Probiotics as a therapeutic strategy in obesity and overweight: a systematic review

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Abstract

Obesity and overweight are two of the most health challenges with an increasing prevalence in recent years, in which several complications have been identified to have a high impact in patients' health conditions. In this vein, an increasing interest in the gut microbiota has emerged as a target for therapeutic strategies in obesity and overweight due to its direct relation with the aforementioned health conditions and complications. Thus, the aim of this study was to evaluate the efficacy of probiotics as a therapeutic strategy in the management of obesity and overweight. A systematic review of randomized controlled trials was carried out in 6 databases until May 2019 to assess the use of probiotics in obesity and overweight patients. The Jadad Scale was used to assess the quality of clinical trials. Twenty-three clinical trials published between 2000 and 2019 met the inclusion criteria. The role of probiotics in reducing body mass index and weight as well as changing the visceral abdominal fat area, waist and hip circumference were shown in 14 of 23 trials (60.87%); 14 trials (60.87%) showed changes on patients' fatty acids and biomarkers; and 4 trials (17.39%) studied the role of the gut microbiota in obese and overweight patients. Some probiotics strains are shown to be effective in reducing body mass index and hip circumference. This review provides evidence of successful results in weight loss using probiotic groups.

Keywords: gut microbiota, obesity, overweight, probiotic

1. Introduction

Two of the most important health challenges worldwide are obesity and overweight, which also constitute a global risk for mortality. In this matter, 1.9 billion adults were overweight in 2016, of whom 650 million were obese (Bentham *et al.*, 2017; Borgeraas *et al.*, 2018; Hadi *et al.*, 2018; WHO, 2018). Moreover, obesity and overweight have been shown to have several medical complications such as cardiovascular diseases, metabolic disorders, respiratory disorders, muscle-skeletal disorders and social and psychological alterations, among others and therefore, the increasing interest for their prevention and treatment acquire great importance between health professionals (Hadi *et al.*, 2018; Hampl and Campbell, 2015; King and Ajjan, 2016; Rizzetto *et al.*, 2018; Wang *et al.*, 2019).

In recent years, the gut microbiota has been widely studied in nutrition for its implication in the pathophysiology for obesity and overweight (Gérard, 2016; Gomes *et al.*, 2018; Maruvada *et al.*, 2017; Turnbaugh *et al.*, 2006). This implication has been shown to be related to its ability to modulate gastrointestinal (GI) functions such as intestinal motility (Fayfman *et al.*, 2019) and permeability (Karl *et al.*, 2017), mucosal immune function (Rizzetto *et al.*, 2018), and activity in the enteric nervous system (Heiss and Olofsson, 2019; Obata and Pachnis, 2016). Obesity is widely associated with a lower bacterial diversity and an increased *Firmicutes*/*Bacteroidetes* ratio, an event known as intestinal dysbiosis (Gomes *et al.*, 2018). It is worth noting that both, a recent systematic review (Crovesy *et al.*, 2020) and a meta-analysis (Mitev and Taleski, 2019), corroborate this imbalance *Firmicutes/Bacteroidetes* ratio in obese individuals, pointing to a different microbiota profile for individuals with obesity, which decreases if the person loses weight.

In this context, intestinal bacteria species are key in the synthesis of short-chain fatty acids (SCFA) by decreasing inflammation (Zhai *et al.*, 2019), intervening in the degradation of complex carbohydrates (Flint *et al.*, 2012) and transforming primary bile acids into secondary ones, which are fundamental for the emulsification, degradation and absorption of cholesterol, fats and fat-soluble vitamins (Ramírez-Pérez *et al.*, 2017).

