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Relationship between probiotics and obesity: a review of recent research

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Abstract

The percentage of obese individuals continues to grow worldwide, and the main factor leading to obesity is the imbalance of energy intake and consumption. The intestinal flora has important regulatory roles in metabolic disorders and obesity. Compared with normal-weight individuals, those that are obese showed remarkable changes in the composition of the intestinal flora. Several studies have reported that probiotics can reverse high-fat diet-induced obesity. Thus, altering the intestinal flora may be an effective approach to control or even prevent obesity, and some probiotics have been demonstrated to have effects on obesity. The purpose of this review is to summarize the experimental means used to study probiotics and obesity and to summarize the weight-loss effects and mechanisms of action of experimental and clinical probiotics, so as to help investigators understand the latest benefits of weight-loss probiotics and to provide a reference for follow-up research in this field.

Keywords: probiotics; obesity; intestine; cardiovascular disease; diabetes.

Practical Application: There are a large number of microorganisms in the human body, among which probiotics are beneficial to the body and can play a role in energy metabolism and weight loss. Understanding the relationship between probiotics and obesity can play a guiding role in the research of probiotics and opening up a new path of weight loss.

1 Introduction

Obesity is a global health problem that affects the quality of life of individuals in all countries (Zhou et al., 2019). Obesity refers to excessive accumulation and/or abnormal distribution of fat in the body. It is a chronic metabolic disease caused by a variety of factors. It is mostly caused by excessive accumulation of fat in the body due to excessive food intake or changes in body metabolism, and some are caused by genetic factors. Presently, when an individual's weight exceeds 20% of the standard weight, or the body mass index (BMI) is greater than 25 kg/m^2, the individual is obese (Shrestha et al., 2016). With improvements in living standards, diets have changed significantly. High calorie intake and low exercise have become the norm, resulting in a rapid increase in the incidence of obesity. Obesity can be divided into two categories, namely, simple obesity and secondary obesity. Simple obesity is mainly due to the excessive consumption of carbohydrates and/or fats. When the intake is higher than the consumption, fat accumulates, which causes obesity. Secondary obesity is mainly due to nutritional and metabolic imbalances, endocrine disorder-related diseases, hypothalamus-pituitary tumors, and other diseases (Herrera et al., 2011). Obesity is often associated with a variety of metabolic syndromes, including hyperlipidemia, type 2 diabetes, cardiovascular and cerebrovascular diseases, and osteoporosis (Finicelli et al., 2019). Regardless, the prevention and treatment of obesity is particularly important, especially with the advent of new scientific concepts and technologies such as artificial intelligence.

Human intestinal micro-ecology is a complex and dynamic ecosystem that is comprised of approximately 10^{14} microorganisms, which include nine main phyla and more than 500 kinds of microorganisms (Scarpellini et al., 2010; Cesaro et al., 2010). The intestinal flora has important roles in protecting host pathogenic microorganisms, regulating immune function, and modulating metabolic processes. The diversity of the intestinal microbial community contributes to the health of the host. A variety of enzymatic reactions carried out by the intestinal flora have roles in host homeostasis, metabolism, micronutrient synthesis, detoxification, immune function, and epithelial cell function (Kinross et al., 2008). For life, probiotics are organisms that promote the health quality of the host. In 2002, who and FAO regarded probiotics as "living microorganisms that will bring health benefits to the host as long as they are ingested in sufficient quantities". Probiotics are a kind of active microorganisms beneficial to the host by colonizing in the human body and changing the composition of flora in a certain part of the host. By regulating the immune function of host mucosa and system, or by regulating the balance of intestinal flora, promoting nutrient absorption and maintaining intestinal health, we can produce single microorganisms conducive to health or mixed microorganisms with clear composition (Zendeboodi et al., 2020). Probiotics are used more and more in the field of food, and more probiotics have been sold as nutritional supplements and food. In order to ensure that probiotics play a functional role in the body, in addition to maintaining the colonization

