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Review Article

The Impact of Prebiotics, Probiotics and Synbiotics on Metabolic Syndrome and Chronic Diseases: A Review

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ABSTRACT

Metabolic syndrome is characterized by a cluster of metabolic abnormalities, including insulin resistance, hypertension, dyslipidemia, and abdominal obesity, which significantly increase the risk of cardiovascular disease and type 2 diabetes. Emerging evidence suggests that metabolic syndrome may play a critical role in the cancer progression and contribute to higher mortality rates. Emerging researches highlight the essential role of the gut microbiota in maintaining health, with dysbiosis being linked to various chronic diseases. This review focused on the potential therapeutic roles of prebiotics, probiotics, and synbiotics in the management and prevention of metabolic syndrome and its associated conditions. Prebiotics support the growth of beneficial gut bacteria, while probiotics are live microorganisms that confer health benefits. Synbiotics, combinations of prebiotics and probiotics, have demonstrated promise in improving gut health and managing metabolic disorders. The article synthesizes clinical and preclinical evidences regarding the effects of these supplements on obesity, diabetes, cancer, inflammatory bowel disease, cardiovascular diseases, and diarrhea. It reviews the efficacy of specific prebiotics (such as inulin and fructooligosaccharides), probiotics (like Lactobacillus and Bifidobacterium), and synbiotics, highlighting their mechanisms of action and clinical outcomes. Additionally, the review emphasized the need for more rigorous clinical trials to establish the safety, efficacy, and optimal use of these supplements in the management of metabolic and chronic diseases.

In conclusion, prebiotics, probiotics, and synbiotics hold significant potential for improving metabolic health and managing chronic diseases. Future researches should prioritize well-designed clinical trials to fully explore their therapeutic potential and refine treatment strategies.

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Introduction

The term "metabolic syndrome" (MetS) describes an extensive medical condition with associated metabolic abnormalities, such as low-grade inflammation, insulin resistance, abdominal obesity, hypertension, and dyslipidemia (1, 2). The prevalence of obesity and type 2 diabetes is frequently correlated with the prevalence of

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metabolic syndrome. About 30.2 million persons in the USA who are 18 years of age or older, or 12.2% of the adult population, have type 2 diabetes, according to Centers for Disease Control and Prevention (CDC) data released in 2017. (3). Individuals with untreated MetS have a higher chance of mortality from cardiovascular and cerebrovascular diseases (4, 5). The hypothesis that MetS may also be a significant etiologic factor for the onset, spread, and overall mortality from cancer is further supported by a number of epidemiological and clinical studies (6).

Intestinal microbiota is important for both human health and diseases. Dysbiosis can arise from disturbances to the gut microflora and chronic diseases may result from an environmental dysbiosis, and it is challenging to restore (7, 8). This dysbiosis is linked to several significant diseases, for which a variety of therapeutic approaches are currently being used with the goal of reestablishing the equilibrium and reconstruction of the intestinal ecosystem (9). By administering probiotics, prebiotics, and their combination (synbiotics), it is possible to eliminate these potentially harmful bacteria and aid in restoring the microbial community's equilibrium (10). So the primary objective of this review was to provide a comprehensive summary of the available evidences regarding the therapeutic potential of prebiotics, probiotics, and synbiotics in managing MetS and chronic diseases. By consolidating the findings, we aimed to highlight the persistent trends in this field of research and suggest directions for future investigations.

Search Methodology

To conduct this review, we searched multiple databases, including Google Scholar, Scopus, Medline, Embase, PubMed for relevant articles on the impact of prebiotics, probiotics, and synbiotics on metabolic syndrome and chronic diseases. The search strategy involved using key terms such as prebiotics, probiotics, synbiotics, metabolic syndrome, obesity, diabetes, cardiovascular diseases, and gut microbiota. Studies were included if they met the criteria of being clinical or preclinical researches focused on the effects of these supplements on metabolic health or chronic conditions, to be written in English, and the full-text to be available. Exclusion criteria were studies with irrelevant outcomes, and studies with insufficient methodological quality.

