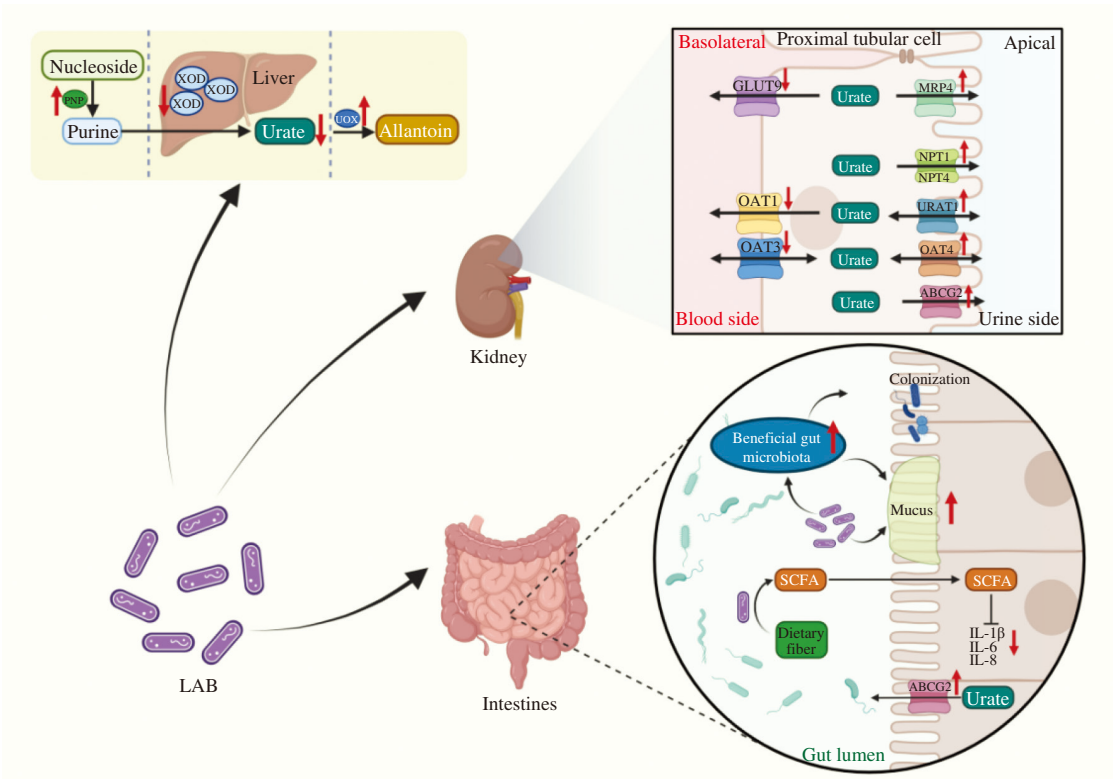

Fig. 4 Mechanisms through which LAB regulate levels of UA.

4.1 LAB reduce UA production by decreasing purine uptake

Purines play a crucial role as biomarkers for HUA, and reducing the accumulation of purines and purine metabolic intermediates represents an efficacious strategy to alleviate HUA. Notably, LAB can modulate host purine absorption by catabolizing excess purines and inhibit the production of UA by interfering with the purine metabolic pathway. *Lactobacillus gasseri* PA-3, a purine-lowering LAB extensively investigated by Meiji Co., Ltd., has demonstrated potential in reducing blood UA concentration in rats through oral administration. Furthermore, consumption of yoghurt containing PA-3 has been shown to effectively suppress the increase of serum UA levels in humans subjects[41-42]. Presumably, this effect is achieved through the ability of PA-3 to degrade nucleosides into purine bases that exhibit limited bioavailability. Additionally, PA-3 has the capability to absorb nucleotides, nucleosides, and purine bases and utilize the assimilated purines for growth and proliferation. Consequently, the absorption of purines from the gastrointestinal tract is reduced[43-47]. Moreover, numerous studies have confirmed that orally administrated LAB can compete with intestinal epithelial cells for nucleosides and degrade purines ingested from food in the intestine. This process can significantly decrease the body's absorption of purines, ultimately resulting in a reduction of serum UA levels. *Lactobacillus shortcombicus* DM9218 has the ability to lower serum UA levels by efficiently taking up purine nucleosides (inosine and guanosine), thereby demonstrating promising potential in reducing serum UA levels for the prevention of HUA[48-49], as well as alleviating high fructose-induced hyperuricemia in mice[50-51]. *Lacticaseibacillus rhamnosus* 1155 and *Limosilactobacillus fermentum* 2644 have also been also reported to decrease serum UA in hyperuricemic animals, which can be attributed to the anabolic effect of purine nucleosides and the intestinal excretion of UA[52]. Similarly, LAB derived from the byproduct of alcoholic fermentation (wine dregs) exhibited the ability to degrade purine comound *in vitro* and demonstrated a UA-lowering effect in mice[53]. Moreover, LAB strains isolated from pickles showed potential in mitigating HUA and kidney injury[54]. Consumption of purine-lowering *Ligilactobacillus salivarius* CECT 30632 resulted in a reduction in gout attacks and the need for gout-related medicines among patients with HUA[55]. In summary, it can be hypothesized that LAB may mitigate UA production by competing with the host for intestinal absorption of purine compounds.

