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REVIEW ARTICLE

THERAPEUTIC DIETARY APPROACH OF CHILDREN WITH AUTISM SPECTRUM DISORDER

ABORDAJE DIETÉTICO TERAPÉUTICO DE NIÑOS CON TRASTORNO DEL ESPECTRO AUTISTA

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ABSTRACT

Introduction: Autism spectrum disorder (ASD) is a neuropsychiatric disease, characterized by deficits in social communication, presence of restricted interests and repetitive behaviors. This review aims to address the different nutrients that can be included in the diet of patients with ASD in order to reduce the different signs and symptoms present in this disorder. Different bibliographic sources were reviewed, such as PubMed, MEDLINE, ScienceDirect, Embase, and SciELO, using the keywords "Probiotics", "Vitamin B", Vitamin C", "Gluten", "Omega-3" and "Autism Spectrum Disorder". It was found that probiotics and gluten improve gastrointestinal symptoms and, in addition, like vitamins B6, B9, B12 and C, as well as omega 3, help improve neurobehavioral symptoms, language and social behavior of children with ASD.

Keywords: Probiotics; Vitamin B; Vitamin C; Omega-3 Fatty Acids; Autism Spectrum Disorder. (Source: MESH-NLM)

RESUMEN

Introducción: El trastorno del espectro autista (TEA) es una enfermedad neuropsiquiátrica, caracterizada por déficits en la comunicación social y la presencia de intereses restringidos y conductas repetitivas. La presente revisión tiene por objetivo abordar los diferentes nutrientes que pueden incluirse en la dieta de los pacientes con TEA con el fin de disminuir los diferentes signos y síntomas presentes en este trastorno. Se revisaron diferentes fuentes bibliográficas como PubMed, MEDLINE, ScienceDirect, Embase, y SciELO, empleando las palabras claves "Probióticos", "Vitamina B", Vitamina C", "Gluten", "Omega 3" y "Trastorno del Espectro Autista". Se encontró que los probióticos y el gluten mejoran los síntomas gastrointestinales y, además, al igual que las vitaminas B6, B9, B12 y C, así como el omega 3, ayudan al mejoramiento de síntomas neuroconductuales, lenguaje y conducta social del niño con TEA.

Palabras clave: Probióticos; Vitamina B; Vitamina C; Ácidos Grasos Omega-3; Trastorno del Espectro Autista. (Fuente: DeCS- BIREME)

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. The World Health Organization estimates the international prevalence of ASD at 0.76%; which represents 16% of the world child population [1]. According to the Centers for Disease Control and Prevention, the prevalence of ASD in the US has increased from 4.5 in 10,000 children in 1966 to 1 in 110 in 2006 and 1 in 59 8-year-olds in 2014, mainly due to increased awareness and better diagnostic methods [2].

According to the Ministry of Health of Peru, until 2019, there were 15,625 people with ASD registered, and of this figure, 90.6% corresponds to children under 11 years of age [3]. Early warning signs for ASD include poor eye contact, poor response to names, lack of showing and sharing, not gesturing at 12 months, and loss of language or social skills [1].

The multidisciplinary evaluation is governed by the Criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) for autism spectrum disorders, which inform both the diagnosis and the interventions that can be carried out for the child with ASD and the family[4].

Gastrointestinal symptoms such as altered bowel habits, chronic abdominal pain, reflux, and vomiting are common in children with ASD. It is noteworthy that untreated gastrointestinal symptoms can increase behavioral problems in children with ASD, as they are associated with a higher rate of irritability, anger, aggressive behavior, and sleep disturbances [5]. The main interventions to alleviate the symptoms of ASD involve psychosocial strategies, such as educational interventions, speech, behavioral, and developmental therapies, and parenting skills training programs, achieving improvements in communication and social behaviors [2].

Studies highlight that dietary and nutritional supplements would help alleviate the symptoms of ASD, as well as improve the effectiveness of established strategies and therapies. The role of probiotics in restoring the balance of the intestinal microbiota, reducing gastrointestinal symptoms, and regulating the "gut-brain axis" with an improvement in the behavior of children with ASD has been highlighted[6].

