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REVIEW ARTICLE

The development of probiotics therapy to obesity: a therapy that has gained considerable momentum

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Abstract

Obesity is a growing epidemic worldwide. The most frequent cause leading to the development of obesity is an imbalance between energy intake and energy expenditure. The gut microbiota is an environmental factor involved in obesity and metabolic disorders which reveals that obese animal and human subjects present alterations in the composition of the gut microbiota compared to their lean counterparts. Furthermore, evidence has so far demonstrated that the gut microbiota, which influences whole-body metabolism, by affecting energy balance, but also inflammation and gut barrier function, integrates peripheral and central food intake regulatory signals, thereby altering body weight. At the same time, these data suggest that species of intestinal commensal bacteria may play either a pathogenic or a protective role in the development of obesity. Though still a relatively nascent field of research, evidence to date suggests that manipulating the gut microbiome may represent effective treatment for the prevention or management of obesity. Various studies have described the beneficial effects of specific bacteria on the characteristics of obesity. However, the available data in this field remain limited and the relevant scientific work has only recently begun. This review aims to summarize the notable advances and contributions in the field that may prove useful for identifying probiotics that target obesity and its related disorders.

Keywords Gut microbiota · Obesity · Probiotics · Treatment · Weight loss

Introduction

Obesity is a metabolic disorder today afflicting people globally which arises as a result of unhealthy eating behaviors and poor diet quality that negatively impacts the manner in which the body controls energy intake, consumption, and storage. The prevalence of obesity has been continuously on the rise worldwide over the last few decades. At present, there are more than 500 million adult humans who are overweight [body mass index (BMI) of 25.0–29.9 kg/m^2] and 250 million that are obese (BMI ≥ 30 kg/m^2) [1]; this accelerating epidemic is now threatening numerous countries. At the same time, obesity-related disorders are also gradually increasing globally. Aside from poor diet choices and genetics, there are many other factors thought to play a role in the emergence of obesity and the metabolic syndrome [2]. Recent human and animal studies have shown the intestinal microbiota to be a potential determinant of obesity [3, 4] given that it plays an important role in the physiologic regulation of metabolic functions in the host [3, 5]. Moreover, certain gut microbial strains have been shown to inhibit or attenuate immune responses associated with chronic inflammation in experimental models. In the meantime, emerging evidence reveals that species of intestinal commensal bacteria may play either a pathogenic or a protective role in the development of obesity. Though still a relatively nascent field of research, evidence to date suggests that the gut microbiome may represent a fertile target for prevention or management of obesity. As a result, the development of therapeutics based on gut microbiota modulation has gained

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considerable momentum. Probiotics can bring about prevention, improvement, and management of obesity by influencing the abundance and functions of several of the intestinal microbiota and regulating several pathogenic alterations [6]. However, the available data in this field remain limited and the relevant scientific work has only just begun. More specifically, recently, new technologies have enabled an attempt at carrying out a systematic intestinal bacterial flora study capable of providing more concrete information about its composition and its pathological variance. This review summarizes cutting-edge research on probiotics treatment for obesity, existing issues in probiotics treatment, the future of probiotics, and microbial therapeutics.

Intestinal microflora

In humans, the gut microbiota is a complex and dynamic ecosystem that has coevolved with its host and represents approximately 1 kg of our body weight [7]. Intestinal microflora consists of approximately 10^4 microbial cells (i.e., a number nearly ten times larger than that of human cells in an adult) and contains six to ten major phylum and three thousand to five thousand species. [6, 8–10]. It is now recognized that the communities of microbes in our gut function as an organ with many metabolic, immunologic, and endocrine-like actions that influence human health [11–13]. The gastrointestinal tract of a fetus is sterile until birth [14]. Following vaginal delivery, bacteria from the mother and the environment rapidly colonize the intestinal tract of an infant [14]. Multiple other factors, such as mode of birth, type of feeding, and hygiene measures, have also been shown to play a role in the composition of gut microbiota [13, 15, 16]. This microbiota changes during the first years of life, under the control of different factors including developmental changes in the gut environment, the genotype, and introduction of solid foods, and a more complex and stable community, close to the adult microbiota, is established at approximately 3 years of age [13, 15]. In adults, the gut microbiota remains remarkably constant slightly fluctuating around an individual core of stable colonizers [17]. Alterations then occur in old age, these brought about by changes in digestive physiology and diet [18–21]. The microbiome endows the host with diverse and powerful health benefits. The vast array of enzymatic reactions, often distinct but essential to those encoded by the human genome, plays a role in host homeostasis, metabolism, synthesis of micronutrients, detoxification, epithelial development, and immune function [22]. Besides its function in metabolism, the gut is a crucial immune organ and contains the biggest lymphoid tissue mass in the human body [23], which might not be surprising considering the intestinal bacterial load. Thus, in addition to contributing to host metabolism, the gut microbiota provides critical signals for the development of host immunity. Hence, gut microbes are crucial for the maintenance of human health and to ward off disease. Disruptions of this intricate balance between host and commensal microbes can therefore exert dramatic effects on human health and disease.