The gut microbiota can be modulated by different ways, such as diet, faecal microbial transplantation (de Groot *et al.*, 2017; Paramsothy *et al.*, 2017), drugs, especially antibiotics (Becattini *et al.*, 2016; Ianiro *et al.*, 2016; Noh *et al.*, 2017), as well as probiotics, prebiotics and symbiotics (Ferrarese *et al.*, 2018). In this sense, probiotics have been defined as living organisms that consumed in adequate amounts provide beneficial health effects (FAO/WHO, 2001). These probiotics and other gut microbiota modulators may alter the secretion of hormones, neurotransmitters, and inflammatory factors, and therefore preventing food intake triggers that lead to weight gain (Aoun *et al.*, 2020). Experimental studies have shown anti-obesogenic effects after probiotics treatments, mainly *Lactobacillus* and *Bifidobacterium*, characterized by a lower weight gain as well as a reduction on fat accumulation (Ejtahed *et al.*, 2019). Some of the mechanisms of action proposed include induction in fatty acid oxidation genes or regulation of the genes involved in lipid metabolism (Dahiya *et al.*, 2017). In addition, some strains of *Lactobacilli* can produce bacteriocins, antimicrobial peptides that are related with body weight. Moreover, probiotics prevent dysbiosis and protect the intestinal barrier through the modulation of cytoskeletal (Cerdó *et al.*, 2019). Another mechanism of action postulated is related to their ability to compete with microorganisms for binding sites by antagonizing these pathogens or by modulating the recipients' immune response. There are several microorganisms recognized as probiotics and not all of them have the same effects and mechanisms of action, and thereby further discussion using probiotics as a therapeutic strategy is needed (Hadi *et al.*, 2018; Sanchis-Chordà *et al.*, 2018; Sarao and Arora, 2017). Thus, the aim of this study was to evaluate the efficacy of probiotics as a therapeutic strategy in the management of obesity and overweight in adults, and their effect in other biomarkers as secondary outcomes.

2. Methods

Search strategy

In May 2019, a systematic review of clinical trials was conducted. The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) statement (Moher *et al.*, 2009). A structured Patient-Intervention-Outcomes (PIO) question was planned as follows (Stone, 2002): *Does probiotics constitute an effective therapeutic strategy in obese or overweight patients?*

This study was carried out in main health science databases: PubMed, Cochrane Library, ProQuest, CINAHL, Science Direct and Scopus; combining natural language and structured language, using the following MeSH terms: "*probiotics*", "*microbiota*", "*obesity*" and "*overweight*". The search strategy used was adapted to each database (see Supplement File 1). The only filter used was "*clinical trials*" as article type in PubMed.

Selection criteria

The following inclusion criteria were used: (i) randomized clinical trials, (ii) papers related to the aim of the study; evaluate the efficacy of probiotics as a therapeutic strategy in the management of loss weight, obesity and/or overweight, (iii) adults aged 18-65 years, (iv) language of publication in English, (iv) included at least one of the following variables: BMI and change in weight, and (v) studies with at least a probiotic intervention. The exclusion criteria were: (i) studies conducted in patients with HIV, cancer, diabetes, cardiovascular diseases, pregnant women, and breastfeeding, (ii) re-publications, and (iii) studies within animals.

Screening of studies

The eligibility of studies was done in three phases. The first phase consisted in reading the title of articles identified throughout the database searching. Once selected, all abstracts were reviewed in a second phase. And finally, full-text reading was used when needed for clarification and in order to discern the suitability of selecting the paper for its analysis. The eligibility process was done by the two first authors (MRA, XM) independently and in duplicate, if consensus could not be achieved, a third author (PR) was consulted. In relation to the included studies, a bibliometric analysis was carried out on the following variables: (i) methods, (ii) participants, (iii) criteria of the studies, (iv) duration of the intervention, (v) probiotics strains used and (vi) results.

Quality of evidence

Besides, a critical reading analysis was performed with the Jadad Scale of Clinical Trials to assess the methodological quality of the analysed studies. This is a scale with five simple items and it has known reliability and external validity. A score below 3 points indicates low quality based on the quality of randomization, double blinding, and drop-outs extracted of each study (Jadad *et al.*, 1996). Any discrepancy was discussed by authors in order to reach a consensus and preserve the reliability of the findings.

3. Results

Study selection

Combining the aforementioned terms resulted in 586 articles [PubMed (n=105), Cochrane Library (n=154), Proquest (n=97), CINAHL (n=98), Science Direct (n=62), and Scopus (n=70)], from which 345 were discarded by duplicity. From the 241 remaining documents, 218 were excluded according to our selection criteria. And finally, a total of 23 documents were included in this systematic review for their analysis. The review and selection processes are detailed in Figure 1.

