


Review Article

Gut microbiota as a therapeutic target in overweight: Role of probiotics, prebiotics, and synbiotics

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	International Archives of Integrated Medicine, Vol. 13, Issue 3, March, 2026. Available online at http://iaimjournal.com/ ISSN: 2394-0026 (P) ISSN: 2394-0034 (O)
	Received on: 21-2-2026 Accepted on: 3-3-2026 Source of support: Nil Conflict of interest: None declared. Article is under Creative Common Attribution 4.0 International DOI: 10.5281/zenodo.19255403
How to cite this article: Arianna Arce Cortés, Tamara Campos Carmona, Grace Quesada Salas, Isaac Sánchez Toruño, Luis Manuel Espinoza López. Gut microbiota as a therapeutic target in overweight: Role of probiotics, prebiotics, and synbiotics. Int. Arch. Integr. Med., 2026; 13(3): 16-25.	

Abstract

Obesity is a multifactorial disease associated with metabolic alterations, and more recently, the influence of the gut microbiome on this condition has been demonstrated, which has driven interest in the study of prebiotics, probiotics, and synbiotics as complementary therapeutic strategies. This study analyzes the available clinical evidence on the use of prebiotics, probiotics, and synbiotics in the management of obesity. For this purpose, a narrative review of the recent scientific literature was conducted, focusing on clinical trials, systematic reviews, and meta-analyses related to gut microbiota and obesity. The analyzed studies show heterogeneous results, which could be explained by differences in the baseline characteristics of patients and in the composition of the gut microbiome. However, the evidence suggests a general favorable trend of prebiotics, probiotics, and synbiotics on metabolically relevant parameters in obesity, such as BMI, waist circumference, and body weight. Despite these findings, limitations persist related to variability in strains, doses, and duration of the interventions. Prebiotics, particularly inulin-type fructans, and next-generation probiotics emerge as promising strategies, although the available clinical evidence is still limited. Therefore, prebiotics, probiotics, and synbiotics may be considered complementary tools in the management of obesity, but they do not replace conventional therapeutic strategies. Well-designed clinical trials and personalized approaches based on the microbiome are required to consolidate their clinical application.

Key words

Gut microbiota, Probiotics, Prebiotics, Synbiotics, Obesity.

Introduction

The increase in overweight over recent decades represents a major global public health problem. It is estimated that approximately 2.6 billion people, corresponding to nearly 40% of the global population, are affected by overweight or obesity [1]. Obesity is considered a multifactorial, chronic, and systemic disease, and its diagnosis is established through the assessment of body composition and a body mass index (BMI) ≥ 30 kg/m² [1, 2, 3].

Despite the fact that many patients with overweight or obesity report adherence to conservative weight loss measures - including dietary modifications, physical exercise, and pharmacological treatment - the results obtained are often limited or not sustained in the long term. Available therapies include recently introduced drugs such as GLP-1 and GIP receptor agonists, as well as treatments with a longer clinical trajectory, such as orlistat, sympathomimetics, antiepileptic drugs, and bariatric surgery [1, 2]. However, a significant proportion of individuals fail to achieve or maintain clinically relevant weight reduction.

The primary cause of overweight and obesity is energy imbalance, in which caloric intake exceeds daily energy expenditure. Nevertheless, multiple additional factors influence the development of this disease, including endocrine alterations, psychological, genetic, socioeconomic, and sleep-related factors. Within this multifactorial scenario, one of the factors that has gained increasing interest in recent years is the role of the gut microbiota in the regulation of body weight and energy metabolism [1, 2].

The gut microbiota refers to the set of microorganisms that inhabit the gastrointestinal tract and play a key role in energy harvest, nutrient absorption, and protection against

pathogens. Throughout human development, the microbiota undergoes progressive changes influenced by factors such as diet, antibiotic use, environmental exposure, and maturation of the immune system, reaching a relatively stable composition in adulthood. This symbiotic interaction between the microbiota and the host is fundamental for the maintenance of metabolic balance [4, 5].

Alterations in the composition of the gut microbiota have been associated with states of low-grade chronic inflammation, insulin resistance, and obesity through mechanisms that include increased intestinal permeability, activation of inflammatory pathways, and metabolic dysfunction [3]. Additionally, it has been observed that microbial composition differs between individuals with obesity and those with normal weight, and that diet significantly influences this variability. For example, hypocaloric diets have been associated with a reduction in the Firmicutes/ Bacteroidetes ratio, whereas vegetarian diets are associated with a greater predominance of *Bacteroides* spp. and a reduction in other bacterial groups [4].

