REVIEW ARTICLE

Psychobiotics in Neurodevelopmental Disorders

Psicobióticos nas Perturbações do Neurodesenvolvimento

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RESUMO

Na última década, a ciência comprovou o papel fundamental que a microbiota intestinal desempenha na regulação do cérebro, cognição e comportamento quer na infância quer na idade adulta.

O distúrbio da homeostase da comunidade bacteriana intestinal exerce um impacto negativo na saúde do hospedeiro, podendo conduzir a patologias distintas, nomeadamente, do foro do neurodesenvolvimento. Neste contexto, os probióticos parecem possuir um papel relevante para a manutenção da eubiose entérica, dando lugar ao conceito emergente de psicobióticos como uma potencial nova arma terapêutica.

Os psicobióticos são culturas vivas de bactérias intestinais benéficas (probióticos) ou substratos de fibras (prebióticos) que aumentam o crescimento e/ou atividade de bactérias intestinais benéficas, que podem produzir benefícios para a saúde de indivíduos com doenças psiquiátricas/neurológicas.

Neste artigo começamos por explorar a relação entre o cérebro e o intestino e, em seguida, revemos as evidências científicas atuais para o uso de psicobióticos em vários distúrbios do neurodesenvolvimento.

PALAVRAS-CHAVE: Disbiose; Eixo Cérebro-Intestino; Perturbações do Neurodesenvolvimento; Probióticos/uso terapêutico

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ABSTRACT

In the last decade, science has proven the fundamental role that the gut microbiota plays in regulating the brain, cognition and behavior, both in childhood and adulthood.

The disturbance of the intestinal community homeostasis has a negative impact on the host's health and can lead to several disorders, namely those related to neurodevelopment. In this context, probiotics seem to play an important role in the maintenance of enteric eubiosis, giving way to the emerging concept of psychobiotic as a potential new therapeutic weapon.

Psychobiotics are live cultures of beneficial gut bacteria (probiotics) or substrates from fibers (prebiotics) that enhance the growth and/or activity of indigenous beneficial intestinal bacteria, which can produce health benefits in individuals with psychiatric/neurological diseases.

In this article we begin by exploring the relationship between the brain and the gut, and then review the scientific evidence available for the use of psychobiotics in various neurodevelopmental disorders.

KEYWORDS: Brain-Gut Axis; Dysbiosis; Neurodevelopmental Disorders; Probiotics/therapeutic use

INTRODUCTION

This review intends to highlight an emerging theme in the Medicine field - the curious communication that is established between the brain and the gut. The role that intestinal bacteria play in the host's health and disease has gained significant prominence in recent years.

The communication between the brain and the gut is dynamic, complex and uses different pathways, forming a bidirectional axis, whose equilibrium depends on the composition of the gut microbial community that inhabits the intestines. The modulating role that this ecosystem plays on the gut-brain axis and, specifically, on neurodevelopment is a fascinating area that is experiencing rapid growth.

The disturbance of the intestinal community homeostasis – dysbiosis - has a negative impact on the host's health and can lead to several disorders, namely those related to neurodevelopment. In this context, probiotics seem to play an important role in the maintenance of enteric eubiosis, leading to the emerging concept of psychobiotic as a potential therapeutic tool.

Numerous studies have indicated the fundamental role that the gut microbiota plays in regulating the brain, cognition and behavior, both in childhood and adulthood.

In this article, we begin by exploring the relationship between the brain and the gut, and then review the scientific evidence available for the use of psychobiotics in various neurodevelopmental disorders.

THE BRAIN-INTESTINE AXIS

The role that the central nervous system (CNS) plays in the intestine has long been recognized, regulating gastrointestinal (GI) functions such as motility, mucin secretion, hormone production; including its immunological component, evident in the cytokine production by immune cells in the intestinal mucosa.[1] However, only recently there is growing recognition of the importance that the enteric nervous system (ENS) seems to have at a central level.

