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Recent Status of Probiotics in the Prevention and Treatment of Hyperuricemia (HUA)

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Abstract:

A metabolic condition called hyperuricemia (HUA) is intimately linked to the beginning and development of numerous chronic illnesses. Increased blood levels of uric acid (UA), or hyperuricemia, are indicative of a higher risk of developing gout and other metabolic problems. Probiotics have been shown to have positive impacts on human health regulation in recent years. These effects include a significant contribution to the control of conditions including type 2 diabetes, obesity, hypertension, and human immunity. Furthermore, pertinent research conducted in the last several years has discovered that probiotics can somewhat alleviate HUA. The use of probiotics for the prevention and treatment of hyperuricemia is discussed in this paper along with the current status of research in this area. Probiotics work by modulating urate metabolism, attenuating inflammatory responses, and improving related metabolic parameters. Additionally, clinical trials assessing the efficacy of specific probiotic strains or blends in reducing serum UA concentrations are included in the analysis, indicating that probiotics could be a future focus for the prevention of hyperuricemia. However, the optimal dose and duration of probiotic supplementation remains to be determined and clinical trials on human subjects should be further expanded. To ascertain the long-term safety and effectiveness of probiotics as an adjuvant treatment for HUA and associated comorbidities, more research is required.

Keywords: List the Hyperuricemia; probiotics; uric acid.

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1. Introduction

An unusually high level of uric acid (UA) in the blood is known as hyperuricaemia (HUA), and it is a prevalent illness affecting millions of people worldwide. Gout, which is linked to a number of metabolic diseases such as type 2 diabetes, mellitus, hypertension, and cardiovascular disease, is also significantly influenced by hyperuricemia. At present, management and intervention are mainly carried out through lifestyle and drugs, but patients have poor compliance with lifestyle intervention and it is difficult to implement. Although drug therapy is the most commonly used treatment in clinical practice, it has the advantages of quick effect and short cycle, but there are certain side effects of drug therapy, easy to cause allergic reactions, great damage to the patient‘s body and expensive, increasing the economic burden of patients, not suitable for all patients, so researchers have begun to explore alternative approaches [1].

Trillions of bacteria make up the gut microbiota, which is essential to both host health and illness. Numerous chronic illnesses are linked to dysbiosis, or an imbalance in the gut microbiota. The part the gut microbiota plays in the aetiology of metabolic disorders like HUA has drawn more attention in recent years. After a study of the literature, it was discovered that the gut microbiota may affect uric acid metabolism via a number of different pathways, including the manufacture of enzymes that break down purines, the creation of precursors to uric acid, and the control of inflammatory pathways that worsen hyperuricemia.

Probiotics have emerged as a promising therapeutic technique for regulating the gut microbiota. Probiotics are described as live bacteria that, when provided in proper proportions, deliver health advantages to the host. According to recent studies, certain probiotic strains can change the ecology in the stomach, which lowers uric acid levels. Probiotic use in the management and prevention of hyperuricemia, however, has not received much attention in the scientific community. Consequently, the purpose of this research is to show that probiotics can be used as a safe and effective adjuvant therapy for hyperuricemia, possibly eliminating the need for stronger pharmaceutical treatments.

2. Epidemiological Features and Classification of HUA

The incidence of HUA has increased significantly worldwide over the past decades, varies between 5%-25%. And in China, adult instances of HUA are approximated to range from 10%-20%. Notably, the occurrence rate is greater among men compared to women and escalates as they age.

There are two main types of hyperuricemia: primary and secondary. Primary hyperuricemia is usually caused by genetic factors that affect uric acid metabolism, resulting in either increased uric acid production or decreased renal clearance. Uric acid is produced during purine metabolism in the body. The process of purine metabolism involves a series of biochemical stages, and the major enzymes that affect the rate of purine and uric acid synthesis include amido-phosphate ribosyltransferase, which converts ribulose-5-phosphate-1-pyrophosphate (PRPP) to ribulosamine 5-phosphate, an early stage of purine synthesis. PRPP itself is produced by phosphoribosyl pyrophosphate synthetase and is an important precursor for purine synthesis. Hypoxanthine phosphoribosyltransferase (HPRT) is involved in the purine recycling pathway, combining hypoxanthine or guanine with PRPP to produce inosine monophosphate or guanosine monophosphate. Defects in HPRT may lead to insufficient purine recycling, which triggers excess uric acid production. In addition, xanthine oxidase (XOD) is a key enzyme in the final stage of uric acid formation, which catalyzes the oxidation of hypoxanthine to xanthine and then xanthine to uric acid. Therefore, inhibition of XOD activity is one of the effective strategies to reduce serum uric acid levels [2]. Secondary HUA can be caused by other systemic diseases, drugs that inhibit UA excretion, or dietary factors such as excessive consumption of purine-rich foods. More UA is produced by enhanced purine metabolism in conditions such as decelerated cellular conversion, proliferative diseases (e.g. leukaemia), after chemotherapy with cytotoxic drugs, haemolysis and rhabdomyolysis [3]. A. large breakdown of skeletal muscle ATP, such as after strenuous exercise, after severe sustained status epilepticus seizures, and certain types of glycogen storage disorders can also lead to elevated UA.