In this context, targeted modulation of the gut microbiota through probiotics, prebiotics, and synbiotics has emerged as a potential therapeutic strategy for the management of overweight. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [6]. Prebiotics are non-digestible substrates that are selectively utilized by host microorganisms, promoting beneficial effects [7]. Synbiotics, in turn, correspond to formulations that combine probiotics and prebiotics with the aim of enhancing their synergistic activity [8].

The aim of this publication is to conduct an updated review of the available scientific evidence on the use of probiotics, prebiotics, and

synbiotics as therapeutic strategies in the management of overweight.

Methodology

This article corresponds to a narrative review of the scientific literature aimed at evaluating the role of probiotics, prebiotics, and synbiotics as therapeutic targets in the management of overweight. To this end, a bibliographic search was conducted in the electronic databases PubMed, ScienceDirect, and Google Scholar.

The search strategy included the terms overweight, obesity, gut microbiota, probiotics, prebiotics, and synbiotics. Articles published in English during the last five years were considered. Original studies, systematic reviews, narrative reviews, and consensus documents relevant to the topic were included.

Investigations conducted in animal models without clinical correlation and those that did not directly address the relationship between gut microbiota and overweight were excluded. Articles were selected according to their relevance to the objective of this review and their methodological quality. The information obtained was analyzed and synthesized narratively, with emphasis on the proposed mechanisms of action, as well as on clinical outcomes and the therapeutic implications of gut microbiota modulation.

Additionally, artificial intelligence-based tools were used as methodological support for the organization of information, thematic grouping of the literature, identification of conceptual relationships among the analyzed studies, and for language translation and manuscript editing.

Gut microbiota and regulation of body weight

The gut microbiota is composed of approximately 10^{14} bacterial cells, corresponding to between 400 and 500 different species per gram of colonic content. It is estimated that around 195 bacterial strains colonize the gastrointestinal tract, of which approximately

101 species are part of the fecal microbiota [2]. During growth, the gut microbiota undergoes a progressive evolution from an initial composition dominated by *Bifidobacterium* and *Lactobacillus* in the first years of life toward an adult microbiota mainly characterized by the phyla *Bacillota* and *Bacteroidota*, together with other less abundant groups such as *Actinomycetota*, *Pseudomonadota*, *Fusobacteriota*, and *Verrucomicrobiota*. In addition, the gut microbiota includes fungi, viruses, bacteriophages, and archaea, with *Methanobrevibacter smithii* standing out. This transition toward a mature microbiota is influenced by factors such as weaning, dietary diversification, environmental exposure, early antibiotic use, and maturation of the immune system [2, 3].

However, it is important to note that there is no universally defined microbial composition that represents a state of metabolic health. This is due to the marked interindividual variability of the gut microbiota, which is influenced by genetic, environmental, dietary, and demographic factors. In this context, metabolically healthy individuals tend to be characterized by greater taxonomic diversity, high microbial gene richness, and preservation of key metabolic functions, such as fermentation of complex polysaccharides with the consequent production of short-chain fatty acids, synthesis of vitamins and essential amino acids, methane production, lipopolysaccharide biosynthesis, oxidative phosphorylation, and modulation of host immunometabolic mechanisms, rather than by the presence of specific bacterial species [2, 9].

Intestinal dysbiosis and overweight

Intestinal dysbiosis is generally characterized by a reduction in microbial diversity, loss of beneficial bacteria, and/or an increase in potentially harmful microorganisms [10]. In this context, lower diversity and gene richness of the gut microbiota have been consistently associated with increased adiposity, insulin resistance, low-

grade chronic inflammation, and alterations in lipid metabolism [9].