[INSERT FIGURE 1 AROUND HERE]

Literature characteristics of included studies

Trials and patients' characteristics are compiled in Table 1. Overall, participants in most of the 23 analysed articles were obese and overweight volunteers, except for five studies (Bernini *et al.*, 2016; Hulston *et al.*, 2015; Leber *et al.*, 2012; Ogawa *et al.*, 2014; Osterberg *et al.*, 2015). In three trials (Bernini *et al.*, 2016; Chung *et al.*, 2016; Zarrati *et al.*, 2013), the gender of participants was not specified and only women participated in Lee and collaborators' (2014) and Madjd and collaborators' trials (2016), as well as only men participated in the study of Osterberg and collaborators' (2015). Inclusion criteria involved an age between 18 and 75 years old (mean age 44.1 years old), enrolling a total of 1996 patients. All manuscripts were published between 2000 and 2019, and 12 clinical trials (52.17%) were not registered in a clinical trial registry. Most of the studies were performed in Asia (n=13), Europe (n=6), America (n=3) and only one was from Oceania (n=1). 12 studies (52.17%) included participants who consumed a single strain of probiotics, and 11 studies (47.83%) included participants who consumed two or multiple strains of probiotics. Also, probiotics were administered in different forms and duration of the probiotic supplementation ranged from 4 weeks to 6 months. One study evaluated the effects of probiotic in two different presentations (Ivey *et al.*, 2014). The range dose was between 10^6 from 10^{12} CFU/day, although in two studies the dose in CFU was not indicated (Hulston *et al.*, 2015; Nakamura *et al.*, 2016). Doses of the same probiotic are evaluated in two studies (Kadooka *et al.*, 2013; Kim *et al.*, 2018) and other two studies compared the effect between heat-killed or living strain (Higashikawa *et al.*, 2016; Pedret *et al.*, 2019). Nevertheless, it is noteworthy that two of the studies analysed evaluate also the effect of prebiotic and symbiotic (Hibberd *et al.*, 2019; Stenman *et al.*, 2016). Moreover, microbial composition changes were reported as outcomes only in 3 studies (13.04%). And finally, 16 studies (69.57%) reported positive results on different parameters (e.g. body weight, fat mass, BMI, biomarkers, etc.), whilst 7 studies (30.43%) reported no impact in their results.

[INSERT TABLE 1 AROUND HERE]

Effects of probiotics in weight and BMI

The role of probiotics in reducing BMI and weight or changing the visceral abdominal fat area, waist and hip circumference was demonstrated in 12 of 23 trials (52.17%) (Bernini *et al.*, 2016; Chung *et al.*, 2016; Higashikawa *et al.*, 2016; Kadooka *et al.*, 2010, 2013; Kim *et al.*, 2018; Lee *et al.*, 2014; Nakamura *et al.*, 2016; Osterberg *et al.*, 2015; Pedret *et al.*, 2019; Stenman *et al.*, 2016; Takahashi *et al.*, 2016). It is interesting to note that 9 of these studies were performed in Asia where the population's BMI is lower than in America or Europe (Castaner *et al.*, 2018).

The probiotics strains employed along these studies were: *Bifidobacterium animalis* subsp. *lactis*, subsp nov. HN019; *Lactobacillus reuteri* JBD301, *Pediococcus pentosaceus* LP28, *Lactobacillus gasseri* BNR17, *Lactobacillus amylovorus* CP1563, *Bifidobacterium animalis* spp. *lactis* BA8145, *Bifidobacterium animalis* spp. *lactis* B420, and *Bifidobacterium lactis* GCL2505. In other clinical trials, probiotics were used in combination (*Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus*, along with *Lactobacillus gasseri* LG2055), (*Streptococcus thermophiles* KCTC 11870BP, *Lactobacillus plantarum* KCTC 107892BP, *Lactobacillus acidophilus* KCTC 11906BP, *Lactobacillus rhamnosus* KCTC 12202BP, *Bifidobacterium lactis* KCTC 11904BP, *Lactobacillus longum* KCTC 12200BP, and *Bifidobacterium breve* KCTC 12201BP), (*Streptococcus thermophilus* DSM24731, and *Lactobacillus acidophilus* DSM24735). The treatment period varied from 4 weeks to 6 months, being the 12-week period the most commonly used. The effects of probiotic over gender were only indicated in the study of Pedret and collaborators (2019), where the probiotic effects were observed only in women.