The human ENS derives from the neural crest and has about 200 to 600 million neurons.[1,2] This represents the largest and most complex neuronal network in the peripheral and autonomic nervous systems. The intestine, together with its neuronal structure, the microbial community and its metabolites, has the ability to modulate the CNS.[2]

The brain and the intestine form a bidirectional communication axis, where information can be generated both at the intestinal and nervous system level.[1,3]

There is growing evidence that the intestinal symbiotic community has a key impact on the dialogue established in the brain-gut axis.[1,3]

In this context, gut microbiota might be a mediator between the environment and the CNS via multiple routes that include neuronal, immune, endocrine and metabolic pathways, namely through vagus nerve modulation, cytokines transmission, activation of the hypothalamic-pituitary-adrenal (HPA) axis and synthesis and release of neurotransmitters like serotonin and dopamine.[4-6]

Disruptions in this axis have been linked to dysfunctions in both the GI tract and the CNS, including inflammatory bowel disease, functional GI disorders, eating behavior disorders (e.g. anorexia and obesity), autism spectrum disorder (ASD), mood disorders, anx-

iety and depression.[1,3,5,7,8] This is further evidence of the importance of the harmonious dialogue between the "upper" and the "lower brain".

INTESTINAL MICROBIOTA

The commensal microbial community that inhabits the enteric lumen has not always been given the importance it deserves. It is currently the subject of growing interest given the recognition of its important contribution to the regulation of numerous physiological functions, from energy production to immunity against pathogens.[9] The complex and dynamic symbiotic gut ecosystem with which human beings are in permanent interaction is called the intestinal microbiota.[1-3,6,9]

The human gut contains 10^{13}-10^{14} microorganisms, a value that is 100 times greater than the number of cells in the human body.[7,10] About 80% of the microbiota is specific to each individual and this exclusive bacterial pattern is in part determined by the host's own genotype.[11] With about 500 bacterial species[11-13] this rich ecosystem is not uniformly distributed throughout the GI tract - the colon is its most densely populated region, which depends on various factors, particularly the local pH.[11-15]

In the human gut microbiota, *Firmicutes* (65%) and *Bacteroidetes* (25%) phyla predominate and account for more than 90% of microbes.[16,17] Anaerobes dominate over aerobes, with the most significant anaerobic genera being *Bacteroides* (from *Bacteroidetes* phyla) and *Bifidobacterium (*from *Actinobacteria* phyla), representing 30% and 25% respectively.[17]

There are several neurotransmitters produced by commensal organisms such as serotonin, gamma-aminobutyric acid (GABA), catecholamines, acetylcholine and histamine.[2] Different studies[18,19] reveal that probiotic bacteria can produce neuroactive substances, which influence the brain-gut axis. Some representatives of the genera *Lactobacillus* and *Bifidobacterium* can produce GABA, while representatives of *Escherichia*, *Bacillus*, and *Saccharomyces* can produce noradrenaline.[8,19] Serotonin is a product of some species of *Candida*, *Streptococcus*, *Escherichia* and *Enterococcus* and is mediated by tryptophan. Other neurotransmitters produced by bacteria are dopamine (*Bacillus*) and acetylcholine (*Lactobacillus*).[8,19] Interestingly, almost half of the dopamine in the human body is produced by microorganisms that inhabit the GI tract.[8]

Human beings, from birth to the end of their lives, are in permanent change and the enteric microbiota, which is an integral part of the host's biology, undergoes the same co-evolutionary process.

