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Symbiosis in the microbiome of people with asd and its effects on the brain-intestine linkage

A simbiose no microbioma de pessoas com tea e seus efeitos na ligação intestino-cérebro

La simbiosis en el microbioma de las personas con tea y sus efectos en la ligación intestino-cerebro

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Cláudia Almeida Alves Vermehren
ORCID: https://orcid.org/0000-0001-8147-7975
Instituto Federal do Amazonas, Brazil
E-mail: claudiaalvesvermehren@gmail.com
Tayna Ofelia Freitas Suarez
ORCID: https://orcid.org/0000-0002-6608-0221
Secretaria de Estado de Educação e Qualidade do Ensino AM, Brazil
E-mail: tayna.suarez@fametro.edu.br

Abstract
Researches show that individuals with Autistic Spectrum Disorder (ASD), present an imbalance in the intestinal microbiota, by the study carried out, there is a possibility of mitigating the characteristic symptoms of Autistic Spectrum Disorder, through the symbiosis in the intestinal microbiome. The objective of this bibliographic review is to analyze the influence of symbiosis on the microbiome in the intestine-brain axis in individuals with ASD and to verify the nutritional needs of this individual, in order to support nutritional strategies. Analyzing the gut-brain axis of children with ASD, verifying the effects of symbiosis on the microbiome and the nutritional needs of autistic people. The approach of this research was qualitative, with a basic purpose, of an observational nature, being cross-sectional bibliographic research. Studies were used to investigate the effectiveness of vitamin and mineral supplementation in the diet of children with autism spectrum disorder. The present study concludes that autistic children are more deficient in the intake of vitamins and minerals, and those who are supplemented with vitamin D had reduced or absent symptoms of ASD. Thus, it will be necessary to offer a greater variety of fruits and vegetables to obtain adequate dosages of micronutrients through food intake, helping with homeostasis in the microbiota in order to achieve a symbiosis in the intestinal microbiome of the child with ASD.
Keyword: Autism nutrition; Autistic spectrum disorder; Microbiota.

Resumo
Pesquisas demonstram que indivíduos com Transtorno do Espectro Autista (TEA), apresenta um desequilíbrio na microbiota intestinal, pelo estudo realizado, existe uma possibilidade de mitigação dos sintomas característicos do Transtorno do Espectro Autista, por meio da simbiose no microbioma intestinal. O objetivo desta revisão bibliográfica é analisar a influência da simbiose no microbioma no eixo intestino-cérebro em indivíduos com TEA e verificar as necessidades nutricionais deste indivíduo, com a finalidade de embasar estratégias nutricionais. Analisando o eixo intestino-cérebro de crianças com TEA, verificando os efeitos da simbiose no microbioma e as necessidades nutricionais de autistas. A abordagem desta pesquisa foi qualitativa, com finalidade básica, de natureza observacional, sendo está uma pesquisa bibliográfica de cunho transversal. Foram utilizados estudos que investigam a eficácia da suplementação de vitaminas e minerais na dieta de crianças com transtorno do espectro autista. O presente estudo conclui que crianças autistas apresentam mais deficiência na ingestão de vitaminas e minerais, e as que são suplementadas com a vitamina D apresentaram os sintomas do TEA reduzidos ou ausentes. Assim será necessário ofertar uma maior variedade de frutas verduras e legumes, para obter dosagens adequadas de micronutrientes por meio da ingestão alimentar, auxiliando com uma homeostase na microbiota afim de alcançar uma simbiose no microbioma intestinal da criança com TEA.
Palavras-chave: Nutrição autismo; Transtorno do espectro autista; Microbiota.

Resumen
Investigaciones demuestran que los individuos con Trastorno del Espectro Autista (TEA), presentan un desequilibrio en la microbiota intestinal, por el estudio realizado, existe la posibilidad de mitigar los síntomas característicos del Trastorno del Espectro Autista, a través de la simbiosis en el microbioma intestinal. El objetivo de esta revisión bibliográfica es analizar la influencia de la simbiosis en el microbioma del eje intestino-cerebro en individuos con TEA y verificar las necesidades nutricionales de este individuo, para apoyar estrategias nutricionales. Analizando el

eje intestino-cerebro de niños con TEA, comprobando los efectos de la simbiosis sobre el microbioma y las necesidades nutricionales de las personas autistas. El enfoque de esta investigación fue cualitativo, con un propósito básico, de carácter observacional, siendo una investigación bibliográfica transversal. Los estudios se utilizaron para investigar la eficacia de los suplementos de vitaminas y minerales en la dieta de los niños con trastorno del espectro autista. El presente estudio concluye que los niños autistas son más deficientes en la ingesta de vitaminas y minerales, y aquellos que reciben suplementos de vitamina D tienen síntomas reducidos o ausentes de TEA. Así, será necesario ofrecer una mayor variedad de frutas y verduras para obtener dosis adecuadas de micronutrientes a través de la ingesta de alimentos, ayudando a la homeostasis en la microbiota para lograr una simbiosis en el microbioma intestinal del niño con TEA.
Palabras clave: Nutrición del autismo; Trastorno del espectro autista; Microbiota.

1. Introduction

According to the Pan American Health Organization (PAHO), 70 million people suffer from a condition that science still does not well understand, Autism Spectrum Disorder (ASD). About 2 million autistic people live in Brazil (Paiva Jr, 2019). ASD is a sequence of conditions characterized by some degree of difficulty in social, language and communication behavior, demonstrating a restricted interest in only some activities, which are specific to the individual and are repeated as a ritual (OPAS, 2017). Presenting in the early years of childhood and consequently lasting throughout the person's life. Autism usually has more than one comorbidity, including depression, anxiety, seizures, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, among other disorders (OPAS, 2017). In addition to presenting disorders in the gastrointestinal system (Adams, Johansen & Poel, 2011).

