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Impact of probiotics and prebiotics targeting metabolic syndrome

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ABSTRACT

Several studies are contributing to the better understanding of the impact of probiotics and prebiotics on the modulation of the intestinal microbiota and subsequent effects on the host's health. This review aimed to discuss the results of studies using different experimental models to evaluate the impact of the supplementation with probiotics and/or prebiotics on the different risk factors related to metabolic syndrome (MetS). A better understanding of the daily supplementation of probiotics and prebiotics regarding the mechanisms involved in the modulation of the intestinal microbiota and the immune system of patients suffering from this metabolic disorder is necessary to establish the efficiency of possible biomarkers that could contribute towards a health claim. Although the results might be promising, the functionality of probiotics and prebiotics on the intestinal microbiota and its relationship with MetS are still poorly understood to indicate their consumption for prevention and management of MetS in clinical practice.

1. Introduction

Due to their diverse health benefits, consumers are increasingly interested in incorporating bioactive compounds into their diets as a functional ingredient (Vo & Kim, 2012). Among these bioactive compounds, probiotic, prebiotic and, synbiotic foods stand out as the most profitable in the functional food market (Cruz et al., 2010).

According to Hill et al. (2014), the International Scientific Association for Probiotics and Prebiotics (ISAPP) proposed a consensus statement on the proper use of the term probiotic: "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". The daily intake of 1×10^9 colony forming units (CFU) per serving is recommended by the public health agency of Canada (Health Canada, 2009) and the Italian Health Ministry (Ministero della Salute, 2013). Both Canada and Italy consider the general benefit of supporting a healthy intestinal microbiota to be a core effect of probiotics (Hill et al., 2014). On the other hand, the Brazilian legislation requires that the probiotic strains have their identity and safety attested. Moreover, the minimum amount suggested to achieve beneficial effects should be established through evidence from animal or human studies, at the end of product shelf life and in the conditions of use, storage, and distribution (Agência Nacional de Vigilância Sanitária, 2018).

On the other hand, many countries categorize probiotic strains into different subcategories in their respective legislations as: (i) biological agent, dietary supplements, medical foods, drugs, and live biotherapeutic agents as intended use in the USA; (ii) natural health products in Canada; (iii) biotherapeutic/pharmaceuticals in Belgium and Germany; (iv) food supplement in Finland, Denmark, and Sweden; (v) functional foods in far eastern countries like Japan, China, and Malaysia (Arora & Baldi, 2015). In this context, the researchers observed that an improper categorization process conducted by the legislation of each country into different subcategories reduced the importance of dose specificity as well as strain specificity (Arora & Baldi, 2015). Nevertheless, the American-European-Asian legislations require scientific evidence on efficacy of probiotic strains through safety studies conducted with clinical trials.

Although many commercial products present probiotic strain quantities ranging from 10^9 to 10^{10} CFU/dose, there are products which demonstrate beneficial effects in lower levels, whereas other products require large amounts; therefore, it is not possible to establish a general dose for products containing probiotic strains (Leo, Ortega, Peñafiel, & Campos, 2019). In this sense, the supplementation time required for health benefits is as important as the choice for a probiotic strain and

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respective dose. In addition, the minimum criteria required for choosing a probiotic microorganism are: (i) the probiotic microorganism should be specified by genus and strain; (ii) it should contain a viable probiotic strain; (iii) to be administered at appropriate doses enough to promote beneficial effects until the end of their shelf life (with minimal variations among batches); (iv) to demonstrate controlled studies in humans that confirm efficacy (International Life Sciences Institute, 1999; Leo et al., 2019).

Among the main patented probiotic microorganisms known, species of lactic acid bacteria (LAB) like *Lactobacillus* (*plantarum, paracasei, acidophilus, casei, rhamnosus, crispatus, gasseri, reuteri, bulgaricus*) are mostly used, as well as *Bifidobacterium* (*longum, catenulatum, breve, animalis, bifidum*) and *Saccharomyces boulardii*. The application of microorganisms like *Enterococcus faecium* and *Bacillus* (*coagulans, subtilis, laterosporus*) are also described (Dixit, Wagle, & Vakil, 2016). Probiotic strains belonging to the genera *Lactobacillus* and *Bifidobacterium* are more common among commercial strains (de Simone, 2019).

The health benefits attributed to the ingestion of probiotic cultures that stand out are: control of the intestinal microbiota; stabilization of the intestinal microbiota after the use of antibiotics; promotion of the gastrointestinal resistance to colonization by pathogens; decrease in the population of pathogens resulting from the production of short-chain fatty acids (SCFA), bacteriocins, and other antimicrobial compounds; modulation of the immune system; increased absorption of mineral salts and vitamin production; and constipation relief (Martinez, Bedani, & Saad, 2015).

Prebiotic ingredients can also be added to different food formulations in order to develop products with functional claims that would attract consumers concerned about health (Hutkins et al., 2016). According to the ISAPP, a prebiotic is currently defined as a "substrate that is selectively used by host microorganisms, conferring a health benefit" (Gibson et al., 2017). The presence of prebiotics in the gastrointestinal tract may induce the development and/or metabolic activation of beneficial microorganisms residing in the intestinal microbiota through the selectivity of the substrate (Martinez et al., 2015).

Currently, the main well-known prebiotics are non-digestible carbohydrates like fructooligosaccharides (FOS) and inulin (Xavier dos Santos et al., 2019; Xavier-Santos, Bedani, Perego, Converti, & Saad, 2019), galactooligosaccharides (GOS) (Fan et al., 2019), and lactulose (Zeng et al., 2019). Other non-digestible carbohydrates have been studied for their prebiotic potential, like soybean oligosaccharides (Ma, Wu, Giovanni, & Meng, 2017), isomalto-oligosaccharides (IMO) (Wu et al., 2017), *xylo*-oligosaccharides (XOS) (Madhukumar & Muralikrishna, 2012), *xylo*-polysaccharide (XPS) (Ho, Kosik, Lovegrove, Charalampopoulos, & Rastall, 2018), polydextrose (Costa et al., 2019), beta glucans (Velikonja, Lipoglavsek, Zorec, Orel, & Avgustin, 2019), and arabinoxylan (Chen et al., 2019). Nevertheless, most of the data available in the scientific literature on prebiotic effects are related to FOS and inulin (Martinez et al., 2015).

The physiological effects promoted by prebiotic supplementation are determined by their chemical structure, especially, non-digestible oligosaccharides, and include several factors like the nature of the glycosidic bonds, degree of polymerization, fermentability, level of solubility, and viscosity (Chen & Karboune, 2019; Rastall & Gibson, 2015; Rastall, 2010; Singh, Jadaun, Narnoliya, & Pandey, 2017). In this sense, the degree of efficacy of a prebiotic is related to the composition of resulting products from its metabolization by the colon bacteria (Chen & Karboune, 2019). According to the researchers, when designating non-digestible carbohydrates as prebiotics, it is important to consider the fact that these compounds will be metabolized distinctly among probiotic bacteria and, thus, the type of prebiotic biomolecule consumed will influence the extent of therapeutic efficacy.

Synbiotic products are made up of a simultaneous addition of probiotics and prebiotics in a food matrix which might lead to a synergic activity (Vrese & Schrezenmeir, 2008; Wu, Liu, Liang, Hu, & Huang, 2018). This interaction *in vivo* might be favoured by an adaptation of the probiotic to prebiotic before the consumption, which in some cases can result in a competitive advantage for the microorganism (Saad, Bedani, & Mamizuka, 2011). According to Kolida and Gibson (2011), a synergistic action occurs when the prebiotic aims to improve survival and growth of the probiotic in the host. On the other hand, in a complementary action, the chosen prebiotic aims to selectively increase concentrations of the beneficial microbiota components. In both approaches, the probiotic is chosen based on its specific beneficial effects on the host. According to Martinez et al. (2015), one of the advantages of a synbiotic is that the effects promoted by its ingestion may be directed to different "target" regions located in the small and large intestine.

Overall, the synbiotic interaction provides great potential for enhancing the efficacy of this class of functional foods. Moreover, this combination between prebiotic ingredients and probiotic microorganisms might offer, not only health to individuals, but also the stability of products throughout their storage period (Kolida & Gibson, 2011; Martinez et al., 2015; Sanders & Marco, 2010).

Much is known about the benefits of probiotic microorganisms and/or the prebiotic substrate on the human body. However, information regarding the effects promoted by these microorganisms and substrates on the parameters associated with the development of metabolic syndrome (MetS) are still not clear. Thus, the aim of this paper is to review the results of studies with different experimental models to evaluate the impact of the supplementation with probiotics and/or prebiotics on the different risk factors related to MetS.

2. Metabolic syndrome (MetS) and consequences on health

2.1. A brief outline on MetS

MetS is a term suggested by the World Health Organization (WHO), in 1998, to universally relate factors that favour a set of metabolic abnormalities associated with the development of coronary heart disease, strokes and cardiovascular mortality (Afsana et al., 2010). On the other hand, it is also defined as a set of metabolic abnormalities and clinical factors like insulin resistance, dyslipidaemia, high blood pressure, abdominal obesity, that together culminate in the increased risk for developing cardiovascular disease and type 2 diabetes mellitus (Jamar et al., 2018; Mazidi, Rezaie, Kengne, Mobarhan, & Ferns, 2016; Medina et al., 2018). Medical disorders stemming from the prevalence of MetS increased in the late 20th century, becoming significant issues worldwide (Chou & Fang, 2010). Some researchers reported that it affects 1 in 5 adults and is considered a new millennium epidemic that will affect the lives of millions of people around the world (Bhatnagar, Arora, Singh, & Bhattacharjee, 2011). Many factors can be considered in the MetS development process as a consequence of the multi-process lifestyle, perinatal programming, and (epi-) genetic pathway (Graf & Ferrari, 2016). Although some therapies have been reported, changes in dietary habits and lifestyle are, undoubtedly, the most important non-pharmacological factors for the prevention and treatment of this syndrome (Kim et al., 2016; Scavuzzi et al., 2015).