The importance of vitamins B6, B9, and B12 lie in their cofactor functions in neurotransmitter synthesis, DNA synthesis and repair, and methionine methylation, which are altered in patients with ASD [7]. Vitamin C prevents brain dysregulation by reducing brain inflammation, improving neurotransmission, mitochondrial dysfunction, and oxidative stress by improving sensorimotor behaviors[8].

In children with ASD, it is thought that polyunsaturated fatty acids (PUFA) metabolism is deficient or abnormal, which leads to a large production of proinflammatory cytokines, an increase in oxidative stress, and instability in the formation and action of neurotransmitters [9]. While gluten-free diet regimens can safely improve manifestations and could be recommended for children with ASD [10].

This review further explores the effects of a diet enriched in probiotic nutrients, vitamins B and C, omega 3 and low amounts of gluten, on the signs and symptoms of children with ASD, emphasizing the metabolic role of each one of them and the relevant findings that the studies carried out so far have shown.

METHODS

This work is a narrative literature review in which various scientific publications have been analyzed in order to describe the effects of a therapeutic dietary treatment in children with ASD, thus fulfilling the objectives already described. A search of journal articles indexed in the following databases was performed: PubMed, MEDLINE, ScienceDirect, Embase, and SciELO. The keywords used to perform the searches were: "Probiotics", "Vitamin B", "Vitamin C", "Omega 3", "Gluten", "Autism Spectrum Disorder", both in Spanish, Portuguese and English. The Boolean operators used were: "AND" and "OR". Articles up to 5 years old after being published, from 2016 to 2021, were considered, except this limit for those that contained highly relevant information. Articles written in Spanish, Portuguese, and English were included.

PROBIOTICS

Several studies have reported alterations in the gut microbiota composition in children with ASD. A greater representation of members of the Clostridiales family and an increase in the populations of Sutterella and Ruminococcus. As a result of intestinal dysbiosis, there is systemic exposure to an excessive amount of LPS (lipopolysaccharides) and other bacterial factors, which through the "gut-brain axis" alter brain function, thus causing the behavioral problems seen in children with ASD [11].

Probiotics are live microorganisms considered beneficial for human health, generally belonging to Gram-positive taxa (that is, Lactobacillus and Bifidobacterium), and recently defined as "psychobiotics", since they could be a therapeutic tool to restore the balance of the intestinal microbiota and promote proper brain function through the "gut-brain axis" [12]. The term "gut-brain axis" refers to a complex two-way communication network between the gut and the brain. This network is involved in neurodevelopment, as well as in a variety of neuropsychiatric diseases, including ASD[11].

The signals from the brain are intended to regulate digestion through the autonomic nervous system and neuroendocrine factors. Signals that originate in the gut on their way to the brain consist of neural messages carried by vagal and spinal afferents, cytokines that represent immune messages, gut hormones, and microbial factors that can reach the brain directly through the bloodstream, but also they can interact with the other signals [13]. According to various studies, the development of systemic and intestinal inflammation development in patients with ASD is evident in alterations in circulating cytokine levels [12].

LPS, after absorption through the enteric mucosa, stimulates the intestinal immune system to produce proinflammatory cytokines and sensitize and stimulate vagal and spinal afferents. On the other hand, through the bloodstream, LPS can directly reach the central nervous system, where they bind with TLR4 receptors to induce the production of proinflammatory cytokines, thus determining the inflammatory processes that alter brain function[13].

It has been shown in various experiments that there is an increase in intestinal permeability in patients with ASD. This results from a decreased expression of proteins that form the mucosal barrier and a low expression of proteins that make up the intercellular junction complexes between neighboring enterocytes. This allows a greater absorption of LPS, and, therefore, a more significant alteration of brain function[14]. (Table 1).

Table 1. Studies of the use of probiotics in patients with ASD.