The role of intestinal microflora in obesity

It must be stressed, however, that the balance between health and commensal microbes is a two-way street: just as host conditions influence microbiota, the presence and properties of microbiota have profound effects on host health and susceptibility to, among other disorders, to obesity [24]. The recognition that gut microbiota is important in the regulation of energy extraction from the diet [25] came from the observation that germ-free mice (raised in the absence of microorganisms) were leaner than mice with a normal gut microbiota, even though mice with a normal gut microbiota were fed 30% fewer calories [26]. Moreover, when germ-free mice were transplanted with gut microbiota harvested from mice with normal gut microbiota, they gained 60% body fat and became insulin-resistant, despite lower food intake [26]. Subsequent studies also demonstrated the role of gut microbiota in regulating energy storage as triglyceride [26, 27] and energy expenditure from fatty acid oxidation [27]. Studies in both mice and humans found that obesity was accompanied by an altered gut microbiota composition. Obesity has further been shown to be associated with altered gut microbial composition in human subjects [28, 29] and mice [30]. Specifically, the guts of obese human subjects were shown to have reduced numbers of *Bacteroidetes* and increased numbers of *Firmicutes* compared with those of their lean counterparts [28]. In a few obese human subjects, an increased proportion of fecal *Bacteroidetes* was found to parallel weight loss on a hypocaloric diet during a 1-year intervention trial [28]. Compared with lean mice, genetically obese mice (leptin-deficient mice) have reduced numbers of *Bacteroidetes* and increased numbers of *Firmicutes* isolated from the distal gut [30]. Recently, Le et al. found that the composition of gut microbiota changed significantly in subjects with obesity. The relative abundance of *Proteobacteria* and *Bacteroidetes* markedly increased. Furthermore, the relative abundance of pathogens such *Campylobacter* and *Shigella* remarkably increased, while the relative abundance of *Akkermansia muciniphila*, which is a species of anti-inflammatory bacteria, significantly decreased. These changes in intestinal microflora can decrease intestinal barrier integrity and increase mucus degradation and oxidative stress by reducing the production of butyrate. [31] After dietary interventions, an increase in the abundance of *Bacteroides fragilis*, *Clostridium leptum*, and *Bifidobacterium catenulatum* and a decrease in the abundance of *Clostridium coccoides*, *Lactobacillus*, and *Bifidobacterium* are notably related to

significant weight loss, regardless of total food intake [31, 32]. Thus, changes in the microbiota play a crucial role in ensuring the efficacy of obesity treatments. Taken together, current evidence supports a role for gut microbiota in the pathogenesis of diet-induced obesity and its related metabolic disorders, which might be reversible with diet and/or gut microbiota manipulation.

Probiotics therapy to obesity

By gaining a better understanding of the gut microbiota as an integral part of our physiology, we may eventually unlock its potential as a diagnostic marker for obesity. We are also only beginning to define the factors needed to implement an effective strategy for manipulating the human gut microbiota and optimizing its performance to improve and manage obesity. Therapeutic interventions with probiotics may offer novel treatments for obesity. Probiotics are nonpathogenic living microorganisms which, when administered in adequate amounts, have been shown to confer health benefits to the host. Accordingly, a great many studies have demonstrated that modulating the gut microbiota may be an effective strategy for the improvement and management of obesity. Meanwhile, the therapeutic effects of probiotics on obesity have also been confirmed in animal and humans.