Metabolic Syndrome

MetS is a complex of metabolic abnormalities, which serves as a risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs). Although research has been carried out in recent decades on MetS, the exact underlying etiology is still not completely understood. Many contributing factors and mechanisms have been proposed, including insulin resistance, adipose tissue dysfunction, chronic inflammation, oxidative stress, circadian disruption, microbiota, genetic factors, and maternal programming, etc. (11, 12).

Prebiotic

In 1995, the prebiotics concept was presented for the first time (13). A prebiotic was characterized as "a non-digestible food ingredient that selectively stimulates the growth and/or activity of one or a limited number of bacteria in the colon, thereby improving host health and having a beneficial effect on the host." Although this original definition has been revised multiple times, the main features have mostly been retained (14). Fructans, glucooligosaccharides, starch, fructooligosaccharides, soybean oligosaccharides (SOS), lactosucrose (LS), lactulose, inulin and glucose-derived oligosaccharides are certain examples of prebiotics (15).

Probiotics

Probiotics are microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host (16, 17). Maintaining a healthy gut is just one of the numerous beneficial health-promoting functions that probiotics play in human physiology. Lactic acid bacteria types, including Lactobacillus, Bifidobacterium and *Streptococcus thermophilus* are the most widely utilized probiotics (18, 19).

Synbiotics

When a product contains both probiotics and prebiotics, it is termed "synbiotics". This word implies synergy, i.e., acting together (20). Prebiotics serve as a nutrient source for probiotics, facilitating their prolonged survival within the gastrointestinal tract. Additionally, synergistic interactions enhance the colonization of live microbial dietary supplements in the colon and stimulate probiotic proliferation. These products typically contain a combination of Bifidobacterium, Lactobacillus, or Streptococcus species and a carbon substrate (e.g., lactose, lactulose, or inulin) supporting the growth of these organisms (21). A combination of Lactobacillus or Bifidobacterium bacteria with fructooligosaccharides is the most common example of a synbiotic (7). Synbiotics can be formulated using two approaches of being a complementary synbiotic, which combines a probiotic and a prebiotic

independently to achieve health benefits, and being a synergistic synbiotic, which combines a live microorganism with a selectively used substrate that allowing them to work together without meeting the minimum criteria for probiotics and prebiotics (22).

Roles of Prebiotics, Probiotics, and Synbiotic Supplements in Various Diseases

1. Obesity

Obesity is a major health issue, causing long-term illnesses and metabolic disorders. Obese individuals have less diverse microbial populations, which can be reversed through weight loss interventions (23, 24). Despite the multifaceted and highly complicated etiology of obesity, a number of studies have demonstrated the potential therapeutic benefits of synbiotics on lipid profiles, body weight, BMI, waist circumference, fat deposition, and chronic inflammation (25, 26). Supplementing with probiotics and synbiotics has gained popularity due to its potential to control body weight and gut microbiota. They can generate short-chain fatty acids, which can improve resting energy and have an impact on hormones that regulate appetite (27, 28). Piyarat *et al.*'s study revealed that combining multispecies probiotics with fructooligosaccharides increased Trolox equivalent antioxidant capacity and decreased malondialdehyde in overweight and obese individuals, suggesting multispecies synbiotic supplementation may improve antioxidant status and gut microbiota composition (29) (Table 1 and Table 2).

2. Diabetes

Type 1 diabetes is characterized by insulin deficiency caused by immune system attacks on beta cells, possibly linked to gut microbiome changes and autoimmune reactions (39). On the other hand, type 2 diabetes, characterized by metabolic abnormalities, is primarily linked to insulin resistance, with gut dysbiosis contributing to chronic inflammation and increased gut permeability (40, 41). Probiotics benefit in normalizing disturbed metabolism (altered gut flora) in diabetic patients. They minimize preprandial glucose and level of insulin depending on the species, probiotic dosage, and efficacy. Probiotic *L. johnsonii* motivates T helper (Th) cell differentiation in the mesenteric gland to develop immunity for protection of T1DM (42). Supplementing with *Bacillus coagulans* synbiotics may help patients with type-2 diabetes's inflammatory response and metabolic parameters (43) (Table 3).

