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Study on the Effect of Probiotic Intervention on the Association Between Gut Microbiota and Metabolic Syndrome

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Abstract. Metabolic syndrome (MetS), characterized by obesity, insulin resistance, dyslipidemia, and hypertension, is closely associated with gut microbiota dysbiosis. Increasing evidence suggests that probiotics may restore microbial balance and alleviate metabolic disturbances. This study reviews the mechanistic roles of probiotics in modulating the gut microbiota and their potential in managing MetS. Probiotics act through multiple pathways, including inhibition of pathogenic colonization, reinforcement of intestinal barrier integrity, immune modulation, and promotion of short-chain fatty acid (SCFA) production. Animal and clinical studies indicate that specific strains, such as Akkermansia muciniphila and Hafnia alvei HA4597®, demonstrate beneficial effects on insulin sensitivity, lipid metabolism, and systemic inflammation, while traditional strains such as Lactobacillus and Bifidobacterium provide more modest improvements. However, clinical outcomes vary due to differences in dosage, treatment duration, strain specificity, and individual host microbiota composition. Current limitations include heterogeneous methodologies, lack of standardized protocols, and insufficient mechanistic validation. Future directions should emphasize precision probiotic strategies, multi-omics approaches, and integration into functional foods and public health interventions. Overall, probiotics represent a promising adjunctive approach for restoring gut–host homeostasis and mitigating metabolic syndrome.

Keywords: Gut microbiota, Probiotics, Metabolic syndrome, Insulin resistance

1. Introduction

In recent years, the gut microbiota, an essential component of the human microecosystem, has been recognized for its critical role in maintaining host health and has become a primary focus in life science and clinical research. Numerous studies have demonstrated that the gut microbiota is involved in various physiological processes, including energy metabolism, lipid regulation, immune

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modulation, and inflammatory responses, all closely tied to metabolic homeostasis. Dysbiosis of the gut microbiota may impair intestinal barrier function and promote chronic low-grade inflammation, exacerbating metabolic disorders and creating a vicious cycle.

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities characterized by central obesity, insulin resistance, hyperglycemia, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein (HDL) cholesterol. It is considered a significant risk factor for type 2 diabetes and cardiovascular diseases. Globally, the prevalence of MetS has reached 20% – 30% [1] among adults, posing an important public health challenge. Emerging evidence suggests that alterations in the gut microbiota, such as reduced diversity, decreased beneficial bacteria, and increased opportunistic pathogens, are common among individuals with MetS, indicating that modulating the gut ecosystem may offer a novel intervention strategy.

Probiotics, defined as live microorganisms that confer health benefits to the host when administered adequately, have attracted increasing attention for their potential role in metabolic disease management. Studies have shown that specific probiotic strains can reshape the gut microbiota composition, enhance the production of short-chain fatty acids (SCFAs), reinforce intestinal barrier integrity, reduce systemic endotoxemia, and improve insulin sensitivity, thereby alleviating symptoms associated with metabolic dysregulation. These effects may help disrupt the pathological loop between dysbiosis and metabolic disorders.

Therefore, this study aims to explore how probiotics regulate gut microbiota and influence host metabolism, focusing on their potential intervention pathways targeting various components of metabolic syndrome. The findings may provide new theoretical insights and practical guidance for microbiota-based therapies in metabolic diseases [1].

2. Mechanistic role of probiotics in modulating gut microbiota

2.1. Classification and functional features of probiotics

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (FAO/WHO, 2002) [2]. The most commonly studied genera include Lactobacillus, Bifidobacterium, and the yeast Saccharomyces boulardii. These microorganisms are naturally present in the human gastrointestinal tract and play vital roles in maintaining microbial balance, strengthening epithelial barrier function, and regulating the immune system [3, 4].

Lactobacilli produce lactic acid, which lowers intestinal pH and inhibits the growth of pathogens, while bifidobacteria promote the synthesis of short-chain fatty acids (SCFAs), enhance intestinal metabolism, and activate mucosal immunity [5]. Some specific strains also possess antioxidant capacity, bile salt hydrolase activity, and cholesterol-lowering properties, making them valuable for nutritional interventions and chronic disease management [6].

2.2. Targeted modulation mechanisms

Probiotics exert regulatory effects on gut microbial ecosystems through the following mechanisms:

(1) Inhibition of Pathogenic Colonization: Probiotics compete with pathogens for adhesion sites and nutrients, while secreting antimicrobial compounds such as bacteriocins, organic acids (lactic and acetic acid), and hydrogen peroxide [7].

