Review

Probiotics: Interaction with gut microbiome and antiobesity potential

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A R T I C L E   I N F O

Article history:
Received 2 January 2012
Accepted 28 July 2012

Keywords:
Probiotics
Obesity
Microbiome
Lactobacillus
Bifidobacteria

A B S T R A C T

Obesity is a metabolic disorder afflicting people globally. There has been a pivotal advancement in the understanding of the intestinal microbiota composition and its implication in extraintestinal (metabolic) diseases. Therefore, any agent modulating gut microbiota may produce an influential effect in preventing the pathogenesis of disease. Probiotics are live microbes that, when administered in adequate amounts, have been shown to confer health benefits to the host. Over the years, probiotics have been a part of the human diet in the form of different fermented foods consumed around the world. Their influence on different physiologic functions in the host is increasingly being documented. The antiobesity potential of probiotics is also gaining wide attention because of increasing evidence of the role of gut microbiota in energy homeostasis and fat accumulation. Probiotics have also been shown to interact with the resident bacterial members already present in the gut by altering their properties, which may also affect the metabolic pathways involved in the regulation of fat metabolism. The underlying pathways governing the antiobesity effects of probiotics remain unclear. However, it is hoped that the evidence presented and discussed in this review will encourage and thus drive more extensive research in this field.

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Introduction

The gut microbiota serves as an ecologic unit harboring $10^{14}$ bacteria [1], including up to 2000 species, and its diversity may shed light on the role of these different bacterial species in the maintenance of health and the development of disease. The advent of 16S rRNA based pyrosequencing has made a significant contribution to the current understanding of the gut microbiota over the past decade [2]. Collectively, the gut microbiota is considered a “virtual organ” and the organisms inhabiting it as a “superorganism” [3]. The physiologic functions attributed to gut microbiota have extended to the extraintestinal tissues, such as the liver, brain, and adipose tissue, constructing novel connections with obesity [4,5], and its sister pathologies, such as type 2 diabetes [6] and atherosclerosis [7].

In general terms, obesity is disequilibrium of the energy balance, with energy intake exceeding energy expenditure. Mechanistically, it is a complex metabolic disorder disturbing the whole-body metabolism in a quest to accommodate the excess energy. Recently, obesity has been correlated with the altered ratio of two dominant microbial groups, Bacteroidetes and Firmicutes, in both rodents [8] and humans [9].

Because the gut microbiota is widely accepted as indispensable in healthy living, the development of therapeutics based on gut microbiota modulation has gained considerable momentum. There are some agents, such as antibiotics, probiotics, prebiotics, and synbiotics, that are endowed with the potential to alter the composition of gut microbiota. However, a new term, pharma-biotic, encompasses any form of therapeutic exploitation of the commensal flora, including the use of live probiotic bacteria, probiotic-derived biologically active metabolites, prebiotics, synbiotics, or genetically modified commensal bacteria [3]. This term has been introduced to widen the scope of these dietary components, whereby any element of these components has the ability to alter the gut microbiota composition.

Probiotics are the live micro-organisms that, when administered in adequate amounts, have been shown to confer health benefits to the host [10]. The growing competence in characterizing and harnessing the potential of these minute, short-lived, health promoting micro-organisms has added new dimensions to the understanding of their usefulness to humans. Although research has strengthened the role of probiotics as effective agents in altering gut microbiota balance, their contribution to the alleviation of chronic intestinal disorders, such as inflammatory bowel disease, traveler’s diarrhea, colitis, Crohn’s disease, and antibiotic-associated diarrhea [11–13] is increasingly being documented. The
hypcholesterolemic potential of probiotics has also been widely studied [14–18]. The obesity properties of probiotics, including their effects on body weight, adiposity, or food intake, are now being extensively explored. Furthermore, the possible cumulative effects of synbiotics (a combination of probiotics and, prebiotics—which are selectively fermented ingredients that allow specific changes in the composition and/or activity in the gastrointestinal microbiota that confer benefits on the host’s well-being and health) on weight management are also being investigated [19]. This review focuses on the interactions of probiotics with other gut microbiota members and their antiobesity potential through regulation of energy homeostasis.