According to the National Cholesterol Education Program, Adult Treatment Panel III (NCEP/ATP III) (Grundy et al., 2005), MetS is characterized by the occurrence of at least three of the following five factors: (1) abdominal obesity (waist circumference of $\geq$88 cm for women and $\geq$102 cm for men); (2) high triglycerides ($\geq$150 mg/dL); (3) reduced high-density lipoprotein cholesterol (HDL-C) ($<$ 50 mg/dL for women and $<$ 40 mg/dL for men); (4) high blood pressure (systolic $\geq$ 130 mmHg or diastolic $\geq$85 mmHg); (5) high fasting glucose ($\geq$100 mg/dL).

2.2. MetS and the development of metabolic disorders

The knowledge of the MetS risk factors assists in developing preventive approaches when metabolic disorders are detected before the

onset of chronic diseases (Martin, Neale, Batterham, & Tapsell, 2016). MetS may be induced through a non-healthy diet with high fat that results in dyslipidaemia, high blood pressure, hyperglycaemia, as well as insulin resistance (Mostafa, Nasra, Zahran, & Ghoneim, 2016; Robberecht, De Bruyne, & Hermans, 2017), increasing the incidence of chronic non-communicable diseases (Bitzur et al., 2016; Monroy-Muñoz et al., 2017). In addition, determination of these parameters is necessary for a treatment that aims to reduce cardiovascular morbidity as a prevention method (Eckel, Alberti, Grundy, & Zimmet, 2010; Westerink et al., 2016).

Obesity, a component of MetS, has been considered its major driving force, leading to both cardiometabolic risk and insulin resistance (Giugliano, Ceriello, & Esposito, 2008; Westerink et al., 2016). Moreover, according to Org, Mehrabian, and Lusis (2015), atherosclerosis risk factors are associated to insulin resistance, bile acid metabolism, and inflammatory processes. These studies also reported that the metabolites derived from the intestinal microbiota contribute to the development of atherosclerosis and cholesterol metabolism through alternative metabolic pathways. According to Hand, Ivan, Ridaura, and Belkaid (2016), the dyslipidaemia process and the cellular composition of the adipose tissue can also be influenced by a metabolically active microbiota via effects on the immune system.

MetS is also characterized by increased renal clearance and hepatic uptake of HDL-C, influencing low levels of HDL-C and increased levels of triglycerides (Gallagher, Leroith, & Karnieli, 2011). Although there are considerable differences in the mechanisms of excessive distribution of abdominal adipose tissue, the clinical diagnosis of MetS does not distinguish between increased amounts of subcutaneous and visceral fat (Eckel, Grundy, & Zimmet, 2005).

Inappropriate activation of the renin-angiotensin system due to the insulin resistance process may induce excess aldosterone and glomerular hypertension (Chou & Fang, 2010). In addition, many researchers associate insulin resistance with the development of metabolic diseases, while cardiologists relate it to cardiometabolic morbidity and mortality in patients (Genser, Mariolo, Castagneto-Gissey, Panagiotopoulos, & Rubino, 2016). Insulin resistance could also be attributed to problems in specific substrate receptors and tyrosine phosphorylation in the liver of rats fed a high-fat diet (Eckel et al., 2005). Moreover, insulin resistance is also related to the accumulation of lipids in insulin-sensitive tissues, so-called ectopic fat deposition (Karpe, Dickmann, & Frayn, 2011; Yki-Järvinen, 2002), mediated by modulation of the function/expression of the transporter proteins (Holloway, Luiken, Glatz, Spriet, & Bonen, 2008; Karpe et al., 2011). Among these risk factors associated with MetS, an experiment conducted with 499 American non-diabetic volunteers from eastern US states suggested that mechanisms related to hyperglycaemia and hypertension are independent of central adiposity or insulin resistance (Boyko et al., 2010).

The process of hyperglycaemia may induce the generation of reactive oxygen which will result in lipid peroxidation that will further aggravate the type 2 diabetes mellitus process (Vangaveti, Jansen, Kennedy, & Malabu, 2016).

Oxidative stress originating from metabolic overload (high caloric intake) can result in cardiovascular risk and low-grade inflammation (Robberecht et al., 2017). Adipose cell enlargement leads to serial proinflammatory response on cells with reduced levels of adiponectin and increased levels of many cytokines and chemokines such as interleukins (IL) IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) (Gustafson, Hammarstedt, Andersson, & Smith, 2007). It is one of the leading global causes of premature mortality due to a range of vision problems, renal dysfunction, disability, coronary heart disease, vascular disease, and physical and cognitive impairment (Noale et al., 2012). Physiologically, it is observed that pancreatic islet ß cells maintain glucose tolerance by their ability to overcome insulin resistance. However, this phenomenon does not occur in people with type 2 diabetes mellitus (Genser et al., 2016; Kahn, 2001).

The modulation of the intestinal microbiota may represent a new disease predictors and, at the same time, a promising approach aiming at the management and prevention of metabolic diseases (Hur & Lee, 2015; Le Barz et al., 2015). The supplementation with probiotics and prebiotics has shown enough evidence for a possible beneficial effect through interventions directed towards treatment of components or complications of MetS (Mazidi et al., 2016).

3. Intestinal microbiota and its relation with MetS

3.1. Intestinal microbiota, dysbiosis process, metabolic endotoxemia, innate immune system, and the development of MetS

The intestinal microbiota is a set of microorganisms that colonize the gastrointestinal tract particularly in a greater number than cells of the human body (Breban, 2016). The microbiota is directly associated with the host's health as well as with the aggravation of diseases, resulting from the great diversity of microorganisms, which makes it the most important environmental agent (Thakur et al., 2016). Although cross-sectional studies and short-term intervention experiments have brought important information on the relationship of the intestinal microbiota and parameters that characterize the MetS, further experiments are still needed to evaluate other parameters that would also be relevant, including the interaction between host genetics, diet, and microbiota in the regulation of the metabolism (Ussar et al., 2015).

According to Rosenbaum, Knight, and Leibel (2015), some specific phyla such as Bacteroidetes (~0 to 25%), Firmicutes (~60 to 65%), Proteobacteria (~5 to 10%), and Actinobacteria (~3%) that make up the intestinal microbiota might represent about 97% of the population of microorganisms. However, Li, Wang, Wang, Hu, and Chen (2016) suggested that the process of colonization and establishment of the intestinal microbiota is complex since numerous microorganism-microorganism and microorganism-host interactions are involved. The researchers stated that this process of colonization is so dynamic that not all bacteria are able to permanently colonize the intestinal microbiota.

Moreover, it is known that an imbalance of the microbiota (dysbiosis) may be a consequence of changes in the nitrogen cycle that would compromise its diversity and amount (Briskey, Tucker, Johnson, & Coombes, 2016). The dysbiosis process can establish a new proportion between the two phyla, Firmicutes and Bacteroidetes, in the intestinal microbiota of obese individuals (Ley et al., 2005; Martinez, Pierre, & Chang, 2016). The dysbiosis process is related to many metabolic disorders through the loss of normal functions provided by a commensal microbiota (Frank, Zhu, Sartor, & Li, 2011). Additionally, a diet rich in fat may further influence the dysbiosis process, leading to increased serum hepatic lipids, increased circulating lipopolysaccharide (LPS), and intestinal barrier dysfunction (Norris, Jiang, Ryan, Porter, & Blesso, 2016). On the other hand, dysbiosis may even further aggravate the pathogenesis of chronic inflammatory disease that remains unexplained to date (Breban, 2016). Due to interactions between genetic and environmental factors, the gut microbiota also contributes to the incidence of obesity, diabetes, and MetS (Ussar et al., 2015). There are several pieces of evidence for the participation of the intestinal microbiota in systemic low-grade inflammation related with obesity and associated metabolic disorders (Cani, Osto, Geurts, & Everard, 2012; Cossío et al., 2017). In this sense, the prevention of intestinal microbiota dysbiosis as well as the maintenance of the intestinal epithelial barrier function are key for the treatment of metabolic disorders and of metabolic endotoxemia related to obesity (Tiange, Gao, Du, & Xueying, 2018).

Metabolic endotoxemia is a clinical condition associated with the low-grade elevation in plasma LPS (endotoxin) from the intestine into the circulation into a heightened proinflammatory and oxidant environment (Boutagy, McMillan, Frisard, & Hulver, 2016; Cani et al., 2007; Derrien, Belzer, & de Vos, 2017). Studies have demonstrated that this endotoxin aggravates the pathogenicity of chronic metabolic

diseases in the subclinical inflammation process and is frequently observed in people with type 2 diabetes mellitus, dyslipidaemia, insulin resistance, and obesity (Frazier, DiBaise, & McClain, 2011; Gomes, Costa, & Alfenas, 2017; Musso, Gambino, & Cassader, 2011).