Some clinicians, however, believe that classifying all people within the autism spectrum in a single group further confuses the diagnosis, as it is often quite complicated. But by putting them together we managed to find something in common, all people with ASD have a clear imbalance in gut bacteria (Veras & Nunes, 2019).

The human body is inhabited by trillions of microorganisms, such as bacteria, viruses and fungi, which we call the microbiome. This microbiome is now known to have important roles in the maintenance of health and the occurrence of disease. The recognition of its genome and influence on health has been the subject of study in numerous scientific investigations (Collen, 2016). Thus, the combination of symbiotics (prebiotics and probiotics), in adequate doses, acting on the intestinal microbiota, can result in varied health benefits.

Their impact is broad, as they have been shown to affect a number of processes, including immune response, metabolism and neurological function. Disruption of the normal commensal microbial community in humans, also called "dysbiosis," is associated with a growing number of disorders such as inflammatory bowel disease, irritable bowel syndrome, obesity, hypertension, diabetes, and autism (Navarro, Liu & Rhoads, 2016).

The intestinal wall of autistics is more permeable. As a result, certain substances can pass through it with great ease, including certain toxins released by *Lactobacillus* bacteria. Once in the bloodstream, these toxins affect the nervous system. Some of these excreted substances are neuroactive and act directly on the functioning of the brain, causing certain behaviors, such as constant body movement, which is common among certain autistics (Bioma4me, 2019). In addition, half of all autistic individuals have populations of one gram-negative bacterium called *Desulfovibrio vulgaris* which is not usually found in the intestines of people without the disorder. And it is a fact, the greater the severity of autism, the greater the presence of this bacterium, marked in genetic screening tests. Therefore, it may be important to also look at the gut when classifying a patient into one of the five grades of the disorder (Bioma4me, 2019).

Autism according to the CDC (2018) is an urgent public health concern, so linking the influence of the symbiosis in individuals with ASD is presented as a possibility to reduce symptoms and improve the quality of life of these individuals, as scientific research applied to the microbiome has shown improvements in people affected with mental disorders such as

autism, depression and dementia, in addition to diseases of the gastrointestinal tract, making the gut-brain connection. The microbiome in the health of individuals, assisted the emergence of new treatments aimed at restoring the symbiosis and the functional reflexes it plays in the host (Malla, Dubey, Kumar, Yadav, Hashem & Abd Allah, 2019)

The aim of this literature review is to analyze the influence of the microbiome symbiosis on the gut-brain axis in individuals with ASD and to verify the nutritional needs of these individuals, in order to substantiate nutritional strategies. To analyze the gut-brain axis of children with ASD, verifying the effects of symbiosis on the microbiome and to verify the nutritional needs of autistic individuals.

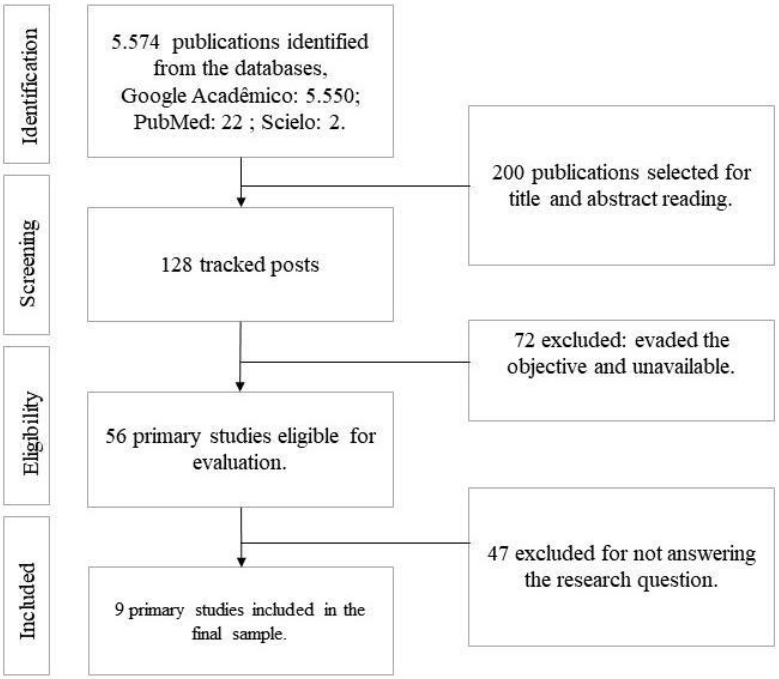
2. Methodology

Among the researches that synthesize findings about a certain phenomenon investigated in primary studies, several terms have been used: integrative review (IR), traditional review, narrative review, systematic review, meta-analysis, meta synthesis, meta summarization, among others (SOARES, 2014). To achieve the objectives proposed in this study, the chosen method was the Systematic Review.The systematic review showed a remarkable contribution in the area of nutrition and use of symbiotic in individuals with ASD in the last decade. This condition seems to be associated with the tendency to understand health care, at the individual or collective levels, as a complex task that requires collaboration and integration of knowledge from different disciplines. This trend is also observed in the area of health care, based on evidence or evidence-based practice, which has been recognizing that the combination of research methods, even under different epistemological matrices, can provide results that benefit nutritionists' care for people with ASD (Soares, 2014). The approach of this research was qualitative, with a basic purpose, of an observational nature, being systematic bibliographical research, of cross-sectional nature.

The data collected for this research were from secondary sources, based on the titles. To search for references in the literature, keywords were used in research platforms and databases PubMed (US National Library of Medicine National Institutes of Health), Scielo (Scientific Electronic Library Online), Google Scholar, in addition to books, magazines and websites of public bodies with the theme of symbiosis, microbiome, ASD, Autism, gut-brain axis and nutrition.