Experimental studies

Convincing evidence from animal studies suggests that probiotic administration may reduce, at least in part, the amount of weight gained in response to a high-fat diet (HFD) (Table 1). At present, most of the research concerns the use of *Lactobacillus* spp. to treat obesity. In 2006, Lee et al. revealed that the administration of probiotic *Lactobacillus rhamnosus* PL60 in diet-induced obese mice resulted in significant body weight loss with a decrease in white adipose tissue mass, although no effect on energy intake was observed. Uncoupling protein-2 expression increased, whereas the expression of fatty acid synthase and serum leptin levels decreased in adipose tissue. The investigators attributed the observed anti-obesity effects to the production of trans-10, cis-12-conjugated linoleic acid (CLA) by the probiotic bacteria [33]. Similarly, another study also revealed that *L. plantarum* PL62 produced CLA and was found to decrease body weight and epididymal, inguinal, mesenteric, and perirenal adipose tissue masses. Leptin levels differed non-significantly, while blood glucose was significantly lowered in the probiotic-treated mice [34]. Park et al. [35] also found that *L. plantarum* Q180 supplement led to a significant reduction of body weight gain, levels of triglyceride and leptin, and epididymal fat weight in HFD mice. Similarly, the incorporation of *L. plantarum* DSM 15313 in the diets of dams (a high-energy-dense diet) decreased body weight gain, retroperitoneal adipose tissue, and leptin levels in pups (results recorded 6 months after birth) [36]. Furthermore, following *L. plantarum* treatment, the viable count of *Enterobacteriaceae* significantly decreased and *Enterobacteriaceae* correlated positively with body weight. In another study, male C57BL/6J mice maintained on a high-fat diet containing probiotic *L. plantarum* LG42 showed lower body weight, with a significant reduction in epididymal and back fat. Serum and hepatic triglyceride, serum insulin, and leptin levels significantly decreased. Meanwhile, the hepatic mRNA expression of peroxisome proliferator-activated receptor α (PPARα) and carnitine palmitoyltransferase-I (CPT-I) were significantly increased, whereas the level of acetyl CoA carboxylase (ACC), sterol regulatory element-binding protein-1 (SREBP-1), and liver X receptor a (LXRα) were significantly decreased. Additionally, the expression of peroxisome proliferator-activated receptor γ (PPARγ) was reduced in epididymal adipose tissue, resulting in inhibition of genes regulated by PPARγ [37]. Likewise, the oral administration of *L. plantarum* TN8 was, on the one hand, noted to induce an increase in anti-inflammatory interleukin-10 (IL-10) cytokine secretion rates and a decrease in pro-inflammatory interleukin-12 (IL-12), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) cytokine production. On the other hand, it improved the hepatic and urinary functions of obese rats by inducing significant decreases in alanine amino transferase (ALAT), gamma glutamyl transferase (GGT), plasmatic triglycerides, total cholesterol concentrations, creatinine, urea, and body weight in diet-induced obese mice [38]. Based on these results, female C57BL/6 mice were fed a high-fat diet and intragastrically administered *L. plantarum* strain No. 14 (LP14) for 11 weeks. LP14 administration significantly reduced body weight gain and mean adipocyte size and tended to reduce white adipose tissue weight and serum total cholesterol and leptin concentrations: these data suggested that LP14 may exert a beneficial effect on the onset of diet-induced obesity by reducing the cell size of white adipose tissues [39]. *Lactobacillus rhamnosus* GG (LGG) as a probiotic bacterial strain has been used for the treatment for many diseases. Some studies also found that *L. rhamnosus* GG additionally has anti-obesity properties. LGG-treated mice showed attenuated weight gain and enhanced insulin sensitivity in the high-fat diet group, while it reduced lipid accumulation by stimulating adiponectin secretion and consequent activation of AMP-activated protein kinase (AMPK), a key enzyme that controls cellular energy status [40]. Ji et al. [41] also showed that LGG and *L. sakei* NR28 resulted in a significant reduction of epididymal fat mass as well as of obesity-related biomarkers like acetyl CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase-1 in the liver. The total number and ratio of the microbial groups, i.e., *Firmicutes*, *Bacteroidetes*,

Table 1 Changes in microbiota composition associated with obesity and probiotics therapeutic strategies

Models	Disease	Implicated microbiota	New therapeutic strategies	Implicated microbiota	Reference
Mice	Obesity	NO	*Lactobacillus rhamnosus* PL60	NO	[33]
Mice	Obesity	NO	*L. rhamnosus* PL60	NO	[34]
Mice	Obesity	NO	*L. plantarum* Q180	NO	[35]
Mice	Obesity	*Enterobacteri-aceae*↑	*L. plantarum* DSM 15313	*Enterobacteriaceae*↓	[36]
Mice	Obesity	NO	*L. plantarum* LG42	NO	[37]
Mice	Obesity	NO	*L. plantarum* TN8	NO	[38]
Mice	Obesity	NO	*L. plantarum* strain No. 14	NO	[39]
Mice	Obesity	NO	*L. rhamnosus* GG	NO	[40]
Mice	Obesity	NO	*L. rhamnosus* GG, *L. sakei* NR28	*Firmicutes*:*Bacteroidetes*↓	[41]
Mice	Obesity	NO	*L. gasseri* SBT2055	NO	[42]
Mice	Obesity	NO	*L. curvatus* HY7601, *L. plantarum* KY1032	NO	[43]
Mice	Obesity	NO	*L. curvatus* HY7601, *L. plantarum* KY1032	NO	[44]
Mice	Obesity	NO	*L. gasseri* BNR17	NO	[45]
Mice	Obesity	NO	A bacteriocin-producing probiotic *L. salivarius* UCC118 Bac+	*Bacteroidetes* ↑, *Enterobacteriaceae* ↑,*Proteobacteri* ↑, *Actinobacteria* ↓	[46]
Mice	Obesity	NO	*L. paracasei* NCC2461	NO	[47]
Mice	Obesity	NO	*Pediococcus pentosaceus* LP28	NO	[48]
Mice	Obesity	NO	*Bacteroides uniformis* CECT 7771	NO	[49]
Mice	Obesity	NO	*Bifidobacterium Bifidobacteria* L66-5, L75-4, M13-4, and FS31-12	NO	[50]
Mice	Obesity	NO	*Bifidobacterium adolescentis*	NO	[51, 52]
Mice	Obesity	*Akkermansia muciniphila* ↓	*Akkermansia muciniphila*	*A. muciniphila* ↑	[53]
Mice	Obesity	NO	*Saccharomyces boulardii Biocodex*	*Bacteroidetes* ↑, *Firmicutes* ↑, *Proteobacteria* ↑,*Tenericutes* ↑	[54]
Mice	Obesity	NO	*L. paracasei* CNCM I-4270, *L. rhamnosus* I-3690, or *Bifidobacterium animalis* subsp.	NO	[55]
Mice	Obesity	NO	Mixtures *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Propionibacterium*	NO	[56]
Mice	Obesity	NO	Cocktail *S. thermophilus*, *L. bulgaricus*, *L. acidophilus*, *Bifidobacterium bifidus*, *L. casei*	NO	[57]
Mice	Obesity	NO	*Bifidobacterium* spp. *B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, and *B. longum* SPM 1207	NO	[58]
Mice	Obesity	NO	*L. salivarius* Ls33, *L. rhamnosus* LMGS-28148, *B. animalis* subsp. *lactis* LMG P-28149, Mix	*A. muciniphila* ↑, *Rikenellaceae* ↑, *Lactobacillaceae*↓	[59]

