



MAJOR APPROACHES TO THE INFLUENCE OF THE MICROBIOME ON THE HEALTH-DISEASE PROCESS AND PROBIOTIC THERAPY: A REVIEW

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ABSTRACT

A healthy intestinal microbiota is responsible for maintaining intestinal barrier homeostasis, non-digestible food metabolism, and protection against pathogens. Fluctuations in the composition of the intestinal ecosystem have been associated with several diseases, such as immune-inflammatory disorders, type I and II diabetes, obesity, intestinal infections or inflammation, autism spectrum disorders, as well as related to stress, anxiety, and depression. Dietary changes or the use of probiotics, prebiotics, and symbiotics can significantly influence the gut microbiota, its functionality, and its relationship to host health. These interventions appear as a therapy aimed at a number of diseases that are affected by, or interact with, an imbalance of the intestinal microbiota. These therapeutic methods have the ability to improve the functionality of the intestinal microbiota by targeting healthy individuals, the elderly, children, immunocompromised patients or genetically susceptible individuals. This review aims to report current literature data on the clinical efficacy of probiotics and prebiotics in the treatment of some disorders correlated with intestinal microbiome imbalance and to verify other types of microbiome-based treatment.

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INTRODUCTION

In mammals there is a high density of cells that make up the intestinal microbiota, this, being the most abundant place where these microorganisms inhabit, which play an important role in the disease health process, is widely studied. According to the HMP (Human Microbiome Project) "The human microbiome is made up of a collection of all the living microorganisms associated with the human body" in different niches like skin, oral and nasal cavities, mucous membranes, gastrointestinal tract (TGI) etc., and is composed of a variety of living things such as prokaryotes, viruses, archaea domain members, and fungi (Bäckhed, 2012). The microbiome has a huge diversity among communities, with different transcriptionally regulated genetic elements. Thus, its composition depends not only on the phenotype of the individual, such as age, ethnicity, gender, and body mass index but also on their immune, emotional state, and diet. The main functionality of these beings is related to the digestion and degradation of sugars, especially those not digested by

humans, and the synthesis of small fatty acids and vitamins. According to Bäckhed (2012), a healthy microbiota is defined as an ecologically stable community, resistant to change in case of stress or that can return to homeostasis after imbalance and several studies have shown the importance of a healthy microbiota in reducing the risk of diseases and diseases maintenance of health (Bäckhed, 2012 and Martinez, 2015). Its functions include an important role in the functional and morphological development of the immune system, functioning as an immune reactor in the first days of life; mucosal barrier fortification, nutrient absorption, angiogenesis, intestinal epithelial permeability, protection against pathogens and production of antimicrobial compounds (Martinez, 2015; Gensollen, 2016 and Di Mauro, 2013). A stable intestinal microbiota is essential for maintaining an individual's homeostasis and reducing the risk of disease, which may be related not only to a pathogen but to dysbiosis caused by treatment with antibiotics, obesity, aging, diet change among others (Blandino, 2016). Understanding this relationship between loss of population in the intestinal microbiome and disease is essential for directing effective therapies for such

health problems, either with individualized dietary interventions or through probiotics, prebiotics or symbiotics. The major disease states or disorders that correlate with the host intestinal microbiota are obesity; insulin resistance; type 2 diabetes; Crohn's disease; autoimmune diseases such as type 1 diabetes; cardiovascular diseases, and neurological disorders, such as depression, anxiety, stress and even autism (Martinez, 2015). Thus, it is necessary to search for new therapeutic methods that can reduce the incidence and even prevent it. In this sense, there is a growing interest in alternatives that may beneficially improve the health status of the individual and the consequent risk of disease development through modulation of the microbiota. Given these discussions, the present study aimed to report data from the current literature on the clinical efficacy of probiotics and prebiotics in the treatment of some disorders correlated with intestinal microbiome imbalance, as well as their advantages and to verify other types of treatment that correlate with the subject matter.

MATERIALS AND METHODS

The proposed revision methodology was performed by searching for articles on PUBMED, NIH, NCBI and Science Direct platforms, and the Human Microbiome Project website with studies on humans and animal models. Using keywords such as “the human gut microbiome”, “gut microbiota and probiotics”, “dysbiosis”, “prebiotics”, “fecal transplant”. The articles used in the discussion have a more clinical aspect considering the treatment methods used for intestinal microbiota homeostasis.