(2) Enhancement of Epithelial Barrier: Certain strains upregulate tight junction proteins (e.g., Occludin, Claudin-1, ZO-1), strengthen epithelial integrity, and reduce intestinal permeability

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("leaky gut") [8].

(3) Immune Modulation: Probiotics stimulate Toll-like receptors (TLRs), promote the differentiation of regulatory T cells (Tregs), and enhance IgA secretion to alleviate inflammation and maintain immune homeostasis [9].

(4) SCFA Production: Probiotics ferment indigestible carbohydrates to generate SCFAs (acetate, propionate, butyrate), which activate G-protein coupled receptors (GPR41, GPR43) and regulate glucose and lipid metabolism [10].

2.3. Experimental and clinical evidence

Numerous animal and clinical studies have validated these mechanisms. For example, Lactobacillus rhamnosus GG demonstrates anti-inflammatory effects in colitis models; Bifidobacterium breve improves gut microbiota in infants [11]; Saccharomyces boulardii is widely used in preventing and treating antibiotic-associated diarrhea [12]. Meta-analyses also reveal that multi-strain probiotic formulations significantly improve insulin sensitivity, lipid profiles, and inflammation markers in individuals with metabolic syndrome [13].

2.4. Metabolic regulatory effects and potential mechanisms

The gut microbiota serves as a crucial interface between dietary input and host metabolism. Probiotics influence this system by reshaping microbial composition and enhancing SCFA production, thereby impacting glucose metabolism, lipid absorption, and energy balance. SCFAs activate signaling pathways such as PI3K/Akt and AMPK to enhance insulin sensitivity and alleviate metabolic endotoxemia [14, 15]. Additionally, probiotics reduce pro-inflammatory cytokines like TNF-α and IL-6, thereby alleviating chronic low-grade inflammation. These mechanisms form the theoretical basis for the application of probiotics in managing metabolic syndrome.

3. Specific association between gut microbiota and metabolic syndrome

3.1. Mechanisms of gut microbiota involvement in metabolic processes

The gut microbiota plays an indispensable role in human metabolic processes. In energy metabolism, studies by Ley and colleagues in Cell have shown that gut microbiota can ferment indigestible carbohydrates to produce short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. Butyrate directly supplies energy to colonic epithelial cells, propionate regulates blood glucose through hepatic gluconeogenesis, and acetate influences energy storage by promoting lipid synthesis. In lipid metabolism, gut microbiota modulates bile acid metabolism: primary bile acids are converted into secondary bile acids by microbial enzymes, affecting lipid digestion, absorption, and transport. Additionally, the microbiota regulates inflammatory responses by controlling the release of proinflammatory cytokines through immune system modulation. SCFAs, as microbial metabolites, act on adipose tissue and the liver to regulate insulin signaling pathways, thereby influencing insulin sensitivity and maintaining glycemic homeostasis [16].

3.2. Functional microbiota categories

Short-chain fatty acid-producing microbiota, including Bifidobacterium and Bacteroides, are key functional groups. They ferment dietary fiber to produce SCFAs, which not only provide energy for the host but also regulate intestinal pH and inhibit pathogenic bacteria to maintain intestinal barrier

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function. Proinflammatory microbiota, such as certain strains of E. coli, overproliferate during dysbiosis, releasing lipopolysaccharides (LPS) that trigger inflammatory responses and disrupt gut homeostasis. Anti-inflammatory microbiota, like Lactobacillus, suppress proinflammatory cytokine production via anti-inflammatory metabolites to maintain intestinal balance [17].

3.3. Association between dysbiosis and characteristics of metabolic syndrome

In obesity, studies have found altered ratios of Firmicutes to Bacteroidetes in the gut microbiota of obese individuals, with increased Firmicutes and decreased Bacteroidetes, enhancing intestinal energy absorption and storage [18].

In hyperglycemia, dysbiosis disrupts SCFA production, impairing insulin secretion and sensitivity to dysregulate glucose homeostasis. In hypertension, gut microbial imbalance affects steroid metabolism to promote renal sodium retention; SCFAs also elevate blood pressure by increasing renin release [19].