On the other hand, 7 trials (30.43%) indicated the poor efficacy of probiotics in reducing BMI, weight or other anthropometric parameters (Hibberd *et al.*, 2019; Hulston *et al.*, 2015; Ivey *et al.*, 2014; Jung *et al.*, 2013; Leber *et al.*, 2012; Lee *et al.*, 2014; Madjd *et al.*, 2016). Only in 3 studies (13.04%) the anthropometric measures were not reported as outcomes (Culpepper *et al.*, 2019; Ogawa *et al.*, 2014; Zarrati *et al.*, 2014). The probiotics used in these studies included *Lactobacillus gasseri* BNR17, *Treptococcus thermophiles*, *Lactobacillus bulgaricus*, *Bifidobacterium lactis* BB, *Lactobacillus acidophilus* LA, *Lactobacillus acidophilus* La5, *Bifidobacterium animalis* subsp *lactis* BB12, *Bifidobacterium subtilis* R0179, *Streptococcus thermophiles* KCTC 11870BP, *Lactobacillus plantarum* KCTC 107892BP, *Lactobacillus acidophilus* KCTC 11906BP, *Lactobacillus rhamnosus* KCTC 12202BP, *Bifidobacterium lactis* KCTC 11904BP, *Lactobacillus longum* KCTC 12200BP, and *Bifidobacterium breve* KCTC 12201BP. The treatment of these studies ranges from 4 weeks to 3 months.

Effects of probiotics in other biomarkers

In reference to the changes on patients' fatty acids and biomarkers, a total of 13 trials (56.52%) showed changes (Agerholm-Larsen *et al.*, 2000; Bernini *et al.*, 2016; Hibberd *et al.*, 2019; Hulston *et al.*, 2015; Ivey *et al.*, 2014; Kadooka *et al.*, 2013; Madjd *et al.*, 2016; Nakamura *et al.*, 2016; Ogawa *et al.*, 2014; Pedret *et al.*, 2019; Stenman *et al.*, 2016; Zarrati *et al.*, 2013, 2014). In that sense, the literature reviewed showed an impact from probiotics treatments, where the improved metabolic health status was indicated as a decrease of total cholesterol, LDL, triglyceride concentration, and a reduction of esterified fatty acid (OFLT), non-esterified fatty acids (NEFA) and triacylglycerol (TAG). Indeed, there were reductions in total cholesterol, LDL, and an increase in the insulin resistance index (HOMA-IR) according to the study of Madjd and collaborators (2016). Likewise, the HOMA-IR was also reduced in Ivey and collaborators' results (2014) and in Pedret and collaborators' (2019). Nevertheless, it was not reported any reduction in total cholesterol, HDL, or triglycerides. On the other hand, a slight improvement was shown in Madjd and collaborators' (2016) and Culpepper and collaborators' findings (2019), but not significant enough to demonstrate the role of probiotics. Conversely, there were studies which showed negative effects correlated with endotoxin levels and total cholesterol, HDL, LDL and triglycerides, but there were no significant changes in their results (Jung *et al.*, 2013; Lee *et al.*, 2014). In the same manner, inconclusive results for changes in these biomarkers were reported in one study (Ivey *et al.*, 2014).

Conversely, impact on immune systems were also reported in 6 studies (Agerholm-Larsen *et al.*, 2000; Bernini *et al.*, 2016; Stenman *et al.*, 2016; Zarrati *et al.*, 2013, 2014). Five of these trials showed changes in levels of zonulin and CRP, a reduction of leptin levels as well as a stimulation of the IL-10 production and therefore an inhibition of TH1 and its cytokines. Concerning to the impact on the gut microbiota, three studies (13.04%) evaluated that relationship between fatty acids reduction and probiotics. Stenman *et al.* (2016) observed an increase of the concentration of faecal propionic acid, butyric acid and valeric acid, as well as total faecal SCFA concentrations. However, no significant changes in SCFA, amino acids were noticed by Hibberd and collaborators (2019) and Pedret and collaborators (2019). In the same line, four studies (17.39%) assessed the effects of probiotics treatments over gut microbiota, which found an increase of bacterial composition. In that sense, Pedret and collaborators (2019) identified an increase in *Akkermansia* spp. after 3 months of treatment with *Bifidobacterium animalis* spp. *lactis*. Takahashi and collaborators (2016) observed an increased number of faecal bifidobacterial after 12 weeks of treatment with *Bifidobacterium lactis* GCL2505. Lee and collaborators (2014) noticed an increase of the levels of *B. breve*, *B. lactis*, and *L. rhamnosus* after the treatment with a probiotic multispecies during 6 weeks. And finally, Osterberg and collaborators (2015) detected greater faecal bacterial enrichment in groups treated with a probiotic multispecies during 4 weeks.

