Chapter 06

Reduction of Body Fat and Alteration of Intestinal Microbiota with Probiotics and Prebiotics in Patients with Obesity and Overweight

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ABSTRACT

Obesity/overweight is caused by imbalanced energy between intake and expenditure of calories, leading to excessive fat accumulation that impairs healthy. As a lifestyle illness, excess body fat is a determinant for numerous chronic conditions and is linked to significant morbidity and mortality. Scientific evidence has in past decades established a connection between the intestinal microbiota and obesity as individuals with obese conditions have shown altered gut microenvironment that contributes to mild forms of inflammation. Since gut dysbiosis promotes overweight and obesity, prebiotic and probiotic therapy has emerged as a potent therapeutic strategy to normalize the intestinal microbiota composition. In this chapter, the mechanisms of select prebiotics and probiotics have been investigated as part of understanding how they help in treating obesity. By enhancing beneficial bacteria and reducing the composition of pathogenic microorganisms, prebiotic/probiotic therapy has been shown to produce anti-inflammatory effects that is crucial in reducing body fat in patients with obesity. It has also been established that prebiotics and probiotics are involved in the expression of hunger-reducing hormones and promotes satiety that is essential in reducing energy intake.

KEYWORDS
Probiotics, prebiotics, Gut-brain axis, Metabolism, Short-chain fatty acids

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INTRODUCTION

According to the World Health Organization (WHO), obesity is an excessive fat buildup capable of impairing health, fundamentally caused by an energy imbalance between caloric consumption and caloric expenditure (Safaei et al., 2021). Obesity and overweight remain a major public health concern globally and represent the main lifestyle illnesses that contribute to further health concerns and are implicated in numerous chronic illnesses like cardiovascular diseases, malignancies, diabetes, and metabolic syndrome. Overweight and obesity rates continue to rise worldwide and are linked with increased chronic morbidity and mortality. The World Obesity Atlas 2023 reports that in 2020, approximately over 2.6 billion people were affected by overweight and obesity globally, and this figure is projected to reach 4 billion by 2035 and representing an increase from 38% to over 50% of the world's population (Lobstein et al., 2023). Figures from the WHO also estimated about 2 billion and 600 million adults with overweight and obesity in 2014 respectively (Simo et al., 2021).

The annual mortality figures show that in 2019, there were an estimated 5 million obesity-related deaths globally, with the age-standardized death rate (ASDR) approximated at 62.59 per 100,000 population (Chong et al., 2023). Despite public health efforts to manage overweight and obesity, the disorders continue to rise and contribute to excess morbidity and mortality. The complex, multifactorial, and relapsing nature of these chronic conditions and associated significant implications for the health of individuals have led scientists to consider novel therapies with the potential to ameliorate the complications (Guerra et al., 2021). Obesity and overweight are significantly linked to premature death and chronic conditions that compromise life expectancy and overall quality of life for patients and the goal of therapy is to improve outcomes for individuals. There is urgency to fully comprehend mediating mechanisms of overweight and obesity since its worldwide prevalence continues to rise as it would inform the discovery of novel targets for safe and effective treatments and to identify biomarkers for tracking the disorder and the efficacy of the strategies to reduce weight (Clark et al., 2023).

Gut Microbiota Role in Obesity

Scientific knowledge of the intestinal microbiome, as well as its intricate relationship to pathophysiology, has grown substantially in recent years. Obesity alters the intestinal microenvironment required for the survival of diverse viral species than those identified in individuals without obesity, leading to susceptibility to detrimental variants capable of causing more serious disorders (Lin and Li, 2021). The gut flora variations alter the weight and metabolism of the host and any microbial population imbalances or 'dysbiosis' results in various diseases. Animal studies show that host-microbiota alteration can lead to mild inflammatory responses marked by moderate increases in proinflammatory gene expression associated with metabolic syndrome, such a Toll-like receptor (TLR) 5, TLR2, and NOD-like receptor family pyrin domain containing 6 genes (NLRP6) (Chassaing et al., 2017). The results of the loss of genes include changed microbiota combination, low levels of inflammation, and a metabolic syndrome-like composition transferrable via fecal transplant. A healthy gut microbiota maintains the metabolism and energy balance of the body by releasing health-beneficial products like neurotoxins, immunotoxins, and carcinogens which infiltrate the blood and directly modulate gene expression and influence the immunity and metabolic processes in humans (Liu et al., 2021). Any imbalance results in metabolic conditions and increased central appetite that cause obesity.