3. Current Therapeutic Strategies

Currently, treatment strategies for HUA mainly include lifestyle interventions and pharmacological treatments. Lifestyle interventions include weight control, adoption of a low purine diet and adequate fluid intake. Obesity is an important risk factor for HUA. Reducing body weight through a balanced diet and regular exercise can improve UA metabolism. The second point is dietary modification. Patients are recommended to limit their consumption of foods high in purines, such as shellfish, offal, and some types of fish. Proper consumption of fluids, particularly water, can lead to the renal elimination of UA. Pharmacological treatment is based on inhibiting UA synthesis (e.g.,

allopurinol) or increasing UA excretion (e.g., fenbutamolone). Medications like allopurinol and febuxostat act as inhibitors of anthine oxidase and diminish the production of UA. Other drugs, such as probenecid and benzbromarone, promote UA excretion. Non-steroidal anti-inflammatory medications (NSAIDs), colliccine, and corticosteroids are used to treat gout attacks by reducing pain and inflammation. Although these treatments are effective in controlling serum UA levels, there are still some limitations, such as the side effects that may result from long-term medication [4].

Probiotic therapy for human HUA does not require restriction of diet or change of eating habits and is relatively easy to obtain and more expensive. Compared with drugs, it is more acceptable to patients. Therefore, it is an effective means for the treatment of HUA and has a good development prospect. Current research shows that probiotics can relieve hyperuricemia in multiple ways, and its mechanism of action mainly includes inhibiting XOD activity, enhancing purine metabolism, repairing intestinal barrier, regulating intestinal microbiota, accelerating UA excretion, and promoting purine degradation or metabolism.

4. Mechanism of Action

4.1 Inhibiting XOD Activity

A crucial enzyme in the synthesis of UA, XOD catalyzes the last stage of purine metabolism, which involves oxidizing hypoxanthine to xanthine, which is subsequently transformed into UA. As a result, XOD activity inhibition works well to lower serum UA levels. According to studies, giving Lactobacillus plantarum UA149 to HUA rats resulted in a considerable reduction in XOD levels and UA production, which in turn led to a drop in blood UA levels [5]. Additionally, compared to the untreated HUA model group, the liver and serum of mice treated with Lactobacillus rhamnosus CCFM1130, CCFM1131, and Lactobacillus reuteri CCFM1132 showed considerably reduced levels of UA and XOD activity [6].

Dysbiosis of the gut microbiota in HUA models frequently results in increased lipopolysaccharide (LPS) levels. Interferon-γ (IFN-γ) and interleukin-1β (IL-1β) are two examples of the inflammatory cytokines that are produced in response to lipopolysaccharide (LPS) and lead to increased UA synthesis and XOD activity [7]. Probiotics have been shown to alleviate HUA by lowering LPS levels, which inhibits XOD action. For instance, the liver concentrations of LPS, IFN-γ, and IL-1β were markedly lowered in fructose-induced HUA mice upon oral administration of Lactobacillus acidophilus DM9218. Furthermore, it has been demonstrated that oral Bifidobacterium treatment dramatically reduces UV-induced XOD activity in mice. This is probably because it reduces the formation of hydrogen peroxide, which in turn inhibits the oxidation of proteins and lipids, hence suppressing XOD activity [8].

4.2 Enhancing Purine Metabolism

Purines primarily exist in the body as purine nucleotides and are gradually converted to UA through the catalytic action of XOD. Serum UA levels increase in purine metabolism disorders, which may result in HUA. Therefore, reducing the absorption of purine nucleotides can help prevent increases in serum UA levels [9]. In mammals, 90% of dietary nucleotides are absorbed by intestinal epithelial cells, including adenosine, guanosine, and inosine. Probiotics can compete with these cells for nucleotides, thereby reducing UA production in the body.