The intestinal microbiota has great resilience and plasticity and is usually able to recover after acute aggressions,[20] such as the use of antibiotics or dietary changes. The impact of diet on the enteric microbiota has been increasingly studied, as strong evidence has emerged about its ability to rapidly induce changes in the composition of the microbiome.[21,22] In fact, it was found that the feces of exclusive breastfeeding infants have 99% of *Bifidobacterium* in their microbiota, unlike those fed with infant formula, which have a more diverse flora.[23]

The theory that the intestine of newborns is sterile at birth is controversial, as there are studies[24-27] that demonstrate possible intestinal colonization in the mother's womb. Jiménez *et al*[24] isolated bacteria from umbilical cord blood of healthy neonates and from murine amniotic fluid, suggesting that term fetuses were not completely sterile and that a prenatal mother-to-child efflux of commensal bacteria might exist. Regardless of one theory or another, it is known that in an initial phase the number and diversity of the bacterial community are extremely reduced,[28,29] going through a process of gradual increase in its complexity, which translates into an immature ecosystem.[28] By age two and a half, the gut microbiota composition stabilizes into a pattern that more resembles an adult-like profile.[30]

The pre and postnatal periods are characterized by intense changes in neuronal organization, being critical phases, in which environmental factors can decisively influence the brain development and behavioral functions.[31] In fact, the behavior of children during the initial three years of life results in significant exposure to several types of microorganisms. The amount and type of exposure depends on factors such as the type of delivery (cesarean *versus* vaginal), oral exploration (including frequent hand-to-mouth contact), choice of breast milk *vs.* artificial milk, food diversification, genetics and the environment (the use of antibiotics, diseases, geographic location).[9,20,21,30,32]

An Irish study from 2013,[33] that analyzed fecal samples from 10 preterm infants, identified a lack of detectable *Bifidobacterium* and *Lactobacillus genera in* preterm infants gut, contrary to what is observed in full-term newborns. The species of *Bifidobacteriums* that colonize the intestine of children are different from those of adults,[32] with a predominance of *Bifidobacterium longum* and *Bifidobacterium bifidum*.

Extensive work using mouse models has shown that several processes in the nervous system are related to the regulatory effect of the gut microbiota, includ-

ing neurogenesis in the hippocampus, the amygdala, myelination, spine density, the synaptic connections, the microglia and the permeability of the blood-brain barrier (BBB).[34]

Another process where the microbiota is involved is neuronal plasticity. Studies with germ-free mice indicated low levels of brain-derived neurotrophic factor (BDNF) expression in the cortex and hippocampus.[35] This factor is associated with brain plasticity and has a regulatory function on neuronal growth, being involved in many behavioral and learning processes, especially those related to working memory.[35] In fact, it has been suggested that decreased serum BDNF levels may have an important role in the pathophysiology of cognitive deficits, depression, schizophrenia, Alzheimer's disease, dementia and autism.[35,36] N-methyl-D-aspartate-activated receptors (NMDAR) are also deeply involved in synaptic plasticity and cognitive function and their production is also dependent on BDNF levels.[36] In fact, low levels of BDNF in germ-free mice inhibits the maintenance of NMDAR production, which affects GABA inhibitory interneurons and, consequently, translates into cognitive deficits.[36]

The intestinal microbiota exerts its action on BDNF through changes in neurotransmitter and modulatory pathways, such as kynurenine (a metabolite of the amino acid – tryptophan), by the action of short-chain fatty acids (SCFAs).[34] Fortunately, studies in mice showed that these low levels of BDNF could be recovered by the direct administration of a strain of *Bifidobacterium longum subspecies infantis*[10] and other probiotics, prebiotics, and antimicrobials that increase the proportion of *Firmicutes*, *Lactobacilli* and *Actinobacteria* and decrease the *Proteobacteria* and *Bacteroidetes* levels in the intestine.[36]

INTESTINAL DYSBIOSIS

The gut microbiota may experience dysbiosis characterized by changes in the quantity and quality of the microbiota colonies when exposed to some factors such as the excessive use of antibiotics, inappropriate diet and lifestyles, infections, cesarean sections and early cessation of breastfeeding maternal abandonment.[37,38]

Gut dysbiosis can negatively influence the physiology of the intestine, causing an inappropriate transmission of stimuli along the gut-brain axis and, consequently, leading to a loss of intestinal barrier integrity and result in an inflammatory condition where the cytokines could get into the bloodstream and reach the brain.[39]

Thus, intestinal dysbiosis can cause changes in CNS functions, leading to various diseases,[39] as the enteric microbiota is essential for the homeostasis of the organism; consequently, dysbiosis—present in both GI and extra-GI conditions[40] —has been associated with alterations in behavior, cognition, and emotions.