4.2 LAB regulate UA levels by inhibiting UA-forming enzymes

Attenuating the production of UA is a critical therapeutic strategy for HUA. The biosynthesis of UA is controlled by purine metabolic enzymes, while its elimination is facilitated by specific transporter proteins. Key enzymes involved in UA formation include ADA and XOD. ADA catalyzes the conversion of adenine nucleosides to hypoxanthine nucleosides, which are subsequently converted to hypoxanthine by PNP, ultimately leading to the generation of UA. XOD is a pivotal enzyme that catalyzes the successive formation from hypoxanthine to xanthine, and from xanthine to UA. Therefore, ADA and XOD represent important therapeutic targets for HUA. Evidence implies that intervention with LAB can suppress the expression or enzyme activity of XOD and ADA, thereby attenuating UA production and effectively mitigating HUA. Cao et al.[56] reported that treatment with *Lactobacillus paracasei* X11 resulted in a significant reduction of 30.59% in ADA activity and 33.69% in XOD activity, while also effectively inhibiting hepatic UA synthesis in hyperuricemic mice. Another study found that *L. fermentum* NCUH003018, *Limosilactobacillus reuteri* NCUH064056, and *L. gasseri* NCUH066006 exhibited a significant reduction in serum UA levels by 20.87%, 14.59%, and 14.84%, respectively, through inhibition of XOD activity[57]. Collectively, these examples highlight the ability of LAB to regulate UA production by suppressing key enzymes involved in its formation, representing an important mechanism for preventing HUA.

4.3 LAB promote UA conversion

Attenuating UA accrual in the body represents another validated approach for mitigating HUA. Historically, research on utilizing LAB to alleviate HUA has predominantly focused on modulating purine metabolism, with less emphasis on directly targeting UA. UOX catalyzes the oxidation of UA to allantoin and hydrogen peroxide[58-59]. Allantoin is a small, non-toxic, water-soluble molecule that can be excreted in urine, thereby preventing its accumulation in the body and subsequently reducing HUA and gout. Despite limited research on UOX-producing LAB and their corresponding UOX. A pioneering was carried out by Handayani et al.[60], who screened 13 UOX-producing LAB strains exhibiting UA-lowering capabilities and identified their potential for both extracellular and intracellular uricase production. The investigation also encompassed the exploration of intracellular UOX activity enhancement through optimal cultivation with UA supplementation[61]. These LAB significantly contribute to augmenting the host's UA metabolism by synthesizing UOX, thereby reducing systemic UA levels.