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of more living bacteria in the body, the metabolites produced by probiotics are also used more and more. Probiotics, living bacteria, their own proteins and metabolites are more used in the health food industry (Champagne et al., 2018). At present, many high-quality probiotics are separated from naturally fermented dairy products. At the same time, probiotics are not only directly used as food or health products, but also used to ferment dairy products, and dairy products are used as carriers to enter the human body to play their activities (Mitra & Ghosh, 2020; Pimentel et al., 2022; Cordeiro et al., 2021). In recent years, the involvement of intestinal flora-related disorders in the occurrence and development of diseases has gained research momentum, and given that this research involves a variety of diseases, especially obesity and related metabolic diseases, probiotics have become the focus of many basic and applied research studies.

2 Influencing factors of obesity

Obesity is a widespread public health problem, and its pathogenesis is complex. Several studies have reported that obesity is determined by congenital genetic factors and acquired environmental factors (Prentice et al., 2008), and obesity is caused by energy intake that exceeds energy consumption. This imbalance leads to a variety of phenomena, including lipid accumulation, insulin resistance, chronic inflammation, and intestinal flora imbalance (Vandevijvere et al., 2015). These symptoms are also the hallmarks of obesity.

2.1 Lipid accumulation

Because the body cannot consume all energy at once, energy is converted into fat and stored in adipose tissues, which increases its weight, especially abdominal white adipose tissue (Gariani et al., 2017). The main components of white adipose tissue are triglycerides. Lipid accumulation or excessive bodily transformation can cause changes in serum lipid levels, increase triglyceride and low-density lipoprotein levels, and decrease the high-density lipoprotein content, resulting in lipid metabolism disorders (Xiao et al., 2011). Lipid accumulation causes chronic inflammation, insulin resistance, and other symptoms (Garcés et al., 2005; Zhao et al., 2015).

2.2 Insulin resistance

Obesity is often accompanied by insulin resistance, which is a state in which various tissues of the body are not sensitive to insulin. In obese people, liver cells, adipose tissues, and other tissues are exposed to high energy compounds for a long time, which reduces the absorption and utilization of glucose by insulin and increases the glucose content in the blood, while the body secretes too much insulin to stabilize the blood glucose level, resulting in insulin resistance (Pan et al., 2003). Excessive energy intake can lead to abnormal glucose metabolism, and excessive carbohydrate synthesis can lead to insulin resistance, resulting in the development of obesity (Xu et al., 2017; Marcovecchio et al., 2017) in patients with type 2 diabetes. Studies have reported that adipokines (leptin, adiponectin, resistin) secreted by adipocytes have important roles in the development of insulin resistance, and obesity caused by lipid accumulation is the most important factor leading to insulin resistance (Li et al., 2017; Nameni et al., 2017).

2.3 Chronic inflammation

Chronic inflammation is a low-level inflammatory reaction that lasts for a long time and produces a harmful impact on the body (Medzhitov, 2008). Studies have reported that chronic inflammation is related to the secretion of adipocytokines and endotoxins, which causes an immune response, while obesity involves chronic inflammation of adipose tissues. Adipose tissues not only store energy, but they are also endocrine organs that can secrete hormones and cytokines, including leptin, adiponectin, resistin, and inflammatory factors (Rosen & Spiegelman, 2014; Trayhurn & Beattie, 2001). In the presence of excessive adipose tissue, numerous adipocytokines and inflammatory factors are produced, which induces an inflammatory response and activates an inflammatory signaling pathway in tissues. Pro-inflammatory factors are overexpressed in adipose tissues in obese patients, which greatly increases the incidence of diabetes, cardiovascular diseases, and cancer (Hotamisligil et al., 1995).