3. Cancer

Uncontrolled cell replication is a

Table 1: The effects and mechanisms of synbiotics on obesity from experimental animal studies.

Synbiotics supplement	Main effect and mechanism
Bifidobacterium, *Lactobacillus*, *Lactococcus*, and *Propionibacterium* plus omega-3 fatty acids	Revealing a positively synergistic effect on reducing hepatic steatosis and lipid accumulation compared to probiotics alone (30).
Bacillus licheniformis plus xylo-oligosaccharides	Supplementation inhibited body weight gain, returned lipid metabolism to normal, and reduced the serum lipopolysaccharides (LPS) level (31).
Lactobacillus plantarum PMO 08 plus chia seeds	Revealing a positively synergistic effect on improving obesity by significantly lower serum total cholesterol, low-density lipoprotein cholesterol levels, and atherogenic index. Increasing *Lactobacillus plantarum* (32).

Table 2: Clinical effects of synbiotics, probiotics, and prebiotics on obesity.

Supplement	Outcome
Synbiotcs	
Bifidobacterium bifidum, *Lactobacillus acidophilus*, *Lactobacillus casei*, plus inulin	Improving lipid profiles and psychological status (33).
Bifidobacterium adolescentis IVS-1, *Bifidobacterium lactis* BB-12, plus galacto-oligosaccharides	Improving intestinal barrier function as single agents. No synergistic effects (34).
Probiotics	
Bifidobacterium lactis	Improving obesity, blood lipids, and inflammatory markers such as TNF-α and IL-6 (35).
Bifidobacterium breve CBT BR3 and *Lactobacillus plantarum* CBT LP3	More effectively improve obese biomarkers in patients with *Prevotella*-rich enterotype than *Bacteroides*-rich enterotype (36).
Prebiotics	
Inulin oligofructose	Decreasing energy intake by modifying appetite (37).
Oligofructose	Improving metabolic endotoxemia (38). Decreasing PAI1 level.

complicated group of disorders known as cancer, necessitating the application of a variety of therapeutic approaches (49, 50). Prebiotics specifically influence the probiotic organisms' growth, allowing them to suppress the malignant growth through immunomodulation. The recruitment of natural killer cells, cytotoxic T cells, and oxidative stress-induced apoptosis in the tumor microenvironment are the mechanisms by which bacteria exert their oncostatic effects. Additionally, methods for using probiotics as an adjuvant in cancer therapy have been explored before (51). Mucositis and gut dysbiosis are the two most common gastrointestinal adverse effects of radiation and chemotherapy (52). These are shown as excruciating mouth and oesophageal ulcers, along with the onset of diarrhea and abdominal pain, which causes patients with solid organ tumors to become malnourished and dehydrated. Several dietary strategies have been employed to improve the gut microbiota and reduce the negative effects of anti-cancer treatments, including prebiotics, probiotics, and, more recently, their combination as synbiotics (53). A clinical study conducted in 2014 on patients with pelvic malignancy found that probiotics (*L. acidophilus and B. longum*) prevented moderate or severe diarrhea caused by radiation therapy in 35% of the probiotic-using patients, compared to 17% in the placebo group (54) (Table 4).

4. Inflammatory Bowel Disorder (IBD)

One of the main causes of IBD has been suggested to be environmental factors generating dysbiosis. It is unclear, though, which pathways, it finally can cause dysbiosis to result in the development of a chronic inflammation (58, 59). Patients with IBD have altered gut microbiota composition in both quantitative and qualitative ways. The most frequent variation is the reduction in the diversity of bacterial species and genera (60, 61). Additionally, there is an alteration in the ratio of various bacterial species; for example, in the feces of IBD patients, there are

Table 3: Clinical effect of synbiotics, probiotics and prebiotics in Type 2 diabetes mellitus.

Supplements	Outcomes
Synbiotcs	
Bifidobacterium, *Lactobacillus*, and *Streptococcus thermophilus* plus fructo-oligosaccharide	Improving HbA1c, BMI, and microalbuminuria. Not affecting fasting blood glucose, lipid profiles, and creatinine (44).
Probiotic yogurt plus *Coix lacryma-jobi*	Reducing body weight and fasting blood glucose (45).
Probiotics	
Bifidobacterium lactis BB-12 and *Lactobacillus acidophilus* La-5	Improving fructosamine, HbA1c and IL-10 levels (46).
Lactobacillus reuteri strain ADR-1 and ADR-3	Decreasing HbA1c and cholesterol levels (47).
Prebiotcs	
Inulin oligofructose	Improving glycemic status, lipid profiles, and immune markers (48).