Instead of making categorical statements about LAB reducing UA levels through UOX production, certain previous studies indicate that they may modulate UA levels by directly absorbing this compound. While the precise mechanism remains unclear, it has been proposed that the bacteria might also synthesize UOX to facilitate the oxidation of UA. A more paradigmatic example is represented by the *L. fermentum* JL-3 strain, which originates from traditional Chinese fermented food slurry water[62]. The high degradation capacity and selectivity of UA have been demonstrated through *in vitro* experiments. Moreover, the efficacy of the JL-3 strain in reducing UA levels has been further confirmed by *in vivo* studies. Additionally, the ingestion of yoghurt containing JL-3 for a duration of 2 months resulted in a significant reduction in UA concentration among HUA patients, highlighting the role of LAB in managing human HUA[63]. Although allantoin was identified as a by-product of JL-3, it was not observed to associate with UOX production. Many LAB intrinsically lack the metabolic capacity for purine and UA utilization[64]. However, studies have demonstrated that domestication of LAB can confer the ability to degrade UA. In the absence of UA induction, *Lactobacillus plantarum* ZXH-1304S intrinsically possesses negligible capacity for UA catabolism. In contrast, induced strains with UA displayed significant degradation of UA in both *in vitro* and *in vivo* experiments. Specifically, during *in vitro* assays, concentrations of UA decreased by 30.75%, while gavage with induced strains resulted in

approximately a 50% reduction in UA levels in hyperuricemic mice[65]. Cumulative evidence indicates that specific LAB can exert their influence on UA through either UOX production to promote UA conversion or by serving as a nitrogen source for strain growth. However, investigations into the mechanisms underlying UA utilization by LAB remain limited, and further studies are necessary to substantiate and elucidate the interplay between these microorganisms and UA.

4.4 LAB increase UA excretion

Approximately one-third of UA undergoes intestinal catabolism, while the 2/3 remaining are predominantly excreted *via* urine. The renal tubules play a critical role in the regulation of serum UA levels, as over 90% of filtered UA is reabsorbed within the proximal tubules. Renal homeostasis effectively maintains plasma urate equilibrium through its excretory capacity, with the urate transport system in the renal proximal tubule playing a crucial role in UA excretion[66]. The urate transport system consists of 2 primary groups: proteins involved in UA reabsorption, such as urate anion transporter 1 (URAT1), organic anion transporter 4 (OAT4), and glucose transporter 9 (GLUT9); and UA efflux transporters including organic anion transporter protein 1 (OAT1), organic anion transporter protein 3 (OAT3), UA transporter protein (UAT), multidrug resistance protein 4 (MRP4/ABCC4), and adenosine triphosphate-binding cassette subfamily G member 2 (ABCG2)[67-69]. Therefore, effective strategies for the treatment of HUA involve regulating the urate transport system and increasing UA excretion, which provides a basis for investigating functionalized LAB strains that can inhibit the expression of proteins responsible for UA reabsorption and stimulate the production of proteins promoting UA excretion. In hyperuricemic rodents, daily oral administration of 10^9 CFU/mL of *L. paracasei* X11 for 28 days resulted in a significant reduction (24.39% and 24.69%, respectively) in the expression of reabsorption transporter proteins GLUT9 and URAT1. Conversely, there was an increase (7.3%) in the expression of excretion transporter proteins. Notably, UA levels decreased by approximately 50%, nearly restoring to normal levels[56]. ABCG2 is a crucial UA transporter involved in impaired cellular UA excretion, hyperuricemia, and early-onset gout development[70]. Experimental treatment of ABCG2 knockout mice with oxalate resulted in a significant reduction (approximately 40%–50%) in intestinal UA excretion[71-72]. Moreover, a study investigating the impact of LAB treatment on ABCG2 indicated that the consumption of LAB increased the levels of ABCG2 in chicken liver[73]. Administering *Lactobacillus ingluviei* through diet led to a notable increase in ABCG2 expression and subsequent modest elevation in UA excretion in hyperuricemic mice. LAB promote UA excretion by amping up the expression of UA transporter proteins while inhibiting urate reabsorption proteins. This is an essential process in the manner that LAB impact HUA[74].

4.5 LAB metabolites lower UA levels

Metabolites produced by LAB, including organic acids, pyruvic acid, lactate, fatty acids, amino acids, and bacteriocins, can can exert crucial roles in lowering UA levels. The regulatory effects of LAB metabolites on HUA occur primarily through the following mechanisms: 1) increasing the excretion of UA to reduce UA concentration; 2) regulating gut microbiota to help improve intestinal flora balance and decrease UA levels; 3) alleviating symptoms-relating physiological basis of HUA and gout, which include inflammatory responses, ameliorating oxidative stress and the inflammatory state; 4) enhancing immunity and increase bodily resilience, potentially aiding in the prevention and treatment of HUA-related illnesses.