2.4 Intestinal flora imbalance

There are approximately 100 trillion different microorganisms in the human intestine, which is more than ten times that of human cells, and the number of genes carried is approximately 150 times that of human genes (Yan et al., 2020; Ley et al., 2008). The intestinal flora is a complex micro-ecosystem, which is comprised of 6-10 categories of bacteria, mainly Firmicutes and Bacteroidetes, which account for approximately 90% of the total proportion (Ley et al., 2008). An increase in the abundance of Firmicutes promotes the intestinal absorption of nutrients, increases the body's energy intake, and causes obesity. Therefore, when the proportions of Firmicutes and Bacteroidetes are altered, obesity develops. In addition, intestinal flora metabolites are key components for host health. Short chain fatty acids (SCFAs), such as butyric acid and propionic acid, are the most abundant compounds in these metabolites, and they regulate energy metabolism. Butyric acid can enhance the function of the epithelial cell barrier in the intestine, reduce intestinal permeability, and prevent endotoxins, such as lipopolysaccharides, from entering the circulatory system (Brahe et al., 2013). Butyric acid can also promote the transformation of white adipose tissue to brown adipose tissue, and improve energy consumption (Bartelt & Heeren, 2014; Nedergaard et al., 2007). On the other hand, propionic acid can bind to free fatty acid receptors on intestinal L cells to promote the secretion of intestinal anorexic hormones, such as peptide YY and glucagon-like peptide-1, and reduce energy intake (Li et al., 2017). Upon an imbalance of the intestinal flora, bacteria producing SCFAs, such as butyric acid and propionic acid, are reduced, and the likelihood of developing obesity is increased.

3 Experimental models for studying the weight-loss effects of probiotics

Obesity models are usually spontaneous single-gene mutation animal models, artificial single-gene mutation animal models,

and high-fat diet-induced obesity animal models (Qian et al., 2007), all of which can be used to study the weight-loss effects of probiotics.

3.1 Animal models of spontaneous single-gene mutations

The spontaneous single-gene mutation animal model of obesity is created by the spontaneous mutation of obesity-related genes. There are three typical models. The ob/ob mouse model is formed by a single base pair mutation of the leptin gene. The db/db mouse model is formed by a single base pair mutation in the leptin receptor gene. Lastly, Zucker (fa/fa) rats have a single base pair mutation in the leptin receptor gene. These animal models are mainly used to study energy regulation. However, the creation of these models is random and uncontrollable. Furthermore, obesity caused by mutations in leptin or its receptor is very rare (Hardie et al., 1996).

3.2 Artificial single gene mutation animal models

The artificial single gene mutation animal model is created by exposing animals to mutagenic chemicals and radiation. The most typical model involves the destruction of the growth hormone receptor (SMA-1), and it can be used to study energy regulation and other physiological functions, except that the establishment of this model is expensive and the model has poor genetic stability. Therefore, this model is rarely applied in research settings (Cornejo et al., 2020).

3.3 Animal models of obesity induced by high-fat diets

Animal models of obesity induced by high-fat diets are mainly created by foods that are high in fat, which leads to excessive energy intake and obesity. They are mainly used to study the effects of the diet, as well as the mechanism of action, on obesity. This model has several advantages, including low cost and easy modeling, and is similar to the human's response to a high-fat diet, which is consistent with obesity caused by a high-fat diet. The animals used in this model mainly include C57BL/6 mice, DBA/2J mice, SD rats, and Wistar rats.