Metabolic interactions between probiotics and gut microbiome: relation to energy derivation

Microbiome is the term used to collectively denote the total genome size of the gut microbiota, which exceeds the human nuclear genome by two orders of magnitude. A human acquires a microbiome from mother’s vaginal tract during birth. This microbiome eventually develops a mutualistic relation with the host [20]. Obesity is reported to be accompanied by the enrichment of a group of bacteria belonging to the Firmicutes, which eventually develops a mutualistic relation with the nuclear genome by two orders of magnitude. A human acquires a genomic and metabonomic approaches using gnotobiotic mice provides insight into interaction of the probiotics species with the possible cumulative effects of synbiotics (a combination of probiotics and, prebiotics—which are selectively fermented ingredients that allow specific changes in the composition and/or activity in the gastrointestinal microbiota that confer benefits on the host’s well-being and health) on weight management are also being investigated [19]. This review focuses on the interactions of probiotics with other gut microbiota members and their antiobesity potential through regulation of energy homeostasis.

The interaction between probiotics and the microbial residents of the gut was evaluated in a simplified germ-free mouse model colonized with Bacteroides thetaiotaomycron, a glycolipolysaccharide exhibiting a vast array of glycoside hydrolases using undigestible carbohydrates for energy production and different probiotic species. Bifidobacterium longum was shown to expand the catabolic activity of B. thetaiotaomycron, especially hydrolysis of mannose- and xylose-containing glycan. Lactococcus casei was also shown to upregulate the genes encoding hexosaminidases and arabinosidases in B. thetaiotaomycron. However, another Bifidobacterium species, Bifidobacterium animalis, was found to dominantly upregulate the genes associated with the transcription and replication of B. thetaiotaomycron, with no change in carbohydrate usage capabilities [26]. This, the study found species-specific alterations in the hydrolyzing ability of B. thetaiotaomycron by different probiotics. A similar upregulation of genes involved in carbohydrate transport and metabolism was reported after a single dose (10^9 CFU) of Lactobacillus plantarum WCFS1 in germ-free mice maintained on high-fat/high-sugar diet, which was coupled with the production of metabolic end-products such as fumarate and alcohol [27].

Probiotic colonization and its impact on gut microbiota members are highly species specific. Fermented milk containing multiple probiotic strains (Bifidobacterium animalis subspecies lactis, two different strains of Lactobacillus delbrueckii subspecies bulgaricus, Lactococcus lactis subspecies cremoris, and Streptococcus thermophilus) were shown to result in the enrichment of only B. animalis in monozygotic twins. In gnotobiotic mice with simplified bacterial community containing 15 bacterial species found in human gut, introduction of the fermented milk was found to upregulate the locus involved in the catabolism of xylo-oligosaccharides and the enzymes catalyzing carbohydrates into propionate [28]. Propionate, produced endogenously by the fermentation of undigestible carbohydrates, has been documented to exhibit hypophagic activity and to modulate gastrointestinal transit [29,30].

Global metabolite profiling of biofluids and tissue extracts by nuclear magnetic resonance was also used to unveil the host response at exposure to probiotics. Colonization of the simplified germ-free mouse model with live Lactobacillus paracasei NCC2461 induced region-dependent changes in the metabolic profiles of the intestinal tissues. The metabolic processes altered were lipid synthesis, nutrient absorption, and intestinal digestion. Oxidative stress was found to decrease as evident from the lowered content of oxidized glutathione and its precursors in the jejunum and ileum. However, no changes in the metabolites of colonic tissue were observed, which may indicate that the regions of the small intestine are the preferable colonization sites for L. paracasei NCC2461 [31]. In another study, the effect of L. paracasei and Lactobacillus rhamnosus supplementation in gnotobiotic mice humanized with infant microbiota was investigated. Probiotic administration lowered the acetate:propionate ratio and increased glucoseogenesis and branched-chain amino acid catabolism. Increased proteolysis and hepatic methylamines levels were accompanied by modulation of bile acid metabolism that favored an increase in the enterohepatic recirculation of bile acids. Lactobacillus paracasei exhibited complex microbiome–metabolome interactions that augmented new links between bile acids and Bacteroides, Staphylococcus aureus, Staphylococcus epidermidis, and L. paracasei. However, L. rhamnosus incorporation did not produce such pronounced effects. Thus, alterations in bile acid metabolism by the gut members occurs species specifically [32].