Development: Diet can have a lasting and sudden impact on the composition, proportion, and functionality of bacteria in the gut microbiome, and consequently these dietary interventions are known as “biological therapies” including probiotics, prebiotics, postbiotics, dietary fibers, and symbiotics, they are used to mediate health status (Barathikannan, ?). Concern about eating habits is growing and also its relationship with health and longevity has leveraged studies in the field of food science and nutrition. microbiome-based therapies aim to improve health by maintaining homeostasis and preventing dysbiosis. Through the proliferation of specific microbiome species known to produce beneficial metabolites and competition for adhesion site and substrate with pathogenic microorganisms, as well as the production of antimicrobial substances by resident microbiota and pH reduction (Martinez, 2015). Probiotics are defined as “living microorganisms which when administered in adequate amounts confer a benefit to the host” (FAO/WHO, 2006).

Potentially probiotic bacteria belong to the group of lactic acid-producing bacteria (LAB), belonging to the *Firmicutes* phylum, a diverse group that includes *Aerococcus*, *Lactobacillus*, *Lactococcus* among others, and *Bifidobacterium*, although they belong to the Phylum *Actinobacteria* (König, 2017). However, for a bacterium to be considered a probiotic and to be incorporated into the diet, it is necessary to fulfill some requirements, such as safety, storage, and distribution method, among others (Martinez, 2015). Probiotics compete with pathogenic microorganisms for adhesion sites and nutrients, increasing the composition of the healthy microbiota. In addition, they produce different bactericidal compounds, thus forming a “resistance colonization” (Saad, 2006). Imbalance of the normal intestinal microbiota may lead to an increase in pathogenic

microorganism populations and, consequently, the occurrence of intestinal infections. Several clinical studies have been or are being conducted to evaluate the use of certain strains for the treatment of intestinal infections with probiotic therapy (Saad, 2013). Studies show that the administration of specific strains at the onset of diarrhea episodes in children led to a reduction in the duration and intensity of the infection (Floch, 2011 and Guarino, 2015). Although most doctors are still afraid of using probiotics as the first line of treatment for intestinal infections, in Europe probiotic therapy is already widely used to treat childhood diarrhea (Wolwers, 2010). However, the results found in the literature show heterogeneity regarding the functionality and benefit of probiotics in *Clostridium difficile* infections after antibiotic therapy. A pioneering study demonstrated the effectiveness of using *Lactobacillus* GG against diarrhea commonly caused by antibiotic use (Vanderhoof, 1999). A systematic review of the effectiveness of probiotics indicated that in the literature the evidence does not support the use of probiotic therapy in the treatment of *C. difficile* infections (Dendukuri, 2005). There are also clinical trials using *Saccharomyces boulardii* yeast to reduce the effects of antibiotic diarrhea (Dendukuri, 2005). Thus demonstrating that although selected probiotics have the ability to reduce the incidence and duration of diarrheal episodes, not all probiotic microorganisms are equally effective in treating diarrhea associated with antibiotic therapy and *C. difficile* infection.

According to the World Health Organization (WHO), obesity and overweight are defined as abnormal or excessive fat accumulation, which poses a health risk (WHO, 2015). Obesity is a risk factor for several chronic diseases, such as diabetes, cardiovascular disease and cancer, and the pivot for the occurrence of metabolic syndrome (Alberti, 2005). In addition to eating excess carbohydrates and saturated fats, genetic and environmental factors, the intestinal microbiota plays an important role in the pathogenesis of obesity. Obesity is associated with the prevalence of the *Firmicutes* population and reduced incidence of *Bacteroidetes*, both in animal models and in obese patients (Le Barz, 2015 and Barrett, 2012). Studies have elucidated in an animal model the mechanisms by which *Firmicutes* affect the absorption of fatty acids and lipid metabolism. The intestinal microbiota promotes the accumulation of fatty acids in the intestinal epithelium, these lipid vacuoles found in these cells are generated by bacterial metabolism; and in association with diet, there is an increase in the number of adipocytes. Thus indicating that fat accumulation also depends on the diet and not only on the presence of the microbiota (Semova, 2012). There are four described mechanisms that lead to fat accumulation i) members of the intestinal microbiota decrease the rate of fatty acid oxidation by decreasing fasting-induced adiposity factor (FIAF) produced in the intestine. FIAF normally inhibits the lipase activity of adipocyte lipoproteins (LPL), thereby reducing the release of fatty acids from circulating triacylglycerols. With the reduction of FIAF, there is an increase in LPL activity, an increase in free fatty acids and an increase in fat storage (Bäckhed, 2004). ii) there is also an indirect increase in carbohydrate and fatty acid absorption by the host intestinal epithelium, through innate physiological changes (Semov, 2012); iii) increased bioavailability of fatty acids by modifying the composition or production of bile acids in various compartments (Swann, 2011). iv) and microorganisms may also perform direct interactions on the luminal lipolytic activity of the host (Semova, 2012).