LAB produce short-chain fatty acids (SCFAs) that modulate purine catabolism and alleviate gout. SCFAs, including acetic acid, propionic acid, and butyric acid, are produced through the fermentation of dietary fibre, oligosaccharides, and other polysaccharides. These acids not only serve as a primary source for colonic and ileal cells in the host but also play a crucial role in maintaining host health by regulating the expression of inflammatory factors that impact intestinal epithelial barrier function and defense mechanisms[75]. For example, butyric acid inhibits the production of cytokines interleukin (IL)-1β, IL-6 and IL-8, which are pivotal in gouty arthritis progression, thereby exerting anti-inflammatory effects[76-77]. SCFAs promote recovery and stabilization of intestinal epithelial cells while amplifying the synthesis of UA carrier proteins such as ABCG2 and SLC2A9 to facilitate increased UA excretion. Pessione et al.[78] revealed that LAB not only directly promote the colon's accumulation of SCFAs through protein production, but also indirectly encourage the production of SCFAs by the endogenous colonic flora. *L. rhamnosus* R31, *L. rhamnosus* R28-1, and *L. reuteri* L20M3 increase the abundance of intestinal bacterial taxa linked to the production of SCFAs. Additionally, these probiotics restore the ratio of anaplasmatoid phyla to thick-walled phyla, which alleviates HUA in mouse models[79].

LAB promotes hepatic primary bile acid biosynthesis and intestinal secondary bile acid biotransformation[80]. Studies have shown that bile acids exert a suppressive effect on UA synthesis by inhibiting the expression and activity of XOD[81]. Secondary bile acids, such as lithocholic acid (LCA) and deoxycholic acid (DCA), are produced by modifying the primary bile acids through fecal bacteria in the intestinal lumen and have a significant impact on regulating bile secretion and lipid digestion[82]. The growth of beneficial bacteria Bacteroides in the gut is promoted by certain secondary bile acids, such as *iso*-DCA, thereby exerting a restorative effect on intestinal flora imbalance in gout patients[83]. Dziedzic et al.[82] showed that LAB possess the ability to bind cholic acid, LCA, and DCA, thereby exerting antagonistic effects on *Escherichia coli*. This beneficial property aids in restoring intestinal dysbiosis and partially alleviating symptoms of hyperuricemia. Lactobacilli also alleviate hyperuricemia by synthesizing choline and conjugated fatty acids (CLA), which serve as vital nutrients for the body. Choline plays a crucial role in diverse biochemical reactions within the human body, and its consumption is intricately associated with the modulation of pro-inflammatory markers that regulate the inflammatory response[84]. Choline deficiency results in renal impairment and hypertension, leading to an unbalanced UA metabolism. Certain LAB possess choline-producing attributes. Stephenson reported the ability of *L. plantarum*, extracted from fermented sauerkraut, to synthesize acetylcholine[85]. Nakamur also isolated and characterized natural lactocholine from *Lactobacillus* fermented foods[86]. LAB is hypothesized to have a beneficial impact on HUA by facilitating the production of CLA. Additionally, CLA

possesses the ability to regulate lipid metabolism disorder and enhance lipolysis[87]. Given that lipid metabolism disorders play a pivotal role in UA-related diseases, modulation of lipid metabolism indirectly alleviates HUA[88-89].