Further animal studies demonstrate the major role gut microbes play in extracting energy from food through diverse mechanisms. Davis (2016) underline how the host cannot digest many polycarbohydrates from plants and starches, and it is the gut microbes that metabolize them to short chain fatty acids (SCFA), such as butyrate, acetate, and propionate that serve as primary energy sources for colonic epithelium and for processes like lipogenesis and glucogenesis in the liver. Germ-free rat models have been used to establish the link between the intestinal bacteria and adiposity, with studies showing conventionally raised mice that ingest less food exhibited 40% higher body fat content and 47% higher gonadal fat content compared with axenic mice. Transplanting the distal colon microorganisms from the normal mice into their gnotobiotic counterparts also resulted in increased body fat by 60% within 2 weeks without food intake increases or obvious variations in energy expenditure. The findings confirmed the role of intestinal bacteria in affecting the phenotype that is linked to host adiposity. Sarmiento-Andrade et al. (2022) confirmed certain groups of bacteria efficiently absorb nutrients and energy and rapidly metabolize nutrients to boost calories absorbed and increase BMI, with examples showing overgrowth of the phylum *Firmicutes* bacteria and *Bacteroidetes* decrease characterize obese mice and human intestines. Through shotgun sequencing, the profile and composition of intestinal microbiota and their effects on human metabolism has been identified. Based on several studies, bacteria number variations in individuals with obesity versus normal weight individuals has been documented, as shown in how gestational obesity alters the gut bacteria where *Bacteroides* increased levels in the third trimester correlates with twice the susceptibility to neonatal obesity (Gorczyca et al., 2022).

Marvasti et al. (2020) study of 50 normal and 50 obese subjects investigated the relative abundance of gut microbiota and their correlative with the body mass index (BMI) of individuals. They examined the ratio of *Firmicutes* and *Bacteroidets* (F/B), which make up the most frequent phyla of gut microbiota, as well as anaerobic intestinal commensal bacteria such as *F. prausnitzii*, *A. muciniphila*, *Bifido-bacterium*, *Roseburia*, and *Prevotella*. The findings showed the F/B ratio was markedly elevated in subjects with obesity versus the control group, and *Firmicutes* abundance significantly increased while *Bacteroidetes* reduced in obese and control groups respectively. *A. muciniphila* relative abundance also significantly reduced in parallel with BMI increase in obese vs. normal weight, and *Bifidobacterium* relative abundance reduced in the obese group. Conversely, there was substantial elevation of *F. prausnitzii* relative abundance in the subjects with adiposity compared to their counterparts with normal weight.

Overview of Probiotics and Prebiotics

Owing to the role of gut dysbiosis in promoting increased weight and adiposity through promoting inflammation, reduced metabolism of fat and cholesterol, and decreased insulin sensitivity, microbial-level intervention with probiotics for gut ecological dysbiosis has been shown to alter gut flora composition. Several novel therapies like prebiotics and probiotics potentially normalize the intestinal flora (Cai et al., 2023). Biomedical research studies of probiotic species have examined the lactic acid bacteria group whereby treatment of subjects with *Lactobacillus* and *Bifidobacterium* have shown to significantly alter the gut microbiota composition (Azad et al., 2018). Probiotics also have effects on appetite and energy homeostasis by increasing SCFA production, with some *Bifidobacterium* spp. and *Lactobacillus* spp. helping the production of prohealthy conjugated linoleic acid (CLA) responsible for body weight control through metabolizing energy and aiding

lipolysis (Wiciński et al., 2020). Prebiotics as well have been considered for managing obesity. The prebiotics that are commonly used are carbohydrate-based, with lactose-produced fructans and Galacto-oligosaccharides (GOS) researched widely. Mechanism of prebiotics in metabolic improvement where they underscore their role in modulating the enteroendocrine function representing their systematic effects on lipid and glucose homeostasis and in controlling satiety. Prebiotic supplementation induces heightened glucagon like peptide-1 (GLP-1) and anorexigenic peptide YY (PYY) circulation induced by SCFA, as well inducing the proliferation of commensal bacteria to alter mucosal architecture (Wang et al., 2023). Based on this background, this chapter sets out to evaluate prebiotics and probiotics anti-adiposity action and altering gut bacteria in obese and overweight individuals.