After identification, the selection of studies was carried out, according to the guiding question and the inclusion criteria already defined. Only literature published in the last twelve years, from 2010 to September 2022, was considered, as well as websites such as WHO (World Health Organization), CDC (Center for Disease Control and Prevention), PAHO (Pan American Health Organization). The studies selected through the search strategy were initially evaluated by analyzing the titles and especially the abstracts, in cases where the abstract titles were not sufficient to define the initial selection, the full article was read. The search identified studies, where duplicate articles or articles that were not related to the specific theme were excluded. At the end, nine selected articles were read in full for the composition of this work.

Figure 1 - Flow diagram of study selection: article search strategy.



Source: Authors.

3. Results and Discussion

3.1 Symbiosis in the intestinal microbiome

The Gut Microbiome exerts a great influence on our body as a whole, it is called our second human genome and considered "a small world in the intestinal tract made up of trillions of multiplying microorganisms" (Kellman, 2017). It is a universe with countless colonies of anaerobic microorganisms living symbiotically in a host, influencing who we are and how we behave.

The variety of genes and genomes within a microbial community is called the Microbiome (Eloe-Fadrosh & Rasko, 2013), this which exerts a great influence on our genetics has the ability to modify gene expression - turn a gene on or off or increase or decrease its volume - is known as epigenetics (Kellman,2017).

Thus, The U.S. National Institutes of Health, which runs the Human Genome Project, along with other studies in laboratories around the world, reveal the dependence our body has on our microbes, to keep us happy and healthy. According to Alanna Collen (2016), every person is far from harboring the same set of microbes. On the contrary, very few groups of bacteria are common to everyone. Each of us contains communities of microorganisms as unique as our fingerprints, that's one of the things that makes us humans unique. According to Frances Blow (2019) it is in the microbial community of the intestine where the main functions related to symbiosis are found.

Gut microbiome symbiosis is an example of functional synchrony, and can be positive or negative, as the microbiome is how our body interacts with the gut universe, in a way, where both have and provide mutual benefits, i.e., reciprocity.

ASD patients have a different macrobiotic composition, raising the hypothesis that nutrition-related factors play a key role in the etiology of ASD and its symptoms (Van De Sande, Van Buul & Brouns, 2014).

The diet of autistic children is mainly related to what is offered to them by their caregivers and the foods that are part of the select acceptance group, which depending on the variety and nutritional quality, can have positive or negative effects on the intestine microbiota.

This is how the balance of the microbiome is essential not only to keep the body healthy and access all the benefits such as, "decrease or eliminate symptoms such as fatigue, anxiety, headaches, acne, eczema, airway congestion, blurred mind, joint pain, frequent infections among others, but to prevent diseases and even reverse some such as: diabetes, heart disease, metabolic syndrome, autism, disorders and other disorders" (Kellman, 2017). The regulation that occurs in the gut by commensal bacterial communities, helps in the response to stress having been shown that modifications in the composition of the microbiota are associated with the development of anxiety and depression (Landeiro, 2016).

Factors that can unbalance this microbiome are stress, poor health and the use of antibiotics, which wreak havoc on our intestinal bacterial flora and compromise our immunity. In addition to concomitant symptoms such as oxidative stress in cells, disruption of tight junctions in the blood-brain barrier, mitochondrial dysfunction and changes in the cortex, amygdala, cerebellum and hippocampus, presented in ASD (autism spectrum disorders) that may be associated with an imbalanced gut microbiota (dysbiosis) in children with ASD (Srikantha & Mohajeri, 2019).

According to Betty Harbolic (2019) When the digestive tract is healthy, it filters out and eliminates harmful elements, such as bacteria, toxins, chemicals, and other waste products. A healthy balance of bacteria helps regulate gastrointestinal motility and maintain intestinal barrier function.

Balancing the number of microorganisms and their strains, as well as what they eat, keeps the various colonies healthy, which comes from a diverse and balanced diet, to preserve beneficial microorganisms.

In research conducted with 53 autistic children, to identify dietary patterns and eating habits in children (ASD), where food intake was recorded for three days, a food frequency questionnaire and the Eating Behavior Inventory (to assess food intake and behavioral problems during meals) were applied. They presented results where a lower consumption of vegetables and fruits was found, revealing a small number of micronutrients, mainly B-complex vitamins, calcium and iron (Siddiqi, Urooj & D'Souza, 2019). Leading to an imbalance in the microbiota and gut bacteria that are beneficial for good intestinal functioning.

Some factors such as lifestyle, diet, antibiotics, probiotics and prebiotics shape our microbiome. Benefits such as modulation of fundamental metabolic processes, signal transduction and immunity are only offered to our human body by coexisting microbes (Malla et al., 2019).

To ensure the balance of the home of our intestinal microbiome, i.e. the human gut, it is necessary to use additives that complement this microbiota and aid in nutrition, these being probiotics and prebiotics. While the probiotic replenishes the bacteria, prebiotics feed them (Kellman, 2017).

This causes a symbiosis in the microbiome, as it begins to function better and produce more efficiently.

> For Raphael Kellman, 2016 "A balanced microbiome regulates the immune system, three-quarters of which is found in the gut. It nourishes and maintains the gastrointestinal tract; it produces vital vitamins and nutrients, including several B vitamins and vitamin K; and it lays the foundation for good mood and optimal brain function by influencing the production of neurotransmitters, hormones and chemicals the brain needs to process thoughts and emotions."

However, this symbiosis can be observed when there is homeostasis between commensal and pathogenic microorganisms (Lopes, 2018).

3.2 Individual with ASD

ASD affects children in the neurodevelopmental process and consequently impairs development in the area of social interaction, verbal communication, i.e., in speech and behavior, and may have repetitive or restricted interests. These characteristics of the disorder present variably, may be milder in some children and more severe in others, or change during the growth of this individual (SBP, 2019) having a higher prevalence among boys than among girls (CDC, 2020).

> "ASD is characterized by neurodevelopmental disturbances and impairments in social interaction and communication, with the presence of repetitive and stereotyped behaviors. Changes in eating habits and disorders of the gastrointestinal tract (GIT), are also described as having a direct interference in the etiology and symptomatology of this condition, being able to impact in a detrimental way or help in the functional balance of the organism" (do Carmo Cupertino, Resende, de Freitas Veloso, de Carvalho, Duarte, & Ramos, 2019).