The first lactobacillus to be found to prevent HUA is *Lactobacillus gasser*i, which is used in functional foods. Hypoxanthine, inosine, and IMP are all absorbed by L. gasseri PA-3 during in vitro growth, according to research. Oral treatment of PA-3 decreased these purine compounds‘ intestinal absorption in rat models [10]. This suggests that by ingesting purines, PA-3 reduces their absorption and contributes to the maintenance of normal serum UA levels. Additionally, a double-blind, randomized, placebo-controlled study showed that yogurt enriched with PA-3 decreased the levels of UA in the serum in patients with HUA [11]. Furthermore, a new purine-degrading strain called L. fermentum 9-4 that was isolated from Chinese fermented rice flour demonstrated effectiveness in breaking down inosine and guanosine, with a guanosine assimilation rate of up to 55.93% [12]. Further studies found that three nucleoside hydrolases in Lactobacillus plantarum, RihA, B, and C, can degrade nucleosides into bases, hypoxanthine, and xanthine. However, L. plantarum lacks the enzymes needed to further convert hypoxanthine and xanthine into UA, partially blocking the UA synthesis pathway and reducing UA levels [13]. Moreover, research suggests that some probiotics can alter purine metabolism pathways, allowing gut strains to use ribose or nucleotides as precursors to synthesize bioamines like thiamine, riboflavin, and folate. As these intermediates decrease, UA synthesis also slows [14].

4.3 Restoring Gut Barrier and Regulating Gut Microbiota Homeostasis

In patients with HUA, excessive accumulation of UA often leads to gut barrier damage. In addition to directly affecting intestinal cells‘ capacity to function normally, elevated UA levels also damage tight junction proteins

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by causing oxidative stress and inflammatory reactions. This increases intestinal permeability and makes it possible for infections and dangerous substances to enter the bloodstream. Studies have shown that probiotics may help repair the intestinal barrier. For instance, *Lactobacillus rhamnosus* GG has the ability to secrete the soluble proteins P40 and P75, which restore the Caco-2 cell barrier damaged by hydrogen peroxide through the mitogen-activated protein kinase pathway. This lowers UA permeability and reduces inflammation [15]. Additionally, it has been demonstrated that probiotic *Akkermansia muciniphila* significantly increases the expression of the tight junction proteins ZO-1, occludin, and claudin in mice, with increases of 70.35%, 179.16%, and 155.02%, respectively. This reduces intestinal permeability and prevents the infiltration of inflammatory cytokines [16]. Additionally, *Lactobacillus delbrueckii* DM9218 improves gut barrier function by lowering LPS permeability, indirectly suppressing XOD expression and activity, and thus reducing UA production [17].

In HUA patients, the compromised gut barrier function leads to increased permeability and a significant decline in microbial diversity, resulting in dysbiosis. Studies on the gut microbiome have revealed that, in comparison to healthy people, HUA patients‘ gut microbiota is less diverse and abundant, and that the abundance of harmful bacteria like Corynebacterium and *Erysipelotrichaceae* is significantly higher [18]. Interventions with probiotics may assist regulate the homeostasis of the gut microbiota and hence lower UA levels. Studies reveal that following *Lactobacillus reuteri* CCFM1132 intervention, there was a large rise in the relative abundance of Firmicutes in the gut microbiota of HUA mice, but there was a significant decrease in the relative abundance of Bacteroidetes [6]. In the stomach of HUA mice, *Lactobacillus paracasei* X11 was shown to raise the abundance of *Faecalibaculum* while lowering the relative abundance of Bacteroides and Proteobacteria. This resulted in a return to normalcy of the Bacteroidetes to Firmicutes ratio [19]. Probiotics L. fermentum F40-4 and L. fermentum GR-3 also lowered UA levels and improved HUA by modulating gut microbiota and reducing inflammation [20].

4.4 Uricase Production

Probiotics work against HUA in a number of ways, one of which is the breakdown of UA by uricase synthesis. Numerous UA-metabolizing enzymes, such as uricase, allantoinase, and allantoicase, can be synthesized by common human gut bacteria, such as Lactobacillus and Pseudomonas species, according to studies. These enzymes then break down UA into 5-hydroxyisourate, allantoin, and ultimately urea [21]. Some probiotic strains may also secrete uricase; *Limosilactobacillus fermentum* JL-3, for example, was isolated from the traditional fermented food „jiangshui“ in Northwest China. In vitro experiments have shown that uricase can significantly improve the HUA by reducing serum UA levels by as much as 31.3% [22]. Furthermore, it has been discovered that certain strains of lactic acid bacteria, such as Lactobacillus sp. OL-5, Lactobacillus plantarum Mut-7, and Lactobacillus plantarum Dad-13, generate intracellular uricase in the gastrointestinal system, continuing to function in the stomach or intestines [23].