Alteration of Intestinal Microbiota

The intestinal microflora of obese subjects potentially promotes more efficient dietary energy extraction and storage as opposed to lean individuals. There is further evidence from research showing that obesogenic intestinal microbiota is associated with intestinal inflammation as proinflammatory tumor necrosis factor-a (TNF-α) messenger RNA levels in the ileum are strongly correlated with increased weight, fat mass, and the levels of plasma insulin and glucose when exposed to a high-fat diet (HFD) (Klancic and Reimer, 2019). Hence, enteric bacteria are essential for triggering intestinal inflammation with an HFD as TNF-α mRNA levels are only upregulated in conventionally raised animals as opposed to germ-free (GF) animals (Malesza et al., 2021). The mechanisms of prebiotics and probiotics alteration of intestinal microbiota in obesity management is a crucial focus of research. Important considerations should be made for how prebiotic therapy acted on *Bifidobacterium* spp. deficiency and promoted SCFA production by the obesogenic intestinal bacteria (Dahiya et al., 2017).

Enhancement of Beneficial Bacteria

Salazar et al. (2015) investigated 30 obese women to determine how inulin-type fructans (ITF) change gut microbiota composition and activity with the goal of determining fecal SFCA concentration disparities and exploring the correlation of *Bifidobacterium*, SCFA, and host metabolism biological markers. The subjects were categorized in two groups that received 16 g of ITF or maltodextrin (placebo group) over 3 months. According to the findings, the post-intervention period showed that the obese women receiving ITF had significantly increased *Bifidobacterium* genus as well as certain species genus as *B. adolescentis*, *B. longum*, and *B. pseudocatenulatum*. Further, a Spearman correlation analysis revealed an inverse association of the alterations in *B. bifidum* and *B. adolescentis* with the percentage of fat mass. The fecal SCFA profiles also indicated that acetate, propionate, and total SCFA markedly reduced after prebiotic treatment. Overall, the findings confirmed that ITF selectively modulated the composition of the intestinal microbiome as exhibited by the *Bifidobacterium* spp. which significantly increased. Accordingly, prebiotic treatment in obese individuals selectively enhance beneficial bacteria mainly identified in the adult intestinal flora (Cerdó et al., 2019). It was also found that *Bifidobacterium* had a negative correlation with anthropometric/biological parameters such as levels of serum lipopolysaccharides (LPS), meaning prebiotics potentially improve metabolic endotoxemia in obesity as they reduce gut permeability. The reduced fecal SCFA further indicated prebiotic treatment potentially reduced adiposity in obese individuals.

Table 1: Mechanisms of Select Prebiotics and Probiotics in Gut Alteration and Body Fat Reduction

Gut Alteration	Prebiotic	Probiotic	References
Enhancing beneficial bacteria	Inulin-type fructans		(Salazar et al., 2015)
		Lactobacillus salivarius, *Lactobacillus rhamnosus*, *Bifidobacterium animalis*	(Chen et al., 2022)
Gut barrier regulation		*Akkermansia, Bifidobacterium, Lactobacillus, Leuconostoc*	(Fijan et al., 2023; Everard et al., 2013)
		Lactobacillus plantarum bacteriocin plantaricin (PlnEF)	(Heeney et al., 2018)
Short-chain fatty acid production	Inulin and GOS		(Holmes et al., 2020)
	VSL#3		(Yadav et al., 2013)
Reduction of Body Fat			
Satiety	Inulin-type fructans		(Hamilton and Bomhof, 2023)
	Polydextrose		(Olli et al., 2015; Daud et al., 2014)