Different studies have identified this correlation between certain pathologies and alterations in the host's microbiota. Unfortunately, investigations about the enteric microbiota-brain interaction are still limited in humans. ASD are among the most studied,[5,7,10,30] with evidence of intestinal dysbiosis.

Regarding neurodevelopmental disorders, intestinal dysbiosis has been studied and identified mainly in patients with ASD.

In 2010, Robinson *et al*[41] had already reported an increase in bacterial diversity in the feces of autistic children when compared to controls, with an increase in some species such as *Bacteroidetes* and *Proteobacteria* and a decrease in others, such as *Actinobacteria* and *Firmicutes*. In 2013, Angelis *et al*[42] found that the gut microbiota of ASD children exhibited lower levels of *Bifidobacterium* and *Firmicutes* and higher levels of *Bacteroidetes*, *Lactobacillus*, *Clostridium*, *Desulfovibrio*, *Caloramator*, and *Sarcina*, than that of neurotypical children. More recently, a systematic review[43] demonstrated there were consistently alterations of gut microbiota in ASD patients compared with controls and it strengthened evidence that dysbiosis of gut microbiota may correlate with behavioral abnormality in ASD.

Several studies[5,30,39,44-46] report that children with ASD tend to suffer from GI disturbs (abdominal pain, diarrhea, constipation, and flatulence), and in this context, it has even been suggested that GI symptoms should be considered as part of the ASD phenotype, like the behavioral symptoms.[5] It was proposed that these disturbs may be due to a disruption of the indigenous gut flora promoting the overgrowth of potentially pathogenic microorganisms, but the mechanism underlying this change has yet to be fully clarified.[44]

The “leaky gut” or increased permeability of the intestinal epithelium is another of the conditions reported in ASD patients.[46-48] A high percentage of abnormal intestinal permeability values was found among ASD patients (36.7%) and their relatives (21.2%) compared with the control group (4.8%).[46] It has been theorized that as a result of this increased permeability, toxins and bacterial products can get into the bloodstream, ultimately affecting brain function and impairing social behavioral scores.[48]

Parracho and colleagues[44] found that the fecal flora of ASD patients contained a higher incidence of the *Clostridium histolyticum* group of bacteria than that of healthy children. *Clostridium* is known for producing neurotoxins that, once released into the bloodstream, can cause systemic inflammation and tissue damage,[44] from mild diarrhea to severe neurological diseases, such as botulism and tetanus, that can lead to respiratory failure and death.[49]

It is worth emphasizing that in children with ASD, the presence of GI dysfunction is often associated with increased irritability, tantrums, aggressive behavior, and sleep disturbances.[45]

The effect of antibiotics on the gut microbiota has been extensively studied in recent times. Some authors[45] have suggested that modulating gut bacteria with short-term antibiotic treatment can lead to temporary improvement in behavioral symptoms in some individuals with ASD.[42] This hypothesis that a gut microbial imbalance, such as the presence of toxin-producing *Clostridium* species, could contribute to ASD behavioral symptoms was addressed in a small study[50] consisting of 11 children with chronic diarrhea and a ASD late-onset phenotype, with no control group. Subjects were treated with vancomycin - an antibiotic used in the treatment of chronic *Clostridium difficile* infections – 500 mg/day given orally three times per day for 8 weeks, followed by 4 weeks of oral treatment with a probiotic mixture of *Lactobacillus acidophilus*, *Lactobacillus bulgaricus* and *Bifidobacterium bifidum*. The results showed that behavior and communication scores improved significantly during the treatment period. However, 2 and 8 months follow-up revealed that the improvement was not sustained and these gains in behavior were lost in most cases after treatment was discontinued. Unfortunately, the authors did not report the GI symptomatology and the fecal flora composition, and their study did not include a control group.