4.5 Accelerating UA Excretion

Approximately two-thirds of UA are eliminated through the kidneys following its synthesis in the liver, with the remaining one-third going through the intestines through the extrarenal excretion pathway. About 90% of HUA cases are related to impaired UA excretion, a process closely associated with UA transporters located on the basolateral and apical membranes. The two primary groups of these transporters are UA reabsorption transporters (OAT4, URAT1, and GLUT9), which reabsorb UA back into the bloodstream, and UA secretion transporters (OAT1, OAT3, and ABCG2), which help move UA from the blood to urine or feces. The risk of HUA can be raised by abnormal expression of these transporters, which can cause an imbalance in UA metabolism [24].

Probiotics may modulate the gene expression of UA transporters to promote UA excretion, thereby reducing serum UA levels. For instance, it has been demonstrated that *Lactobacillus paracasei* MJM60396 dramatically increases the expression of OAT1 and OAT3 in the kidneys of mice, thus downregulating the expression of GLUT9 and URAT1, thereby decreasing UA reabsorption and increasing its excretion [25]. Additionally, intervention with Lactobacillus paracasei X11 reduced the expression levels of GLUT9 and URAT1 in mice by 24.39% and 24.69%, respectively , further enhancing UA excretion [19].

5. Safety

A commonly used standard for evaluating the efficacy, safety, and quality of probiotic strains in food is provided by the FAO/WHO Guidelines for the Evaluation of Probiotics in Food [26]. Although toxicological studies have demonstrated the safety of high-dose use of *Bacillus coagulans* and *Clostridium butyricum* in rats, it has been noted that most clinical studies have not adequately evaluated the safety of probiotics. The Agency for Healthcare Research and Quality (AHRQ) has also indicated that the existing literature is insufficient to definitively

establish their safety [27]. Furthermore, probiotics may cause serious infections and increase all-cause mortality in immunocompromised individuals. Certain strains may lead to d-lactic acidosis, biogenic amine-related reactions, lipid metabolism issues, and even intestinal ischemia and increased mortality in patients with severe acute pancreatitis. Overgrowth of probiotics can also result in brain fog, bloating, and gastrointestinal discomfort, especially in patients with inflammatory bowel disease, and may contribute to the horizontal gene transfer of antibiotic resistance [28].

6. Limitation

Although there has been a significant increase in research on the relationship between probiotics and HUA, existing studies still have some limitations. For example, the majority of dietary purines are absorbed into the bloodstream after passing through the stomach and small intestine, meaning that only a small portion of purines really make it to the colon. Therefore, the likelihood of probiotics directly degrading dietary purines in the colon is relatively low. Additionally, many studies rely on fecal analysis to explore the gut microbiome. However, the quality of DNA extraction may be impacted by differences in fecal consistency and the presence of microbial contaminants, which could then have an impact on how sample α-diversity is interpreted [29].

While probiotics have shown promising effects in regulating UA levels in in vitro simulation studies, there is a relative paucity of in vivo research and clinical application studies. The effects of probiotics in people still need to be confirmed by clinical trials because in vitro trials might not accurately mimic the intricate physiological and metabolic systems found in the body. Furthermore, studies on the application of probiotics to treat HUA are still in their infancy, and the underlying mechanisms are still unclear. Different probiotics may operate through different mechanisms, and whether other potential mechanisms exist remains uncertain. The antibiotic resistance and safety of probiotics have also not been comprehensively studied. Thus, more thorough investigation and copious data are required to gain a deeper comprehension of the function of probiotics in the management of HUA.

7. Conclusion

The epidemiological characteristics of HUA indicate it‘s a health issue that demands concentrated consideration. Probiotics, serving as a harmless and efficacious supplementary treatment, have demonstrated encouraging uses in both preventing and curing HUA. Probiotics, by maintaining the balance of gut microecology, enhancing metabolic activities, aiding in lowering serum UA concentrations. Nonetheless, more investigation is required to understand the precise operational process of probiotics and to identify the most efficacious strains. In addition, due to certain physiological and metabolic differences between animals and human, it is difficult to fully reflect the effect of human beings even if animal experiments have achieved good clinical effects. Future research should focus on in vivo trials and clinical trials, and further improve the research level of probiotics in alleviating hyperuricemia, increase research efforts, and apply them to clinical practice. Furthermore, it is crucial to consider how individual variances impact probiotic effectiveness to develop more accurate health management approaches.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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