Additional research has been done examining the reshaping of obesity-related gut dysbiosis using multi-strain probiotic supplementation as well as its effects on lipid metabolism in managing obesity. In a study by Chen et al. (2022), they treated 82 overweight and obese children with three strains of supplementary prebiotics: *Lactobacillus salivarius* AP-32, *L. rhamnosus* bv-77, and *Bifidobacterium animalis* CP-9. The analysis showed that probiotic supplementation significantly reduced BMI, total cholesterol (TC), low-density lipoprotein (LDL), leptin, and TNF-a in the subjects and there was an alteration of the gut microbiota composition, such as significant increase of the beneficial bacteria *B. animalis* after prebiotic administration. Investigations of gut microbial communities after treating obese diabetic mice with prebiotics have also reported increased *Bifidobacterium* spp. and the *Eubacterium*

rectale/Clostridium coccoides groups while reducing Firmicutes and *Roseburia* spp. (Everard et al., 2011). The gut bacterial populations also showed significant phylum-wide shift where Bacteroides increased while Firmicutes decreased after prebiotic treatment, and Actinobacteria and Proteobacteria also increased. These gut microbiota composition alterations were associated with significantly reduced levels of fasting glycemia and improved glucose tolerance. When treated with dietary α-cyclodextrin prebiotics, HFD-fed obese mice exhibited increased total number of bacteria: *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*, which were reduced in gut microbiota after feeding the HFD (Nihei et al., 2018).

Regulating Gut Barrier Function

Excessive adiposity correlates with gut permeability as exhibited by the loss of epithelial integrity causing upregulated LPS infiltration and the circulation of other inflammation agents (Di Vincenzo et al., 2024). The shift if gut microbiome adversely affect intestinal permeability and probiotic intervention may attenuate this negative impact by promoting beneficial bacteria. Probiotics role in restoring gut permeability after the effects of excess adiposity. They noted that dysbiosis, inflammatory cytokines, immune cell activation, and enterocyte health alter intestinal permeability (DiMattia et al., 2023). Pro-inflammatory agents like interferon-γ (IFN- γ) and TNF-α temporarily compromised the gut barrier integrity through tight junction (TJ) protein rearrangement in the enterocyte membrane via myosin light chain kinase (MLCK) gene activation (Al-Sadi et al., 2016). Evidence shows that probiotic supplementation ameliorates increased intestinal permeability by potentially promoting the production of TJ protein, increasing mucus secretion and the metabolism of ethanolamine, and producing butyrate that enhances enterocyte health.

Heeney et al. (2018) also assessed the ability of *Lactobacillus plantarum* bacteriocin plantaricin EF (PlnEF) to maintain gut barrier integrity when administered to a mouse model of diet-induced obesity. PlnEF, a two-peptide bacteriocin, has been confirmed to induce cell membrane disruption in bacteria. The mice exhibited significantly increased production of the TJ protein Zonula Occludens-1 (ZO-1) when fed with *L. plantarum* with an HFD, and the transcript levels of ZO-1 mRNA were also elevated in whole ileal tissues. Further, PlnEF peptides prevented IFN-γ and TNF-α induced reductions in transepithelial resistance. Overall, LP probiotics fortified TJ between intestinal epithelial cells as PlnEF peptides sufficiently prevented cytokine-induced disruptions to epithelia barrier integrity. *Akkermansia muciniphila* probiotic has also been investigated for safeguarding gut barrier integrity when a prebiotic like oligofructose is administered (Everard et al., 2013). The evidence showed that *A. muciniphila* normalized metabolic endotoxemia, adiposity, and the CD11c adipose tissue marker. The enhancement of gut barrier function by *A. muciniphila* was linked with epithelia signaling mechanisms by acting on the intestinal mucosa that secretes antimicrobial peptides for innate immunity to maintain the gut barrier.

Production of Short-Chain Fatty Acids

SCFAs are carboxylic acids produced when microorganisms ferment various dietary compounds, majorly fibers. Propionate (Prop), butyrate (Bu), and acetate (Ac) are the most extensively studied as they are produced in the colon (Ilyés et al., 2022). Studies have shown that microbial action of fermenting indigestible dietary carbohydrates to produce SCFAs has proven to be critical in protecting against pediatric obesity and metabolic syndrome. Holmes et al. (2020) conducted an *in vitro* study to examine fecal microbiota production of SCFAs from 17 children with obesity treated with over-the counter (OTC) prebiotic supplements. From the assessment of diverse prebiotic supplements like inulin and GOS, it was proven that administration showed efficacy in increasing the total SCFAs. SCFA production after administering prebiotics also correlated with the relative abundance of beneficial bacterial genera, including *Akkermansia*, *Methanobrevibacter*, and *Lactobbacillus*.