Some hypotheses throughout decades of research, divided several opinions about what triggered autism, among them environmental, genetic, epigenetic, immune system factors, among others. No conclusion was drawn as to what would be the key factor in the disorder (Laurent, 2014).

Until a recent scientific study that showed that genetic factors have a great influence on the spectrum.

> "The causes of autism increasingly point to genetics. Confirming previous recent studies, a 2019 scientific paper showed that genetic factors are the most important in determining the causes (estimated at 97% to 99%, with 81% being inherited - and linked to more than 900 genes), in addition to environmental factors (1% to 3%) may also be associated, for example, advanced paternal age or the use of valproic acid during pregnancy. There are currently 913 genes already mapped and implicated as risk factors for the disorder, 102 being the main ones" (Revista Autismo, 2020).

According to the CDC (Center for Disease Control and Prevention - Center for Disease Control and Prevention of the United States Government), the latest prevalence data for autism, presented on December 2, 2021, is 1 in 44, having an increase of 22% over previous figures (Junior, 2021).

A study published in the Journal of Autism and Developmental Disorders (2020), indicates that there is one case of ASD for every 32 children aged 6 to 12 years (prevalence of 3.1%) (Junior, 2020). This reveals that it is a disorder that is affecting more and more children worldwide.

Signs of autism appear in infancy, but sometimes the traces of the disorder are so faint that parents or guardians often do not notice the differences between a child with ASD and a neurotypical child during early childhood development.

According to the Pediatric Society (2019), the difference between children who receive an early diagnosis and those who receive a diagnosis later in life is striking. Being that the diagnosis of ASD occurs around 4 to 5 years of age.

Starting interventions, the earlier it is detected is better due to the level of transformation of neuronal synapses, which are still flexible, since neuronal plasticity is present at these ages. In addition to mitigating the functional limitations of origin (Costa, 2014).

Iron deficiency is a frequent comorbidity in autism spectrum disorder. For it negatively affects the functions of psychomotor and cognitive development, and can influence the decrease or increase of deficiency of other important nutrients for the organism (Pivina, Semenova, Doşa, Dauletyarova, & Bjørklund, 2019). Which is probably one of the factors that cause problems of delay in fine motor development, learning and cognitive performance in the school phase, which influences little or less learning during the school period.

According to the Pan American Health Organization (2017), based on evidence, psychosocial interventions, such as behavioral treatment and parenting skills training programs, can reduce and improve communication and social behavior difficulties, creating a positive impact on the well-being and quality of life of caregivers, family members and people with ASD.

3.3 Gut-Brain Axis

The complex and dynamic way in which the brain and the gut communicate through different pathways forms the bidirectional axis. The balance of this axis needs the microbial composition that inhabits the gut and the influence that this ecosystem exerts on human behavior is important (Silvestre, 2015).

The set of neuronal pathways and ganglia, involving the Central Nervous System (CNS), the Autonomic Nervous System (ANS) and the Enteric Nervous System (ENS), together with afferent and efferent neural pathways, in addition to the endocrine and immune systems, form the gut-brain axis. The hypothalamus-pituitary-adrenal connection is noted as the control center of the response and adaptation to any type of stress, as it provides extensive regulation of various bodily mechanisms such as intercellular signaling, intestinal permeability, immune activation and neuroendocrine signaling (Zorzo, 2017).

The gut-brain axis has its functioning influenced by the relationship of the microbiome with the Central Nervous System (Zorzo, 2017). So too, the microbiome, plays a fundamental role in modulating the intestinal barrier, maintaining the production of a tightly connected mucosal barrier and tight junctions of enterocytes (Stilling, van de Wouw, Clarke, Stanton, Dinan, & Cryan, 2016).

The relevance of understanding the gut-brain connection is to acknowledge the possible negative changes it can bring to the organism such as mental morbidity conditions, depression, anxiety, mental developmental delay and ASD (Allen, Dinan, Clarke, & Cryan, 2017).

3.4 Effects of symbiosis on the microbiome in the gut-brain axis

Communication between these systems has great influence on nutritional homeostasis, insulin release and even appetite balance, constituting a network of interconnections that links the gut-brain, hypothalamic-pituitary-adrenal axis and the immune system, since the endocrine and immune systems are also linked to the digestive and brain systems (Pereira & Gouveia, 2019).

Symbiosis makes the microbiome healthier for the host, bringing benefits in the production of hormones and fundamental chemicals for the regulation of the metabolisms of the intestinal microbiota. Inflammation caused by intestinal hypersensitivity and imbalance in the microbiome can cause alterations in brain chemistry (Kellman, 2017), these changes are highly influenced by diet (Zarrinpar, Chaix, Yooseph, & Panda, 2014).

Highlighting the importance of symbiosis in the gut microbiome of autistic children, in a study conducted with biochemical analysis of the urine of 120 children (60 children with ASD and 60 neurotypical children), in order to test possible changes in metabolism due to simultaneous deficiencies of vitamins B6, B9 and B12 and their influence on phenotypic aspects of ASD, it was concluded that intestinal dysbiosis as the main cause of a decrease in their absorption and genetic mutation in a specific gene (Belardo, Gevi, & Zolla, 2019).

Therefore, symbiosis in the gut microbiome is beneficial for improving vitamin absorption, decreasing nutritional and functional deficiency of the metabolism of the child with ASD, positively influencing brain chemical changes.

The microbiota plays an important role in certain points of neurodevelopment, neuroinflammation and behavior that, with recent studies in order to clarify the bidirectional pathway between the gut and the CNS, we can assert that this axis is increasingly related to pathophysiology and neural disorders such as autism (Cryan, O'Riordan, Sandhu, Peterson, & Dinan,

2020). Immunomodulation, nutritional input and resistance to colonization by pathological bacteria are some of the functions of the microbiome (Paixão, 2016).