NO refers to no test or no research

Clostridium clusters I and XIVab, and *Lactobacillus* spp., were modulated in the small intestine and the *Firmicutes*:*Bacteroidetes* ratio was decreased [41]. In another study, Miyoshi et al. [42] investigated the effect of probiotic *L. gasseri* SBT2055 (LG2055) on C57BL/6 mice fed a 10%-fat diet, showing that consumption of LG2055 significantly prevented body weight gain, fat accumulation, and pro-inflammatory gene expression, including chemokine (C–C motif) ligand 2 (CCL2) and chemokine (C–C motif) receptor 2 (CCR2), in adipose tissue. Relatively lower triglyceride levels and reduced expression of lipogenic genes, including acetyl CoA carboxylase 1 (ACC1), fatty acid synthase (FAS), and sterol regulatory element-binding protein 1 (SREBP1), were also observed in the liver. It is suggested that improvement in the inflammatory state of adipose tissue might be a possible mechanism underlying the anti-obesity effect of LG2055. Several other *Lactobacillus* strains have been tested as agents with potential anti-obesity effects. Probiotic supplementation with *L. curvatus* HY7601 or *L. curvatus* HY7601 in combination with *L. plantarum* KY1032 effectively suppressed body weight gain and reduced adipose tissue weight and cholesterol content in mice fed a high-fat high-cholesterol diet for 9 weeks. Notably, the combination was more effective for inhibiting gene expressions of various fatty acid synthesis enzymes, concomitant with decreases in fatty acid oxidation-related enzyme activities and their gene expressions [43]. In another study by the same group, mice were fed a HFD for 8 weeks to induce obesity and then randomized to receive HFD plus *L. curvatus* HY7601 and *L. plantarum* KY1032 or placebo for another 10 weeks. Obese mice treated with probiotics showed reduced body weight gain and fat accumulation as well as lowered plasma insulin, leptin, total cholesterol, and liver toxicity biomarkers compared to obese mice treated with probiotics. Meanwhile, the food efficiency ratio was reduced significantly in mice supplemented with probiotics, indicating lower weight gain per gram of food consumed. Further study found that the diversity of the gut microbiota and its composition were significantly altered in the obese mice and after probiotic treatment. At the same time, the authors observed concurrent transcriptional changes in adipose tissue and the liver. In adipose tissue, pro-inflammatory genes (TNF-α, IL6, IL1β, and MCP1) were downregulated in mice receiving probiotic treatment. In the liver, fatty acid oxidation-related genes (PGC1α, CPT1, CPT2, and ACOX1) were upregulated in mice receiving probiotic treatment [44]. Similarly, Kang et al. [45] also found that the administration of *L. gasseri* BNR17 significantly reduced body weight and white adipose tissue weight in high-sucrose diet-fed mice. More specifically, following *L. gasseri* BNR17 supplement, mRNA levels of fatty acid oxidation-related genes (ACO, CPT1, PPARα, PPARδ) significantly increased and those of fatty acid synthesis-related genes (SREBP-1c, ACC) decreased. Meanwhile, the expression of GLUT4, the main mediator of insulin-stimulated glucose uptake, was elevated in BNR17-fed groups. *L. gasseri* BNR17 also reduced the levels of leptin and insulin in serum. These results suggest that the anti-obesity actions of *L. gasseri* BNR17 can be attributed to elevated expression of fatty acid oxidation-related genes and reduced levels of leptin. Additionally, the data that pointed to the antidiabetic activity of *L. gasseri* BNR17 may be due to elevated GLUT4 and reduced insulin levels. Probiotic supplementation with a bacteriocin-producing probiotic (*Lactobacillus salivarius* UCC118 Bac^+) effectively suppressed body weight gain in mice fed a high-fat diet for 20 weeks. Meanwhile, the bacteriocin-producing probiotic, though having no significant impact on the proportions of *Firmicutes*, resulted in a relative increase in *Bacteroidetes* and *Proteobacteria* and a decrease in *Actinobacteria* [46]. Finally, the supplementation of *L. paracasei* NCC2461 for 11 weeks decreased body weight gain and abdominal fat in rats maintained on a high-fat diet, with no effects on food consumption. To investigate the mechanisms, *L. paracasei* NCC2461 was injected intraduodenally, which resulted in increased activity of the sympathetic nervous system in white and brown adipose tissue. Intragastric administration of the probiotic increased thermogenesis in brown adipose tissue and lipolysis in white adipose tissue [47]. The investigators thus attributed the anti-obesity effects of *L. paracasei* NCC2461 to its excitation of the sympathetic nervous system, which facilitated lipolytic and thermogenic responses.