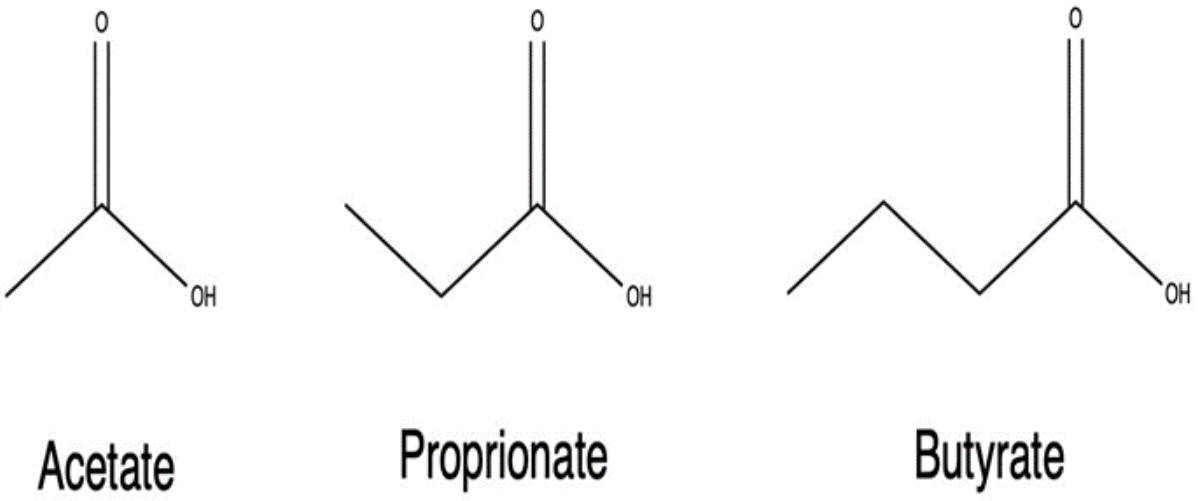

Fig. 1: Short-Chain Fatty Acid Substrates

Yadav et al. (2013) investigated VSL#3 probiotic beneficial metabolic effects when administered to HFD mice to counter obesity and diabetes. Their findings showed that probiotic supplementation reduced the gain in weight corresponding to feeding with a low-fat diet (LFD) while further decreasing fat depot size, fat mass, and adipocyte size without alteration in lean mass. The mechanism of enhancing metabolism in obesity/overweight was linked to significant decrease in the circulating levels of IL-6, TNF-a, and MCP-1, further resulting in decreased food intake, body weight gain, and enhanced glucose homeostasis. The enhanced metabolic function was also exhibited by the decreased insulin, triglycerides, free fatty acids (FFAs), and resistin while adiponectin was elevated and anti-inflammation improved. It was additionally noted that VSL#3 probiotics promoted GLP-1 secretion, mediated by butyrate, from the intestinal L-cells as it modified gut microbiota and altered the level of gut hormones involved in food intake regulation. GLP-1 is a hunger reducing hormone, which was significantly increased with probiotic supplementation. The process causing the upregulation of GLP-1 was the marked decrease in Firmicutes and an upsurge in Bacteriodetes and Bifidobacteria (Cabral et al.,2021). Gut flora alterations were linked to the increased levels of SCFA butyrate as the gut flora composition alterations contributed to the transformed gut metabolic environment.

Prebiotic and Probiotic Reduction of Body Fat

A. Stimulating the Expression of Satiety Hormones

Scientists have documented the role of inulin-type fructans (ITFs) in stimulating anorectic gut hormones release that act to reduce appetite and energy intake. In a randomized crossover study of ITFs mechanisms of inducing satiety, Hamilton and Bomhof (2023) administered sweetened milk (SM) or sweetened milk plus oligofructose-enriched inulin (OI) to participants and recorded the perceived measures of hunger after intervention. In this human trial involving 14 participants between the ages of 18 and 50 years, the subjects exhibited increased GLP-1 and PYY concentrations post-treatment. The appetite perceptions also showed that SM+OI reduced overall hunger relative to SM, and a tendency towards reduced satisfaction with prebiotic supplementation. There was further increased flatulence for SM+OI compared to SM, and increased abdominal discomfort was marked with SM+OI. Hence, the study reported the acute effect of OI after exercise as long-term physical activity is usually related to increased hunger and energy compensation. Overall, OI prebiotics elevated GLP-1 and PYY while reducing acyl-gherin post-exercise, with evidence of OI fermentative activity in the gut.