Fluctuations in the composition of the intestinal microbiota may lead to instability or intestinal dysbiosis, which is correlated with disease states such as obesity, with a prevalence of dysbiosis observed in obese or overweight patients. In addition to the previously mentioned bacterial populations, there are important members of human diners who also relate to obesity dysbiosis. Some bacteria from the family *Prevotellaceae* and *Enterobacteriaceae* have been associated with obesity (Iqbal, 2014 and Yakovlieva, 2015). However, bacteria from the *Christensenellaceae* family are abundant in individuals with low body mass index (Iqbal, 2014), and there is a prevalence of *Lactobacillus* in adolescents who recently lost weight (Huang, 2013). Thus, in addition to understanding the mechanisms by which microbiota can lead to weight gain in association with a high-fat diet, it is also necessary to understand which microbiota components are involved in obesity or non-obesity. In this sense, it is essential to study the dynamics of the microbiome to provide new treatments and a better understanding of susceptibility biomarkers for obesity and other diseases, in which obesity is an aggravating factor.

In addition to the use of probiotics to combat intestinal infections, studies also discuss possible treatments for obesity based on changes in microbiome composition (Barathikannan, ?). Considering the relationship between obesity and metabolic disorders, and the ability of the microbiota to mitigate some of these interactions, recent studies focus on the modulation of the intestinal microbiota of obese to neutralize such metabolic deficits as insulin resistance, intolerance to glucose, high blood glucose levels, and adiposity. In studies performed on lean Zucker mice, Hatstra *et al.* (Hartstra, 2015) found that administration of *Lactobacillus gasseri* SBT 2055 led to a reduction in mesenteric adipose tissue, adipocyte size, and reduced serum leptin levels. Similarly, increased insulin sensitivity was observed following administration of *Lactobacillus casei* of the Shitora strain in obese mice fed a high-fat diet, as well as a decrease in glucose intolerance (Le Barz, 2015). In addition to the effects observed in animal models, studies have demonstrated the impact of probiotic therapy in humans to improve metabolic conditions. Preventing gestational diabetes mellitus in overweight and obese pregnant women (Callaway, 2019), reducing fat mass in obese adults (Kim, 2018), improving high-intensity cholesterol (HDL) (Minami, 2018) and increasing weight gain during obesity. pregnancy or at birth (Okesene-Gafa, 2019).

The TGI has an intrinsic nervous system, also called the Enteric Nervous System (SNE), which has several physiological functions, such as gastrointestinal motility control, fluid secretion, absorption and redirection of blood flow (Furness, 2012). Concomitantly with the colonization of TGI, there is the maturation of the mucosal immune system and neuronal and cognitive development. Disorders in early bowel colonization in early postnatal life, such as early maternal separation and formula feeding can trigger dysfunctions such as depression and anxiety (Borre, 2014). Monoamines, such as serotonin, are responsible for regulating cardiovascular function, gastric motility, maintaining body temperature, vasodilation and also participating in the immune response. About 90% of serotonin (5-hydroxytryptamine, 5-HT) is produced by enterochromaffin cells, endocrine cells that make up the intestinal epithelium (O'Mahony, 2015). And recent studies demonstrate the participation of microbiota in the induction of intestinal biosynthesis of 5-HT through the

production of short-chain fatty acids (Yano, 2015 and Reigstad, 2015). Studies carried out in germ-free mice transplanted with the microbiota of conventional animals have shown that the microbiota exerts a 5-HT-dependent modulation in the anatomy of the SNE in adults (De Vadder, 2018), which in the SNE has neurogenerative and neuroprotective functions (Liu, 2009). Consequently, a serotonergic pathway-related TGI dysfunction may result in brain disorders correlated with sleep, mood, and behavior (Berger, 2009). Evidence supported by another study with germ-free mice, in which serum serotonin levels decreased and depression and anxiety behaviors increased (Neufeld, 2011). Given these findings, it is also important to understand how diets that impact the composition of the microbiota can impact the individual's mental state. One study revealed that a high-carbohydrate, low-fat diet is related to changes in the gut microbiome, and thus promotes a state of reduced synaptic plasticity, which causes glutamate receptor hypoactivity, and susceptibility to anxiety symptoms (Degruittola, 2016). Some studies elucidate the relationship between Autistic Spectrum Disorder (AED) and schizophrenia, and that there is still a high incidence of intestinal diseases caused by *Clostridium difficile* (Louis, 2012 and Argou-Cardozo, 2018). Many of these patients still have what is called a 'loose bowel', with high intestinal permeability. Studies have also shown that lactose malabsorption in women was correlated with depression. This impairment occurs due to the high concentrations of intestinal lactose that affects serotonin signaling (Ledochowski, 1998). And it is well documented that the improvement of lactose digestion through the use of probiotics is correlated with the reduction of the existing brain condition (Kadooka, 2010).