Tejada-Simon, Lee, Ustunol, and Pestka (1999) reported that the increased inflammatory process is influenced by some components of the bacterial cell on the immunomodulatory activity in the lymphoid tissue. According to the researchers, cell membrane components such as peptidoglycans and LPS are responsible for the signalling and translocation of antigens by the intestinal mucosal barrier. The proinflammatory effect occurs by activation of the immune system through a cascade reaction when LPS and peptidoglycan bind to toll-like receptors 4 (TLR4) and nucleotide-binding oligomerization domain (NOD), respectively (Amar et al., 2011; Miremadi, Sherkat, & Stojanovska, 2016; Schertzer et al., 2011). Serum LPS levels are twice as high in obese, diabetic or individuals with a high fat diet as a consequence of decreased permeability of the intestinal barrier, elevation of chylomicron formation during the digestive process, and reduction of alkaline phosphatase activity which is responsible for the cleavage of this endotoxin in the intestine (Delzenne, Neyrinck, & Cani, 2011). In addition, this chronic exposure to serum LPS has induced the characteristics of MetS for its interaction with the innate immune system, promoted through LPS-binding protein (LBP) and the co-receptor CD14 (Awoyemi, Trøseid, Arnesen, Solheim, & Seljeflot, 2018).

According to He, Shan, and Song (2016), the development of MetS is an interaction between the innate immune system and the intestinal microbiota. Recent approaches have aimed to establish the intestinal homeostasis through a specific diet that can restore the underlying immune system or promote changes in the microbiota (Thakur et al., 2016). In addition, it was evidenced in experimental models that strain specificity on the gut microbiota is important for the attenuation of certain immune responses related to chronic inflammation (Kang, Cai, & Zhang, 2017). Although the intestinal microbiota of adults presents stability, changes can occur due to diet, genotypic/epigenetic composition, and immuno-metabolic function (Ling, Ting, Lei, Chen, & Ping, 2015). As reported by Moran and Shanahan (2014), different signalling pathways are used as a mean of communication between the microbiota and the host, involving different classes of effector ligands required to modulate the immune system.

Inflammatory biomarkers present in oxidative and endoplasmic stress induced by diabetes aggravate the synthesis of β-cells influencing the levels of insulin sensitivity and glucose homeostasis (Hasnain et al., 2014; He et al., 2016). It is important to emphasize that the more invasive and inflammatory the composition of the intestinal microbiota, the greater the changes in the immune environment adipose compartment from M2 to M1 macrophages that may contribute to the development of the MetS (Burcelin, Garidoua, & Pomié, 2012; Hand et al., 2016). Besides, according to Breban (2016), the components of the intestinal microbiota promote anti-inflammatory effects on intestinal cells both by reducing nuclear factor kappa B (NF-κB) levels and synthesis of pro-inflammatory cytokines by the microbiota.

4. Influence of probiotics and/or prebiotics on parameters related to MetS

4.1. Modulation of the intestinal microbiota through consumption of probiotic microorganisms and prebiotic ingredients

The diet may change the composition of the gut microbiota, influencing the physiopathology of nutritional disorders such as obesity, severe acute malnutrition, and anorexia nervosa (Alou, Lagier, & Raoult, 2016). The intake of specific nutritional supplements contributes to the modification of the microbiota composition (Hussey & Bergman, 2014). Furthermore, the advent of treatments composed by probiotics and prebiotics becomes a promising alternative to the "pharmaco-nutritional" approach aiming at reversing the host metabolic disorders associated to the dysbiosis process observed in obese individuals (Cani & Delzenne, 2011). According to Shang et al. (2017), the intestinal microbiota becomes a desired target for the MetS management through supplementation with probiotics and prebiotics. Thus, it represents the alternative mostly used to restore the balance or keep a healthy microbiome when it is believed that the homeostasis process has been upseted through an adverse condition (Quigley, 2019). The presence of prebiotics in the diet improves the growth of beneficial species, modifying the intestinal microbiota composition in a way that can promote beneficial effects on the host's health (Alou et al., 2016). Additionally, interest of the consumer market in supplementing food with probiotic microorganisms is growing since evidence has shown that certain probiotic strains could modulate the inflammatory response, which could help to reduce the risk of MetS (Penga et al., 2014). Along this line, a meta-analysis conducted by John et al. (2018) showed that gut microbiome-modulating dietary agents (probiotics/prebiotics/synbiotics) can lead to significant decreases in body mass index (BMI), body weight, and fat mass when compared to placebo. The authors further concluded that additional studies are necessary to identify the better supplementation and specific populations of overweight patients who could benefit from gut microbiome modulation.

The modulation of the intestinal microbiota through probiotics and/or prebiotics consumption associated to improvements in the parameters that characterize the MetS described in this topic are summarized in Fig. 1.

4.2. Pre-clinical studies using animal models

Several studies have suggested the consumption of products containing probiotics, prebiotics, and synbiotics as nutritional therapies to prevent MetS (Scavuzzi et al., 2015). Table 1 displays some studies with animal models showing the probiotic and prebiotic effects on risk factors related to MetS.

In this context, a study performed with hypercholesterolemic Sprague-Dawley rats, the daily supplementation with 2 mL (10^9 CFU/mL) of *Lactobacillus plantarum* Lp3 over 7 weeks led to a modulation of the lipid profile (Ding et al., 2017). According to the researchers, the probiotic strain contributed to the decline in levels of total cholesterol and triglycerides both plasmatic and hepatic. Moreover, a study performed with Wistar rats fed a high-cholesterol diet showed a reduction in the total cholesterol levels, low-density lipoprotein cholesterol (LDL-C), and triglycerides at the end of 42 days of supplementation with *Saccharomyces cerevisiae* ARDMC1 isolated from traditional rice beer starter cake (Saikia et al., 2017).

On the other hand, Hashmi et al. (2016) reported that hypercholesterolemic female Sprague-Dawley rats supplemented with galactooligosaccharides (GOS) (110–198.4 mg/250 g body weight) along with a high-fat diet for 60 days showed a significant decrease in serum triglycerides, total cholesterol, LDL-C, and VLDL-C when compared to the control group lipid profile.

Singh, Zapata, Pezeshki, Reidelberger, and Chelikani (2018) evaluated the influence of the administration of different concentration of inulin (2.5%, 10%, and 25%) and 25% cellulose or pair-fed to 25% inulin on diet of SD rats over 3 weeks. The results suggested that inulin dose-dependently improved glucose tolerance and increased the presence of microorganisms like *Bacteroidetes* and *Bifidobacterium* spp. on the intestinal microbiota of these animals.

The effects of probiotic *Lactobacillus paracasei* HII01 (10^8 CFU/mL), prebiotic XOS (10%), and synbiotic (combination of both) on the improvement of gut dysbiosis and gut inflammation of Wistar rats during 12 weeks of intervention were evaluated by Thiennimitr et al. (2018). The authors concluded that the supplementation with pro-, pre-, and synbiotic lead to an equal improvement in the dyslipidaemia process and the insulin sensitivity in obese rats, thereby improving the metabolic dysfunction of these animals.

Maciel et al. (2016) reported that the supplementation with Kefir

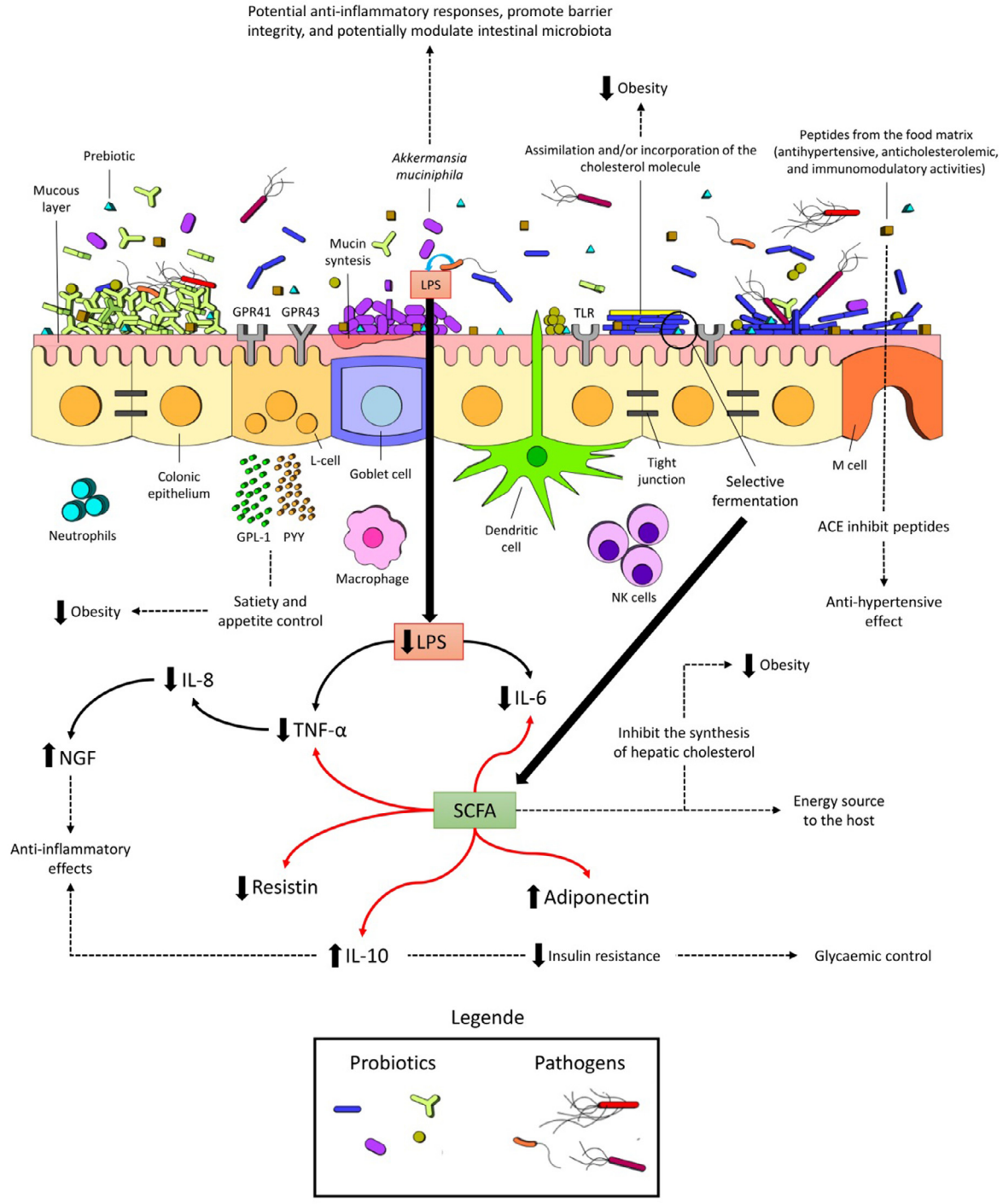

Fig. 1. Intestinal homeostasis process regarding modulation of parameters associated with the development of metabolic syndrome through supplementation with probiotics and/or prebiotics.