Other probiotics shown to have anti-obesity effects include the plant-derived lactic acid bacterium *Pediococcus pentosaceus* LP28 [48], *Bacteroides uniformis* CECT 7771 [49], *Bifidobacterium* [50–52], *Akkermansia muciniphila* [53], and *Saccharomyces boulardii Biocodex* [54]. Accordingly, *Pediococcus pentosaceus* LP28 supplementation reduced body weight gain, liver lipid contents (triglyceride and cholesterol), and abdominal visceral fat in mice fed a high-fat diet for 8 weeks. Further examination showed that lipid metabolism-related genes, such as *CD36*, *SCD1* encoding stearoyl-CoA desaturase 1, and *PPARγ* encoding peroxisome proliferator-activated receptor gamma, were downregulated by taking LP28 continuously, when compared with those of the control group [48]. Likewise, oral administration of *B. uniformis* CECT 7771 reduced body weight gain, liver steatosis and liver cholesterol, and triglyceride concentrations and increased small adipocyte numbers in HFD-fed mice. The strain also reduced serum cholesterol, triglyceride, glucose, insulin, and leptin levels and improved oral tolerance to glucose in HFD-fed mice. The bacterial strain also reduced dietary fat absorption, as indicated by the reduced number of fat micelles detected in enterocytes. Moreover, *B. uniformis* CECT7771 improved immune defense mechanisms, impaired in obesity. Namely, the administration of *B. uniformis* CECT 7771 increased TNF-α production and phagocytosis and restored the capacity of dendritic cells (DCs) to induce a T-cell proliferation response. HFD induced marked changes in gut

microbiota composition, which was partially restored by the intervention [49]. A recent study compared the effects of four *Bifidobacteria* strains (*Bifidobacteria* L66-5, L75-4, M13-4, and FS31-12) on lipid metabolism in high-fat diet obese mice. All the four strains were associated with reductions in serum and liver triglycerides and significantly alleviated lipid deposition in the liver. Only *Bifidobacterium* L66-5 and *Bifidobacterium* FS31-12 decreased cholesterol liver content significantly. Specifically, *B.* L66-5 was the only one that resulted in a significant reduction in body weight [50]. In keeping with these results, oral supplementation of *Bifidobacterium* adolescentis for 12 weeks was shown not only to reduce body weight gain but also to improve diet-induced nonalcoholic steatohepatitis (NASH). Furthermore, mice treated with the probiotic had significantly decreased liver damage, which was associated with inhibition of lipid peroxidation, nuclear factor κB (NFκB) activation, and, importantly, inflammation of the liver [51]. Chen et al. [52] found that *B. adolescentis* also reduced body and fat weight in HFD-fed rats. *Akkermansia muciniphila* is a mucin-degrading bacterium that resides in the mucus layer [53, 60]: it is a dominant intestinal bacterium and composes about 3–5% of the intestinal microflora in normal individuals [60, 61]. High numbers of these bacteria negatively correlates with body weight and decreases in response to a HFD [53]. Moreover, daily administration of *A. muciniphila* to HFD-induced obese mice for 4 weeks reduced body weight and improved body composition (i.e., fat mass:lean mass ratio) without changes in food intake [53]. Meanwhile, *A. muciniphila* treatment completely reversed diet-induced fasting hyperglycemia by reducing in hepatic glucose-6-phosphatase expression [53] and, most importantly, improving insulin sensitivity. Meanwhile, it increased the mRNA expression of markers of adipocyte differentiation and lipid oxidation without affecting lipogenesis markers. Prebiotics (oligofructose) completely restored *A. muciniphila* counts in high-fat (HF)-fed mice and leptin-deficient obese mice. Finally, the anti-obesity properties of a probiotic yeast were examined for the first time in a recent study by Everard et al. [54]. *Saccharomyces boulardii* administration reduced body weight gain, fat mass, hepatic steatosis, and inflammatory tone in obese and type 2 diabetic mice and significantly changed the gut microbiota composition with an increased proportion of *Bacteroidetes* and a decreased amount of the phyla *Firmicutes*, *Proteobacteria*, and *Tenericutes*. Of note, the gut microbiota changes in response to *S. boulardii* were correlated with several host metabolism responses. In keeping with these observations, it has recently been reported that 12-week dietary supplementation in HFD-fed mice with either *L. paracasei* CNCM I-4270, *L. rhamnosus* I-3690, or *Bifidobacterium animalis* subsp. *lactis* I-2494 significantly attenuated weight gain and macrophage infiltration into epididymal adipose tissue and markedly improved glucose-insulin homeostasis and hepatic steatosis despite no reductions in food intake. In parallel, the probiotic strains shifted the overall structure of the HFD-disrupted gut microbiota toward that of lean mice fed a normal (chow) diet. *L. paracasei* CNCM I-4270 and *L. rhamnosus* I-3690 increased cecal acetate but did not affect circulating lipopolysaccharide-binding protein; in contrast, *Bifidobacterium animalis* subsp. *lactis* I-2494 did not increase acetate but significantly decreased adipose and hepatic tumor necrosis factor-α gene expression, indicating that *Lactobacillus* and *Bifidobacterium* differentially attenuate obesity in part through strain-specific impacts on obesity-associated phylotypes of gut microbiota in mice [55].