Author(s)	No. Patients	Procedure	Results
Liu, et al. 2019 (17)	n=80 7-15 years	Lactobacillus plantarum. 1 capsule daily for 1 month.	Decrease in symptoms: anxiety, hyperactivity and impulsivity and defiant attitude.
Kaluzna, et al. 2012 (68)	n=22 4-10 years	Lactobacillus acidophilus. 2 times a day for 2 months.	Significant decrease in D-/L-arabinitol (DA/LA) in urine.
Niu, et al. 2019 (16)	n=77	Lyophilized, water-soluble powder containing 6 strains of bacteria.	Decrease in symptoms (83.8% of cases).
Sanctuary A, et al. 2019 (69)	n=8 2-11 years	Bifidobacterium longum supbsp. Infantis.1 time a day for 12 weeks.	Significant improvement in irritability and stereotypy scores.
Shaaba N, et al. (2018) (70)	n=30 5-9 years	Lactobacillus acidophilus, rhamnosus and Bifidobacterium longum.	Significant decrease in symptoms.
Tomova, et al. 2015 (71)	n=9 2-9 years	Lactobacillus, Bifidobacteria, Streptococcus. 3 times a day for 4 months	Increased levels of TNF-α associated with increased severity of ASD.

West R, et al. 2013 (72)	n=33 3-16 years	Lactobacillus acidophilus, casei y delbrueckii. 3 times a day for 21 days	Behavior improvement (ATEC scores and participant feedback)
Parracho, et al. 2010 (73)	n= 39 4-16 years	Lactobacillus plantarum	Lower levels of Clostridium in feces. No big differences in behavior.

ATEC: Autism Treatment Evaluation Checklist

Probiotics may represent a treatment in disorders where dysbiosis and increased intestinal permeability have been reported. Probiotics can stabilize the mucosal barrier by increasing mucin expression, its antiproliferative activity in Clostridium species, stimulating mucosal immunity (secretory IgA) and synthesizing antioxidant substances[11].

They can reduce intestinal permeability by upregulating the proteins that make up the tight junctions between enterocytes, strengthening the mucosal barrier through increased mucin production, and through their direct anti-inflammatory effects[15].

The effect of probiotics to improve the behaviors of patients with ASD is also due to the relief of gastrointestinal disorders. The most frequently reported gastrointestinal symptoms in children with ASD are altered bowel habits, chronic abdominal pain, reflux, and vomiting. Of note, untreated gastrointestinal symptoms may increase behavioral problems in children with ASD[11].

In a study by Manman et al., thirty-seven children with ASD were treated with 4-week applied behavior analysis (ABA) training in combination with probiotics. The dose used was 6 g per day (36 billion CFUs in total). During the study, both groups were prohibited from using antibiotics, other probiotics, prebiotics, or any other treatment that could alter the gut microbiota. After the month of treatment, the researchers found a decrease in ASD symptoms and a decrease in gastrointestinal symptoms[16].

Kaluzna-Czaplinska et al. They administered an oral supplement of Lactobacillus acidophilus twice a day for 2 months to a group of children with ASD, finding significant metabolic changes and an improvement in the ability to follow orders and in concentration after this period of time[11].

Yen et al. found a decrease in ASD symptoms, anxiety, hyperactivity and impulsivity, and defiance after 1 month of treatment based on Lactobacillus plantarum PS128, 3 × 1010 CFU in capsules. Participants were allowed to continue their regular medications and therapies, with the exception of antibiotics, and were asked to refrain from consuming yogurt or probiotic products during the study period[17].

Some studies have reported minor gastrointestinal symptoms, such as nausea, loose stools, flatulence, and taste disturbances in subjects receiving probiotics[18]. With regard to the safety of probiotic intake, cases of infection by lactobacilli and bifidobacteria are extremely rare and are estimated to represent between 0.05% and 0.4%[19].

Existing probiotic lactobacilli and bifidobacteria are suitable for babies and children. Several studies have shown that products containing lactobacilli and bifidobacteria are well tolerated in this age group[20].

VITAMINS B6, B9 and B12

Vitamin B6 (pyridoxine) is a water-soluble vitamin that acts as a coenzyme[21] important in several reactions involved in the metabolism of lipids, carbohydrates, and amino acids.

There are three inactive conformations of vitamin B6 (pyridoxal, pyridoxine, pyridoxamine), which are converted to its biologically active form, pyridoxal 5'-phosphate (P5P). Low concentrations of P5P were found in autistic children in combination with low activity of the enzyme pyridoxal kinase that converts pyridoxal to P5P[22].