containing 10^{10} CFU/g of LAB (*Lactobacillus* sp., *Lactococcus lactis*, *Streptococcus thermophilus*, *Leuconostoc* sp.) and 10^{4}–10^{7} CFU/g of yeast improved the anti-inflammatory response of diabetes-induced Wistar rats. According to the researchers, there was an elevation in the IL-10 and IL-17 cytokine levels synthesized by cells responsible for the immune system (natural killer cells, dendritic cells, macrophages, and neutrophils) along an 8-week daily intervention period with the probiotic product. In addition, the supplementation of C57BL/6N rats with fermented milk containing 10^{8} CFU/mL of *Bifidobacterium bifidum* JLAU4, *Lactobacillus casei* B10, and *L. plantarum* CGMCC NO.11172 for 6 weeks reduced the levels of serum alanine aminotransferase (ALT), LPS and liver tumour necrosis factor-α (TNF-α) compared to the control group (Zhang et al., 2017b).

Rault-Nania et al. (2008) evaluated the potential effect of the administration with different inulin-type fructan fractions against general characteristics of the MetS in a rat model of this syndrome (fructose-fed rat). The authors showed that oligofructose-enriched inulin and long-chain inulin administration prevented fructose fostered elevated blood pressure, susceptibility to renal damages and heart peroxidation. Moreover, all inulin-type fructan containing diets prevented fructose induced hypertriglyceridemia.

The results suggest that the modulation of the intestinal microbiota

Table 1
Studies reporting the effects of probiotics and/or prebiotics in animal models.

Condition	Animal model	Product	Pro- and/or Prebiotics (dose)	Results	References
Atherosclerosis	Male Sprague Dawley rats	Probiotic conveyed by water	*Pediococcus acidilactici* AS185 (10^9 CFU/mL) (1 × daily for 8 weeks)	Reduction: TG, TC, OX-LDL-C, LDL-C, TNF-α, IL-1β, IL-6, and IFN-γ Increase: HDL-C and IL-10	Wang et al. (2019)
Chronic inflammation	Male and Female Sprague Dawley rats	Probiotic culture, prebiotic, and oil conveyed by skim milk	*Lactobacillus plantarum* LS/07 CCM7766 (10^9 CFU/mL), 8% BeneoSynergy1 (oligofructose-enriched inulin), and 4% oil (enriched with flax-seed oil) (1 × daily for 28 weeks)	Reduction: IL-2, IL-6, IL-17, NF-κB, and TNF-α Increase: IL-10	Štofilová et al. (2015)
Heart dysfunction	Sprague Dawley rats	Probiotic culture conveyed by PBS	*Lactobacillus reuteri* GMNL-263 (Lr263) (4 × 10^9 CFU/mL) (1 × daily for 8 weeks) *Lactobacillus reuteri* GMNL-263 (Lr263) (2 × 10^{10} CFU/mL) (1 × daily for 8 weeks)	Reduction: TC and TG	Liao et al. (2016)
Hypercholesterolemia	Male C57BL/6 mices	Probiotic conveyed by double-coated	*Lactobacillus plantarum* KCTC3928 – live cell (10^9 CFU/mL) (1 × daily for 4 weeks) *Lactobacillus plantarum* KCTC3928 – dead cell (10^{10} CFU/mL) (1 × daily for 4 weeks).	Reduction: TG, LDL-C, HDL-C/TC, HDL-C/LDL-C, AST, and ALT (live cell) Increase: HDL-C (dead cell)	Jeun et al. (2010)
Hypercholesterolemia	Male Sprague Dawley rats	Prebiotic conveyed by saline solution	100 mg/kg fucoidan solution, or 800 mg/kg galactooligosaccharides solution, or a combination (1 × daily for 8 weeks)	Reduction: TC, LDL-C, and LPS (galactooligosaccharides and fucoidan) Increase: HDL-C (galactooligosaccharides and fucoidan)	Chen et al. (2019a)
Hypertension	Male Sprague Dawley rats	Probiotic conveyed by blueberry powder	Combination of *Lactobacillus plantarum* DSM 15313 (10^9 CFU) mixed with the blueberry powder (2 g) (1 × daily for 4 weeks)	Reduction: SBP and DPB	Ahrén et al. (2015)
Hypertension	Male SHR rats	Probiotic conveyed by fermented milk	*Lactococcus lactis* NRRL B-50571 (10^6–10^7 CFU/mL) (1 × daily for 6 weeks)	Reduction: ACEI, NO, CAT, and GPx.	Beltrán-Barrientos et al. (2018)
Metabolic syndrome	Male ZDF (*Lepr^{fa}*) rats	Probiotic conveyed by saline solution	*Lactobacilus fermentum* NCIMB 5221 (2 × 10^{10} CFU/mL) (1 × daily for 8 weeks)	Reduction: INS, HOMA-IR, TG, LDL-C, TG/HDL-C, and LDL-C/HDL-C	Tomaro-Duchesneau et al. (2014)
Metabolic syndrome	Male *db/db* (C57BLKS/J-leprdb/+) and *db/db* (C57BLKS/J-leprdb/leprdb) mices	Prebiotic conveyed by water	0.6 g oligofructose/mice (1 × daily for 8 weeks)	Increase: IL-10	Cossío et al. (2017)
Metabolic syndrome	Male Wistar rats	Probiotic conveyed by saline solution	*Bifidobacterium longum* BIF CGMCC NO.2107 (2 × 10^9 CFU/mL) (1 × daily for 12 weeks)	Reduction: BW, SBP, BG, TG, and INS	Chen, Wang, Li, and Wang (2011)
Metabolic syndrome	Female BALB/c mices and male Sprague-Dawley rats	Probiotic conveyed by PBS	*Enterococcus faecium* WEFA23-H (5 × 10^9 CFU/mL) (1 × daily for 5 weeks)	Reduction: BW, TC, TG, LDL-C, BG, and HOMA-IR	Zhang et al. (2017a)
Metabolic syndrome	Male C57BL/6J mices	Prebiotic conveyed by water	80 mg Dfuc-*Pg* (fucoidan oligosaccharide)/kg body weight (1 × daily for 6 weeks) 80 mg Dfuc-*Ib* (fucoidan oligosaccharide)/kg body weight (1 × daily for 6 weeks)	Reduction: FSG, TNF-α, LPS, CD68-positive, TC, and TG (Dfuc-*Pg*) Reduction: FSG, TNF-α, LPS, TC, and TG (Dfuc-*Ib*)	Li et al. (2019a)
Metabolic syndrome	Male BALB/c mices	Prebiotic conveyed by water	0.25% polysaccharides from *Laminaria japonica* solution (1 × daily for 10 weeks)	Reduction: LDL-C Increase: HDL-C, and HDL-C/LDL-C	Duan et al. (2019)
Obesity	Male Syrian golden hamsters	Probiotic conveyed by water	1.5 × 10^{10} CFU of *Streptococcus thermophilus* (CNCM strainnumber I-1630), *Lactobacillus bulgaricus* (CNCM strain numbers I-1632 and I-1519); *Lactobacillus lactis* subsp. *lactis* (CNCM strainnumber I-1631); *Lactobacillus acidophilus*; *Streptococcus thermophiles*; *Lactobacillus plantarum*; *Bifidobacterium.lactis* (CNCM I-2494); *Lactobacillus reuteri* (DSM 17938) (3 g/200 mL for each animal) (1 × daily for 4 weeks)	Reduction: BW	Avolio et al. (2019)
Obesity	Male C57BL/6J mices	Probiotic conveyed by PBS	*Lactobacillus rhamnosus* GG (1 × 10^7 CFU/mL) (1 × daily for 10 weeks)	Reduction: BW, IL-12p70, and Leptin Increase: AD	Ji et al. (2018)
Obesity	Male C57BL/6J mices	Prebiotic conveyed by water	200 mg blueberry polyphenol extract/kg body weight (1 × daily for 12 weeks)	Reduction: BW, TC, and TG	Jiao et al. (2019)
Obesity	Male C57BL/6J mices	Prebiotic conveyed by water	200 mg hydroxysafflor yellow A/kg body weight (1 × daily for 6 weeks)	Reduction: BW, FA, INS, HOMA-IR, and FSG	Liu et al. (2018)
Obesity	Male C57BL/6J mices	Prebiotic, probiotic, and synbiotic conveyed by MRS broth	*Bifidobacterium animalis* subsp. *lactis* DSM 10140 and *Lactobacillus paracasei* subsp. *paracasei* DSM 46331 (10^8 CFU) (1 × daily for 12 week) 1 g oat β-glucan (80% purity)/kg body weight (1 × daily for 12 weeks)	Reduction: BW, HOMA-IR, INS, LBP, and TC (Prebiotic) Reduction: INS, HOMA-IR, and LBP (Probiotic)	Ke et al. (2019)