High-fat diet-induced mouse obesity models are often used in probiotic research. In recent years, many researchers have studied the relationship between the intestinal flora and the host energy metabolism and reported that the intestinal flora can regulate metabolic processes and energy storage to maintain energy balance (Turnbaugh et al., 2006). The ratio of the intestinal flora characterized by high lipophilic bacteria increased, while the ratio of the intestinal flora characterized by high lipophilic bacteria decreased (Turnbaugh et al., 2008; Cani et al., 2007; Ley et al., 2006). In addition, the intake of lactic acid bacteria can change the composition of the intestinal flora, and its metabolites can affect certain metabolic processes such as energy metabolism, reduce fat weight and cholesterol content, repair the mucosal barrier, reduce intestinal permeability, lower the inflammatory response, inhibit the colonization of pathogenic bacteria in the intestine, and regulate the number and diversity of intestinal flora (Wu et al., 2015; O'Shea et al., 2012). Presently, there are many studies on lactic acid bacteria employing the high-fat diet-induced obesity model. The administration of *Lactobacillus fermentum* CECT5716 by gavage can improve obesity induced by foods that are high in fat by fixing the microbial imbalance in the intestine. Furthermore, *Lactobacillus fermentum* CECT5716 exhibits an anti-inflammatory effect and regulates the microbial community, thereby partially reversing obesity, restoring the abundance of *Akkermansia* sp., reducing the proportions of *Erysipelotrichi* and *Clostridium*, and increasing the abundance of *Bacteroides* (Molina-Tijeras et al., 2019). *Lactobacillus plantarum* K50 (K50) isolated from kimchi was orally administered to mice given a high-fat diet for 12 weeks, and the weights of the epididymis, mesenteric and subcutaneous adipose tissues, and liver were significantly reduced. In K50-treated obese mice, serum triglyceride levels decreased and HDL cholesterol levels increased. Intestinal flora analysis revealed that *Lactobacillus plantarum* K50 treatment reduced the ratio of *Firmicutes* to *Bacteroidetes* and improved the composition of the intestinal flora (Joung et al., 2021). In addition, this model is very reproducible. Therefore, it is an ideal model to study the pathogenesis of obesity and to evaluate the preventive effects of lactic acid bacteria, which has been widely used by researchers.

4 Characteristics of intestinal flora in obese populations

The intestinal microbial community is less rich in obese individuals than that in normal-weight individuals, and the change in the microbial community at the genus level is closely related to obesity. The relative proportions of *Proteobacteria*, *Firmicutes*, and *Actinobacteria* in the intestine of obese individuals increased significantly, while the relative abundance of *Bacteroides* decreased significantly. These changes decreased butyrate production, which in turn reduced the integrity of the intestinal barrier and increased mucus degradation and oxidative stress (Zuo et al., 2011). After intervention with functional foods, the proportions of *Bacteroides fragilis*, *Clostridium flexis*, *Lactobacillus*, and *Bifidobacterium* were increased, indicating that they significantly associate with weight loss (Chatelier et al., 2013). Studies have reported differences in the composition of the intestinal flora due to differences in the eating habits of individuals in different countries. For example, the proportion of *Firmicutes* in the intestine of individuals in western countries is high, while the proportion of *Bacteroides* in Chinese and Korean individuals is high, and the proportion of *Actinomycetes* in the intestine of Japanese individuals is high. For those eating high-fat foods on a regular basis, the microbial community will not only change, but the distribution of tight binding proteins and the permeability of the intestinal wall will be altered, which will stimulate the production of fat. Probiotics may have a similar role in weight loss, that is, they may have beneficial effects on human health by changing the microbial community. Gut microbes secrete bioactive compounds by fermentation, which induce a variety of responses in the intestinal mucosa, and simultaneously affect metabolic processes in the liver and adipose tissues, thereby regulating lipid and glucose homeostasis (Delzenne et al., 2011). The gut microbiota can also regulate the intestinal barrier and endocrine function, thereby affecting the transport and absorption of nutrients. Thus, the regulation of the gut microbiota is an effective strategy to reverse and manage obesity, and probiotics can provide a new treatment method for obesity.