The microbiome is indispensable in the production of the right chemicals and in the right amounts, since when this is dysregulated, it can produce symptoms such as anxiety, memory problems, clouded mind and depression. On the other hand, the chemical it produces, serotonin, allows us to feel self-confidence, optimism and serenity (Kellman, 2017).

In the lumen of the intestine, interactions occur between microorganisms and the host through various types of molecules, some examples of compounds generated by the intestinal microbiota are dopamine, noradrenaline, nitric oxide and the inhibitory neurotransmitter GABA, which interact with the human endocrine system, known as microbial endocrinology (Lerner & Matthias, 2016).

Microbial metabolites exert influence on brain function and behavior and have as main products of the microbiota short chain fatty acids (SCFAs) and butyric acid. This being a functionally occasional molecule and produced in the mammalian gut by fermentation of dietary fibers (Stilling et al., 22016), leading to the conclusion that in various diseases, such as diabetes, intestinal inflammation, obesity, colorectal cancer and neurological disorders, butyrate shows interesting results in addition to being necessary for the immune system (Stilling et al., 2016).

3.5 Gut-brain relationship in children with ASD

With the microbiome in homeostasis, consequently the gut-brain axis will be in balance, providing the individual with ASD with varied benefits. With a healthy microbiome there is a better functioning of the gut (balancing the chemicals produced there), in addition to providing clearer thinking, calmness, physical disposition and optimism (Kellman, 2017). Since gastrointestinal problems and neurodevelopmental behavioral changes have been linked to changes in the gut microbiota of people with ASD (Dias, 2016).

In this sense the ideal for autistics is to keep the microbiome in perfect functioning to avoid dysbiosis and all its consequences.

> According to Piranavie Srikantha and Hasan Mohajeri (2019), "various altered levels of metabolites have been observed in the blood and urine of autistic children, many of which are of bacterial origin, such as short-chain fatty acids (SCFA), indoles and lipopolysaccharides (LPS). A less integrative intestinal barrier abounds in autistic individuals. This explains the leakage of bacterial metabolites in patients, triggering new body responses or altered metabolism. Other concomitant symptoms were also detected, such as mitochondrial dysfunction, oxidative stress in cells, altered tight junctions in the blood-brain barrier, and structural changes in the cortex, hippocampus, amygdala and cerebellum."

There is a link between gut dysbiosis and autism because the gut microbiota suffers an imbalance. Therefore, to provide intestinal homeostasis, the consumption of probiotics is necessary to improve health and not cause side effects to the host (Adams et al., 2011). This occurs due to "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" (Hill, Guarner, Reid, Gibson, Merenstein, Pot, & Sanders, 2014), aiding microbial symbiosis.

Evidence with animal studies reveals that the serotonergic system can be influenced with the administration of pro- and prebiotics as it reduces intestinal permeability. Then, according to clinical studies, there were improvements in microbiome imbalance and metabolism, in addition to improvements in symptoms characteristic of ASD (Berding, & Donovan, 2016). One way to improve the health of the intestinal microbiome was the administration of microorganisms that were found in lower quantities in the intestinal flora, thus reinforcing the army of beneficial bacteria for the host.

Thus, gut modulation with the use of specific antibiotics, probiotics and restrictive diets are promising adjuvant therapies (Srikantha & Mohajeri, 2019).

A literature review study with 11 scientific publications on gluten-free and casein-free diets concluded the possible improvements or elimination of symptoms characteristic of ASD, with the implementation of a low-cost and easy to accept diet (Moraco & Nunes, 2017). Restriction diets can be beneficial, since substances that generate inflammation, malabsorption of nutrients and cause damage to the health of the individual are eliminated from all meals, causing significant benefits.

Treatment with restrictive diets such as soy-free, gluten-free, lactose-free and the administration of digestive enzymes, carnitine, essential fatty acids, some specific types of minerals, vitamin supplements, Epsom salt baths, provide significant improvements in non-verbal intellectual capacity, according to clinical evaluations (Adams et al., 2011). According to Silva (2011), children with ASD who adhere to gluten- and casein-free diets show significant improvements in symptoms characteristic of ASD, as they cause feelings of pleasure, lack of concentration, hyperactivity, irritability and difficulties in social relationships.

A checklist equivalent to 274 children with ASD was completed to assess serum levels of vitamins and minerals, being 97 neurotypical children of the same age. The following methods were used: vitamin A was detected by high performance liquid chromatography (HPLC); vitamin D, folate, vitamin B12 and ferritin by immunoassay method and minerals such as calcium, copper, magnesium, iron and zinc by atomic absorption spectrophotometry. In conclusion the study found a higher deficiency of minerals and vitamins in children with ASD than in neurotypical children (Wang, Lu, Wang, Zhang, Ungvari, & Xiang, 2018). In another study, 80 children (40 children with ASD and 40 control children) were evaluated in a case-control study, assessing levels of folate and vitamin B12, administered in both serum and diet, and found that children with ASD were significantly deficient in these vitamins and highlighting the need to ensure sufficient intake of essential nutrients to minimize or reverse potential nutritional deficiencies (Al-Farsi, Waly, Deth, Al-Sharbati, Al-Shafaee, Al-Farsi, & Ouhtit, 2013). Both studies show micronutrient (vitamin and mineral) deficiencies, especially at the stage of child development when the nutritional need is so necessary.

In a study of 738 children with ASD and 302 neurotypical children, nutritional status was assessed by biochemical screening of micronutrients, anthropometric measurements, provision of questionnaires and a food frequency questionnaire (FFQ) to guardians. Micronutrients correlated with ASD development and symptoms were vitamin A, vitamin D, zinc and folate. The results showed an increased risk of nutritional deficiencies in children with ASD compared to neurotypical children, as well as highlighting nutritional differences in children from different regions, so nutritional interventions should be individualized in children with ASD (Zhu, Guo, Yang, Lai, Tang, Chen & Li, 2020). This study reveals that, depending on the region of the country, vitamin and mineral deficiencies may vary, possibly due to soil enrichment, climate, water availability, purchasing power, among others, which may influence adequate nutritional intake.