LAB also produces various vitamins and amino acids that mitigate HUA. Vitamins B and K, along with gamma-aminobutyric acid (GABA), are essential for tissue health and plays a crucial role in the energy metabolism of food breakdown. Studies have indicated a link between folic acid and HUA, where an increased intake of vitamin B is associated with a reduced risk of developing HUA[90]. Folic acid is regarded as a potent inhibitor of mammalian XOD, which reduces the production of UA[90-91]. Multiple lines of evidence indicate that LAB possess the ability to synthesize vitamin B[92-95]. Meanwhile, there is a correlation between vitamin K and the development of chronic kidney disease. The utilization LAB that synthesize vitamins as an adjunctive therapy holds promise for mitigating adverse side effects in patients afflicted with various inflammatory conditions, including gout[96]. GABA has been found to possess antihypertensive, antidiabetic, anticancer, antioxidant, anti-inflammatory, antimicrobial, antiallergic, hepatoprotective, nephroprotective, and enteroprotective properties[97]. Multiple studies have demonstrated that GABA exerts its therapeutic effects on gout through diverse pathways. Primarily, GABA exhibits the potential to decrease the incidence of gout attacks by suppressing UA synthesis in patients with gout, thereby decreasing the accumulation and crystallisation of UA. A study by Pyo et al.[98] found that GABA derived from soybean fermentation lowered UA production by inhibiting XOD. Secondly, GABA lowers pain and inflammatory response among gout patients by controlling inflammation and blocking cytokine production[99]. LAB are crucial GABA producers[100-101], and supplementation with GABA-producing LAB holds potential as a therapeutic approach for HUA. In conclusion, the metabolites derived from LAB demonstrate therapeutic properties against hyperuricemia; however, further investigations are necessary to elucidate their precise effects.

4.6 Modulation of HUA by LAB through effective regulation of intestinal flora

Dysregulated gut ecology is considered a pivotal factor in the pathogenesis of gout. Dysregulation of gut microbiota has been found in patients with HUA and gout, showing a significant deviation from the gut microflora in healthy individuals, characterized by significant reductions in gut microbial diversity and beneficial bacteria[102-103]. During the course of HUA, the dynamic fluctuations in both UA levels and intestinal barrier function were accompanied by a reduction in key beneficial bacteria, including Prevotellaceae, *Muribaculum*, *Parabacteroides*, *Akkermansia*, and *Bacteroides*, and coincided with an increase in pathogenic bacteria such as *Oscillibacter* and *Ruminiclostridium*[104]. A macrogenomic analysis of 307 faecal samples from 102 gout patients and 86 healthy controls learned that the relative abundance of *Prevotella*, *Clostridium*, and *Synechococcus* was significantly increased in gout patients, while the relative abundance of Enterobacteriaceae and butyric acid-producing bacteria showed a notable decrease[105]. The α-diversity of gut microbiota was significantly reduced in the gout group than in the healthy group, suggesting a potential association between decreased gut microbial diversity and gout. Previous studies have provided evidence that the gut microbiome of gout patients is more abundant in carbohydrate metabolism but has less capacity for purine metabolism[106]. Elevated levels of UA cause intestinal dysbiosis, exacerbating chronic gut inflammation and impairing UA excretion. Consequently, this dysbiosis disrupts purine metabolism, leading to elevated UA levels and establishing a detrimental cycle[107]. Certain intestinal microorganisms secrete UA transporters, while an imbalance in UA absorption and excretion in the gut is mediated by dysbiosis of the intestinal flora. A research by Kasahara et al.[108] implies that these intestinal microorganisms are vital for maintaining host purine homeostasis and serum UA levels. Intestinal LAB serve as beneficial microbiota in the gastrointestinal tract, contributing to regulating intestinal disorders and promoting anti-inflammation and the catabolic metabolism of intestinal bacterial purines[109]. The microbial community shift likely contributed to elevated lipopolysaccharide (LPS) and proinflammatory cytokine levels, ultimately promoting metabolic inflammation. Particular types of LAB shield the intestinal and renal functions of the host by regulating their intestinal flora and lessening oxidation and inflammation, resulting in increased UA excretion and decreased blood UA concentrations. Following a 5-week probiotic treatment, hyperuricemic mice exhibited higher levels of *Bifidobacterium* and *Lactobacillus* in their gut, lower LPS levels, and a significant reduction in serum UA[56].