The above data concern a monostrain probiotic effect in diet-induced obese mice. In fact, a multi-strain mixture has also been tested for its ability to improve and manage obesity. Short-term courses of probiotic mixtures containing concentrated biomass of 14 live probiotic strains (*Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Propionibacterium*, *Acetobacter*) in newborn Wistar rats were shown to significantly reduce total body and visceral adipose tissue weight (epididymal, perirenal, and omental fat), together with achieving improvement in insulin sensitivity [56]. Poutahidis et al. [57] also examined human subjects and mouse models consuming a Western "fast food" diet: the authors observed CD4+ T helper (Th) 17-biased immunity and changes in microbial communities and abdominal obesity in genetically outbred Swiss mice after eating Western chow. In striking contrast, feeding mice Western chow together with probiotic yogurt containing a microbial cocktail including *S. thermophilus*, *L. bulgaricus*, *L. acidophilus*, *Bifidobacterium bifidus*, *L. casei*, and *L. rhamnosus* inhibited age-associated weight gain. The authors went on to examine whether a species of bacteria / a bacterium found in yogurt may serve to lessen fat pathology in mice by the use of purified *Lactobacillus reuteri* ATCC 6475 in their drinking water. Surprisingly, oral *L. reuteri* therapy alone was sufficient to change the pro-inflammatory immune cell profile and prevent abdominal fat pathology and age-associated weight gain in mice regardless of their baseline diet. These beneficial microbe effects were transferable into naive recipient animals by purified CD4+ T cells alone. Specifically, bacterial effects depended upon active immune tolerance by induction of Foxp3+ regulatory T cells (Treg) and interleukin (Il)-10 without significantly changing the gut microbial ecology or reducing ad libitum caloric intake. Similarly, it has been shown that administration of *Bifidobacterium* spp. (*B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, and *B. longum* SPM 1207) can reduce blood serum levels (TC, HDL-C, LDL-C, triglyceride, glucose, leptin, AST, ALT, and lipase levels) and harmful enzyme activities (β-glucosidase, β-glucuronidase, and tryptophanase), and significantly increase fecal *B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, and *B. longum* SPM 1207 counts [58]. All in all, these data suggest that the *Bifidobacterium*

spp. used in this study may have beneficial anti-obesity effects. In another study by the same group, mice received a once-daily oral administration of *L. salivarius* Ls33, *L. rhamnosus* LMGS-28148, and *B. animalis* subsp. *lactis* LMG P-28149 (Mix) for 1 week, the mice being randomly assigned to be fed with an HFD [59]. The administration of a combination of *L. rhamnosus* LMG S-28148 and *B. animalis* subsp. *Lactis* LMG P-28149 (Mix) significantly reduced adiposity and body weight gain and ameliorated insulin resistance and dyslipidemia through adipose tissue immune cell-remodeling, mainly affecting macrophages. At the gut level, the mixture modified the uptake of fatty acids and restored the expression level of the short-chain fatty acid receptor GPR43. These beneficial effects were associated with changes in microbiota composition, such as the restoration of the abundance of *Akkermansia muciniphila* and *Rikenellaceae* and the decrease of other taxa as for example *Lactobacillaceae*. Using an in vitro gut model, the authors further showed that the probiotic mixture favors the production of butyrate and propionate. By comparing the effects of the Mix with the effect of the individual strains, it was clear that *B. animalis* subsp. *lactis* LMG P-28149 alone significantly reduced body weight, epididymal adipose tissue mass, and blood leptin levels as efficiently as the mixture, while *L. rhamnosus* LMG S-28148 did not yield such effects. Conversely, both strains similarly decreased the expression levels of macrophage-specific genes (*F4/80*, *Cd68*, *Cd11b*, and *Cd11c*) in epididymal adipose tissue. However, the Mix and the *B. animalis* subsp. *lactis* strain alone led to the observed increased of the abundance of *A. muciniphila*, compared with HFD-fed mice, while *L. rhamnosus* even decreased these levels. Taken together, these findings provide crucial clues for the design and use of more efficient probiotic preparations in obesity management and may bring new insights into the mechanisms by which host-microbe interactions confer such protective effects.