5 Research status of lactic acid bacteria in the prevention and treatment of obesity

Obesity, a chronic metabolic disease, has a variety of causes, but its root lies in the imbalance between energy intake and consumption, which leads to lipid accumulation and obesity. Presently, many studies have reported that lactic acid bacteria can prevent and improve obesity by regulating the intestinal flora, maintaining the micro-ecological balance in the intestine, promoting lipid metabolism, reducing serum lipid levels, and regulating immune function (Figure 1). The probiotic strain *Lactobacillus fermentans* CQPC07 isolated from pickled vegetables, which can prevent and treat obesity, was used as a daily supplement in high-fat diet-induced obese mice, and it was demonstrated that this strain can improve obesity, hyperlipidemia, and liver injury caused by chronic low-grade inflammation and obesity. The mechanism of action may involve antioxidants and the regulation of lipid metabolism (Wu et al., 2021). In another study, lactic acid bacteria with cholesterol-lowering ability from traditional fermented yak yoghurt were examined, and their probiotic effects in high-fat diet-induced obese rats were evaluated. The results showed that the *Lactobacillus plantarum* Lp3 strain could reduce the cholesterol level by 73.3% in simulated gastrointestinal fluid. In rats fed a high-cholesterol diet, Lp3 could significantly reduce the contents of cholesterol and triglycerides in the serum and liver, and reduce lipid deposition in the liver, indicating that *Lactobacillus plantarum* Lp3 may be a potential probiotic for the treatment of hyperlipidemia (Won et al., 2020). The metabolic effects of *Lactobacillus paracasei* K56 and prebiotic α-galacto-oligosaccharides in regulating obesity were also investigated, and it was demonstrated that high-fat diet-induced obese mice exhibited weight gain, abnormal glucose levels, and abnormal lipid metabolism. Treatment with *Lactobacillus paracasei* K56 and α-galacto-oligosaccharides significantly reduced body weight and fat mass, especially when α-galacto-oligosaccharides were given with a high concentration of *L. paracasei* K56. In addition, both α-galacto-oligosaccharides and *Lactobacillus paracasei* K56 significantly modulated obesity and improved lipid metabolism (Min et al., 2020). After examining the prebiotic effects of *Lactobacillus fermentum* CECT5716 in high-fat diet-induced obese mice, this prebiotic was demonstrated to possess anti-obesity and anti-inflammatory properties, improve endothelial dysfunction and intestinal dystrophy, restore the abundance of *Akkermansia*, reduce the proportions of *Erysipelotrichi* and *Clostridium*, and increase the abundance of *Bacteroidetes*. Furthermore, *Lactobacillus fermentum* CECT5716 can reduce obesity by modulating the gut microbial community, and its research has lead to the identification of different bacteria that play key roles in the pathogenesis of obesity (Molina-Tijeras et al., 2019). After investigating the anti-obesity effects of *Lactobacillus sackii* ADM14 in high-fat diet-induced obese mice and the resulting changes in the gut microbial community, the results showed that *Lactobacillus sackii* ADM14 reduced body weight and epididymal fat weight, decreased total blood cholesterol and glucose levels, significantly decreased the expression of lipid-related genes in epididymal fat, restored the ratio of *Firmicutes* to *Bacteroidetes*, and increased the relative proportions of *Bacteroides faecichinchillae* and *Alistipes*. *Lactobacillus sackii* ADM14 regulates the gut microbial community, alters short-chain fatty acid production in the caecum, and improves butyrate production. In general, *Lactobacillus sackii* ADM14 shows potential as a probiotic supplement for the treatment of metabolic disorders. For instance, in a clinical study of 210 overweight subjects, some individuals drank 7 ounces of fermented milk per day, while others drank fermented milk fortified with different amounts of