More recently, a small (n = 18) open-label clinical trial[51] evaluating the impact of fecal microbiota transfer (FMT) in 18 ASD-diagnosed children reported an improvement in both ASD-related behavior and GI symptoms (80% reduction) after 8 weeks. FMT is designed to alter the entire microbiome by transferring fecal material containing microbiota from a healthy donor to another person with an impaired gut microbiota.[5] In this study, the abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* increased following the 8 weeks of FMT treatment. A new article[52] was published reporting the follow-up with the same 18 participants two years after treatment was completed. Remarkably, most improvements in GI symptoms were preserved, and ASD-related symptoms improved even more after the end of treatment.

A study[53] that investigated the fecal microflora of autistic *versus* control children, showed that *Bacteroidetes* were found at high levels in the severely autistic group, while *Firmicutes* were more predominant in the control group. Furthermore, *Desulfovibrio species* and *Bacteroides vulgatus* are present in significantly higher numbers in the stools of severely autistic children than in controls. Another study[54] evaluated the concentrations of SCFAs in fecal samples (48h) from children of similar age with ASD (n = 23), and without ASD (n = 31), and concluded that fecal SCFAs concentrations were significantly higher in children with ASD.

Pequegnat *et al*[55] have reported *Clostridium Bolteae* species as being over-represented in the intestinal microbiota in ASD, in such a way that its capsular polysaccharide (consisting of rhamnose and mannose units), has been proposed as a potential viable vaccine to reduce *Clostridium Bolteae* colonization of the intestinal tract of autistic patients.

Several authors studied the impact of exposure to breast milk in the gut microbiota and its relation to the development of ASD and GI ASD symptoms. We know that formula-fed infants showed higher levels of *Clostridium difficile* in comparison with breastfed infants.[56] Additionally, breastfeeding over 6 months has been associated with a lower risk of ASD development and GI ASD-related symptoms.[57]

PROBIOTICS

The recognition and use of food products with beneficial properties for health are quite remote, as more than 1000 years ago, in the Caucasus, *Kefir* was already used. It is a product resulting from the fermentation of milk by a colony rich in bacteria and fungi. At the time, its chemical and metabolic characteristics were unknown. Currently, the literature recognizes it as a natural source of probiotics, whose name appears to derive from the Turkish word *kief* which means "good-feeling". Evidence that bacteria played a beneficial role in health emerged at the beginning of the 20th century. Later, the name probiotic come to light, which derives from the Greek and means "for life". This term was first introduced by Lilly and Stillwell[58] in 1965, referring to substances secreted by one microorganism that stimulated the growth of others. Currently, the concept is slightly different, and probiotics are defined as live microorganisms that, when administered in appropriate amounts (approximately 1 x 10^9 cells/day), confer a health benefit on the host organism.[15,59-61]

This complex and numerous community with around thirty identified species includes *Lactobacillus helveticus*, *Lactobacillus brevis*, *Lactobacillus kefir*, *Lactobacillus plantarum*, *Lactobacillus acidophylus*, *Lactobacillus kefiranofaciens*, *Kluyveromyces lactis and Saccharomyces lipolytica*, among others.[62,63] Nowadays, the species *Lactobacillus* spp. and *Bifidobacterium* spp. are the most commonly used probiotics.[15]

There are still several not understood aspects regarding the mechanisms of action of probiotics. Probiotic bacteria can act via their structures such as DNA, peptidoglycan, lipopolysaccharides (LPS) and flagellin and/or through metabolites such as SCFAs, particularly acetic acid, propionic acid and butyric.[64] Their action may be direct, related to their digestive colonization, or indirect because these strains modulate the microbiota by increasing the inoculum of bacteria with beneficial effects.[64]