There are already some experimental advances, demonstrating the efficacy of the administration of *Bacteroides fragilis* and *Bifidobacterium*, in the correction of intestinal permeability and improvement of communication, stereotypic and anxiety behaviors observed in AED; and reestablishment of norepinephrine in the central nervous system, reduced inflammation or gastrointestinal infection and anxiety symptoms in mice with maternal contact deprivation, symptoms observed in schizophrenic patients, respectively (Hsiao, 2013 and Dickerson, 2014). However, there is still little clinical progress on the efficacy of probiotic treatment to improve the psychiatric and mental picture of patients with AED or schizophrenia. Given the above, it is reasonable to suppose that the intestinal microbiota influences cerebral neurobiochemistry, regardless of central autonomic modulations or inflammatory state, and that changes in intestinal microbiome stability may contribute to psychiatric disorders in patients with intestinal disorders. Prebiotics are classified as non-digestible food products that selectively benefit the host by promoting the growth and development as well as the activity of one or more species of microbiome bacteria (Pineiro, 2008). These compounds are non-digestible and non-hydrolyzable by digestive enzymes such as fructooligosaccharides (FOS), soybean oligosaccharides, galactooligosaccharides (GOS), inulin, cyclodextrins, isomalto-oligosaccharides (51). Like probiotics, for human dietary use, prebiotics needs to be specific, selective and fermentable by one or more beneficial TGI bacteria. Fiber is prebiotic that after its metabolic conversion by the host microbiota, it may confer health benefits, such as improved glycemic control in patients with type 2 diabetes (Zhao, 2018). The type of bacterial community that results from fiber consumption will depend on the molecular structure of the

fiber, the enzymatic potential for degradation and utilization of microorganisms and their ability to tolerate changes in the fermentation-mediated gastrointestinal environment. There is growing evidence indicating the positive influence of prebiotic therapy on microbiota composition, increasing the growth of *Bifidobacterium* and *Lactobacillus* populations in the gastrointestinal tract of obese animals (Barathikannan, ?). Milk oligosaccharides, commonly found in human breast milk, promote the multiplication of beneficial bacteria such as *Bacteroides* and *Bifidobacterium*, which compete for local pathogens (Underwood, 2015) in humans. Evidence also indicates the role of oligofructose as a beneficial microbiota substrate in promoting glucose homeostasis and increasing leptin sensitivity in mice (Everard, 2011) and in treating patients with recurrent intestinal infection by *C. difficile* (Lewis, 2005).

Although there are no clinical studies on the efficacy of using prebiotics to improve schizophrenia, studies in animal models reveal the effect of GOS prebiotic therapy in reducing neuroinflammation and anxiety, indicating this as a possible treatment for patients with neuropsychiatric disorders (Savignac, 2016). In addition, GOS administration in healthy human patients revealed suppression of neuroendocrine stress response and increased processing of positive responses to negative situations (Schmidt, 2015). Recently, fecal microbiota transplantation (TFM) has been seen as a widely used clinical treatment method because of its safe, innovative and easy-to-handle approach to treat difficult diseases such as recurrent intestinal infection by *C. difficile* (Gough, 2011). Being 92% of the cases of *C. difficile* infections, eliminated through the TFM (De Vos, 2013). TFM involves transplantation of the intestinal microbiota from a specific donor to a recipient; however, there are some donor-excluding factors. These include i) infectious diseases; ii) age above 50 years; iii) personal or family history of infectious diseases or gastrointestinal malignancy; iv) recent trips to endemic sites of gastrointestinal pathogens, and v) antibiotic therapy in the last 6 months (Zhang, 2019). TFM can occur through the ingestion of frozen oral capsules, enemas, nasojejunal tube administration, and colonoscopy (Madar, 2019).