Research has shown that a compromised intestinal barrier occurres with elevated UA and intestinal permeability progressively increases with the progression of HUA[104]. LAB can increase the proportion of microbiota exhibited negative correlations with intestinal permeability, thereby repair and enhance the ability of the intestinal barrier. *L. paracasei* MJM60396, recognized for its UA level regulation, can restore the intestinal barrier by increasing the quantity of intestinal probiotics, enhancing the presence of *Trichoderma reesei*, which is associated with intestinal barrier integrity, and elevating the expression of tight junction proteins ZO-1 and occludin. The intestinal barrier was repaired by *L. paracasei* MJM60396 through the upregulation of tight junction proteins ZO-1 and occludin, thereby regulating UA levels[109]. *Bifidobacterium animalis* subsp. *lactis* XLTG11 significantly increases the expression of aquaporin and tight junction proteins, and inhibited toll-like receptor 4 activation of the nuclear factor-κB signaling pathway, significantly increased the levels of anti-inflammatory cytokines, and decreased levels of pro-inflammatory cytokines[110].

However, it is possible that most LAB act through a combination of one or several mechanisms, depending on the effector molecules they express. The major effectors have yet to be conclusively determined. Table 1 outlines some of the LAB that have demonstrated the ability to lower UA through a combination of several mechanisms.

5. LAB mitigate chronic diseases causally related to HUA

Disorders affecting UA metabolism can be associated with the pathological mechanisms of various conditions, such as diabetes[116-117], cardiovascular disease[118], and renal disease[119-120]. The presence of these ailments can lead to an elevation in the levels of UA within the body, causing its accumulation and initiating a harmful cycle. Several studies indicate the prevalence of HUA in patients with chronic kidney disease and diabetes mellitus[121-123]. HUA has been

Table 1
Mechanism of targeted gut microbiota in the treatment of HUA.

Strains	Source	UA-lowering mechanism and effect
L. rhamnosus Fmb14[111]	Yoghourt	The biosynthesis of XOD was reduced in hepatocytes and enterocytes, leading to a decrease in the body's digestion and absorption of inosine. Additionally, UA secretion was enhanced through the promotion of ABCG2 and inhibition of GLUT9. Following 8 weeks of oral administration, serum UA levels exhibited a significant reduction by 36.8% in rats.
L. plantarum Q7[112]	Yak milk	By degrading nucleotides, nucleosides, purines and UA, down-regulating serum biochemical indices, reversing organ damage, regulating the expression of UA-metabolizing enzymes and transporter proteins, improving intestinal flora imbalance, suppressing inflammation and alleviating UA.
L. paracasei MJM60396[109]	Fermented food	Regulates UA by absorbing purines, inhibiting XOD to reduce UA synthesis and regulating the UA transporter to increase UA excretion.
L. paracasei X11[56]	Yak yogurt and pickles	Inhibits renal pro-inflammatory cytokines by degrading nucleotides and nucleosides, regulates the expression of ADA, XOD and transporters (GLUT9, NPT1 and URAT1) to normal levels, restores intestinal flora and reduces serum UA.
L. rhamnosus R31, *L. rhamnosus* R28-1, *L. reuteri* L20M3[79]	Healthy human subjects	Effectively mitigates hyperuricemia in mice by enhancing short-chain fatty acid production, leading to reduced serum and urine UA concentrations as well as decreased serum and liver tissue XOD activity. This mechanism alleviates hepatic inflammation and mild kidney injury without relying solely on purine catabolism.
L. plantarum FS4722[113]	Unknown	The inhibition of hepatic XOD and purine nucleoside phosphorylase activity leads to a reduction in urate synthesis. Additionally, the ribonucleoside hydrolase RihA-C facilitates the hydrolysis of nucleosides into nucleobases that are poorly absorbed by epithelial cells, thereby decreasing intestinal UA absorption.
L. rhamnosus 1155 and *L. fermentum* 2644[114]	Traditional fermented dairy products	The UA transporter ABCG2 gene expression was upregulated by LR1155 and LF2644, with LR1155 significantly inhibiting XOD activity. Additionally, LF2644 improved intestinal barrier function in hyperuricemic rats by upregulating the expression of occlusion and mucin2 genes while while reducing the inflammatory indices of LPS and interleukin 1β (IL-1β).
Lactobacillus acidophilus F02[115]	Traditionally fermented sourdough	*L. acidophilus* F02 degrades inosine strongly, inhibits the activity of XOD and ADA, suppresses the NLRP3 inflammasome expression, regulates bacterial taxa composition in hyperuricemic mice, and promotes UA excretion.