Probiotics have an excellent safety profile, with special emphasis on the genera *Bifidobacterium* and *Lactobacillus*, that have proven their safety in their long history of use in fermented food and milk. *Lactobacilli*, *Bifidobacteria*, *Lactococci*, and yeasts are classified in the category of organisms Generally Regarded As Safe (GRAS).[64] However, cases of septicemia (bacterial and fungal) and endocarditis have been reported, which, although rare, should not be neglected.[65-67] A recent review[67] reported cases of *Lactobacillus* bacteremia (LB), their epidemiology, and examined the role of *Lactobacillus*-containing probiotics in LB. The authors mention that LB is typically linked to individuals with underlying health conditions or weakened immune systems. In fact, LB has been reported in patients with cancer, serious GI disorder (i.e., hepatic cirrhosis, cholecystolithiasis, chronic pancreatitis), ischemic or ulcerative colitis, those who are immunocompromised (HIV, chronic steroids, chemotherapy, or transplant patients), those who have undergone surgery, prior hospitalization or previous antibiotic treatment, those who have used central venous devices, and in preterm neonates with underlying conditions (short bowel syndrome, growth restriction).[67] It is important to mention that this review of the literature (from 1980 to 2023) found 23 cases where the blood isolate from a bacteremic patient was identical to the probiotic strain the patient had been taking.[67] One the other hand, this review also revealed 49 case reports of LB without any history of probiotic use.[67] These authors conclude that even though the risk of LB in patients taking probiotics is low, caution is advisedwhen probiotics are administered in vulnerable populations.[67]

PREBIOTICS

Prebiotics are non-digestible food components that selectively stimulate the growth and activity of the gut microbiota.[15,68,69] They essentially consist of carbohydrates, namely, oligosaccharides and polysaccharides that are not digestible by intestinal enzymes, selectively stimulating the growth and activity of the gut microbiota.[15] These food components play an important role for the host, as they act as substrates, nourishing a selective group of microorganisms that live in the intestine, stimulating their growth and the production of SCFAs that are used by the body as a source of energy,[69] thus promoting a healthier microbial community.

Inulin, fructose-oligosaccharide (FOS), lactulose and galacto-oligosaccharide (GOS) are some examples of the most studied prebiotics.[15,69] GOS is found in human breast milk.

Currently, in the national market, it is easy to find an extensive list of food products that have probiotics and/or prebiotics, such as yogurts, cheeses, biscuits, and baby food, among others. Dairy products are, in general, the most selected foods for their transmission.

SYNBIOTICS

Nowadays, mixtures of probiotics and prebiotics,[15,69] which are named synbiotics, are often used in order to take advantage of their synergic effects in application to food products.

PSYCHOBIOTICS

In 2013, psychiatrist Dinan and his collaborators[18] were the progenitors of a new concept – psychobiotics - to define a living organism that, when ingested in adequate quantities, provides a health benefit to individuals suffering from a mental illness. They are live cultures of beneficial gut bacteria (probiotics) or substrates from fibers (prebiotics) that enhance the growth and/or activity of indigenous beneficial intestinal bacteria, which can produce health benefits in individuals with psychiatric or neurological diseases.[4]

There were already several studies that sought to explore the possible contribution of probiotics in psychiatric disorders, but a specific terminology had not yet been assigned until that moment.[70,71]

Psychobiotics are a class of probiotics capable of produce and/or regulate neuroactive substances, such as GABA, serotonin, glutamate and BDNF, which act on the gut-brain axis, and play important roles in con-

trolling the neural excitatory-inhibitory balance, and have a beneficial effect on mood, anxiety, memory and cognition.[7,18]

The literature identifies and reinforces the idea that only specific classes of probiotics can act as psychobiotics and be useful as a new therapeutic weapon in favor of mental health. The bacteria known so far with these psychotropic properties belong to the genus *Lactobacillus* and *Bifidobacterium*.[72,73]

The action mechanisms by which bacteria exert their psychobiotic potential has not been completely elucidated, but it is known that they act on the microbiota-gut-brain axis through three mechanisms: by affecting the HPA axis stress response and reducing systemic inflammation; by a direct effect on the immune system; by the secretion of molecules such proteins, SCFAs and neurotransmitters such as GABA, serotonin, glutamate and BDNF, which play an important role in mood, cognitive functions, learning processes and memory.[74]

PSYCHOBIOTICS IN NEURODEVELOPMENTAL DISORDERS

A growing body of evidence supports the usefulness of psychobiotics in neurodevelopmental disorders.