Studies also show that patient acceptance of treatment is high, even considering the unpleasant nature of the procedure (Kahn, 2013). A survey conducted in Romania also found that there is a low percentage of medical students who know about the treatment of FMD, studied about or would indicate as the first line of treatment for recurrent *C. difficile* infections (Madar, 2019). Although TFM is a promising therapy for treating disorders associated with intestinal dysbiosis, there is little evidence of its efficacy in treating metabolic disorders, AEDs and schizophrenia. There are currently some registered clinical trials for the treatment of obesity with FMD in humans. Most studies focus on the use of probiotics, prebiotics, and TFM as microbiome-based biological therapies, which is a methodology for bringing the patient to health status. However, it is also worth mentioning the use of probiotics and prebiotics in the food industry, with the use of *Lactobacillus casei*, *B. lactis*, *L. rhamnosus* strains, to modulate the immune response (Ashraf, 2014), adipokine inhibition and adipose tissue reduction, promoted by the presence of *L. gasseri* BNRH; reduction of oxidative stress by *L. casei* (Sharma, 2016) and hypocholesterolemic effects promoted by *L. acidophilus*, *B. longum*, *L. casei* (Kang, 2013 and Scheiman, 2019). In addition to these benefits for

maintaining body homeostasis, studies also demonstrate the potential use of probiotics for performance improvement. In the analysis of the stool sample of marathon athletes, it was found in abundance, post-marathon, the genus *Veilonella*. After isolating this strain, the bacteria were administered to mice submitted to an exhaustive treadmill test, and it was observed that they had a longer exhaustive run time compared to animals administered placebos. In a metabolomic analysis, researchers have elucidated the mechanisms by which this intervention improves performance, thus demonstrating the ability of *Veilonella* atypical bacteria to metabolize lactate to propionate, a short-chain fatty acid. Both the presence of *V. atypical* and rectal propionate infusions have been shown to have the same effect on the animals' athletic performance. Although there are no studies to prove the efficacy of *V. atypical* as probiotic or propionate as postbiotic in humans, this study opens the door for future studies on the efficacy and applicability of these dietary supplements for improving or improving exercise (Scheiman, 2019).

Final Considerations

The interactions between microbiota and humans are studied. A healthy microbiota is responsible for maintaining intestinal barrier homeostasis, human-indigestible food metabolism, and protection against pathogens. In addition to these functions, the microbiota is responsible for the maturation and development of the mucosal immune system, as well as the establishment of an inflammatory tone that prevents the exacerbation of an immune response in the presence of antigens originating from the microbiota and ingested food. Changes in diet regarding the amount, type and balance of macronutrients (carbohydrates, proteins, and fats) can significantly affect the diversity of intestinal microbiota, with the prevalence of some populations that may have negative effects on host health. It is therefore of interest to study how this microbiota behaves in the face of fluctuations in its composition and organization. Such changes, known as dysbiosis, are associated with diseases such as obesity, intestinal inflammation, neuropsychiatric and autism spectrum disorders, which involve changes in catecholaminergic and serotonergic pathways. Ingestion of probiotic and prebiotic microorganisms is an alternative microbiome-based biological therapy that beneficially influences the interaction of the intestinal microbiota with the host, maintaining intestinal and metabolic homeostasis and controlling dysbiosis, even when pathogen-induced, improving the health of the individual. Several studies suggest the efficacy and clinical applicability of probiotics and prebiotics as therapy for the treatment of intestinal infections, mainly recurrent ones caused by *Clostridium difficile* and anti-obesity therapy or attenuation of metabolic changes caused by obesity. There are still a few human studies on the efficacy of these therapies for the treatment of AED and schizophrenia. Although promising results have already been shown in modulating behaviors of stress, anxiety, and depression, among other symptoms that characterize AED and schizophrenia in animal models. Another promising treatment with a safe and easy approach is the microbiota fecal transplantation (TFM), which consists of healthy microbiota transplantation for patients with recurrent intestinal infection by *C. difficile*, with perspectives for the treatment of obesity and diabetes type 2. In addition to the benefits of treating disease and maintaining health, there are already animal model studies demonstrating the functionality of microbiota in improving exercise performance, thus

pointing to new areas of study and perspectives for the future of therapies based in the microbiome. Still, further studies are needed on the impact of these therapies on disease prevention and control and may boost their use in the medical and nutritional setting.

Declaration of conflicts of interest: The authors declare nothing.

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