Quality assessment

The average quality of the analysed studies scored 3.52 in the Jadad Scale (Table 2). Its variability was ranged from 2 (in four studies), 3 (in eight studies), 4 (in six studies) to 5 (in five studies), and none had an unacceptable reporting quality (lower than 1). As for potential sources of sponsorship bias, 8 analysed studies received funding from different manufacturers (Bernini *et al.*, 2016; Chung *et al.*, 2016; Hibberd *et al.*, 2019; Hulston *et al.*, 2015; Lee *et al.*, 2014; Nakamura *et al.*, 2016; Ogawa *et al.*, 2014; Takahashi *et al.*, 2016).

[INSERT TABLE 2 AROUND HERE]

4. Discussion

The aim of the present study was to evaluate the efficacy of probiotics as a therapeutic strategy against obesity and overweight on humans. In this sense, this systematic review from 23 randomized controlled trials showed the beneficial effects that probiotics may have in obesity and overweight management. That is, a reduction in BMI and weight among other anthropometric measures, which were observed in 12 of 23 trials (52.17%); along with 14 trials (60.87%) that showed changes on patients' fatty acids and other biomarkers. Our results are according to other found in previous reviews about the topic (Azad *et al.*, 2018; Borgeraas *et al.*, 2018; Rouxinol-Dias *et al.*, 2016; Wang *et al.*, 2019).

There exists a wide variety of strains which can be used in order to obtain these beneficial health effects. Thus, *Streptococcus thermophilus* strain was the most widely used (Bernini *et al.*, 2016; Kadooka *et al.*, 2013; Lee *et al.*, 2014; Osterberg *et al.*, 2015; Zarrati *et al.*, 2014). Almost half of the reviewed manuscripts employed a multi-strain probiotics (Agerholm-Larsen *et al.*, 2000; Culpepper *et al.*, 2019; Ivey *et al.*, 2014; Kadooka *et al.*, 2010, 2013; Lee *et al.*, 2014; Madjd *et al.*, 2016; Ogawa *et al.*, 2014; Osterberg *et al.*, 2015; Zarrati *et al.*, 2013, 2014), which seems to be more effective than a single strain according to a recent meta-analysis (Koutnikova *et al.*, 2019). Regarding the duration of the intervention, the most common treatment was 12 weeks, that seems to be enough to demonstrate changes in body weight. Others authors, such as Bernini and collaborators (2016), Madjd and collaborators (2016), or Ogawa and collaborators (2014), among others, used *Lactobacillus bulgaricus* strain with similar significant results in a length of time alike. Many authors (Agerholm-Larsen *et al.*, 2000; Chung *et al.*, 2016; Higashikawa *et al.*, 2016; Kadooka *et al.*, 2010; Kim *et al.*, 2018) agree in the positive effects of probiotics for changing metric parameters like weight and BMI, particularly in the abdominal region, waist and hip circumference, diastolic blood pressure, fat percentage, whole body fat, and visceral fat. In this sense, Pedret and collaborators' results (2019) demonstrated how the consumption of probiotics such as BA8145 improves biomarkers of anthropometric adiposity such as visceral fat area, BMI, waist circumference, waist-to-hip ratio and conicity index, particularly in women, and appears to constitute a complementary strategy in obesity.

Regarding to the effects of probiotics in other biomarker measures, Stenman and collaborators' (2016), and Zarrati and collaborators' results (2014) among others revealed how this process induced changes at protein levels like levels of zonulin and CRP, besides immunology and metabolic changes. For that matter, Ogawa and collaborators (2014) showed how levels of post-nephric NEFA and levels of TAG in the active fermented milk (FM) period were lower ($p < 0.005$) than in the FM control group.