A systematic review[4] carried out in the United Kingdom and published in January 2022 evaluated the efficacy of psychobiotic interventions (with an active treatment with pre- and probiotic supplements and a placebo) on stress, anxiety, and cognition outcomes in children and adolescents (aged 6–25 years). The administration of a pro and prebiotic combination (i.e., synbiotics) was one of the exclusion criteria. A total of 19 eligible studies (6 with probiotics,[10,75-79] and 13 with prebiotics[80-92]) evaluated cognitive outcomes. Among the 6 probiotic studies, a variety of probiotic species and strains were used. Probiotic dosages ranged between $1x10^9$ and $3x10^{10}$ CFU (colony forming unit), administered once or twice a day and the intervention length was between 28 and 84 days. Significant effects were found in only 2[75,78] of the 6 studies. In contrast, prebiotic supplementation used mostly PUFAs, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), with some using GOS or FOS. Total daily dosage ranged between 400 mg and 5500 mg, with an intervention duration between 21 and 121 days. Significant effects were found in 8 [80,82,84, 87-92] of the 13 studies. While most probiotic studies were conducted on healthy participants, prebiotics studies involved clinical samples, including children with attention-deficit hyperactivity disorder (ADHD), learning disabilities, and mood disorders. Moreover, the authors concluded that therapeutic psychobiotic use for cognitive improvements in development is encouraging, with 50% of studies reporting success.

In a study by Hsiao EY *et al*[48] the administration of a single strain of the human commensal *Bacteroides fragilis*, was able to ameliorate social deficit in a mice model, as well as to correct gut permeability and altered microbial composition.

Another review article[7] published in 2019, brings together several articles that have been published about the use of psychobiotics in mental health, neurodegenerative and neurodevelopmental disorders. Regarding neurodevelopment, the authors identified 10 clinical trials with probiotic interventions in ASD patients. One of the reported studies is a randomized pilot trial carried out in the USA studying[93] the effects of *Visbiome extra strength* (a probiotic product which contains 8 strains of probiotics) on the GI symptoms in children with ASD. In another clinical trial, performed in Italy,[94] including children aged between 18 and 72 months, the primary outcome was the change in the severity of ASD measured using Autism Diagnostic Observation Schedule-2 (ADOS-2), after using a product containing multiple probiotic species called *Vivomixx*. Despite the lack of a significant overall effect, subgroup analyses indicated potential benefits: in children without GI symptoms, probiotic supplementation was associated with a reduction in autism severity scores compared with placebo, while in children with GI symptoms, probiotics appeared to improve GI manifestations, adaptive functioning, and sensory processing relative to placebo. An open-label trial conducted in Egypt[95] used 3 probiotics strains (*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Bifidobacterium longum*) and evaluated their effects on GI and ASD symptoms in children between 5 and 9 years old. According to the results of this study, both autism severity and GI symptoms, assessed using the Autism Treatment Evaluation Checklist (ATEC) and the 6-item GI severity index (6-GSI) respectively, were improved after the three-month intervention. Some other studies evaluating the adverse effects of using probiotics in patients with ASD were included in this review,[7] but they were still ongoing. In summary, what has been demonstrated in this review is that probiotics, whether including multiple or single species, can improve GI symptoms and even ASD-related symptoms

in children with ASD. In the same article,[7] a reference is still made to 3 studies[96-98] that evaluated the effects of psychobiotics on ADHD. According a randomized double-blind trial,[96] infants who received *Lactobacillus rhamnosus GG* instead of placebo for six months presented a reduced risk of developing ADHD. Another study[97] included 20 children with ADHD (10 children treated with Ritalin and 10 with dietary supplements) reported that the use of dietary supplements containing *Lactobacillus acidophilus* improved attention and self-control in children with ADHD and suggest that food supplement treatment of ADHD may be of equal efficacy to ritalin treatment. According to one case report,[99] a FMT used to treat a child with Tourette syndrome (TS) dramatically ameliorates the symptoms 8 weeks after the treatment.