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Table 1 (*continued*)

Condition	Animal model	Product	Pro- and/or Prebiotics (dose)	Results	References
			Synbiotic is a combined dose of the pro- and prebiotics (1 × daily for 12 weeks)	Reduction: BW, HOMA-IR, INS, LBP, and TC, and FSG (Synbiotic)	
Obesity	Male BALB/c mices	Prebiotic conveyed by water	0.2% polysaccharides from *Gracilaria lemaneiformis* (1 × daily for 10 weeks)	Reduction: TC and LDL-C Increase: HDL-C	Sun et al. (2018)
Obesity	Male C57BL/6J mices	Prebiotic conveyed by salad oil	0.18 mg chlorophyll-rich spinach extract/10 g body weight (1 × daily for 13 weeks)	Reduction: TC and TG Increase: HDL-C	Li et al. (2019b)
Obesity	Male C57BL/6J mice	Probiotic conveyed by saline solution	*Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus* LA1/K8, a mixture of *Bifidobacterium lactis* Bi1, *Bifidobacterium breve* Bbr8, and *Bifidobacterium breve* BL10 (B. mix), or a mixture of *Lactobacillus bulgaricus* Lb2 and *Streptococcus thermophilus* Z57 (10^9 CFU) (1 × daily for 12 weeks)	Reduction: TG, LDL-C, and BW Increase: HDL-C, $CD4^+$, Leptin, TNF-α, IL-1β, IL-6, IFN-γ, IL-4, IL-10, and TGF-β	Roselli et al. (2018)
Type 1 diabetes mellitus	Male Wistar rats	Probiotic conveyed by fermented milk	Kefir culture, with 10^{10} CFU/g of lactic acid bacteria and 10^4–10^7 CFU/g of yeast, containing *Lactobacillus* sp., *Lactococcus lactis* subsp., *Streptococcus termophilus*, *Leuconostoc* sp. grains and yeast (1 × daily for 8 weeks)	Reduction: FSG Increase: BM (body mass) and INS	Maciel et al. (2016)

ACEI, angiotensin-I converting enzyme inhibition activity; AD, adiponectin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BG, blood glucose; BM, body mass; BPS, phosphate buffered saline; BW, body weight; CAT, catalase activity; $CD4^+$, cluster of differentiation 4^+; CD68, cluster of differentiation 68; DBP, diastolic blood pressure; *Dfuc-Ib*, fucoidan from *Isostichopus badionotus*; *Dfuc-Pg*, fucoidan from *Pearsonothuria graeffei*; FA, fat accumulation; FSG, fasting serum glucose; GPx, glutathione peroxidase; HDL-C, high-density lipoprotein cholesterol; HDL-C/LDL-C, high-density lipoprotein/low-density lipoprotein cholesterol; HDL-C/TC, high-density lipoprotein/total cholesterol; HOMA-IR, homeostasis model assessment index-insulin resistance; IFN-γ, Interferons-γ; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; IL-12p70, interleukin-12p70; IL-17, interleukin-17; IL-2, interleukin-2; INS, insulin; LBS, LPS-binding protein; LDL-C, low-density lipoprotein cholesterol; LDL-C/HDL-C, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol; LPS, lipopolysaccharide; LPS, lipopolysaccharides; MRS, Man, Rogosa and Sharpe; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; OX-LDL-C, oxidized low density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TG/HDL-C, triglycerides/high-density lipoprotein; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α.

Table 2
Studies reporting the effects of probiotics and/or prebiotics on different risk factors related to the development metabolic syndrome in clinical trials.

Conditions	Study design	Product	Pro- and/or Prebiotics (dose)	Results	References
Dyslipidaemia	Randomized double-blind placebo-controlled crossover trial	Capsules containing lyophilized probiotic culture	Combination of *Bifidobacterium animalis* subsp. *lactis* MB 2409 (DSM 23733), *Bifidobacterium* MB 109 (DSM 23731), *Bifidobacterium longum* subsp. *longum* BL04 (DSM 23233) (10^9 CFU/g) (1× daily for 12 weeks)	Reduction: TC, and LDL-C Increase: HDL-C	Guardamagna et al. (2014)
Dyslipidaemia	Randomized double-blind placebo-controlled trial	Capsules containing lyophilized synbiotic	Combination of *Lactobacillus acidophilus* CHO-220 (10^9 CFU/g) and 0.2 g Inulin (4× daily for 12 weeks)	Reduction: TC and LDL-C	Ooi, Ahmad, Yuen, and Liong (2010)
Gestational diabetes mellitus	Randomized double-blind placebo-controlled trial	Capsules containing lyophilized probiotic culture	Combination of *Lactobacillus acidophilus, Lactobacillus casei*, and *Bifidobacterium bifidum* (2×10^9 CFU/g) (1× daily for 6 weeks)	Reduction: FSG, INS, HOMA-IR, TG, and VLDL-C	Karamali et al. (2016)
Healthy adults	Double blind, parallel group, placebo controlled trial	Capsules containing lyophilized probiotic culture	*Lactobacillus fermentum* PCC (2×10^9 CFU) (2× daily for 10 weeks)	Not effective: lipid profile	Simons, Amansec, and Conway (2016)
Healthy adults with obese tendencies	Randomized double-blind placebo-controlled trial, cluster cross-over	Fermented milk containing probiotic culture	*Lactobacillus gasseri* SBT2025 (5×10^{10} CFU/100 g) (1× daily for 12 weeks)	Reduction: BMI, BW, WC, AV, BFM, and SFA	Kadooka et al. (2010)
Hypercholesterolemia	Single-arm, open-label pilot study	Capsules containing probiotic culture	*Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 (1.4×10^{10} CFU) (2× daily for 8 weeks)	Reduction: RLP-P	Ryan, Hanes, Schafer, Mikolai, and Zwickey (2015)
Hypertensive adults	Double-blind placebo controlled trial	Fruit drink with probiotic bacteria	*Lactobacillus plantarum* DSM 15313 (1×10^9 CFU/daily dose) (1× daily for 12 weeks)	Not effective: blood pressure parameters	Xu et al. (2015)
Hypertensive overweighed women	Double blind, randomized trial	Cheese with probiotic bacteria	*Lactobacillus casei* 01 (10^8 CFU/g) (1× daily for 4 weeks)	Reduction: TC, LDL-C, TG, and SBP, and DBP Increase: HDL-C, HB, and HE	Sperry et al. (2018)
Metabolic syndrome	Randomized double-blind placebo-controlled trial	Yogurt milk containing probiotic culture and prebiotic	*Bifidobacterium lactis* Bb-12 (10^7 CFU/g) and 6 g inulin (2× daily for 10 weeks)	Reduction: BFM, BFP, WC, HOMA-IR, and TG Increase: 25(OH)D, HDL-C, and QUICKI	Mohammadi-Sartang et al. (2018)
Metabolic syndrome	Randomized double-blind placebo-controlled trial, cluster cross-over	Fermented milk containing probiotic culture	*Bifidobacterium animalis* ssp. *lactis* HN019 (2.72×10^{10} CFU/mL) (1× daily for 45 days)	Reduction: BMI, TC,TNF-α, IL-6, and LDL-C	Bernini et al. (2016)
Metabolic syndrome	Randomized double-blind placebo-controlled trial	Packages containing probiotics culture and synbiotic	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and *Bifidobacter longum* (1.5×10^9 for each; 6 g daily for 24 weeks), synbiotics comprising the mentioned-above probiotics plus inulin as prebiotic	Reduction: HDL-C (probiotic group)	Kassaian et al. (2018)
Metabolic syndrome	Randomized double-blind placebo-controlled trial	Yogurt milk containing probiotic culture	*Bifidobacterium lactis* Bb-12 (3.6×10^6 CFU/300 g) and *Lactobacillus acidophilus* La-5 (4.4×10^6 CFU/300 g) (1× daily for 8 weeks)	Reduction: BG, INS, and HOMA-IR Increase: QUICKI	Rezazadeh, Gargari, Jafarabadi, and Alipour (2019)
Obesity	Randomized double-blind placebo-controlled trial	Packages containing prebiotic	0.29 g oligofructose/kg body weight and 0.14 g oligofructose/kg body weight (1× daily for 120 days)	Reduction: BW, WC, BMI, INS, HOMA-IR, and LDL-C	Genta et al. (2009)
Obesity	Randomized double-blind placebo-controlled trial	Capsules containing lyophilized probiotic culture	Two capsules (400 mg/capsule) of low dose (10^9 CFU) or high dose (10^{10} CFU) of *Lactobacillus gasseri* BNR17 (2× daily for 12 weeks)	Reduction: WC in both dose (high and low), and VAT (high dose)	Kim, Yun, Kim, Kwon, and Cho (2018)
Overweight	Randomized, controlled, parallel, double-blind, factorial trial	Probiotic yoghurt and capsules containing lyophilized probiotic cultures	*Lactobacillus acidophilus* La-5 (3×10^9 CFU) and *Bifidobacterium animalis* Bb-12 (3×10^9 CFU) (1× daily for 6 weeks)	Not effective: lipid profile and blood pressure	Ivey et al. (2015)
Overweight and obesity	Randomized double-blind placebo-controlled trial	Packages containing prebiotic	21 g oligofructose (1× daily for 12 weeks)	Reduction: BG, BW, and INS	Parnell and Reimer (2009)
Type 2 diabetes mellitus	Randomized double-blind placebo-controlled trial	Packages containing prebiotic	10 g chicory inulin enriched with oligofructose (1× daily for 8 weeks)	Reduction: FSG, HbA1c, AST, SBP, DBP, SC, and ALP	Farhangi, Javid, and Dehghan (2016)
Type 2 diabetes mellitus	Randomized double-blind placebo-controlled trial	Packages containing prebiotic	10 g oligofructose enriched inulin (1× daily for 8 weeks)	Reduction: IL-12,BMI, WC, DBP, and IFN-γ Increase: IL-4	Dehghan et al. (2016)
Type 2 diabetes mellitus					