A study with 252 food records evaluated to compare nutrient intakes in foods, ingested by children with and without ASD, checking for nutrient deficiencies and excesses, concluded that children consume fewer nutrients and foods than recommended. Highlighting the need to include nutritional surveillance as primary care for all children (Hyman, Stewart, Schmidt, Cain, Lemcke, Foley, & Ng, 2012).

Micronutrient intake is very important for hormonal, metabolic and synthesizing regulation, among others. The possibility of a diet with variety and adequate amounts of food, allows providing appropriate doses of minerals and vitamins, making up for micronutrient deficiencies, with the intake of carbohydrates, proteins and lipids, allowing a better functioning of the organism.

In one study, with 215 children with ASD and 285 neurotypicals, 37 children of the 215 with ASD received vitamin D treatment. Symptoms were then evaluated with the application before and after 3 months of treatment, of the Autism Behavior Checklist (ABC) and the Childhood Autism Rating Scale (CARS) and serum levels of 25(OH) D. They concluded that vitamin D deficiency contributes to the cause of ASD and presents better results in younger (Feng, Shan, Du, Wang, Li, Wang & Jia, 2017).A single-blind, randomized, controlled treatment study that followed 67 autistic participants, including children and adults, where a vitamin/mineral supplement was administered for twelve months, associated with a healthy diet, essential fatty acids, digestive enzymes, homocysteine, carnitine and Epson salt baths, showing positive results, where they concluded that the healthy diet and nutritional supplements caused improvements, increasing the learning capacity due to better brain functioning, increased daily life skills, social, non-IQ -verbal and by the substantial 18-month increase in developmental communication skills (Adams, Audhya, Geis, Gehn, Fimbres, Pollard, & Quig, 2018).

Diet should be taken into consideration in the improvement of symptoms characteristic of ASD, because in addition to being a non-invasive and easy to administer method, since parents or caregivers can prepare it and offer it to the child, it is low cost, and preserves the gastrointestinal tract, where digestion and absorption of food occurs. Strict feeding patterns of children with ASD due to food selectivity are commonly reported by parents and/or caregivers (Berding, & Donovan, 2016).

A study with 61 children with ASD, randomized double-blind and placebo crossover, showed a partial and significant reduction in the gastrointestinal symptoms that are usually present in these individuals and a decrease in the severity of the behavior (socio-relational aspect, maladaptive behaviors and the level of parental stress). perceived), with the administration of these specific probiotics: *Streptococcus thermophilus*, *Bifidobacterium longum*, *Limosilactobacillus fermentum* and *Ligilactobacillus salivarius*. The presence of these taxa related to the cited species was present in fecal samples, indicating intestinal colonization by probiotics in these patients (Guidetti et al., 2022).

It is necessary to assess nutritional problems in children with ASD from an early age, in order to develop effective and individualized strategies (Marta, 2020). Since each individual within the spectrum is unique, presenting numerous different eating habits, selectivity and eating problems.

With its onset in infancy and consequently lifelong, the signs of ASD manifest in the first five years of the autistic person's life. They usually present more than one comorbidity, including depression, anxiety, seizures, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder among other disorders (OPAS,2017).

Table 1 compiles the results and discussion on micronutrients and vitamin D supplementation in autistic children on the studies reviewed.

11Author (Year)	Sample	Nutrients	Results
Hyman *et al.* (2012)	(n=252) food records	Vitamins A, E, K, C, D and minerals (calcium, copper, potassium, selenium, sodium) and fibers	Concluded that children with ASD, like neurotypical children, consume less nutrients than the recommended amounts for their nutritional needs.
Al-Farsi *et al.* (2013)	(n=80) Children	Vitamins B9 and B12	Children with ASD showed significant deficiencies of these vitamins and highlighted the need to ensure sufficient intake of essential nutrients.
Feng et al. (2016),	(n=285) Children	Vitamin D	Concluded that vitamin D deficiency contributes to the cause of ASD, and also showed better outcomes in younger children with ASD.
Adams et al. (2018)	(n= 67) Children and adult	Vitamin/mineral supplementation, Essential Fatty Acid supplementation, Epsom salt baths, carnitine supplementation, digestive enzyme supplementation, and a healthy, casein- and gluten-free diet.	The results concluded that the healthy diet and nutritional supplements led to improvements, increasing the learning capacity due to better brain functioning. Increased daily living, social and communication skills and non-verbal IQ.
Guo et al. (2018)	(n=274) Children	Vitamin A, D, B9, B12. Minerals calcium, copper, ferritin, iron, magnesium and zinc.	A higher mineral and vitamin deficiency was found in children with ASD than in neurotypical children.

Siddiqi et al (2018).	(n=53) Children	B complex vitamins, calcium and iron.	The results have revealed that the consumption of vegetables and fruits is lower, revealing a low number of micronutrients, mainly B-complex vitamins, calcium and iron (SIDDIQI, 2018).
Belardo et al. (2019)	(n=120) Children	Vitamins B6, B9 and B12.	Conclusion that intestinal dysbiosis may be the main cause of a decrease in its absorption and genetic mutation in a specific gene.
Zhu, et al. (2020)	(n=738) Children	Vitamin A, D, B9, B12 and the mineral zinc	Concluded that there is an increased risk of nutritional deficiencies in children with ASD compared to neurotypical children, and also highlighted nutritional differences in children from different regions.
Guidetti et al. (2022)	(n=61) Children	*Streptococcus thermophilus*, *Bifidobacterium longum*, *Limosilactobacillus fermentum* e *Ligilactobacillus salivarius*	It concludes that the use of specific strains of probiotics obtains positive results related to the symptoms present in individuals with ASD, such as a reduction in the severity of gastrointestinal symptoms and behavior (socio-relational aspect, maladaptive behaviors and the level of perceived parental stress).