Table 4: The role of probiotics for the alleviation of chemotherapy-associated symptoms.

Beneficial Mechanism of Probiotics	Type of Probiotics	Relevance to Chemotherapy
The colonization and normalization of dysbiotic gut microbiota	*Bifidobacterium, Lactobacillus reuteri, Lactobacillus rhamnosus GG, Butyricicoccus pullicaecorum, Faecalibacterium prausnitzii*	The gut microbiota may become dysbiotic as a consequence of chemotherapy. It has been suggested that probiotics can aid in the restoration of the gut's microbial environments. This has been shown to be effective in lowering the gastrointestinal adverse effects of chemotherapy, such as mucositis and diarrhea (55).
The modulation of the immune system	*Lactobacillus salivarius, Lactobacillus helveticus, Lactobacillus acidophilus, Bifidobacterium breve, and Bifidobacterium bifidum*	Chemotherapy may impair the immune system's capacity for defense against infection. By modifying the actions of immune cells such as dendritic cells, macrophages, T and B lymphocytes, and others, probiotics control the immunological response (56).
Cell adhesion	*Lactobacillus rhamnosus, Lactobacillus johnsonii*	Chemotherapy destroys the intestinal mucosa and causes the gut flora to disappear. Due to their ability to stick, probiotics can increase the number of helpful microorganisms in the stomach by adhering to the mucosa (57).

more Proteobacteria and fewer Firmicutes than in the control group (60, 62). According to other researches, there is a decrease in anti-inflammatory bacterial species (like *Faecalibacterium prausnitzii*) and an increase in pro-inflammatory bacterial species (like *E. coli*) in IBD patients (63, 64). Probiotics have been used in clinical trials to treat IBD and prevent dysbiosis during immunosuppressive or long-term antibiotic therapy. They have also been used to treat dysbiosis in patients with newly diagnosed IBD or who have experienced an exacerbation of the disease (17, 65, 66).

Prebiotics appear to have potential benefits, particularly for patients with minimal disease activity or for preserving remission. The majority of prebiotics utilized in research involving IBD patients belong to the oligosaccharide and inulin classes (17, 67). Prebiotic fructans and resveratrol were reported to increase the quantity of Bifidobactrium and Lactobacillus in the colon of IBD-induced mice and rats in animal experiments (68). Psellyllium husk was found to reduce gastrointestinal symptoms in individuals with ulcerative colitis (UC) in remission of clinical studies such as IBD (69). In Japan, a clinical study was carried out to treat UC using germinated barley food (GBF) products that are mainly composed of dietary fiber and glutamine-rich protein. The research indicated that GBF could potentially decrease clinical activity in individuals with mild to moderate UC, and it seems to be a useful treatment for maintaining remission in these people (70). Several studies have documented the beneficial effects of synbiotics on IBD. Furrie *et al.* demonstrated that a synbiotic formulation containing *Bifidobacterium longum* and oligofructose-enriched inulin reduced both macroscopic and microscopic inflammatory lesions in the colon, as assessed by sigmoidoscopy and histopathological examination, respectively. Additionally, the synbiotic treatment lowered the levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). This was observed in a randomized, double-blind, placebo-controlled trial in 18 patients with UC (71).

5. Cardiovascular diseases (CVDs)

Heart diseases, or cardiovascular diseases, encompasses four conditions of cerebrovascular diseases, peripheral artery diseases (PADs), aortic atherosclerosis, and coronary artery diseases (CADs), also called coronary heart diseases (CHDs) (72). Consuming probiotics may improve serum lipid profiles and have anti-hypertensive effects. The consumption of probiotics, prebiotics, or a combination of the two, known as synbiotics, may help prevent and treat cardiovascular diseases, according to more recent *in vivo* trials. Few studies have looked specifically at the role of probiotics in this regard, and it is still unknown what the precise therapeutic and preventive doses for humans are (73).