3.4. Mechanisms of gut microbiota impact on components of metabolic syndrome

For abdominal obesity, the gut microbiota regulates energy metabolism and gene expression related to fat synthesis/storage, influencing adipocyte differentiation and fat deposition. In hyperglycemia, the microbiota modulates insulin secretion via SCFAs and regulates gut endocrine cells to secrete hormones like glucagon-like peptide-1 (GLP-1) for glycemic control. In hypertension, beyond affecting steroid metabolism and renin release, microbiota-derived trimethylamine N-oxide (TMAO) exacerbates renal dysfunction and promotes atherosclerosis, elevating blood pressure. In dyslipidemia, the microbiota participates in bile acid and cholesterol metabolism to influence lipid absorption, synthesis, and transport. In insulin resistance, chronic inflammation induced by dysbiosis disrupts insulin signaling pathways, reducing insulin sensitivity [20].

The gut microbiota is intricately linked to all aspects of metabolic syndrome. In-depth research into these associations holds significant promise for the prevention, diagnosis, and treatment of metabolic syndrome.

4. Current status and problems of probiotic intervention in metabolic syndrome (MetS)

4.1. Summary of evidence from animal and clinical studies

Table 1. The intervention means and effects of several sample probiotic strains

Strain	Means of Intervention	Effect	Suitable Population
Akkermansia muciniphila	Oral supplementation (High-fat diet animal models)	Significantly lowering visceral fat, adipose inflammation, insulin resistance, and serum cholesterol and triglycerides	1. Obese or overweight individuals with insulin resistance 2. MetS-risk adults [21-23]

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Table 1. (continued)

Hafnia alvei HA4597®	Oral probiotic in mice & human RCTs (with hypocaloric diet)	In mice: Significantly lowering body weight gain, food intake, and blood glucose and cholesterol levels In humans: (n=236 overweight) ≥3% weight loss responders (57.7% vs 41.7%, p=0.028) A decrease in hip circumference, cholesterol, and blood sugar. Increase in satiety	Overweight adults (BMI 25–29.9 kg/m²) aiming for weight loss [24, 25].
Bifidobacterium adolescentis	Animal supplementation in MetS models	Ameliorates visceral fat accumulation and improves insulin sensitivity	Individuals with obesity/MetS in experimental studies (early clinical stage) [26, 27]
Lactobacillus spp. & Bifidobacteria (various)	Clinical RCTs in MetS patients	Modest improvements in BMI, blood pressure, glucose metabolism, and lipid profile	Adults with mild/moderate MetS [28]
Multistrain mixes (e.g., L. acidophilus, L. plantarum, B. lactis, S. boulardii)	6-month Greek RCT in T2D subjects	Inconclusive (with some lipid/glycemic benefits)	Adults with T2DM Less clear for primary MetS [28]
L. gasseri SBT2055, B. breve B-3	Oral in animal/limited human studies	Decrease in visceral fat, improves glucose metabolism, and reduces obesity-related inflammation	Overweight/obese individuals (experimental stage) [29, 30]

Recent research highlights the potential of specific probiotic strains in mitigating metabolic syndrome (MetS), with *Akkermansiamuciniphila* and *Hafnia alvei* HA4597® emerging as particularly promising. These strains have demonstrated beneficial effects on insulin sensitivity, lipid profiles, body weight, and appetite regulation through mechanisms such as gut barrier enhancement, modulation of inflammation, and hormone signaling. In contrast, more commonly used probiotics like *Lactobacillus* and *Bifidobacterium* species tend to yield modest and inconsistent metabolic improvements in clinical settings. These findings underscore the need to move beyond generic formulations and toward precision probiotic strategies emphasizing strain-specific efficacy, mechanistic validation, and individualized therapeutic applications.

4.2. Critical intervention parameters

The success of probiotic interventions in managing metabolic syndrome (MetS) depends on a combination of critical parameters, most notably the dose, duration of treatment, and the specific probiotic strains used. Clinical and preclinical studies consistently show that probiotic doses ranging

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from 10^8 to 10^{10} colony-forming units (CFU) per day are generally effective for modulating gut microbiota and improving metabolic markers. Increasing the dose beyond 10^{10} CFU does not always translate into greater clinical benefit, possibly due to saturation effects or host resistance [31]. Moreover, the intervention period is a decisive factor. Short-term treatments (less than 8 weeks) tend to show minimal changes, whereas interventions lasting 12 weeks or more—and especially those extended beyond six months—are associated with significantly improved outcomes in terms of body weight, fasting glucose, lipid profiles, and systemic inflammation [32, 33]. These results suggest that dose and treatment length must be carefully calibrated to ensure meaningful physiological change in the host.