4. Conclusion

It was found that people on the Autistic Spectrum have more deficiency in the intake of vitamins and minerals, not reaching the needs recommended by the DRIs. However, with the use of supplementation of vitamins, minerals, essential fatty acids, associated with a healthy diet, they showed reduced or absent symptoms characteristic of ASD. Being interesting the adequate administration of macronutrients in order to a quantitative and qualitative intake that can offer a greater variety of fruits and vegetables, to obtain adequate dosages of micronutrients with food intake, helping a homeostasis in the microbiota in order to reach a symbiosis in the intestinal microbiome, with ingestion of prebiotic foods, modulating with specific strains of probiotics, strengthening the intestine-brain axis so that there is a significant improvement in the characteristic behavioral and gastrointestinal symptoms in individuals with ASD. It is important to encourage healthy and eating habits to improve the quality of life of people with Autistic Spectrum Disorder and their family members/caregivers. Carrying out new studies focusing on design of experimental, that is, targeting studies aimed at sample groups by age group, levels of cognitive and behavioral impairment, socioeconomic status, standardization of diet and medication reconciliation.

References

Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal flora and gastrointestinal status in children with autism–comparisons to typical children and correlation with autism severity. *BMC gastroenterology*, *11*(1), 1-13.

Adams, J. B., Audhya, T., Geis, E., Gehn, E., Fimbres, V., Pollard, E. L., ... & Quig, D. W. (2018). Comprehensive nutritional and dietary intervention for autism spectrum disorder—A randomized, controlled 12-month trial. Nutrients, 10(3), 369.

Al-Farsi, Y. M., Waly, M. I., Deth, R. C., Al-Sharbati, M. M., Al-Shafaee, M., Al-Farsi, O., ... & Ouhtit, A. (2013). Low folate and vitamin B12 nourishment is common in Omani children with newly diagnosed autism. *Nutrition*, *29*(3), 537-541.

Allen, A. P., Dinan, T. G., Clarke, G., & Cryan, J. F. (2017). A psychology of the human brain–gut–microbiome axis. Social and personality psychology compass, 11(4), e12309.

Belardo, A., Gevi, F., & Zolla, L. (2019). The concomitant lower concentrations of vitamins B6, B9 and B12 may cause methylation deficiency in autistic children. The Journal of nutritional biochemistry, 70, 38-46
.
Berding, K., & Donovan, S. M. (2016). Microbiome and nutrition in autism spectrum disorder: current knowledge and research needs. Nutrition reviews, 74(12), 723-736.

Bioma4me. (2019). O elo entre o autismo e as bactérias intestinais. URL:https://bioma4me.com.br/autismo-bacterias-intestinais/

Blow, F., Gioti, A., Goodhead, I. B., Kalyva, M., Kampouraki, A., Vontas, J., & Darby, A. C. (2019). Functional genomics of a symbiotic community: shared. *Microbiol. Mol. Biol.* Rev, 73, 775-808.

Cani, P. D. (2018). Human gut microbiome: hopes, threats and promises. *Gut*, *67*(9), 1716-1725.

Collen, A. (2016). 10% humano: como os micro-organismos são a chave para a saúde do corpo e da mente. Sextante.

Costa, D. C. F. D. (2014). Intervenção precoce no transtorno do espetro do autismo (*Doctoral dissertation).*

Cryan, J. F., O'Riordan, K. J., Sandhu, K., Peterson, V., & Dinan, T. G. (2020). The gut microbiome in neurological disorders. *The Lancet Neurology*, *19*(2), 179-1Dias, B. P. (2016). Relação entre a microbiota intestinal e o autismo. Trabalho de Conclusão de Curso – Centro Universitário de São Lucas, Porto Velho.

Do Carmo Cupertino, M., Resende, M. B., de Freitas Veloso, I., de Carvalho, C. A., Duarte, V. F., & Ramos, G. A. (2019). Transtorno do espectro autista: uma revisão sistemática sobre aspectos nutricionais e eixo intestino-cérebro. *ABCS Health Sciences*, *44*(2).

Eloe-Fadrosh, E. A., & Rasko, D. A. (2013). The human microbiome: from symbiosis to pathogenesis. *Annual review of medicine*, *64*, 145.

Feng, J., Shan, L., Du, L., Wang, B., Li, H., Wang, W., ... & Jia, F. (2017). Clinical improvement following vitamin D3 supplementation in autism spectrum disorder. *Nutritional neuroscience*, *20*(5), 284-290.

Furness, J. B., Rivera, L. R., Cho, H. J., Bravo, D. M., & Callaghan, B. (2013). The gut as a sensory organ. Nature reviews Gastroenterology & hepatology, 10(12), 729-740.

Guidetti, C., Salvini, E., Viri, M., Deidda, F., Amoruso, A., Visciglia, A., ... & Caucino, A. C. (2022). Randomized Double-Blind Crossover Study for Evaluating a Probiotic Mixture on Gastrointestinal and Behavioral Symptoms of Autistic Children.Journal of clinical medicine, 11(18), 5263.

Harbolic, Betty. (2019). Probióticos. URL:https://www.medicinenet.com/probiotics/article.htm.

Herath, M., Hosie, S., Bornstein, J. C., Franks, A. E., & Hill-Yardin, E. L. (2020). The role of the gastrointestinal mucus system in intestinal homeostasis: implications for neurological disorders. *Frontiers in Cellular and Infection Microbiology*, 248.

Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., ... & Sanders, M. E. (2014). The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature reviews Gastroenterology & hepatology*, *11*(8), 506-514.

Hsiao, Elaine. (2013). Probióticos podem atenuar sintomas do autismo. *Investigadores do California Institute Technology (Caltech).* URL:https://www.caltech.edu/.