New probiotics such as *Akkermansia muciniphila* have a negative correlation with overweight and obesity (Vallianou *et al.*, 2020). Results from both preclinical and clinical research have showed declined abundance of *A. muciniphila* in obesity and metabolic syndromes (Xu *et al.*, 2020). This probiotic has been effective to improved metabolic biomarkers like insulin sensitivity, total cholesterol and also decrease inflammation (Depommier *et al.*, 2019; Li *et al.*, 2016). The role of *A. muciniphila* in body metabolism revealed to be a great option treatment of metabolic disorders associated with obesity. In fact, *A. muciniphila* impacts on SCFA production, which can have effects on glucose and lipid homeostasis (Xu *et al.*, 2020).

In this matter, a recent review points out to three mechanism of probiotics action over obesity: antimicrobial activity, immunomodulation and reduction of permeability barrier (Abenavoli *et al.*, 2019). Treatments with a mixture of probiotics have been shown effective to alter host inflammation, adipose tissue hormone levels, and intestinal microbial composition. In that sense, Al-Muzafar and Amin's results (2017) showed that co-administrated with a high fat diet induced changes in intestinal microbiota, which reduced serum lipid profiles and inflammatory biomarkers. Furthermore, some studies indicate that certain bacterial strains are able to decrease the inflammatory environment associated with gastrointestinal dysfunction in animal models of obesity and obese patients, whereas others find changes in levels of certain proteins involved in the energy balance (Park *et al.*, 2019; Sun *et al.*, 2020; Zarrati *et al.*, 2013).

One possible mechanism of action of probiotics over obesity could be their impact on cytokines induction (Maldonado-Galdeano *et al.*, 2019). Thereby, Zarrati and collaborators (2013) showed that probiotics (*Lactobacillus acidophilus* LA5, *Bifidobacterium* BB12 *and Lactobacillus casei* DN001) also stimulate the production of IL-10 and therefore inhibit TH1 and its cytokines in an 8-week period. As these probiotics can also modify lipid and glucidic homeostasis, mRNA levels of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and PGC-1α, proteins that interact with PPAR-γ were significantly elevated, promoting the interaction of both and improving obesity in HFD mice after the administration of *L. amylovorus* KU4 (Park *et al.*, 2019).

In this sense, treatments with *L. plantarum* CGMCC1.557, *L. fermentum* CGMCC1.1880, *B. breve* CICC 6182 and *L.casei* CRL 431 showed an improvement in the composition of the intestinal bacteria, along with reduced levels of IL-1β, IL-6, IL-17, TNF-α and LPS and increased levels of IL-10, which had anti-inflammatory properties in mice fed with high-fat diets (HFD mice) and *E.coli*-induced endotoxemia (Novotny-Núñez *et al.*, 2015; Sun *et al.*, 2020). Similarly, a probiotic mixture containing *B. animalis* VLK and VKB and *L. casei* IMV B-7280 increased the levels of IL-4, IL- 10 and TGF- β in rats with monosodium glutamate-induced obesity (Falalyeyeva *et al.*, 2017). In this vein, *L. plantarum* was shown as a promising strain for the reduction of hypercholesterolemia and adipogenesis in vitro experiments (Huang *et al.*, 2019).

In spite of the consistency among the reviewed trials, discrepancies in strain differences and individuals' genotype were found. So, both Hulston and collaborators (2015), Leber and collaborators (2012), as well as Madjd and collaborators (2016) showed poor effects of probiotics over anthropometric parameters. In the same line, a recent metanalysis showed that oral probiotics and/or symbiotic administration have no effect on body weight or BMI, although reduced minimally waist circumference (Suzumura *et al.*, 2019). However, there are only two studies that did not find different effects between control and probiotics groups (Jung *et al.*, 2013; Lee *et al.*, 2014). That aside, despite there were no significant changes in body weight (Lee *et al.*, 2014) and total cholesterol, HDL, LDL and triglycerides levels (Jung *et al.*, 2013), an increase in bacteria composition was observed.

It is interesting to note that the form of the probiotic has been also compared in some of the studies reviewed. Ivey and collaborators (2014) found that probiotic yogurt (PY) increased the HOMA-IR and fasting glucose concentration whilst the probiotic capsules did not. Also, heat-killed strain seems to be more effective than live strain (Higashikawa *et al.*, 2016; Pedret *et al.*, 2019).