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Table 2 (*continued*)

Conditions	Study design	Product	Pro- and/or Prebiotics (dose)	Results	References
	Randomized double-blind placebo-controlled crossover trial	Packages containing synbiotic	Combination of *Lactobacillus sporogenes* (10^7 CFU/g), 0.1 g inulin and 0.05 g β-carotene (3× daily for 6 weeks)	Reduction: INS, HOMA-IR, HOMA-B, TG, VLDL-C, and TC/HDL-C ratio Increase: NO and GSH	Asemi, Alizadeh, Ahmad, Goli, and Esmaillzadeh (2016)
Type 2 diabetes mellitus	Randomized triple-blind placebo-controlled trial	Packages containing prebiotic	10 g Inulin (1× daily for 8 weeks)	Reduction: FSG, INS, HOMA-IR, HbA1c, hs-CRP, TNF-α, and LPS	Dehghan, Gargari, Jafar-Abadi, and Aliasgharzadeh (2014)
Type 2 diabetes mellitus	Randomized double-blind placebo-controlled trial	Packages containing synbiotic	*Lactobacillus acidophilus* [2×10^9 colony forming units (CFU)], *Lactobacillus casei* (7×10^9 CFU), *Lactobacillus rhamnosus* (1.5×10^9 CFU), *Lactobacillus bulgaricus* (2×10^8 CFU), *Bifidobacterium breve* (3×10^{10} CFU), *Bifidobacterium longum* (7×10^9 CFU), *Streptococcus thermophilus* (1.5×10^9 CFU), and 100 mg oligofructose (1× daily for 6 weeks)	Reduction: FPG Increase: HDL-C	Razmpoosh et al. (2019)
Type 2 diabetes mellitus	Randomized double-blind placebo-controlled trial	Packages containing synbiotic	*Lactobacillus* + *Lactococcus* (6×10^{10} CFU/g), *Bifidobacterium* (10^{10} CFU/g), *Propionibacterium* (3×10^{10} CFU/g), *Acetobacter* (1×10^6 CFU/g) (1× daily for 8 weeks)	Reduction: HOMA-IR, TNF-α, and IL-1β	Kobyliak, Falalyeyeva, Mykhalchyshyn, Kyriienko, and Komissarenko (2018)
Type 2 diabetes mellitus with coronary heart disease	Randomized double-blind placebo-controlled trial	Packages containing probiotics culture Packages containing selenium	200 μg/day selenium plus 8×10^9 CFU/g probiotic (*Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each) (1× daily for 12 weeks)	Reduction: FPG, INS, and HOMA-IR (Consuming probiotic plus selenium) Reduction: TG, VLDL-C, TC, and hs-CRP Increase: NO, TAC, and GSH (Co-supplementation)	Raygan, Ostadmohammadi, and Asemi (2019)

25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; AST, aspartate aminotransferase; AV, abdominal visceral; BFM, body fat mass; BFP, body fat percentage; BG, blood glucose; BMI, body mass index measure; BW, body weight; DBP, diastolic blood pressure; FSG, fasting blood glucose; GPA, glutathione peroxidase activities; GSH, total glutathione; HB, haemoglobin; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HE, haematocrit; HOMA-B, homeostasis model assessment index-β-cell; HOMA-IR, homeostasis model assessment index-insulin resistance; hs-CRP, high-sensitive C-reactive protein; IFN-γ, interferons-γ; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-4, Interleukin-4; INS, insulin; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharides; NO, nitric oxide; QUICKI, quantitative insulin sensitivity check index; RLP-P, remnant lipoprotein particle; SBP, systolic blood pressure; SC, serum calcium; SFA, subcutaneous fat areas; TAC, total antioxidant capacity; TAS, total antioxidant status; TC, total cholesterol; TG, triglycerides; TNF-α, tumour necrosis factor alpha; VAT, visceral adipose tissue; VLDL-C, very low-density lipoprotein cholesterol; WC, waist circumference.

of animals stimulated through the administration of probiotic microorganisms and prebiotic ingredients showed satisfactory results regarding the improvement of the parameters associated with the development of MetS. On the other hand, the heterogeneity among studies, including factor like time of intervention, number of animals, animal model (e.g., rat, hamster, mouse), species (e.g., Sprague Dawley, C57BL/6J, Wistar, BALB/c), gender (male or female), feeding form (e.g., water, phosphate buffered saline), environmental conditions of cage, diet control, show an important limitation of these studies; thus, results are still preliminary.

4.3. Clinical trials

Although several clinical trials withstand the hypothesis that probiotics and/or prebiotics present positive effects on MetS, other studies have shown conflicting results (Table 2). Ivey et al. (2015) found that the probiotic strains *Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis* ssp. *lactis* Bb-12 did not improve the blood pressure and serum lipid parameters in overweight individuals. Xu et al. (2015) also verified that the consumption of live *L. plantarum* DSM 15313 or bilberries fermented by the same probiotic strains for 3 months did not reduce the blood pressure in adults with hypertension.

It is noteworthy that studies evaluating the impact of probiotics and/or prebiotics on MetS, particularly clinical trials, are still limited, which justifies the need to conduct further research to introduce these functional foods in clinical practice.

Following this line, the interest in the exploration of the anti-obesity potential of probiotic strains has been growing in recent years (Kovatcheva-Datchary & Arora, 2013). A clinical trial performed with 134 volunteers (body mass index between 28.0 and 34.9) showed a reduction in the waist circumference by 2.4% (2.4 cm) after a daily supplementation with sachets containing 10^9 CFU of *B. animalis* ssp. *lactis* 420 (B420) for 6 months (Stenman et al., 2016). In addition, Jung et al. (2015) observed that daily supplementation of 120 overweight volunteers with a sachet containing 2 g of *L. plantarum* KY1032 and *Lactobacillus curvatus* HY7601 (2.5×10^9 CFU, each) influenced the reduction by 0.56% (0.5 cm) of waist circumference during the period of 3 months of intervention. Although both studies have shown significant reductions in waist circumference, it is important to note that the shorter intervention time and strain specificity may be responsible for the lower reduction in this parameter found in the last study. Moreover, studies suggest that a 2 cm reduction of waist circumference might be considered as clinically significant in the context of obesity since this could mean a reduction in mortality from stroke, heart disease, and other chronic diseases (Lemes, Turi-Lynch, Cavero-Redondo, Linares, & Monteiro, 2018). Dehghan, Gargari, and Jafar-Abadi (2014) reported that daily supplementation of 10 g of oligofructose-enriched inulin also contributed to the reduction of body weight and BMI of women with type 2 diabetes mellitus over 8 weeks of supplementation. Similar behaviour was observed by Dehghan, Farhangi, Tavakoli, Aliasgarzadeh, and Akbari (2016) in a clinical trial conducted with diabetic female patients. According to the researchers, daily supplementation with 10 g of oligofructose-enriched inulin during 2 months helped to decrease the BMI, waist circumference, and diastolic blood pressure of these patients.

Jones, Martoni, Pietro, Simon, and Prakash (2012) evaluated the influence of the daily intake of two capsules containing 2.9×10^9 CFU of *Lactobacillus reuteri* NCIMB 30242 in a randomized, multi-centre, placebo-controlled design. The authors reported that the probiotic strain did not influence the glycaemia levels of 124 hypercholesterolemic volunteers during 9 weeks of intervention. On the other hand, Ejtahed et al. (2012) evaluated the glycaemia levels of 60 diabetic patients who consumed 300 g/day of probiotic yogurt containing 1.8×10^6 CFU/g of *B. animalis* subsp. *lactis* Bb-12 and 1.9×10^6 CFU/g of *L. acidophilus* La-5 for 6 weeks of supplementation. According to the researchers, the changes in the intestinal microbiota related to the presence of probiotic microorganisms possibly contributed to a reduction in fasting glucose levels throughout the intervention period.

A systematic review and meta-analysis of 23 randomized, controlled clinical trials comparing the efficacy of synbiotic supplementation in obese individuals with placebo or no treatment (control) showed that synbiotic interventions including capsule and food (bread, dessert, beverage, and pomegranate) was able to reduce body weight and waist circumference (Hadi, Alizadeh, Hajianfar, Mohammadi, & Miraghajani, 2018). On other hand, it did not have any effects on the BMI and on the body fat. In a study with normocholesterolemic individuals, Sperry et al. (2018) found a significant decrease in total cholesterol, LDL-C cholesterol, triglycerides, diastolic and systolic pressure and an increase in HDL-C, haemoglobin, and haematocrit levels in 30 hypertensive overweighed women volunteers who consumed a probiotic cheese with *L. casei* 01 (10^8 CFU/g) during 4 weeks.

On the other hand, Xavier-Santos, Lima, Simão, Bedani, and Saad (2018) reported that daily consumption of either a synbiotic mousse containing *L. acidophilus* La-5 and the prebiotics inulin and fructooligosaccharides or the placebo product led to the reduction of total cholesterol and HDL-C in volunteers with MetS, suggesting that the presence of probiotic microorganisms and prebiotic ingredients in the diet mousse did not influence significantly the lipid profile of subjects with MetS.