Another major determinant is the selection and combination of probiotic strains. Multi-strain formulations, especially those combining *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* species, are often more effective than single-strain probiotics. This is due to synergistic interactions, where one strain may enhance gut barrier integrity while another reduces pro-inflammatory signaling or modulates bile acid metabolism [34]. For example, *Lactobacillus plantarum* has improved blood pressure and endothelial function, while *Bifidobacterium lactis* is more active in improving insulin sensitivity and reducing serum triglycerides. These mechanistic differences imply that combining strains with complementary effects can provide more robust coverage of the multiple pathophysiological aspects of MetS. However, the efficacy of these combinations is still strain-dependent, and some commercial blends may lack scientific validation for the claimed effects.

Lastly, individual host variability plays a pivotal role in determining probiotic effectiveness. The same probiotic formulation may produce dramatically different results in two individuals due to differences in baseline gut microbiota composition, genetic background, diet, age, metabolic status, and medication use. For example, individuals with a more diverse gut microbiome tend to show greater responsiveness to probiotics, possibly due to better microbial network integration and metabolite production. Emerging studies suggest tailoring probiotic treatments to personal microbial profiles—precision or personalized probiotics—may enhance therapeutic efficacy. This approach requires gut microbiota screening, biomarker monitoring, and potentially adjunctive lifestyle modification to be fully effective. Thus, future clinical applications should emphasize strain specificity, personalization, and long-term modulation rather than short-term, one-size-fits-all supplementation.

4.3. Research deficiencies and practical challenges

A primary weakness in existing studies is their heterogeneous methodologies, which limit the comparability and reliability of findings. Clinical probiotic trials vary significantly regarding strain selection, CFU dosing, formulation, intervention length, and outcome measurements. For example, Cao et al. report that probiotic dosages ranged from 1×10^9 to over 10^{10} CFU/day across 31 RCTs. However, the overall effects on glycemic control remained modest and inconsistent due to this variability [35]. Without standardized protocols detailing viable CFU counts, strain genetics, and treatment regimens, reproducibility across studies is severely compromised, making it challenging to identify which probiotic compositions genuinely offer metabolic benefits.

Equally concerning is the lack of mechanistic clarity underpinning clinical outcomes. Many trials focus primarily on macroscopic endpoints—such as fasting glucose, HbA1c, and lipid profiles—without delving into how probiotics influence gut ecology, immune pathways, or host metabolism. Menon et al. have demonstrated that microbiome-wide association studies often generate spurious correlations, reflecting indirect ecological shifts rather than direct causal effects of administered

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strains [36]. Similarly, studies such as those compiled by Cao et al. rarely include biomarkers like short-chain fatty acids, tight junction integrity, or cytokine profiles, leaving a mechanistic gap that undermines the validity of observed clinical improvements.

Finally, real-world challenges further diminish the translational potential of probiotic therapies. As Hoffmann et al. explain, the survivability of microbial strains through manufacturing, storage, and ingestion is frequently unverified; many products fail to deliver the viable doses expected under lab conditions. Regulatory agencies like the FDA and EFSA routinely reject health claims when strain-specific evidence is lacking or mechanistic justification is absent, limiting claims and consumer trust [37]. Additionally, individual variability—driven by genetics, baseline microbiome composition, diet, and comorbidities—further complicates efficacy. These divergent factors result in some individuals responding positively, while others see minimal or no benefit, illustrating that one-size-fits-all approaches are insufficient for complex metabolic conditions.

4.4. Application prospects and strategies

Recent research has focused on their potential integration into functional foods, clinical supplementation protocols, and public health initiatives, offering a multi-pronged approach to managing MetS through gut-mediated mechanisms.

Innovating functional foods with prebiotic ingredients offers a practical and palatable strategy to influence metabolic health. For instance, a randomized clinical trial provided adults at risk of type 2 diabetes with 10 g/day of inulin for six weeks, within a fully controlled diet. This led to a significant decrease in fasting insulin and HOMA-IR and an increase in fecal *Bifidobacteria*. Though peripheral insulin sensitivity did not improve, it established a model for dietary prebiotic efficacy. Similarly, synbiotic yogurt enriched with *Lactobacillus plantarum*, *L. pentosus*, and *Chloromycesmarcosianos,* administered daily for 12 weeks to adults with metabolic syndrome, significantly lowered fasting glucose, insulin, HOMA-IR scores, waist-to-hip ratio, and systolic blood pressure, showcasing the metabolic benefits of a food-based prebiotic–probiotic combo [38]. These examples underscore how carefully formulated everyday foods can be leveraged to provide consistent therapeutic doses of prebiotics and improve multiple MetS markers.