By lowering increased cholesterol levels, probiotics may aid in the prevention and treatment of some cardiovascular disorders (74). Probiotic use can significantly reduce total cholesterol and low-density lipoprotein cholesterol in people with hypercholesterolemia that was reported in a recent meta-analysis by Mo *et al.* (75). In a model of hypercholesterolemia in rats, Parnell and Reiner found that probiotic treatment reduced the total serum cholesterol (76). Synbiotics have shown encouraging hypercholesterolemic characteristics, according to several investigations. According to Haghighat *et al.*'s study, hemodialysis patients who took a 12-week synbiotic supplement had lower concentrations of intracellular adhesion molecule type 1 (ICAM-1) as a risk factor for CVDs (77). Probiotics, prebiotics, and synbiotics all have poorly understood modes of action. Before these drugs may be used to effectively prevent and cure CVDs, more experimental researches are required, especially well-designed clinical trials (73).

6. Diarrhea

The World Health Organization defines diarrhea as the presence of three or more loose or watery stools in a 24-hour period. Over the past 20 years, several studies on probiotic bacteria were conducted *in vitro*, *in vivo*, and in appropriately designed clinical trials and have confirmed the benefits of probiotic ingestion in controlling various forms of diarrhea (78). Regarding an acute infectious diarrhea, probiotics of *L. rhamnosus GG* and *S. boulardii CNCM I-745* have been suggested by the World Gastroenterology Organization Global Guidelines for the treatment of acute infectious diarrhea (79). Three key outcomes of the probiotic impact were demonstrated to be a decrease in the average length of diarrhea, a decrease in the frequency of diarrheal stools lasting at least four days, and a decrease in the frequency of diarrheal stools on the second day of diarrhea (80). In antibiotic-associated diarrhea (AAD), diarrhea can often be brought on by antibiotic treatments that disturb or destroy the natural microbiota. It has been demonstrated that *L. rhamnosus GG* and *S. boulardii CNCM* I-745 are useful in treating II. AAD patients and that a combination of *L. acidophilus CL1285, L. casei LBC80R*, and *L. rhamnosus CLR* is effective in preventing AAD (81). In relation to traveller's diarrhea, an estimated 20-60% of travelers worldwide were shown to suffer from travelers's

diarrhea. Lactobacillus *GG* showed efficacy against viral and idiopathic diarrhea, while *S. boulardii* was found to be more efficient against bacterial diarrhea. To avoid traveler's diarrhea, prophylactic usage of Lactobacilli, Bifidobacteria, Enterococci, and Streptococci has been implemented (82).

Clinical Validation of Prebiotics, Probiotics, and Synbiotic Supplements

The Centers for Disease Control and Prevention stated that probiotics and prebiotics available over-the-counter can be taken safely by healthy people. Probiotics produced as pharmaceuticals, as opposed to dietary supplements, are exempt from regulatory assessment since they do not have to back up statements regarding the efficacy or safety of food or supplements. This is a significant contributing element to the dearth of knowledge regarding the safety and efficacy of most products that are promoted (83). It is essential to consider individual health status and potential interactions when using probiotics and synbiotics. While probiotics are generally safe, certain populations may require cautious use. Individuals with weakened immune systems, pregnant or breastfeeding women, and those with premature infants should consult with a healthcare provider before taking probiotics. Additionally, individuals with severe immune system disorders or specific gastrointestinal diseases may need to avoid or use caution with synbiotics (83, 84).

Synbiotics might interact with some medications, such as antibiotics or immunosuppressants. Clinical validation helps identify these interactions and provides guidance on safe use. While extensive research exists on the use of probiotics in humans, information regarding prebiotics and synbiotics remains relatively limited. The efficacy of these interventions in promoting health benefits requires robust clinical validation through well-designed, large-scale trials. It is essential to acknowledge the diverse bacterial carbohydrate utilization patterns among different strains and species, which necessitates a tailored approach to developing novel synbiotic formulations. A comprehensive understanding of these factors is crucial for optimizing the efficacy and safety of synbiotic interventions (19, 85).