Vitamin B6 also participates in the synthesis of neurotransmitters such as serotonin, aminobutyric acid, dopamine, noradrenaline, and epinephrine [23]. Abnormal biochemical synthesis of these neurotransmitters, as well as mineral and vitamin deficiency associated with abnormal bowel function and impaired immune systems, occur in individuals with ASD.

.High-dose vitamin B6 supplementation with magnesium has been studied in many double studies. blinded placebo-controlled studies, and almost all reported improvements in behavioral manifestations [24], therefore, the studies recommended the beneficial effect for patients with ASD (Table 2).

Table 2. Participation of Vitamin B6, B9 and B12 in patients with ASD.

Author(s)	No. Patients	Procedure	Results
Obara T, et al. 2018 (22)	n=17 8.8 years	Vit B6 Administration.	Improvement in 17% of cases.
Altun H, et al. 2018 (23)	n=105 3-12 years	Vit B6, B9 and B12 measurement, ELISA analysis.	Significantly low levels.
Khan F, et al. 2021 (24)	n=50	Randomized, double-blind, placebo-controlled trial.	Vit B6 and magnesium combination: neurobehavioral improvement.
Rossignol et al. 2021 (25)	-	Systematic review of 17 publications.	Vit B12 effectiveness: very well tolerated and safe.
Zhang Y, et al. 2016 (28)	n=64	Postmortem samples from the frontal cerebral cortex.	Abnormally lower Vit B12 levels.
Raghavan R, et al. 2017 (29)	n=1257	Prospective study	In optimal concentrations: improvement of signs and symptoms.
Zhang Z, et al. 2018 (30)	n=401	DNA extraction from blood cells.	Genetic disorders in the metabolism of Vit B12 and B9 increase the risk of ASD.
Belardo et al. 2019 (31)	n=120 3-8 years	Urine collection and metabolite extraction.	Reduced concentrations of Vit B6, B9 and B12.

Vitamin B12 (cobalamin) exists in multiple forms, including methylcobalamin and adenosylcobalamin, cofactors for methionine synthase and methylmalonyl CoA mutase, respectively [25]. The metabolically active form of vitamin B12, methylcobalamin, is an essential cofactor for the folate-dependent methylation of homocysteine to methionine by methionine synthase.

ASD is associated with decreased absorption of vitamin B12 which has been attributed to poor dietary intake of vitamin B12 [26], dysbiosis in the lining of the intestine leading to malabsorption of B12, autoimmune antibodies, neurotoxin and heavy metal intoxication[27]. that render neurons insensitive to standard doses of B12. High concentrations of methylcobalamin are required to regenerate neurons and the myelin sheath

of the spinal cord[28], which is necessary for the relief of ASD symptoms.

Folic acid, a component of the B complex, is involved in different reactions such as DNA synthesis and repair and in methylation pathways, in particular, it helps prevent the fetus from developing major congenital deformities [29] of the brain or spine, including neural tube defects. Patients with ASD have been found to have folic acid deficiency in the cerebrospinal fluid (CSF). This deficit can be explained by the action of circulating serum antibodies against folate receptors. Antibodies to folate bind to folate receptors and block folic acid synthesis[30], thereby inhibiting folate transport to the CSF in autistic patients with cerebral folate deficiency syndrome. This mechanism may be a common factor in the pathogenesis of ASD.

Several studies have shown in their results some altered pathways due to vitamin B6, B9 and B12 deficiency [31], including the methionine transmethylation and transsulfuration pathways, which justifies the well-known protein and DNA hypomethylation observed in ASD.

VITAMIN C

Vitamin C supplements reduce brain inflammation, improving pathological behavior problems in people with ASD [32]. In patients with ASD, mitochondrial dysfunction and oxidative stress are common, which can be treated with vitamin C [33]. In a randomized, double-blind, placebo-controlled vitamin and mineral treatment study, children with ASD treated with vitamin C significantly reduced oxidative stress. These increased levels of vitamin C were suggested to be beneficial in significantly reducing oxidative stress in these patients [34].