Clinical studies

Recent evidence suggests that the gut microbiota is involved in the control of body weight, energy homeostasis, and inflammation and thus plays a role in the pathophysiology of obesity [62]. Probiotics are of interest because they have been shown to alter the composition of gut microbiota and to affect food intake and appetite, body weight, and composition and metabolic functions through gastrointestinal pathways and modulation of the gut bacterial community [63, 64]. The anti-obesity effects of probiotics have already been investigated in some placebo-controlled randomized clinical trials (Table 2). Roux-en-Y gastric bypass (RNYGB) surgery offers an effective and enduring treatment for morbid obesity. However, gastric bypass may alter gastrointestinal (GI) flora, possibly resulting in bacterial overgrowth and dysmotility. In 2009,Woodard et al. [65] completed a randomized placebo-controlled trial conducted on 44 patients undergoing RNYGB. By comparison with the control group, the probiotic *Lactobacillus* group significantly alleviated bacterial overgrowth and improved vitamin B_{12} availability and weight loss after RNYGB. In 2010 and 2013, Kadooka et al. [66, 67] studied the effects of the probiotic *L. gasseri* SBT2055 (LG2055) on abdominal adiposity, body weight, and other body measures in adults with obese tendencies by means of a multicenter, double-blind, randomized, placebo-controlled intervention trial. Abdominal visceral and subcutaneous fat areas significantly decreased in the probiotics group versus the control group. Furthermore, BMI, waist and hip circumferences, and body fat mass were also significantly decreased. A recent randomized double-blind clinical investigation has also examined the effects of probiotic *L. amylovorus* (LA) and *L. fermentum* (LF) yogurt administered orally to healthy but overweight participants [68]. The study demonstrated that body fat mass was reduced in all treatments, with the

Table 2 Changes in microbiota composition associated with obesity and probiotics therapeutic strategies

Models	Disease	Implicated microbiota	New therapeutic strategies	Implicated microbiota	Reference
Human	Obesity	NO	*Lactobacillus* species	NO	[65]
Human	Obesity	NO	*L. gasseri* SBT2055	NO	[66, 67]
Human	Obesity	NO	*L. amylovorus*, *L. fermentum*	*Clostridial cluster IV*↓, *Lactobacillus*↑	[68]
Human	Obesity	NO	*L. gasseri* BNR17	NO	[69]
Human	Obesity	NO	*L. plantarum* TENSIA	NO	[70]
Human	Obesity	NO	*L. rhamnosus* GG	NO	[71]
Human	Obesity	NO	*L. rhamnosus* CGMCC1.3724	*Lachnospiraceae*↓, *Subdoligranulum*↓, *Lactobacillus rhamnosus* CGMCC1.3724↑	[72]

NO refers to no test or no research

greatest reduction via LA consumption. Meanwhile, the abundance of *Clostridial cluster IV* from LA consumption was significantly reduced, albeit the abundance of *Lactobacillus* in both LF and LA treatments significantly increased. The results suggest that modulation of gut microbial composition through probiotic consumption may contribute to altered energy metabolism and body composition. The use of probiotic *L. gasseri* BNR17 isolated from human breast milk may be beneficial in the management of obesity. A recent study evaluated the effects of treatment with BNR17 or placebo for 12 weeks in obese and overweight adults (BMI $\geq$23 kg/m^2) [69]. After probiotic treatment, a decrease in weight and waist and hip circumference was observed. However, there were no significant differences between the two groups. In this report, Sharafedtinov et al. [70] examined whether an intervention with probiotic *L. plantarum* TENSIA for 3 weeks could reduce some symptoms of metabolic syndrome in Russian adults with obesity and hypertension using a randomized, double-blind, placebo-controlled, parallel pilot study. A reduction of body weight was observed in the active treatment group as compared with the control group. Furthermore, administration of *Lactobacillus plantarum* TENSIA also helped to significantly reduce BMI and arterial blood pressure (BP) values, recognized symptoms of the metabolic syndrome. This study also evaluated the impact of perinatal probiotic intervention on childhood growth patterns and the development of overweight during a 10-year follow-up. Administration of *L. rhamnosus* GG started 4 weeks before expected delivery with an extension of 6 months postnatally modified the growth pattern of the child by restraining excessive weight gain during the first years of life. The most pronounced changes were observed at the age of 4 years, with lack of efficiency in the later stages of development [71]. In a recent randomized clinical trial, the treatment of healthy but overweight or obese women (BMI between 29 and 41 kg/m^2) for 6 months with *L. rhamnosus* CGMCC1.3724 (LPR) led to significant weight loss which was associated not only with significant reductions in fat mass and circulating leptin concentrations but also with the relative abundance of bacteria of the *Lachnospiraceae* family and the *Subdoligranulum* genus in feces [72]. Of note, the present study shows that the *Lactobacillus rhamnosus* CGMCC1.3724 formulation helps obese women to achieve sustainable weight loss. Taking into account all these data, the mounting evidence that probiotics improve the host metabolism by manipulating the gut microbiota and restoring the physiological bacterial flora has today gained considerable interest. Moreover, while the benefits of probiotics for general health are increasingly being accepted, its application as a useful therapeutic agent specifically for obesity is also gaining ground.