The consumption of synbiotic (fructo-oligosaccharides plus Lactobacillus helveticus Bar13 plus B. longum Bar33) was demonstrated to produce changes in the concentrations of SCFAs, ketones, carbon disulfide, and methyl acetate in healthy subjects [33]. In addition, symbiotic supplementation (Lactobacillus acidophilus, B. longum, and fructo-oligosaccharides) was found to increase amino acid absorption and prevent the accumulation of toxic byproducts of amino acid fermentation, such as amines and ammonia, in healthy subjects. An increase in fermentation metabolites such as acetate, butyrate, and lactate was also found [19]. However, the administration of galacto-oligosaccharides and L. rhamnosus in axenic mice colonized with human infant microbiota had a minimal effect on SCFA production, but increased the excretion of amino acids. Lower levels of plasma lipoproteins, hepatic triacylglycerols, and kidney lipids were also observed. Compared with the prebiotic alone, the symbiotic treatment increased the deconjugation of bile salts. The alteration of transmethylation pathways (homocysteine–betaine) in liver and pancreas also occurred as a consequence of symbiotic treatment [34].

Thus, the impact of supplementation of a handful beneficial probiotic bacteria in the diet is not confined to gut but extends to extraintestinal tissues including the liver and kidney [35]. The presence of the probiotic produces effects on lipid and bile acid metabolism. It also modulates the pattern of nutrient use, bestows other gut members with the activation of hydrolases that allows more efficient energy derivation from the undigestible polysaccharides, and drives effective absorption of nutrients in the different intestinal regions. However, these studies were carried out in gnotobiotic mice whose intestinal physiology differs from that of conventional mice. They exhibit decreased...
intestinal vascularity, muscle wall thickness, and digestive enzyme activities [3]. Nevertheless, metagenomics and metabonomics have proved useful in providing a better understanding of host–microbiomic interactions under controlled conditions in these mice. Therefore, applications of these approaches in obese mouse models may help shed further light on the antiobesity potential of probiotics.

Antiobesity potential of probiotics

With the startling increase in obesity and increasing evidence supporting the role of gut microbiota as an important element in the regulation of energy homeostasis and weight management [36], the studies discussed in this section unveil the potential of probiotics as antiobesity agents in experimental animals (Table 1) [37–50].

The administration of L. rhamnosus PL60 in diet-induced obese mice resulted in a significant body weight loss with 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 antiobesity effects to the production of trans-10, cis-12 conjugated linoleic acid (CLA) by the probiotic bacteria [37]. Besides the production of CLA by bacteria, it is also found in beef and dairy foods. A body of literature supports the antiobesity potential of CLA in laboratory animals, but the results in humans have been inconsistent [51]. Lactobacillus plantarum PL62 also produced CLA and was found to decrease body weight and epididymal, inguinal, mesenteric, and perirenal adipose tissues masses. Leptin levels differed non-significantly, whereas blood glucose was significantly lowered in the probiotic-treated mice [38].