Several studies have shown that populations in industrialized countries exhibit lower microbial diversity compared with those maintaining traditional lifestyles, a phenomenon that has been linked to the increased prevalence of obesity and other metabolic disorders [9]. In individuals with obesity, a decrease in the abundance of genera such as *Akkermansia*, *Faecalibacterium*, *Oscillibacter*, and *Alistipes* has been described, while elevated levels of *Lactobacillus reuteri* have been associated with greater weight gain. In contrast, species such as *Bifidobacterium animalis*, *Methanobrevibacter smithii*, and others of the genus *Lactobacillus* predominate in lean individuals. Likewise, microorganisms such as *Eubacterium ventriosum* and *Roseburia intestinalis* have been associated with obesity, whereas *Oscillospira* spp. and *M. smithii* are more frequent in individuals with lower body mass index. Additionally, the abundance of *Bacteroides thetaiotaomicron*, a commensal involved in glutamate fermentation, is reduced in obese individuals, and its administration in murine models has demonstrated a protective effect against increased adiposity. Taken together, these findings suggest that modulation of the gut microbiota could constitute a promising strategy for body weight control [2, 9].

Factors such as urbanization, changes in dietary patterns, improved hygienic conditions, and especially the use of antibiotics have been proposed as contributors to the progressive loss of microbial diversity. Although a direct causal relationship has not yet been fully established, there is evidence that certain dietary interventions can improve microbial richness and, in parallel, favor metabolic parameters in individuals with overweight or obesity [9, 11].

From a functional perspective, the gut microbiota associated with obesity exhibits a greater capacity to extract energy from the diet. Studies conducted in germ-free murine models have

shown that colonization with microbiota from obese individuals increases body fat accumulation, even under similar dietary conditions, suggesting greater efficiency in lipid absorption and a promotion of weight gain [11].

Probiotics as a therapeutic strategy in overweight

Probiotics can positively influence the gut microbiota by modulating its composition and metabolic activity. Among their main effects is an increase in the production of beneficial metabolites, such as short-chain fatty acids (SCFAs), which contribute to strengthening the intestinal epithelial barrier and regulating inflammatory processes [10, 12].

Various probiotic strains have been investigated for their potential in the treatment of overweight and obesity. Among the most studied is *Lactobacillus gasseri*, which has been associated with reductions in adipose tissue and body mass index, as well as *Lactobacillus rhamnosus*, recognized for its anti-inflammatory effects and its ability to improve gut microbiota composition. Other species of the genus *Lactobacillus*, such as *L. acidophilus* and *L. plantarum*, frequently used in multistrain formulations, have shown beneficial effects on the intestinal barrier and various metabolic parameters. Within the genus *Bifidobacterium*, *B. animalis* subsp. *lactis* stands out for its clinical evidence, as it promotes short-chain fatty acid production, increases the abundance of *Akkermansia*, and improves insulin sensitivity. Likewise, strains such as *B. breve* and *Streptococcus thermophilus* have been shown to reduce weight gain in high-fat diet models, while *Akkermansiamuciniphila* has recently emerged as a microorganism of interest due to its effects on inflammation and glucose metabolism [12, 13]. Complementarily, both live and inactivated probiotics and postbiotics have been shown to modulate key metabolic pathways, promoting lipid oxidation, inhibiting lipogenesis, and improving insulin sensitivity, in addition to stimulating the production of beneficial

metabolites such as short-chain fatty acids, GLP-1, and bile acids. Even inactivated forms and pasteurized *A. muciniphila* have been shown to reduce fat accumulation and improve lipid profiles in obesity models [14].

In a review that included 23 randomized controlled trials, nearly half of the studies reported significant reductions in body mass index, body weight, or waist circumference, and more than 60% showed improvements in lipid profiles, inflammatory markers, and intestinal permeability parameters. Multistrain formulations, particularly in interventions of approximately 12 weeks, showed greater efficacy and were associated with positive changes in the gut microbiota, such as increased short-chain fatty acids and beneficial taxa such as *Akkermansia* and *Bifidobacterium* [12]. Consistently, another systematic review that analyzed 27 clinical trials found that most reported significant effects on body weight and other anthropometric parameters. In addition, the most recent evidence (2020–2021) reinforces these results, as six of seven studies published during this period showed significant reductions in weight, BMI, waist circumference, or body fat, mainly through multistrain formulations of *Lactobacillus* and *Bifidobacterium*, with interventions lasting 8 to 36 weeks. From a mechanistic perspective, studies based on network pharmacology approaches suggest that prebiotics, probiotics, and postbiotics can integratively modulate metabolic and signaling pathways involved in obesity, such as AMPK, PPAR, and PI3K/Akt, supporting the effects observed in preclinical and clinical studies [15]. Taken together, these findings support the use of probiotics as a complementary strategy in the management of overweight and obesity, dependent on the strain, dose, and duration of the intervention [13].