Reduced vitamin C (dehydroascorbate, DHA) can directly regenerate vitamin E after it is converted to ascorbate, its oxidized form. Thiol antioxidants such as glutathione can convert ascorbate to DHA, which is then available to regenerate vitamin E again. Therefore, vitamin C is particularly effective in reducing oxidative damage when used in conjunction with vitamin E. Vitamin E, vitamin C, and glutathione systems act synergistically, cells have low steady-state concentrations of vitamin E and ascorbate radicals, and vitamin loss or consumption is prevented.

Vitamin C is a powerful antioxidant that can neutralize and eliminate oxidants, such as highly reactive molecules generated in metabolic processes in the brain, but also in other organs. It is vital in tissue growth, synthesis of vasoactive agents, immune regulation, and many other metabolic functions. The biological importance of this vitamin in the brain is related to the development of neurons, their functional maturation and antioxidant responses. When there is a deficiency of vitamin C, neurons show decreased growth and activity, as well as increased susceptibility to oxidative damage [35].

Vitamin C is an essential cofactor for proline hydroxylase involved in collagen synthesis. Most organs are affected by its presence or absence, and its deficiency usually leads to corkscrew or dystrophic hairs, gingival hyperplasia, and weakened blood vessel walls. As a result of the weakening of the blood vessel walls, people with vitamin C deficiency often experience bleeding into the skin, joints, and other organs [36].

In a study of 182 treated with vitamin C, it also improved health in patients with ASD, such as constipation in 12% of cases and heart problems (27%) [37]. When children with ASD were supplemented for 30 weeks, a significant improvement in sensorimotor behaviors could be observed due to the dopaminergic effects of this vitamin[33,38]. (Table 3)

Table 3. Studies of the role of vitamin C in developing signs and symptoms in patients with ASD.

Author(s)	Patients	Procedure	Results
Núñez, et al. 2020 (32)	-	Nutrition in relation to etiology and symptomatology.	Improve behavior problems.
Pangrazzi, et al. 2020 (33)	-	Summary of studies using antioxidants in their interventions for ASD.	Vit C supplementation improved sensorimotor behaviors.
Karhu, et al. 2021 (34)	-	Summary of studies on dietary supplements (vitamins A, C, B6 and B12; magnesium and folate).	Vit C significantly reduced oxidative stress.
Pangrazzi, et al. 2020 (35)	-	Studies on deficiencies in the vitamin-based antioxidant network.	Glutathione, Vit C and NAC: behavior improvement.
Raffe, et al. 2019 (36)	n=1	Single case report.	Vit C deficiency.
Adams, et al. 2021 (37)	n=1286	National Survey on the efficacy of treatment focused on nutraceuticals.	Improvement of constipation, aggression, agitation, and gastrointestinal problems.
Bjørklund et al. 2019 (38)	-	Efficiency and safety in vitamin treatments.	Improved sensorimotor behavior.

NAC: N-acetylcysteine

GLUTEN

For decades, gastrointestinal conditions have been considered an important part of autistic patients [39]. These symptoms are generally: constipation, diarrhea, abdominal pain, and reflux, their prevalence in children with ASD ranges from 23% to 70%, since the degree of severity of ASD correlates with the appearance of symptoms [40,41].

Gluten is a protein complex found in foods that come from wheat, oats, rye, and barley, among other foods [42]. It is composed of two main classes of proteins: 90% gliadin (a prolamin) and glutenin (a glutelin) , lipids (8%), and carbohydrates (2%) [43]. Gluten digestion begins with the enzymes gastrointestinal elastase 3B (CEL3B), elastase 2A (CEL2A), and carboxypeptidase A1 (CBPA1) enzymes, capable of digesting gluten in humans [44]. Then, through various studies, it was possible to determine that the intestinal permeability increased by gluten is due to a protein called zonulin, which is going to be in charge of opening the pores of the intestinal wall. Furthermore, tests in healthy subjects of a gluten-free diet suggest that it produces a reduction in the intestinal flora, an increase in opportunistic pathogens, and immunosuppressive effects [41]. In patients with ASD, it is possible to demonstrate a dysbiosis generated by the imbalance of intestinal bacteria, which is why toxins that are released by said bacteria are present in the bloodstream, causing the activation of TNFα, which is responsible for producing proinflammatory cytokines[45].