Another study reported a decrease in average adipocyte size in mesenteric and retroperitoneal adipose tissues and serum leptin concentration in rats fed L. gasseri SBT2055 [39]. No effect on body weight, total adipose tissue mass, hepatic lipids, and serum adiponectin levels was observed. Hamad et al. [40] extended this study and found that L. gasseri SBT2055 supplementation resulted in the lowering of mesenteric adipose tissue mass, adipocyte size, and serum leptin levels in lean Zucker rats. The decrease in serum and hepatic cholesterol coupled with an increased excretion of fecal fatty acids and total neutral sterols was observed in obese and lean Zucker rats. The observed effects were attributed to a decrease in the maximum lymphatic absorption of triacylglycerols, phospholipids, and cholesterol. Another strain of L. gasseri, BNR 17, isolated from human breast milk was demonstrated to decrease body weight gain and fat pad mass in diet-induced overweight rats. The levels of total cholesterol, triacylglycerols, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were not altered after probiotic administration [41]. However, a decrease in fasting and postprandial blood glucose levels and an improvement in glucose sensitivity occurred [42]. Similarly, the L. casei Shirota strain was shown to improve insulin sensitivity and decrease glucose intolerance in diet-induced obese mice. It also decreased lipopolysaccharide binding protein [43], which has been found to increase obesity-associated inflammation and metabolic abnormalities. However, no change in intra-abdominal fat mass occurred [6]. Lactobacillus fermentum, produced by the fermentation of wheat and barley flour with multiple lactic acid bacteria, decreased body weight gain, perirenal and epididymal fat pads, total serum cholesterol, and total triacylglycerol levels in animals fed a high-fat diet [44].

Supplementation of multiple strains of

| Table 1 Antiobesity effects of probiotic in animal studies |
|---|---|---|---|---|---|---|
| Animal strain | Duration of study | Diet | Probiotic strain | Dose | Mode of delivery | Effects |
| Sr.No. | | | | | | |
| 1 | C57/B16 mice | 8 wk | HFD | L. rhamnosus HMR 60 | 1 × 10^9 CFU/d PBS | Y |
| 2 | C57/B16 mice | 8 wk | HFD | L. plantarum PL62 | 6 × 10^9 CFU/d | Y |
| 3 | Sprague-Dawley rats | 4 wk | HFD | L. plantarum SBT2055 | 1 × 10^9 CFU/d | Y |
| 4 | Zucker obese and lean rats | 11 wk | HFD | L. casei Shirota | 1 × 10^10 CFU/mouse | Y |
| 5 | Sprague-Dawley rats | 4 wk | HFD | L. plantarum 14 | 1 × 10^10 CFU/mouse | Y |
| 6 | Sprague-Dawley rats | 12 wk | HFD | L. gasseri BNR 17 | 2 × 10^10 CFU/mouse | Y |
| 7 | Sprague-Dawley rats | 12 wk | HFD | L. gasseri SBT2055 | 2 × 10^11 CFU/mouse | Y |
| 8 | Sprague-Dawley rats | 4 wk | HFD | L. rhamnosus PL60 | 1 × 10^10 CFU/mouse | Y |
| 9 | Sprague-Dawley rats | 4 wk | HFD | L. rhamnosus PL60 | 1 × 10^10 CFU/mouse | Y |
| 10 | Zucker rats | 11 wk | HFD | L. casei Shirota NS | 0.05% (w/w) mixed in diet | Y |
| 11 | Sprague-Dawley rats | 5 wk | HFD | L. plantarum DSM 15313 | 10^9 CFU/d | Y |
| 12 | Wistar rats | 12 wk | HFD | B. longum sp. Bi 88 | 1 x 10^9 CFU/animal | Y |
| 13 | C57/B16 mice | 5 wk | HFD | B. longum sp. Bi 88 | 1 x 10^9 CFU/animal | Y |
| 14 | Sprague-Dawley rats | 2 wk before parturition | HFD | L. plantarum SBT2055 | 10^9 CFU/mouse and 6 mo to pups | Y |

AT, adipose tissue mass; BWG, body weight gain during the dietary intervention with probiotic supplementation; H, food intake; HCD, high-carbohydrate diet; HFD, high-fat diet; ND, normal diet; PBS, phosphate buffered saline

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Bifidobacteria produced significant decreases in body weight gain and blood glucose and leptin levels without any significant change in fat pad weights in rats [45]. The incorporation of L. plantarum in the diets of dams decreased body weight gain, retroperitoneal adipose tissue, and leptin levels in pups (recorded 6 months after birth) [46].