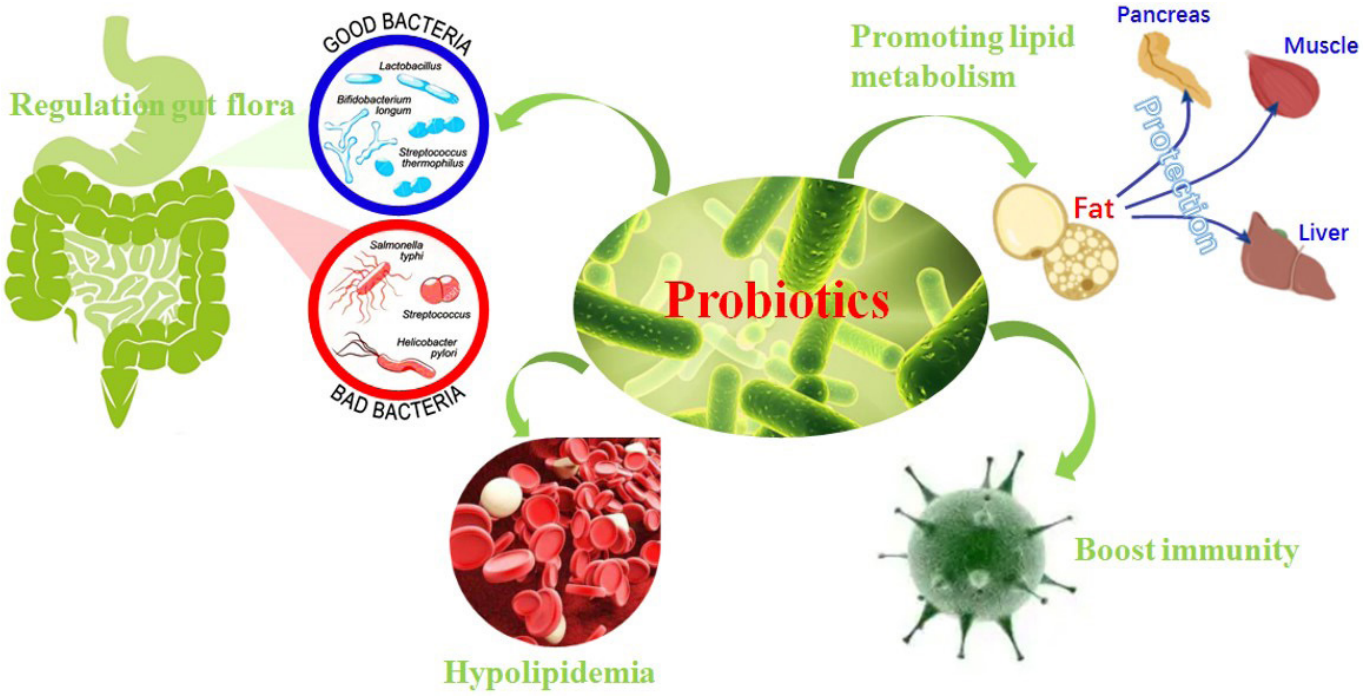

Figure 1. The mechanism of action of probiotics on obesity.

probiotics that had been linked to weight loss in past studies. After 12 weeks, the individuals who drank the probiotic-containing formula lost about 8-9% of their visceral fat (the unhealthy type of fat surrounding the heart and other internal organs). The study also revealed that individuals in both groups who drank probiotic-supplemented milk lost 1-3% of their belly fat (Won et al., 2020). Probiotic drinks do not contain sibutramine, ephedrine, dihydroclenbuterol, indole, and other drugs with obvious side effects, as well as other prohibited ingredients, so they are safe. Thus, probiotics can be used to effectively remove the stubborn fat in the abdomenal area, and they can quickly enter the human intestine; accelerate the combustion, decomposition, and transformation of fat; and improve metabolism, so as to achieve rapid weight loss (Zhang et al., 2020).

6 Conclusions

Probiotics have no side effects, require no exercise, and are simple to use. The problems of weight loss and the side effects of traditional diet pills have been solved, and obesity is no longer a problem that affects individuals. Presently, the screening of probiotics with weight-loss effects is still at an early stage of research. Nevertheless, recent findings have put forward new solutions to the problem of obesity. With future advancements in science and technology, such as studies on the meta-genome and the culture of fecal probiotic bacteria, targeted microbial therapy will play an important role in obesity intervention.

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