On the other hand, dietary interventions have been evaluated in two studies (Madjd *et al.*, 2016; Osterberg *et al.*, 2015). Relevant results were obtained from Osterberg and collaborators (2015) who observed that a multispecies probiotic reduced the increase in body weight caused by a high-fat diet. The relationship between gut microbiota, obesity, diet and other factors such as physical exercise has been reviewed (Brahe *et al.*, 2016). In fact, an increase of intestinal bacteria was detected in those patients who experienced weight loss through diet and exercise. As Hadi and collaborators' (2018), and Prados-Bo and collaborators' results (2015) suggest, the effectiveness of lifestyle interventions in weight loss seems to be influenced by the composition of each individual's microbiota. It is well-known that one of the main activities of the intestine bacteria is to break down substrates like dietary fibre. As result of this degradation, SCFA are produced, interplaying between diet, gut microbiota and host energy metabolism. SCFA exert multiple effects on host metabolism by acting on glucose and lipid metabolism in various tissues, notably in liver, adipose tissue and muscle in which they act on insulin signalling and even, with a key role in gut-brain axis (Hadi *et al.*, 2018; Rizzetto *et al.*, 2018).

Regarding potential mechanism to explain the aforementioned effects, there is growing evidence that support a link between the gut microbiota, SCFAs and obesity (Wang *et al.*, 2019). Gut microbiota has been evaluated only in four studies, but all of them found an increase of bacterial diversity or richness or an increased abundance in certain species (Lee *et al.*, 2014; Osterberg *et al.*, 2015; Pedret *et al.*, 2019; Takahashi *et al.*, 2016). This bacterial richness will modify the production of SCFA and consequently will lead to beneficial metabolic impact. In that matter, only Stenman and collaborators' results (2016) showed an increased in the concentration of faecal propionic acid, butyric acid and valeric acid, as well as total faecal SCFA concentrations, whilst no significant changes in SCFA were observed by Hibberd and collaborators (2019) and Pedret and collaborators (2019).

Other systematics reviews and metanalysis have evaluated the effects of probiotics treatments in obesity (Aoun *et al.*, 2020; Borgeraas *et al.*, 2018; Cerdó *et al.*, 2019; Dahiya *et al.*, 2017; Ejtahed *et al.*, 2019; Koutnikova *et al.*, 2019; Suzumura *et al.*, 2019). Their results are according to our systematic review, showing that probiotics consumption improves anthropometric parameters and BMI. However, the exact mechanism of action still needs to be elucidated as it seems to be specific for each probiotic species and strain.

Nevertheless, more studies are necessary according to López-Moreno and collaborators (2020), due to the high variability between studies and lack of standardized protocols.

Limitations

Nevertheless, there is a number of limitations to consider when interpreting the results of this review. First, the number of excluded studies has been noteworthy due to its low methodological quality. Indeed, twelve clinical trials were not registered, which may have a risk of reporting bias. Our findings are based on consistent trials, following Jadad Scale. In addition, differences on strains, length of interventions and population of the studies may constitute confounding factors, and thereby generalizations should be made with caution. Due to the limited number of studies included, the effects of probiotics treatments in the prevention and treatment of overweight and obesity still need more consistent work, specially to identify potential mechanisms of action. Lastly, a wider strategy was used, using both probiotic and microbiota as natural and structured terms, to include the use of specific genera as some authors refer to probiotics by the specific genus used in their studies.

In summary, this study contributes to the existing literature proving the efficacy of probiotics as a therapeutic strategy against obesity and overweight on humans. Further research is needed with larger sample groups and length of interventions in order to confirm the beneficial effects of probiotics as a therapeutic strategy.

5. Conclusions

In conclusion, our findings showed that some probiotics strains (*Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, among others) are a valid therapeutic strategy to use against obesity and overweight by modifying metric parameters and other biomarkers, especially when multi-strains rather than single strains are used. The beneficial variation among different strains has been similar and thereby, all of them may be considered as a possible strategy to regulate the gut microbiota, being a 12-week treatment the most widely used and effective. Furthermore, these probiotics have showed to be more effective in reducing BMI and hip circumference. Also, probiotics administration could produce a beneficial effect in many biomarkers, such as cholesterol, LDL, triglyceride concentration or in HOMA-IR. In this vein, the composition of each individual’s microbiota seems to have an influence in avoiding a body weight increase during dietary interventions, where multispecies probiotics have been shown to be effective.

Conflict of interests

The authors declare no conflict of interests.

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