Clinical validation ensures that synbiotics provide the claimed benefits, such as improved gut health, enhanced immune function, or relief from gastrointestinal symptoms. Evidence-based research supports claims made by manufacturers, providing assurance to consumers and health professionals. Validation builds trust by providing evidence that the supplements are effective and safe. Consumers are more likely to use products that have been scientifically proven to deliver the advertised benefits. Consumer education is crucial for better understanding of health benefits, potential risks, and safe and effective use of synbiotics. Investing in clinical validation is a strategic move for supplement brands seeking to differentiate themselves in the competitive market. By demonstrating the efficacy and safety of their products through rigorous scientific research, brands can establish credibility and build trust with consumers (19, 86).

Long-term studies are essential to fully understanding the effects of prolonged probiotic and synbiotic use. These studies help identify potential cumulative effects, long-term risks, and the overall impact of these interventions on health outcomes. Clinical validation is crucial for determining whether the observed changes are beneficial or detrimental over time. Clinically validated supplements are more likely to meet regulatory standards, be manufactured in GMP-compliant facilities, and undergo independent testing. By emphasizing these factors and transparently disclosing product formulations and scientifically supported health claims, brands can build trust with consumers and establish themselves as leaders in the sports nutrition market. Clinical trials monitor potential side effects such as gastrointestinal discomfort (e.g., bloating, gas), allergic reactions, or any adverse effects associated with the synbiotics. In summary, clinical validation is essential for establishing the efficacy and safety of prebiotic, probiotic, and synbiotic supplements, addressing contraindications, and ensuring long-term safety. Effective marketing and consumer education, grounded in clinical evidence, support informed decision-making and promote trust in the brand (19, 84-86).

Future Perspective of Prebiotic, Probiotic, and Synbiotic Supplements

Future research on prebiotics, probiotics, and synbiotics could significantly advance their applications in various health conditions. For instance, exploring their potential in combination with other therapies, such as medications or lifestyle interventions, could enhance their effectiveness in managing complex diseases like metabolic syndrome. Synbiotic supplementation may serve as a complementary therapeutic approach for individuals with Parkinson's disease. However, additional research is necessary to validate this finding (87). Probiotics hold promise as potential therapeutic agents for cardiovascular health. Ongoing researches aim to uncover their specific effects and mechanisms of action in preventing and managing conditions like

heart attacks and atherosclerosis (87). Prebiotics, probiotics, and synbiotics offer significant potential for improving metabolic health and managing chronic diseases; further research is crucial to fully understand their mechanisms, optimize their use, and ensure their safety. Future studies should focus on well-designed clinical trials to validate these findings and guide effective therapeutic applications.

Conclusion

Recent studies suggest that prebiotics, probiotics, and synbiotics may be beneficial adjuncts in managing MetS and related chronic conditions. The reviewed clinical and preclinical evidences demonstrated that these interventions can positively modulate the gut microbiota, which subsequently influence various metabolic and health parameters. Prebiotics like inulin and fructooligosaccharides support beneficial gut bacteria growth, while probiotics such as Lactobacillus and Bifidobacterium help maintain microbial balance. Synbiotics, combining prebiotics and probiotics, enhance the growth and function of beneficial microbes. In obesity, these supplements may improve metabolic biomarkers. For diabetes, probiotics have shown promise in regulating glucose and insulin, with synbiotics potentially offering additional benefits. They are also valuable in managing gastrointestinal issues from cancer treatments and may aid in preventing cardiovascular diseases and diarrhea. Despite these encouraging findings, further rigorous clinical trials are necessary to confirm efficacy and safety. Future researches should focus on large-scale studies to validate benefits, understand mechanisms, and optimize treatment protocols, considering individual variations and interactions with other therapies. Overall, while prebiotics, probiotics, and synbiotics hold potential as complementary treatments, further researches are needed to fully establish their therapeutic value and ensure their effective clinical application.

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Authors' Contribution

NDP, RL: Writing original draft, writing review and editing. GG, DN, SR: Conceptualization, supervision, writing review and editing.

Conflict of Interest

None declared.

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