The intragastric administration of L. plantarum 14 was also found to decrease mean adipocyte size and tended to lower adipose tissue weight, serum cholesterol, and leptin in C57/BL6 mice fed a high-fat diet, although no change in body weight gain and serum CLA concentration was recorded. This probiotic did not produce any decrease in the serum triacylglycerol concentration after olive oil administration to mice treated with the lipoprotein lipase inhibitor (Triton WR1339). Thus, L. plantarum 14 exert its antiobesity effects by a mechanism that does not involve either CLA production or the decreased absorption of fat [47].

The coupling of antiobesity effects of probiotics with a decrease in inflammation was also observed. Esposito et al. [48] supplemented the high-fat diet of mice with a commercially available probiotic mixture, VSL#3, containing multiple strains of Lactobacilli, Bifidobacteria and S. thermophilus. They reported decreases in fat mass and liver weights despite no change in body weight gain and food intake. The supplementation of VSL#3 also resulted in decreased oxidative and inflammatory liver damage as indicated by decreases in hepatic tumor necrosis factor-α levels and the expression of inducible nitric oxide synthase. The administration of B. longum and a high-fat diet suppressed high-fat diet-induced metabolic alterations in the gut, by effectively decreasing body weight gain, fat deposition, serum glucose and triacylglycerol levels, and increasing insulin sensitivity. These effects were accompanied by changes in the expression of RegI endotoxin levels, clearly indicating a reduced intestinal inflammation [49]. Restoration of oxidative stress (induced by thermally oxidized soybean oil) with the inclusion of Bifidobacteria BB-12 in the diet was also reported [52].

To gain mechanistic insights, a microarray-based study was carried out whereby acidified milk containing L. paracasei F19 or L. acidophilus NCFB1748 was administered to germ-free mice and was found to elicit the expression of genes that regulate fat and sugar metabolism. Increased expression of the insulin-sensitizing hormones, adipisin and adiponectin, paralleled with the decreased expression of resistin-like β, known to induce insulin resistance, was observed [53].

It has been recently shown that the colonization of germ-free mice with whole-gut mouse microbiota promoted adiposity by the downregulation of fasting-induced adipocyte factor/angioptiotin-like protein-4, a lipoprotein lipase inhibitor [5]. Supplementation of L. paracasei F19 in mice fed a high-fat diet resulted in an increase in the circulating levels of angioptiotin-like protein-4 accompanied by a decrease in whole-body fat and an increase in the triacylglycerol content of the very low-density lipoprotein fraction. Coculture experiments of colonic cell lines with F19 increased the expression of angioptiotin-like protein-4, which was mediated by the action of some unknown secreted factors on peroxisome proliferator-activated receptors (α and γ). Monocolonization of gnotobiotic mice with F19 similarly increased the triacylglycerol content in very low-density lipoprotein and angioptiotin-like protein-4 [54].

The supplementation of L. paracasei NCC2461 for 11 wk decreased body weight gain and abdominal fat in rats maintained on a high-fat diet, with no effects on food consumption. To investigate mechanisms, L. paracasei NCC2461 was injected intraduodenally, which resulted in an increased activity of the sympathetic nervous system in white and brown adipose tissues. Intragastric administration of the probiotic increased thermogenesis in brown adipose tissue and lipolysis in white adipose tissue [50]. Thus, the investigators credited the antiobesity effects of L. paracasei NCC2461 to its excitation of the sympathetic nervous system, which facilitated lipolytic and thermogenic responses.