Concluding remarks

Obesity and its related complications constitute worldwide a major burden for the status of health of millions as well as economically for healthcare systems [73]. The human gut hosts trillions of microorganisms collectively named bacterial flora or the gut microbiota. The human gut microbiota is a complex ecosystem that has evolved with us and interacts with all of our daily functions. Crucially, growing evidence strongly suggests that the gut microbiota plays a pivotal role in regulating energy homeostasis and, as a result, the development and progression of obesity and its associated metabolic disorders. Mechanistic studies have also revealed that the gut microbiota may perform specific functions in the metabolic, neurohormonal, and immune dysfunction associated with obesity, with these particular species of intestinal commensal bacteria capable of playing either a protective or pathogenic role in its development. In this context, a large number of studies conducted in both animal models and humans have shown that an effective strategy of preventing and managing obesity could be the targeting of the gut microbiota, probiotics being able to confer notable health benefits by modulating the composition of gut microbiota and restoring the physiological bacterial flora [74–77]. However, while an increasing number of studies have pointed to the therapeutic effects of probiotics on obesity, the available data in this field remain limited and the relevant scientific work is still in its early stages. Among the most serious limitations of the clinical trials conducted to date are their small sample sizes and the absence of long-term follow-up.

Firstly, as is well known, the gut microbiota is of enormous complexity, as is also highly complex the process involving the onset of obesity. Thus, it is as yet unclear whether alterations of gut microbiota lead to the development of obesity or whether, in contrast, it is the onset of obesity that brings about changes in the gut microbiota. In order to make optimal use of probiotics for the treatment of obesity, an in-depth understanding of the mechanisms of action between the gut microbiota and the host is needed. In this respect, it is evident that more studies will need to be conducted in different human populations and mammal models. Secondly, studies on the gut microbiota studies must also be carried out as they may hold an important key to a deeper understanding of obesity pathogenesis: for example, identification of bacteria (and/or microbial functions) that cause obesity is essential. Thirdly, as attractive as the use of probiotics may seem to be to counteract the obesity problem, we are still far from being able to provide guidelines for its clinical application. Hence, many more placebo-controlled randomized clinical trials are required that will elevate our scientific knowledge to such a level as to

make available firm evidence regarding specific strains, length of treatment, and the dose that needs to be administered. The latter guidance and recommendations are not, however, likely to be effective until and unless we take into consideration not only the current microbial communities and metabolic alterations but also the genetic background and lifestyle habits of each individual that are known to influence the gut ecosystem. Fourth, it will also be important to determine how probiotics change the composition of the gut microbiota (i.e., restore bacterial flora) and how relevant this is to obesity. To date, only a handful of studies have investigated the alteration of the gut microbiota in pre- and post-probiotics treatment among obesity patients. Fifth, most medications for the treatment of obesity have been withdrawn from the market because of their adverse effects. The development of therapeutics based on gut microbiota modulation has therefore gained considerable momentum. At the same time, in lieu of developing new anti-inflammatory drugs, it might be more cost-effective to devote greater effort to new approaches. One of the latter is monitoring the human intestinal microbiota and manipulating it, if required, through the use of probiotics, since the opportunity exists to develop new probiotics based on the knowledge of the interaction between the microbiota and obesity. Moreover, it is possible to develop probiotics from the gut microbiota of a healthy group [78]. At present, most important effects of probiotics on host metabolism and obesity from human studies are reported chiefly for *Lactobacillus* and/or *Bifidobacterium* strains. More potential bacterial candidates should be identified along with the mechanisms of action governing their beneficial effects on obesity. Sixth, functional foods, including fermented dairy products containing probiotics, are attracting growing attention in many countries, for children in particular, but little research has been carried out on the connection between these products and weight gain. There is definitely a pressing need to promptly carry out studies on the effects of these functional foods in different populations. All in all, we have opened up an entirely new approach to the understanding and treatment of obesity. Probiotics treatment may be considered a potentially useful therapy for obesity in the future, but research has just started in this field. Certainly, further research is urgently required.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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