Prebiotics and their impact on the gut microbiota and body weight

Prebiotics constitute a promising strategy for the management of overweight and obesity, due to

their ability to modify the gut microbiota and correct states of dysbiosis associated with metabolic alterations [16]. Obesity is associated with intestinal dysbiosis characterized by a lower abundance of *Bacteroidetes* and *Actinobacteria* and a predominance of *Firmicutes*. In this context, prebiotics promote the proliferation of beneficial bacteria such as *Bifidobacterium* and the production of short-chain fatty acids, which are linked to improvements in energy metabolism and adiposity [17]. Intestinal bacteria ferment prebiotics, favoring the production of short-chain fatty acids such as acetate, propionate, and butyrate, which are key in the regulation of lipid and glucose metabolism, the improvement of insulin sensitivity, and the strengthening of the intestinal barrier. Likewise, these metabolites influence enteroendocrine function by promoting the release of hormones related to satiety and appetite control, such as GLP-1 and PYY [16].

Among the most investigated and clinically used prebiotics, inulin stands out. It is a soluble short- to medium-chain fructan (degree of polymerization, DP 2–60) present in foods such as chicory and Jerusalem artichoke. This compound reaches the colon almost undigested, where it is fermented mainly by *Bifidobacterium* and other short-chain fatty acid-producing bacteria [18, 19]. Clinical trials in pediatric populations with obesity have shown that inulin supplementation increases the alpha diversity of the microbiota, increases the abundance of beneficial genera such as *Bifidobacterium*, *Blautia*, and *Megasphaera*, and is associated with a reduction in BMI z-score and a higher percentage of fat-free mass [17, 18].

Similarly, fructooligosaccharides (FOS) or enriched oligofructose (OI) have shown reductions in BMI z-score and endotoxemia, mainly through the stimulation of bifidobacterial growth and increased production of short-chain fatty acids. Other prebiotics, such as galactooligosaccharides (GOS) derived from lactose, promote bifidobacterial colonization and

improve immune responses, especially in infants. Xylooligosaccharides (XOS) are associated with improvements in glucose and cholesterol metabolism, in addition to enhancing mineral absorption and immune function, while chitooligosaccharides (COS) exhibit anti-inflammatory properties and beneficial effects on bone health. Lactulose contributes to lowering intestinal pH, increases fecal biomass, and stimulates SCFA synthesis, and resistant starch promotes the growth of beneficial bacteria and has been linked to protective effects at the colonic level. Finally, polyphenols, including flavonoids, exert anti-inflammatory effects and promote a healthier microbial composition [20].

However, although several preclinical and clinical studies have shown beneficial effects on body weight and metabolic parameters, the results remain inconsistent, highlighting the need for more standardized clinical trials to more precisely define the type, dose, and optimal duration of prebiotic supplementation [16, 17].

Synbiotics: current evidence and therapeutic potential

Based on the consensus of the International Scientific Association for Probiotics and Prebiotics, synbiotics are classified as complementary and synergistic, a key distinction from both the formulation design perspective and the understanding of their biological effects [21, 22].

Complementary synbiotics combine probiotics and prebiotics with individually demonstrated benefits, representing a conceptually straightforward strategy to enhance host health. From a theoretical standpoint, this approach allows the integration of safe and well-studied microorganisms, mainly *Lactobacillus* and *Bifidobacterium*, together with digestion-resistant prebiotics that selectively promote their growth in the intestine. By simultaneously providing the microorganism and its substrate, complementary synbiotics may improve the stability and functionality of the gut microbiota

to a greater extent than probiotics or prebiotics administered separately [22]. In contrast, synergistic synbiotics combine beneficial microorganisms with substrates specifically designed to selectively stimulate their growth, allowing them to overcome common limitations of probiotics or prebiotics administered alone, such as competition with the resident microbiota and variability in host response. By promoting probiotic colonization and activity through a specific substrate, these formulations may generate more consistent and predictable effects on host health [22, 23].