Children with ASD sometimes have digestive and extra digestive symptoms. Digestive symptoms include abdominal pain, heartburn, chronic diarrhea, flatulence, hypersalivation, vomiting, regurgitation, weight loss, rumination, bruxism, irritability, dysentery, constipation, fecal impaction. Regarding extra digestive symptoms, respiratory, neurological, and dermatological disorders can be found, such as upper respiratory tract infections, eczema, atopic dermatitis, and pruritus[46].

Children with ASD who consumed cow's milk or gluten-containing foods have been shown to have higher levels of proinflammatory cytokines and increased symptoms(48) (Table 4).

Table 4. Participation of gluten in the diet of patients with ASD.

Author(s)	Patients	Procedure	Results
Marí S, et al. 2016 (47)	n=105	Gluten-free and casein-free diet / regular diet.	Gluten-free diet improves quality of fat intake.
Serrato S, et al. 2018 (74)	n=15 3-12 years	Gluten-free and casein-free diet with omega-3 supplementation Duration: 8 weeks	Behavior improvement.
Hernandez A, et al. 2017 (75)	n=26 3-12 years	Gluten-free and casein-free diet. Duration: 10 weeks	Decrease in gastrointestinal symptoms.
Gonzales D, et al. 2020 (76)	n=37	Gluten-free and casein-free diet / regular diet. Duration 12 months	No significant results.
Ghalichi, et al. 2016 (77)	n=80	Autism Diagnostic Interview-Revised (ADI-R). ROME III questionnaire. GARS-2 questionnaire.	Gluten-free diet is effective in controlling gastrointestinal and behavioral symptoms.
Hyman, et al. 2016 (78)	n=14 3-5 years	Gluten-free and casein-free diet Duration: 30 weeks	Provides no evidence to support use.
Harris C,Card B. 2012 (79)	n=13 5 - 12 years	free diet casein	Continued and well-controlled r esearch is needed.

GARS: Gilliam Autism Rating Scale

Many people with ASD have an intolerance(47) or food hypersensitivity to different proteins, so it is advisable to follow a gluten-free diet in this case since an improvement in intestinal problems has been seen [49].

OMEGA-3

Omega 3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the fatty acids found in fish oil. These acids reduce the synthesis of proinflammatory mediators by acting as competitive inhibitors of omega 6. The important role of omega 3 highly unsaturated fatty acids is to reduce plasma triglyceride levels and optimize cholesterol concentrations. They also have antithrombotic, antiarrhythmic, and vasodilator properties, which protect the cardiovascular system and significantly reduce cardiovascular mortality(50). EPA and DHA are crucial for fetal development and neuronal, retinal, and immunological functions [51].

There has been an increased interest in the action of omega-3 fatty acids in psychiatric patients and the treatment of various mental illnesses. The fundamental reason is its main action in modifying the synaptic membrane. Among psychiatric diseases, one of them being ASD, long-chain omega-3 fatty acids have been tested for treatment [50].

Some evidence showed that omega-3 could improve the course of chronic inflammatory diseases related to the pathophysiology of ASD [51]. In 2017, through 3 Randomized Clinical Trials (RCTs), only a small but not

significant benefit of omega-3 was reported, concluding that it cannot be recommended as an alternative to support behavioral therapies for infants with ASD. Large, high-quality RCTs are needed to clarify further the role of omega-3 fatty acids[52,59].

Studies from 2019 only found small improvements in hyperactivity, lethargy, and stereotypies but no significant effect on global functioning or social interactions[53].

The two neurodevelopmental disorders becoming more prevalent are ASD and ADHD (Attention Deficit Hyperactivity Disorder). High omega 6 intakes and lower omega-3 intakes may be found to be associated with this increase. Lately, there are lower levels of DHA in children with ASD; this is because DHA is very important in the last trimester of pregnancy because it is crucial for optimal neurological development. This means that the excellent supply of DHA through the maternal diet or breastfeeding may increase neuronal protection in the offspring, indicating that DHA may act as a modifiable risk factor for ASD[54].