A four-week, randomized, double-blind, placebo-controlled study published in 2019,[10] investigated the effects of *Lactobacillus plantarum PS128* (PS128) in male children between 7 and 15 years old with ASD in Taiwan. Thirty-six boys in the PS128 group and 35 in the placebo group were analyzed. This *Lactobacillus plantarum PS128* was isolated from a product commonly used by Taiwanese tribes as a food ingredient - *fu-tsai* – which results from the spontaneous fermentation of mustard. Exclusion criteria included consumption of prescribed antibiotics and yogurt or probiotic products two weeks before enrollment. Participants were allowed to continue their usual medications, treatment and therapies. The results showed that the use of PS128 significantly reduced the scores for anxiety, rule-breaking behavior, SNAP-IV-inattention, SNAP-IV-hyperactivity/impulsivity, SNAP-IV-opposition/defiance and total score compared to the placebo group. Additionally, the efficacy of PS128 intervention seemed to be age-dependent, with better results being observed in younger children, which highlights the importance of early intervention. No adverse event was reported.

A more recent systematic review,[8] published in July 2022, which included 5 publications[10,95,101-103] on the use of probiotics in ASD. The participants were under 25 years of age and the duration of the intervention ranged from four weeks to six months. The probiotic species reported in all studies except for one was *Lactobacillus plantarum*. Probiotic intervention improved results in the scales that assess the severity of ASD in all studies. The beneficial effects included increased attention, communication skills, sociability, interaction and personal autonomy, sensory/cognitive awareness, reduced anxiety, opposition/aversion, rule-breaking behavior and hyperactivity/impulsivity. Nevertheless, the truth is that despite the positive effect of probiotics in relieving ASD symptoms, in the studies involving control groups, the results did not differ significantly from those obtained in the placebo arm. In addition, the participant`s age was very heterogeneous, making it difficult to determine the effectiveness of the treatment and compare the results obtained for a group of preschoolers [101] and school-age children or adolescents.[10] A positive aspect of the obtained results was the lack of important adverse effects. However, none of the studies investigated the influence of discontinuing supplementation on the maintenance of improvement or worsening of ASD symptoms. On the other hand, most publications did not mention the exclusion of the consumption of other supplements during the intervention that could have had an additional effect on the evaluated outcome. In fact, only in one study were participants required to eliminate yogurt from their diet.[10]

CONCLUSION

The knowledge that some bacteria can positively influence health has been gaining prominence in scientific literature. It is now well known that gut microbiota influence health and disease, at least from birth to old age. It is also widely recognized that some intestinal bacteria are able to synthesize neuroactive molecules, and emerging evidence suggests that they can play a role in several neurodevelopmental domains, such as attention, communication skills, learning, anxiety, oppositional behavior and even in cognition, acting as psychobiotics. There is also a growing body of evidence showing probiotics ameliorate GI-ASD-related symptoms.

It is important to note that most studies conducted in ASD children are non-interventional, and many do not adequately record details about medication use and dietary information. In fact, the interventional studies are few, and of small sample size.

Despite the current encouraging evidence, the mechanism of action of psychobiotics is not fully understood, nor has it been established which psychobiotic, in what dose, administered with what frequency and for how long, has a specific effect on a particular symptom or neurodevelopmental disorder. More studies are therefore needed before psychobiotics can be used as an alternative therapy in clinical practice.

DECLARAÇÃO DE CONTRIBUIÇÃO /CONTRIBUTORSHIP STATEMENT

BV, AC. DG, IVM, SS, CP - Elaboração do manuscrito e revisão final

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