Hyman, S. L., Stewart, P. A., Schmidt, B., Cain, U., Lemcke, N., Foley, J. T., ... & Ng, P. K. (2012). Nutrient intake from food in children with autism. *Pediatrics*, *130*(Supplement_2), S145-S153.

Kellman, R. (2017). A dieta do microbioma: uma maneira definitiva e cientificamente comprovada de emagrecer, restabelecendo a saúde intestinal. *São Paulo: Ed. Cultrix*.

Landeiro, J. A. V. R. (2016). Impacto da microbiota intestinal na saúde mental (Doctoral dissertation).

Laurent, É. (2014). A batalha do autismo: da clínica à política. *Editora Schwarcz-Companhia das Letras.*

Lerner, A., & Matthias, T. (2016). GUT-the Trojan horse in remote organs' autoimmunity. *J Clin Cell Immunol*, *7*(401), 10-4172.

Lopes, N. (2018). O que é simbiose e disbiose?.URL:https://nutritotal.com.br/pro/o-que-a-simbiose-e-disbiose/

Maenner, M. J., Shaw, K. A., Baio, J., Washington, A., Patrick, M., DiRienzo, M., ... & Dietz, P. M. (2020). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveillance summaries*, *69*(4), 1.

Malla, M. A., Dubey, A., Kumar, A., Yadav, S., Hashem, A., & Abd_Allah, E. F. (2019). Exploring the human microbiome: the potential future role of next-generation sequencing in disease diagnosis and treatment. Frontiers in Immunology, 9, 2868.

Marta, J. P. (2020). Problemas Alimentares e Nutricionais em Crianças com Perturbação do Espectro do Autismo (Doctoral dissertation).

Moraco, J. D., & Nunes, C. P. (2017). Dietas livres de gluten e casíena no autismo: uma revisão sistemática. *Revista da Faculdade de Medicina de Teresópolis*, *1*(01).

Navarro, F., Liu, Y., & Rhoads, J. M. (2016). Can probiotics benefit children with autism spectrum disorders? *World journal of gastroenterology*, *22*(46), 10093.

OPAS – Organização Pan Americana da Saúde. (2017). Transtorno do espectro autista. Folha informativa. URL:https://www.paho.org/bra/index.php?Itemid=1098.

Paiva Jr, F. (2019). Quantos autistas há no Brasil? *Revista Autismo.* São Paulo, ano V, (4), 20-23.

Paiva Jr, F. (2020). Prevalência de autismo nos EUA sobe 22%: agora é para 44. *Revista Autismo.* São Paulo, ano VI, (8), 8.

Paixão, L. A., & dos Santos Castro, F. F. (2016). Colonização da microbiota intestinal e sua influência na saúde do hospedeiro. *Universitas: Ciências da Saúde*, *14*(1), 85-96.

Pereira, M., & Gouveia, F. (2019). Modulação intestinal: fundamentos e estratégias práticas. *Brasília: Trato*.

Pivina, L., Semenova, Y., Doşa, M. D., Dauletyarova, M., & Bjørklund, G. (2019). Iron deficiency, cognitive functions, and neurobehavioral disorders in children. *Journal of Molecular Neuroscience*, *68*(1), 1-10.

Siddiqi, S., Urooj, A., & D'Souza, M. J. (2019). Dietary patterns and anthropometric measures of Indian children with autism Spectrum disorder. *Journal of autism and developmental disorders*, *49*(4), 1586-1598.

Silva, N. I. D. (2011). Relação entre hábito alimentar e síndrome do espectro autista (Doctoral dissertation, Universidade de São Paulo).

Silvestre, C. M. R. F. (2016). O diálogo entre o cérebro e o intestino: qual o papel dos probióticos*?: revisão de literatura (Doctoral dissertation).*

Sociedade Brasileira de Pediatria (2019). Transtorno do Espectro Autista. Departamento Científico de Pediatria do Desenvolvimento e Comportamento. *Manual de orientação.*

Srikantha, P., & Mohajeri, M. H. (2019). The possible role of the microbiota-gut-brain-axis in autism spectrum disorder. *International Journal of molecular sciences*, *20*(9), 2115.

Stilling, R. M., van de Wouw, M., Clarke, G., Stanton, C., Dinan, T. G., & Cryan, J. F. (2016). The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis?. *Neurochemistry international*, *99*, 110-132.

Vanti, N. A. P. (2002). Da bibliometria à webometria: uma exploração conceitual dos mecanismos utilizados para medir o registro da informação e a difusão do conhecimento. *Ciência da informação*, *31*, 369-379.

Van De Sande, M. M., van Buul, V. J., & Brouns, F. J. (2014). Autism and nutrition: the role of the gut–brain axis. *Nutrition research reviews*, *27*(2), 199-214.
Veras, R. D. S. C., & Nunes, C. P. (2019). Conexão cérebro-intestino-microbiota no Transtorno do Espectro Autista. *Revista de Medicina de Família e Saúde Mental*, 1(1).

Wang, F., Lu, L., Wang, S. B., Zhang, L., Ng, C. H., Ungvari, G. S., ... & Xiang, Y. T. (2018). The prevalence of autism spectrum disorders in China: a comprehensive meta-analysis. *International journal of biological sciences*, *14*.

Zarrinpar, Amir, et al. Diet and eating patterns affect the daytime dynamics of the intestinal microbiome. Metabolismo de células, EUA, 2014, p. 1006-1017, 2014.

Zhu, J., Guo, M., Yang, T., Lai, X., Tang, T., Chen, J., ... & Li, T. (2020). Nutritional status and symptoms in preschool children with autism spectrum disorder: a two-center comparative study in Chongqing and Hainan Province, China. *Frontiers in pediatrics*, *8*, 469.

Zorzo, R. A. (2017). Impacto do microbioma intestinal no eixo cérebro-intestino. *International Journal of Nutrology*, *10*(S 01), S298-S305.