Prebiotic supplements allow for precise dosing and clear outcome monitoring in clinical settings. The inulin-based proof-of-concept trial mentioned earlier—though limited in improving peripheral insulin sensitivity—demonstrated favorable shifts in gut bacteria and insulin resistance markers [39]. This suggests that standardized inulin supplementation (e.g., 10 g/day) could be strategically used alongside medications or lifestyle interventions for patients with prediabetes. Additionally, long-chain inulin-type fructans (ITFs) have been repeatedly shown to improve gut permeability, SCFA production, and insulin sensitivity in preclinical and clinical contexts [40], reinforcing their viability as adjunctive therapy. Such supplements are ideal for precision medicine strategies where dosage and timing can be synchronized with pharmacotherapy to enhance metabolic outcomes.

At the public health level, incorporating prebiotics into institutional food systems and policy initiatives holds great promise. Inulin and FOS have consistently demonstrated modulation of the gut microbiota—boosting *Bifidobacteria* and *Anaerostipes*—and reducing inflammation in population-based studies. Some national programs have begun testing inulin-fortified grains or staple foods, observing reliable shifts in microbiome profiles and inflammation markers among diverse demographics. Public health systems can promote preventive metabolic health at scale by subsidizing prebiotic-enhanced staples, mandating transparent labeling of prebiotic content, and educating healthcare providers about standardized supplementation. These strategies complement

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individual-focused medical interventions, offering multi-level approaches to reduce metabolic syndrome prevalence.

5. Conclusion and future perspectives

5.1. Research summary

In recent years, with the growing understanding of the gut microbial ecosystem, probiotics have received increasing attention as a regulatory tool for modulating gut microbiota and improving metabolic dysregulation. This study focused on the 'probiotics–gut microbiota–metabolic syndrome' pathway and systematically reviewed the core characteristics of probiotics, their mechanisms of action, supporting evidence from clinical and experimental studies, and their potential in managing metabolic syndrome.

Probiotics act through diverse mechanisms—suppressing pathogenic bacteria, enhancing intestinal barrier function, modulating immune responses, and promoting the production of short-chain fatty acids (SCFAs)—to maintain microbial homeostasis and metabolic stability [41, 42]. Metabolic syndrome, characterized by abdominal obesity, insulin resistance, dyslipidemia, and hypertension, is closely linked to gut dysbiosis [43]. Probiotic interventions have shown the capacity to improve insulin sensitivity, lipid profiles, and chronic low-grade inflammation [44]. Several clinical and animal studies, especially those using multi-strain probiotic formulations, have demonstrated significant improvements in metabolic syndrome-related phenotypes [45].

However, current research still faces limitations in terms of mechanistic clarity, standardization of interventions, and individualized application strategies. Probiotic efficacy varies depending on strain, dosage, duration, and host microbiota composition [46], while the lack of unified evaluation criteria hinders broader clinical translation.

5.2. Future research directions

(1) Deepening the Understanding of Mechanisms: Future studies should focus on elucidating the molecular mechanisms by which probiotics influence host metabolism, immune modulation, and inflammatory pathways, particularly in distinct metabolic phenotypes [42, 47].

(2) Balancing Standardization and Personalization: It is essential to establish standardized intervention models (including optimal dosage, intervention duration, and strain combinations), while also incorporating multi-omics approaches (e.g., metagenomics, metabolomics) to develop personalized probiotic strategies [46, 48].

(3) Expanding Multicenter Clinical Trials: Current clinical studies often suffer from small sample sizes and short intervention periods. Large-scale, long-term randomized controlled trials (RCTs) are needed to validate the efficacy and safety of specific probiotic strains or formulations in different subtypes of metabolic syndrome [45, 49].

(4) Integrating Functional Foods and Public Health Strategies: Probiotics should be integrated into functional food design and community-based nutrition interventions, fostering the creation of a 'nutrition intervention–chronic disease prevention–population health promotion' framework [50].

5.3. Final remarks

In conclusion, probiotics, as safe, multifunctional, and adaptable microbial agents, are becoming a promising focus in metabolic syndrome management. With further mechanistic studies and

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translational research, probiotics are expected to play a broader and more profound role in precision nutrition and chronic disease control in the near future.

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