One of the arms of energy balance i.e., energy intake has been shown to be regulated centrally through the hypothalamic appetite centers. Intracerebroventricular administration of L. acidophilus supernatants was reported to decrease body weight with no apparent effect on food intake, which was attributed to the increased expression of leptin in the cerebral cortex, thalamus, hypothalamus, and choroid plexus [55]. Lesniewska et al. [56] observed no effect on food intake despite increases in plasma levels of peptide YY and neuropeptide Y when rats were fed a mixture of symbiotics containing L. delbrueckii, B. lactis, and a fermentable fructan polymer, inulin. Peptide YY and neuropeptide Y are generally known to regulate food intake centrally [57]. Intraduodenal administration of L. paracasei NCC2461 resulted in the decrease in c-fos expression in the paraventricular nucleus and, suprachiasmatic nucleus, which is involved in the communication between the liver and the hypothalamus. The investigators proposed that the suprachiasmatic nucleus might receive abdominal signals and relay them to the paraventricular nucleus, thus affecting the peripheral autonomic nervous system [50]. Figure 1 illustrates the summary of the different proposed mechanisms of the antiobesity action of probiotics. However, despite numerous evidences pointing toward the obesity-lowering potential of probiotics, their use in increasing the weight of farm animals has been reported [58,59]. It is suggested that it was due to an increase in the proportion of Firmicutes involved in energy derivation in the gut. In another study, probiotic (B. longum, L. acidophilus, and Enterococcus fæcalis) supplementation resulted in a lesser decrease of weight loss after severe head injury in rats. However, the effect was positive because probiotic supplementation improved gut absorptive capacity (as evident from the increased villus surface area), thus helping in better recovery [60].

There are few human trials that have been carried out to test the efficacy of probiotics as antiobesity agents. Fermented milk containing L. gasseri SBT2055 (200 g/d) was administered to healthy overweight subjects in a randomized, placebo-controlled intervention. After administration, there was a significant decrease in visceral and subcutaneous fat, which may be linked to decreased fat absorption. Body weight and body mass index were also significantly decreased compared with the control group. However, serum high-molecular-
weight adiponectin levels increased in both probiotic and control groups, suggesting the effect of fermented milk independent of the probiotic [61]. In a randomized, double-blind, crossover trial, satiety-inducing effects of a beverage fermented with _L. acidophilus_ and _Propionibacterium freudenreichii_ were observed in healthy female subjects. These effects were associated with a non-significant decreasing trend in ad libitum food consumption. The appetite-decreasing effects were ascribed to the production of propionate by _P. freudenreichii_ [62]. A recent study reported that _Lactobacilli_ species when given in capsule form to morbidly obese patients undergoing gastric bypass surgery resulted in significantly greater weight loss and an increase in vitamin B12 levels, suggesting a smaller number of B12-catabolizing intestinal bacteria in the probiotic group. This could be beneficial to gastric bypass surgical patients because they have an increased risk of vitamin B12 deficiency. A significant decrease in bacterial overgrowth was also observed, which may arise postoperatively due to alterations in gut microbiota [63].

In a 10-y follow-up study, pre- and postnatal _L. rhamnous_ GG (1 × 10^10 CFU) interventions inhibited excessive weight gain in children [64]. A series of studies conducted in healthy pregnant women showed that probiotic (_L. rhamnous_ GG and _B. lactis_ intervention and dietary counseling resulted in the lowering of blood glucose levels [65], lower frequencies of gestational diabetes mellitus [66] central abdominal adiposity [67], and increased colostrum adiponectin levels [68].

Although there is clearly literature to support the antiobesity effects of probiotics, the underlying mechanisms of action governing these effects are far from clear. The antiobesity effects of probiotics may be multifatorial in nature and thus result in the regulation of overall metabolism. Further research on the safety of probiotics coupled with real-time measurements (of probiotic numbers in the product) and support from human trials, which could assist in the elucidation of the role of probiotics in the regulation of metabolic pathways involved in energy homeostasis, will be instrumental in the development of “antibiostes” probiotic products.

**Conclusion**

The purpose of this review was to discuss, using the literature, the antiobesity potential of probiotics. The review also focused on the host-microbe-probiotic interactions and their effect on the metabolic reactions that are involved in the regulation of energy homeostasis. Probiotics confer alterations in the properties of gut microbiota members, which range from their growth to their metabolism and use of nutrients; these alterations appear to influence glucose and fat metabolism in the host. Probiotics also display weight-lowering properties in different animal and human trials. Various factors have been put forward to explain these antiobesity effects. However, the species specificity of the probiotics poses problems in assigning a dedicated pathway for their mechanism of action. It is necessary to obtain data from human trials that could reveal subtle differences at microbiomic and metabolomic levels so as to harness the potential of probiotics in the amelioration of obesity and related metabolic diseases.

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