Although this combination presents clear conceptual advantages, clinical evidence in obesity and metabolic disorders has shown inconsistent results, suggesting that the simple addition of components does not always translate into superior benefits and that more targeted design strategies are required to maximize efficacy [22]. This may be explained by the possibility that the prebiotic is consumed by a commensal intestinal microbe that competes with or inhibits the growth or biological activity of the administered probiotic, resulting in a null effect [21].

The benefit of synbiotics on body weight remains debatable, as different published studies and clinical trials show inconsistent results. Some clinical trials report improvements in lipid profiles and psychological status in obese patients but do not demonstrate significant changes in BMI, body weight, waist circumference, blood pressure, or glucose levels. Likewise, meta-analyses and studies using different combinations of probiotics and prebiotics have not demonstrated clear synergistic effects on body weight or fat mass. Overall, these findings suggest that optimized synbiotic formulations and additional clinical trials are required to confirm their metabolic and anti-obesity benefits [23, 24].

Limitations of the current evidence

The analyzed reviews present limitations that reduce the robustness of the evidence. The methodological quality of clinical trials is heterogeneous; some studies show low scores on the Jadad scale or lack prior registration, which increases the risk of publication bias. Likewise, there is marked variability in the probiotic strains used, the doses administered, and the duration of the interventions, making comparisons between studies difficult. In addition, in many trials probiotics, prebiotics, and synbiotics were evaluated in combination with hypocaloric diets or exercise programs, preventing the isolation of their specific effects [12, 13]. Furthermore, several of the proposed mechanisms are based on preclinical studies whose results are not always extrapolable to humans. Regarding synbiotic research, most studies use synbiotic formulations without independent control groups for probiotics and prebiotics, which limits the assessment of whether a true synergistic effect exists. This is compounded by the frequent use of suboptimal doses of prebiotics in commercial products, interindividual variability of the microbiome, and limited stratification of participants according to their microbial profile [21, 25]. Finally, the diversity of the studied populations, variable sample sizes, incomplete information on product composition, viability, stability, and safety, together with the lack of standardized protocols and long-term follow-up data, limit the reproducibility and clinical applicability of the results [12, 13].

Future perspectives

The available evidence indicates that prebiotics, probiotics, and synbiotics could play a relevant role as complementary therapies in the management of obesity and its comorbidities. However, their clinical application requires the development of more optimized formulations and the support of rigorous clinical trials that confirm their efficacy and safety [12, 14, 16]. In this context, next-generation probiotics (NGP) have emerged as one of the most promising strategies, as their identification through next-generation sequencing techniques and bioinformatic

analyses allows the precise selection of strains with specific mechanisms of action and well-defined safety profiles. Future perspectives are oriented toward the design of personalized therapies based on the individual microbiome profile, the application of synthetic biology tools and genetic editing for the development of strains with targeted therapeutic functions, and the implementation of advanced delivery systems that optimize their viability and clinical efficacy. Likewise, the harmonization of regulatory frameworks and the integration of NGP with prebiotics, postbiotics, or conventional treatments will be essential to facilitate their transition from research to clinical practice [26, 27].

Conclusions

Obesity is a multifactorial disease that represents one of the main challenges in current medical practice. In this context, prebiotics, probiotics, and synbiotics have emerged as complementary strategies with clinical support, since although the available evidence shows inconsistent results, it suggests an overall favorable trend of prebiotics, probiotics, and synbiotics on metabolically relevant parameters in obesity. Nevertheless, this heterogeneity highlights the need for better standardized clinical trials that allow a more precise definition of optimal doses, composition, and duration of these interventions.

Despite these limitations, the study of the effects of biotics on anthropometric parameters such as body mass index and waist circumference, as well as on metabolic variables related to insulin resistance, appears promising. These potential benefits go beyond aesthetic aspects and could contribute to a comprehensive approach to the current obesity pandemic. Likewise, advances in the understanding of the intestinal microbiome and in analytical technologies open the possibility of developing personalized medicine approaches based on individual microbiota characteristics.

Finally, the use of prebiotics, probiotics, and synbiotics also represents an area of interest in the management of childhood obesity, a population in which scientific evidence is still limited. In this regard, further studies specifically designed in children and adolescents are required to evaluate their long-term efficacy and safety. Until more robust evidence is available, these interventions should be considered as a complement to conventional obesity treatment and not as a substitute for established therapeutic strategies.

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