Subclinical inflammation is an important indicator of metabolic risk of obesity (Devaraj, Singh, & Jialal, 2009; Pahwa, Adams-Huet, & Jialal, 2017; Robberecht & Hermans, 2016), relating to high sensitivity C-reactive protein (CRP) (Williams, Richardson, Johnson, & Churilla, 2017) as well as to other inflammatory biomarkers like leukocyte, neutrophil, and lymphocyte, associated with prevalence of MetS (Meng et al., 2017). Barreto et al. (2014) showed that the consumption of fermented milk containing *L. plantarum* Lp 115 led to a significant decrease in IL-6 levels in patients with MetS after 90 days of intervention.

Despite limitations involving clinical trials, it seems that probiotics and/or prebiotics could positively modulate the risk factors related to MetS. Nevertheless, differences found among the results of individual studies can be attributed to different protocols of administration and doses of probiotics and prebiotics products, besides differences between probiotic strains of the same species. In this sense, clinical trials using randomized, placebo-controlled experimental design, a large number of participants and a longer period of intervention should be conducted to clarify the efficacy of probiotics, prebiotics and synbiotics against MetS (Xavier-Santos et al., 2018). The daily supplementation with prebiotics and/or probiotics is an interesting non-pharmacological strategy for modulating the intestinal microbiota and, consequently, promoting improvements in the parameters associated to MetS, as shown in animal and human studies. However, it is important to note that there is a discrepancy in the results obtained among these clinical studies with animal and human, which may be due to the interaction between the microorganisms present in the intestinal microbiota and the host. Moreover, particular genotypes are also important factors that should be considered in clinical trials.

5. Mechanism of action of probiotics and prebiotics in the context of MetS

The mechanism of action of probiotics and/or prebiotics on the host has not yet been clearly elucidated. However, several studies using *in vivo* and *in vitro* models have supported the hypothesis that probiotics and/or prebiotics could reduce the risk factors related to MetS (Daliri & Lee, 2015; Scavuzzi et al., 2015). However, there is a consensus in the scientific community that the mechanisms of action of probiotic microorganisms are strain-specific (Higashikawa et al., 2010; Ooi & Liong, 2010).

5.1. Hypocholesterolemic effect

Probiotics, prebiotics, and synbiotics can be involved, for example, in the reduction of cholesterol levels, but the mechanisms have not been fully elucidated (Bedani et al., 2015; Miremadi et al., 2016; Zhang et al., 2017b). The main mechanism of action of prebiotics is based on their ability to reduce lipid levels in the bloodstream by the presence of SFCA produced upon selective fermentation of the prebiotic substrate by the intestinal microbiota (Miremadi et al., 2016). SCFAs are absorbed and used as an energy source to the host. On the other hand, they are also known to play an important role as metabolic regulators (Tremaroli & Bäckhed, 2012). In general, SCFAs produced from a prebiotic substrate can inhibit the synthesis of hepatic cholesterol and/or assist in the redistribution of cholesterol from the plasma to the liver (Al-Sheraji et al., 2012; Fernández et al., 2016; Wong, de Souza, Kendall, Emam, & Jenkins, 2006).

One of the mechanisms responsible for the hypocholesterolemic effect of probiotics is related to the assimilation and/or incorporation of the cholesterol molecule into the bacteria cell membrane during the microbial growth phase (Alhaj, Kanekanian, Peters, & Tatham, 2010; Kumar et al., 2012). On the other hand, the binding of cholesterol to the cell surface can occur independently of the physiological state of the cell (living or dead) (Kimoto, Ohmomo, & Okamoto, 2002). Nevertheless, the researchers still reported that some microorganisms in the growth phase can remove higher levels of cholesterol compared to the dead cell. Along this line, Choi and Chang (2015) demonstrated in an *in vitro* study that *L. plantarum* EM has a great ability to bind the cholesterol molecule to its cell surface, regardless of its viability. Thus, this mechanism of action may reduce the cholesterol absorption from the gastrointestinal tract after the binding of this lipid molecule to the probiotic cell surface (Lye, Rahmat-Ali, & Liong, 2010). Besides this, the inhibition of bile acid reabsorption mediated by bile acid hydrolase from some probiotic bacteria that catalyse the deconjugation of bile acid salts, releasing free bile acids excreted in faeces; the co-precipitation of cholesterol with deconjugated bile salts; and the conversion of cholesterol in coprostanol are other possible mechanisms that could explain the potential hypocholesterolemic of some probiotic strains (Ooi & Liong, 2010).

5.2. Anti-hypertensive effect

Some studies indicate that daily supplementation with *L. plantarum* and *L. casei* strains showed a potential anti-hypertensive effect in hypertensive volunteers (Nakajima et al., 1995; Naruszewicz, Johansson, Zapolska-Downar, & Bukowska, 2002). As observed by Lollo et al. (2015) in a study conducted with rats, probiotics contributed towards the reduction of blood pressure through the degradation of proteins from the food matrix, mainly milk protein, releasing bioactive peptides with a hypotensive effect that act on the renin-angiotensin system. Thus, proteolytic activity of various probiotics through the fermentation process can help to release ACE inhibitory peptides responsible for a blood-pressure lowering effect (Fekete, Givens, & Lovegrove, 2013; Gonzalez-Gonzalez, Gibson, & Jauregi, 2013; Mazidi et al., 2016).

5.3. Modulation on obesity-related parameters

The supplementation with prebiotic ingredients can contribute to the anti-obesity potential through the stimulation of physiological functions responsible for insulin secretion (Kovatcheva-Datchary & Arora, 2013), through the multiplication of β-pancreatic cells (Delzenne, Cani, & Neyrinck, 2007; O'Connor, Chouinard-Castonguay, Gagnon, & Rudkowska, 2017; Panwar, Rashmi, Batish, & Grover, 2013; Roberfroid et al., 2010). Moreover, the stabilization of the gut microbiota composition of obese individuals alters adiposity and influences the metabolic capability of peripheral organs, which are responsible for satiety control in the brain; secretion of intestinal hormones such as PYY and GLP-1 (Tremaroli & Bäckhed, 2012), responsible for appetite control (Kovatcheva-Datchary & Arora, 2013), reduced risk of MetS, chronic non-communicable diseases (obesity, type 2 diabetes), intestinal inflammation, colon cancer, energy metabolism, and satiety (Martinez-Gutierrez et al., 2017; Morris & Morris, 2012).

The SCFAs modulate uncountable specific cellular functions from the interaction with specific receptors inserted into the G protein coupled receptors such as GPR41 and GPR43 (Tremaroli & Bäckhed, 2012). These receptors are responsible for the secretion of intestinal hormones like glucagon-like peptide-1 (GLP-1) that prolong the gastric phase and time of intestinal transit, and consequently, the rate of nutrient absorption becomes higher (Kaji, Karaki, & Kuwahara, 2014; Remely & Haslberger, 2017; Wichmann et al., 2013), while protein YY (PYY) is important for other functions such as controlling caloric intake and appetite, inhibits intestinal motility and stomach emptying, besides contributing to the increased absorption of nutrients, water, and electrolytes in the gastrointestinal tract (Remely & Haslberger, 2017; Wu, Zhou, Hu, & Dong, 2012).

However, evidence suggests that the composition of the intestinal microbiota might influence the loss of function of the toll-like receptor-5 (TLR-5) in humans (Hartstra, Nieuwdorp, & Herrema, 2016). In this sense, Al-Daghri et al. (2013) suggest that the loss of the human TLR5 function may protect from weight gain; on the other hand, in analogy with the animal model, the nonsense allele may predispose to type 2 diabetes. The authors reported that these findings reinforced the hypothesis that metabolic diseases are associated with immune dysregulation. It remains to be determined whether these effects on the loss of function of TLR5 in humans influence modifications in the microbiota composition.

5.4. Glycaemic control

A clinical trial conducted by Tonucci, Santos, Oliveira, Ribeiro, and Martino (2017) lead to the conclusion that daily consumption of probiotic fermented milk containing *L. acidophilus* La-5 and *B. animalis* subsp *lactis* BB-12 improved glycaemic control in volunteers with type 2 diabetes mellitus, suggesting that the presence of probiotic microorganisms in the drink contributed to the control of diabetes. The researchers hypothesized that immune modulation contributed for improved glycaemic control after supplementation with probiotic strains. In this sense, glycaemic control and insulin resistance are associated with the interaction of a set of key inflammatory and anti-inflammatory cytokines like adiponectin, resistin, IL-6, and TNF-α that contribute directly to glucose homeostasis (Fasshauer & Paschke, 2003; Magrone & Jirillo, 2013; Tonucci et al., 2017).

In this sense, Cossío et al. (2017) verified that the chronic administration (8 weeks) of oligofructose to obese and type-2 diabetic db/db mice (mouse model of MetS) improved excessive food ingestion and glycemic dysregulations (insulin resistance and glucose tolerance) and increased the plasma levels of IL-10 (anti-inflammatory cytokine) and hypothalamic mRNA expression of the anorexigenic cytokine IL-1ß. The authors also detected signs of improved blood-brain hurdle integrity in the hypothalamus of oligofructose-treated db/db mice (normalized expression of narrow junction occludin and proteins ZO-1).