shown to predict hypertension and act as an independent predictor of it[124]. As illustrated in Fig. 5, hypertension, hyperglycaemia, hyperlipidaemia, and HUA are significant factors in the development of UA-related illnesses, and HUA is acknowledged as an indicator of metabolic syndrome, chronic kidney disease, cardiovascular disease, and diabetes mellitus[125-126]. The association between gout and HUA, along with the presence of comorbidities such as diabetes, hypertension, hyperlipidemia, cardiovascular disease, renal disease, and obesity, suggests that HUA may play a pivotal role in the pathogenesis of metabolic syndrome[127]. The kidneys play a pivotal role in the body's metabolism, and metabolic disorders can cause eventual kidney damage. The therapeutic potential of LAB lies in its ability to ameliorate hyperuricemia and attenuate symptoms associated with gout. The study conducted by Wang and colleagues suggests that the presence of *Bifidobacterium bifidum* and *L. rhamnosus* can ameliorate gut dysbiosis and inflammation, thereby mitigating diabetes symptoms in mice[128]. Huang et al.[129] conducted a screening of *Lactobacillus casei* and *L. plantarum* to evaluate their potential in scavenging indole and *p*-cresol, regulating dysbiosis of the intestinal microbiota, and restoring renal injury as well as intestinal barrier disruption. The results provide evidence that interventions with LAB can be beneficial for the prevention and treatment of chronic kidney disease (CKD). A study investigated the impact of LAB supplementation on obese adults demonstrated favorable effects on the intake of LAB in overweight or obese individuals, including reduced levels of low density lipoprotein (LDL) cholesterol and total cholesterol, as well as improvements in fasting blood glucose and triglycerides under specific conditions[130]. Several studies have also shown the potential of LAB in reducing blood pressure and conferring cardiovascular benefits. Furthermore, numerous studies have demonstrated the potential of LAB in reducing blood pressure and conferring cardiovascular benefits, thus presenting a promising non-pharmacological approach for managing hypertension[131].

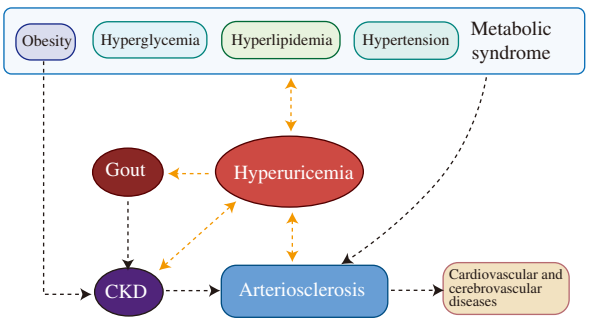

Fig. 5 Relationship between HUA and gout, chronic kidney disease, metabolic syndrome, atherosclerosis, and cardiovascular disease.

6. Conclusion and future perspectives

HUA is emerging as an increasing global public health problem and a potential risk factor associated with multiple diseases, which necessitates the development of novel safe, efficacious treatments without side effects that are currently available in clinical chemotherapy methods. Emerging evidence consistently supports the efficacy and safety of anti-HUA LAB as a viable dietary intervention for the prevention and management of HUA and gout. The latest investigations have revealed potential underlying mechanisms, including: 1) direct breakdown of nucleosides by LAB to acquire purines that are difficult to absorb; 2) competition with small intestinal epithelial cells for nucleosides and purines leading to reduced absorption in the human body; 3) regulation of UA levels through UOX production by LAB, which can either directly break down UA or inhibit purine metabolism enzymes such as XOD; and 4) regulatory effects on transport proteins, intestinal flora, and intestinal barrier repair by LAB and their metabolites that may also aid in regulating UA levels. The mechanisms are likely to be implemented in concert for the remission of HUA, owing to the diversity of substrate availability and active metabolites of LAB. However, further investigation is still required to elucidate the

unique role played by each mechanism. Meanwhile, LAB with anti-hyperuricemic or purine-lowering properties also exhibit favorable impacts on chronic kidney disease and metabolic syndrome associated with HUA, thereby serving as efficacious interventions for preventing and treating HUA and gout.

Conflict of interest

The authors declared no competing interests in this paper.

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