In another study, Olli et al. (2015) investigated the polydextrose (PDX) prebiotic for its postprandial effects on satiety hormone responses in obese participants with subjective feelings of appetite. The trial involved 18 subjects who consumed a high-fat meal with or without PDX (15 g) assessed postprandial concentrations of peptides ghrelin, cholecystokinin (CCK), GLP-1, and PYY, as well as SCFAs and lactic acid. The subjects exhibited elevated levels of GLP-1 release into the plasma after PDX consumption compared to the placebo, while the rest of the peptides did not show statistically different variations. Lactic acid concentrations significantly decreased post-treatment, and acetic acid marginally reduced. PDX significantly reduced hunger during the satiety period (40.4%), and marginally enhanced satisfaction by 22.5% compared to the placebo. Overall, the downregulated concentrations of postprandial plasma lactate after PDX in obesity implied that prebiotics have a lipolytic effect after consuming an HFD. The reduced food intake due to prebiotic promotion of satiety translates too reduced body fat for individuals and improved obesity outcomes. Daud et al. (2014) investigate 22 healthy overweight and obese participants, oligofructose prebiotics reduced hunger and motivation to eat and decrease energy intake (EI). Slight reductions in intrahepatocellular lipids (IHCL) and glutamyl transferase gamma (γGT) suggested how prebiotics protected against fat accumulation in the liver. More trials can be done to determine the fat-reducing effects of prebiotics and probiotics in obesity.

B. Gut-Brain Axis Modulation

Gut microbiota interacts with diverse organs such as the brain as they might target the brain directly through vagal stimulation or indirectly via immune-neuroendocrine mechanisms (Asadi et al., 2022). Research supports the bidirectional signaling within the gut-brain axis (GBA) in obesity pathophysiology facilitated by mechanisms like the metabolic, endocrine, neural, and immune system. The role of intestinal microbiota in obesity is also linked with regulating adiposity, homeostasis and energy balance, and central appetite and food reward signaling (Rautmann and de La Serre, 2021). The nervous system is instrumental among the probiotic pathways in lipid metabolism regulation, with SCFAs and secondary bile acids induced by probiotic metabolism triggering the intestinal-brain axis by prompting intestinal hormone production. The hypothalamus activation by gut hormones like GLP-1 and PYY alters the intake and expenditure of energy to achieve metabolism balance (Song et al., 2023). Additionally, leptin hormones secreted by the adipose tissue affects appetite when probiotics are administered as the hormones synthesize fat by preventing fatty acid synthase expression and suppressing appetite by stimulating hypothalamic receptors, which also alter the consumption of energy, and enhancing nervous system lipid metabolism.

Wang et al. (2020) have reported on the effects of intestinal bacteria in neuroendocrine modulating carbohydrate and lipid metabolism, specifically focused on the microbiota-gut-brain-liver axis. They noted that intestinal microbiota affected intestinal movement, metabolism, immune responses, and behaviors through the mediation of enteric neurons. SCFAs, such as acetate, propionate, and butyrate activate the vagal afferent pathway and suppress consumption of food. The intestinal LPS influence the vagal pathway and instigates inflammatory responses and obesity, with TLR4 receptor expressed on the afferent fibers capable of sensing LPS and transferring the signal to the brain. Prebiotic and probiotics

induce gut peptides that act through the vagal and non-vagal neuronal relays that trigger the gut-to-brain signaling pathways to reduce the ingestion of food and increase energy expenditure (Bauer et al., 2015).

Conclusion

Obesity and overweight remain a significant public health concern worldwide and is one of the major lifestyle diseases contributing to further health concerns and numerous chronic illnesses. The burden of disease has made it an imperative to consider the mediating mechanisms of obesity as this would inform novel therapies after the discovery of new targets. The association between the gut microbiome and obesity has been documented in research, which makes prebiotics and probiotics potential therapeutic candidates for reducing body fat and altering intestinal microbiota. SCFA production and elevated levels of GLP-1 and PYY peptides, as well as proliferation of beneficial bacteria are likely mechanisms through which prebiotics and probiotics modulate obesity outcomes. Future research focused on the metabolic effects of different strains of prebiotics and probiotics can be considered, as well as combination therapies.

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