On the other hand, supplementation with *Bifidobacterium* and *Lactobacillus* strains, together, tend to improve glucose tolerance due to elevation of SCFA and butyrate that induce GLP-1 production in the intestinal microbiota (Kassaian, Feizi, Aminorroaya, & Amini, 2018; Yadav, Lee, Lloyd, Walter, & Rane, 2013). It is noteworthy that the meta-analysis conducted by Zhang, Wu, and Fei (2016) suggested that probiotic strains might improve the glucose metabolism slightly. However, this activity might by highly increased if the duration of the supplementation period is longer than 8 weeks or when multiple species are consumed simultaneously. Thus, the results obtained by Razmpoosh et al. (2019) suggest that other forms of administration (capsule, etc.) and a longer period of intervention are needed to evaluate the influence

of other important factors that may contribute to improve parameters associated to MetS.

5.5. Modulation of the process of low-grade inflammation

Clinical and epidemiological studies have indicated that low-grade inflammation may contribute for the development of obesity-associated metabolic disorders (Cani & Hul, 2015; Febbraio, 2014). In this sense, evidence demonstrate that markers of systemic inflammation should be included in the definition of MetS since it plays an important role in this pathogenesis (Synetos et al., 2016).

Furthermore, Cani et al. (2009) observed that the increase of the endogenous production of glucagon-like peptide-2 (GLP-2) in function of the supplementation with prebiotics may contribute to the reduction of metabolic endotoxemia, and, consequently, to the reduction of the process of low-grade inflammation. On other hand, the gut microbiota composition is directly associated to metabolic disturbances and increased obesity. In this case, the supplementation with probiotic strains has become a promising non-pharmacological alternative in the prevention of metabolic endotoxemia and weight gain, contributing to the prevention of the process of dysbiosis associated with obesity (Lee et al., 2014). Thus, the administration of probiotic strains and/or prebiotics in the diet of individuals with MetS might contribute to the reduction of Gram negative bacteria in the intestinal microbiota, preventing the development of metabolic endotoxemia by reducing serum LPS levels, and, consequently, the inflammatory process.

Thakur et al. (2016) observed that among *Lactobacillus* strains, only *L. casei* Lbs (MTCC5953) showed the ability to reduce the secretion of the tumour necrosis factor alpha (TNF-α) and IL-6 after induction by the presence of LPS in an *in vivo* assay with rats. Besides, *L. rhamnosus* GG showed the ability to modulate the immune system through the reduction in IL-8 levels induced by TNF-α (Zhang, Li, Caicedo, & Neu, 2005). Consequently, in addition to inhibiting the secretion of IL-8, this strain stimulated increased levels of nerve growth factor (NGF), responsible for the anti-inflammatory effects (Ma, Forsythe, & Bienenstock, 2004). According to Jakobsdottir, Nyman, and Fak (2014), an unbalanced intestinal microbiota originating from a dysbiosis process may act as a driving force for the beginning of low-grade systemic inflammation in subjects with MetS.

The scientific literature has also presented much evidence of the probiotic potential of *Akkermansia muciniphila* for the prevention and treatment of metabolic disorders associated with the development of cardiometabolic diseases (Zhou, 2017). This bacterium belongs to the *Verrucomicrobia phylum*, is strictly anaerobic, and is found along the mucosal surface of the gastrointestinal tract (Collado, Derrien, Isolauri, de Vos, & Salminen, 2007; Huang et al., 2015). The surface colonization of the intestinal mucosa by *A. muciniphila* may become more stable when associated with other beneficial microorganisms of the gut microbiota (Derrien et al., 2017). Everard et al. (2013) showed that the daily administration of *A. muciniphila* for 4 weeks in the diet of obese and diabetic mice reversed high-fat diet-induced obesity, insulin resistance, and type 2 diabetes. Additionally, the abundance of this species negatively correlated with the levels of gut permeability and inflammation markers. Zhou (2017) hypothesized that the reduction of the endotoxemia induced by elevated serum LPS levels, responsible for inflammation and metabolic disorders, may be mediated by the activity of metformin in the intestinal microbiota, since this drug can increase the presence of *A. muciniphila* in the gut. Besides, *A. muciniphila*, as a mucin-degrading bacterium that resides in the mucus layer, can also stimulate mucin synthesis (Derrien et al., 2017). These studies also reported that reduced levels of this microorganism have been found in individuals with inflammatory bowel diseases and metabolic disorders.

In general, studies have suggested that *A. muciniphila* can cross-talk with the host, present potential anti-inflammatory responses, promote barrier integrity, and potentially modulate resident intestinal microbiota (Derrien et al., 2017). Therefore, *A. muciniphila* could induce specific host responses compared with other potential beneficial microorganisms (Everard et al., 2013).

5.6. Reduction of trimethylamine-N-oxide levels

Several studies have explored the effects of probiotic consumption on the control of cardiovascular risk factors and the possibility of manipulating the composition and metabolism of the intestinal microbiota through the use of probiotics is an exciting aspect to be considered in the context of MetS (Org et al., 2015). In this regard, modulation of the intestinal microbiota composition through the ingestion of probiotic microorganisms to cause a decrease in trimethylamine (TMA) production and trimethylamine-N-oxide (TMAO) levels in the host has attracted the attention of the scientific community (Tang & Hazen, 2015).

TMAO is an intestinal microbial co-metabolite that has drawn a lot of attention both as a biomarker for CVD risk and as a promoter of atherothrombotic diseases, which has supported the link between the gut microbiota and CVD (Brown & Hazen, 2018). According to the researchers, the control of TMAO pathway could be considered as a promising target for CVD drugs focused on the intestinal microbiome.

The TMAO biosynthesis may occur in response to dietary intake of nutrients that contain a TMA [$N(CH_3)_3$] moiety, such as phosphatidylcholine, choline, and L-carnitine (Battson, Lee, Weir, & Gentile, 2018; Tang, Bäckhed, Landmesser, & Hazen, 2019). Examples of dietary sources rich in these nutrients are red meat, fish, dairy, and egg yolk (Drosos, Tavridou, & Kolios, 2015). In the intestines, the microbial catabolism of these nutrients occurs through the action of microbial TMA-lyase (CutC) and its activactor CutD (Schiattarella, Sannino, Esposito, & Perrino, 2019; Tang et al., 2019). TMA produced in the gut is absorbed and enters the portal circulation and subsequently it is transferred to the liver where it is oxidized into TMAO by hepatic flavin monooxygenases (FMO), particularly FMO3. Afterwards, TMAO enters the systemic circulation (Tang et al., 2019). According to the authors, the specific receptor or chemical sensor for TMAO that promotes the atherosclerotic process remains unknown.

Although TMAO, an intestinal microbiota metabolite, has been shown to be a predictor of incidental cardiovascular events, unfortunately clinical trials have shown that supplementation with probiotic strains were not able to influence TMAO levels (Borges et al., 2018; Boutagy et al., 2015; Halloran & Mark, 2019; Tripolt et al., 2015). According to Tripolt et al. (2015), some limitations should be considered in clinical trial when evaluating the modulation of intestinal microbiota based on TMAO levels: (i) pilot studies are insufficient to provide a robust response on the probiotic influence in the formation of TMAO; (ii) as in any clinical trial, a sum of nutritional factors may result in antagonistic effects in results; (iii) the dose used in studies may be insufficient to promote health benefits; (iv) administration time may be short to influence the formation of TMAO. Thus, the authors suggest that clinical trials with human volunteers are needed to evaluate whether different probiotic strains are sufficient to intervene in the production of TMAO.

6. Conclusions and future prospects

Recently, the manipulation of the intestinal microbiota employing specific microorganisms and substrates to benefit the host metabolism has received substantial interest. Overall, there are several findings showing that the beneficial modulation of the intestinal microbiota and the immune system using probiotics and/or prebiotics can improve the characteristic parameters of MetS. Nevertheless, more properly designed animal and human trials may disclose further knowledge to clarify controversies about the effects of pro- and prebiotics and their doses on the risk factors of MetS and to provide a more comprehensive understanding of the mechanism of actions involved. Factors to be clearly elucidated include the minimum amount necessary to achieve beneficial effects, the supplementation period, the endurance of this

effect, and possible contraindications. Various mechanisms have been proposed to explain the benefits of probiotic microorganisms on MetS; however, it is noteworthy that the strain specificity and time of administration are important aspects that must be considered in relation to probiotic effects and their mechanisms of action. In addition, the chemical structure of prebiotic compounds is a key factor and should be considered for modulation of intestinal microbiome promoted by microorganisms. In this context, clinical randomized placebo controlled studies, using, for example, a large number of subjects, must be performed in order to clarify the effectiveness of probiotics and prebiotics on the prevention and management of MetS, supporting their potential use in clinical practice.

In addition, paraprobiotics and postbiotics are attractive options as functional foods for modulating the intestinal microbiota aiming at enhancing the parameters associated with the development of MetS. Paraprobiotics are defined as "inactivated (non-viable) microbial cells, which, when administered in sufficient amounts, confer health benefits to the consumers" (Guimarães et al., 2019). On the other hand, postbiotics are "metabolic byproducts of LAB which are excreted into cell-free supernatant of bacterial suspension during the bacterial growth" (Moradi, Mardani, & Tajik, 2019).

Based on the review by Gibson et al. (2017), the plant polyphenols have demonstrated a great prebiotic potential. In this sense, they also have the ability to favor the development of beneficial microorganisms in the intestinal microbiota (Thilakarathna, Langile, & Rupasinghe, 2018) and might contribute for potential effects in the context of MetS. Therefore, future perspectives indicate that modulation of the microbiome by polyphenols and probioactives (paraprobiotics and postbiotics) is a promising therapeutic alternative for improving the health of individuals with MetS.

Ethics statement

The authors state there are no Ethical matters involved in the study, since the study did not enroll human beings and, also, did not deal with animals.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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