A deficit of PUFA (polyunsaturated fatty acids) omega-3 during pregnancy is associated with maternal depression and the neurological development of the child. Likewise, there is a greater production of IL6 in brain tissues and a poorer spatial memory. Epidemiological studies have indicated that low or no consumption of seafood containing omega-3 PUFAs results in offspring with poorer performance on neurodevelopmental measures[56].

Something very important to note about the mother's PUFAs is that they represent the only source of omega-3 long-chain PUFAs for the fetus. The recommendations established by the National Health Security Agency (ANSES), the European Scientific Committee for Food (ESCF), and the International Society for the Study of Fatty Acids and Lipids (ISSFAL) for excellent development is around 500 mg/day of EPA and DHA. In pregnant women, it can fluctuate between 200 and 1000 mg/day[57].

The consumption of omega 3 is very important in the third trimester of pregnancy since it is there where they are incorporated into the retinal and neuronal tissues (it affects cognition, learning, behavior, and reproduction), also after birth, during the following 10 months of life [58]. In 2016, the evidence that could be obtained from three RCTs was insufficient at that time to determine if HUFAs (highly unsaturated fatty acids) are beneficial for ASD. In the first RCT, which was double-blind, randomized, and placebo-controlled, was carried out in 13 children between the ages of 5 and 17 years with ASD. Taking 840 mg/day of EPA plus 700 mg/day with DHA showed improvements after six weeks in hyperactivity and stereotypic behaviors.

In the second double-blind, placebo-controlled RCT, favorable results on core symptoms of ASD were not obtained in a group of 48 children with ASD for six months with DHA 200 mg/day supplementation. And finally, in the third RCT, it did not support the hypothesis that supplementation with high doses of HUFA (1.5 g EPA AND DHA/day) in children with ASD provides any benefit in improving central symptoms.

In a case report study, improvements were found after treatment with EPA administered at a dose of 1g/day for the first time, then ascending to a dose of 3g/day, all over a period of four weeks. Finally, the expected results of the eight-month follow-up were beneficial [59]. In 2021, the effects of omega-3 polyunsaturated fatty acids were studied. The results of several RCTs showed improvement in some core symptoms of ASD, such as hyperactivity, lethargy, and stereotypy.

The first RCT treated fifty-seven children with ASD who presented hyperactivity, for six weeks with a dose of 1.3g/day of omega-3 polyunsaturated fatty acids in parallel with a placebo. Several improvements in stereotypy and lethargy were found.

In the second RCT, seven children with ASD were treated for 4 months with large doses of AA (arachidonic acid) and DHA, in parallel with six children receiving a placebo. The result shown was an improvement in social withdrawal, stereotypy, and in communication. In the third RCT with forty-eight children, the desired results were not achieved. In another RCT, they found that AA, EPA, and DHA supplementation over a period of 21 days led to better behavior in 20 children out of a total of 30 children with ASD; the authors concluded that PUFA supplementation could play a very important role in improving autistic characteristics as well as in their ability to concentrate, eye contact, motor skills, and language development. A fifth RCT with 68 children with ASD with PUFA supplementation, the authors found that during the trial, there is an improvement in social motivation; in addition, patients who had very low initial levels of omega - 3 / - 6 managed to show a greater effect. Finally, in the year 2021 a final investigation, the authors discovered the benefits with omega-3 treatment that included stereotyped behavior and social communication, as well as in the Gilliam Autism Assessment Scale (GARS) score in parallel with the control group [55]. (Table 5)

Table 5. Clinical studies of the role of Omega-3 in patients with ASD.

Author(s)	Patients	Procedure	Results
Sheppard, et al. 2017 (60)	n=31 18-38 months	Administration of omega-3, omega-6 and omega-9.	Improvement in language, combined gestures and BITSEA ASD scale score.
Pallerada, et al. 2017 (61)	n=68 5-17 years	Administration of omega-3 and vitamin E as a stabilizer.	Improvement in social motivation and global clinical impression.
Raine, et al. 2018 (62)	n=282 7-16 years	Administration of omega-3.PO	Decreased aggressiveness and antisocial behavior.
Keim, et al. 2018 (63)	n=31 18 a 38 months	Administration of omega-3-6-9 vs canola oil.	According to the BITSEA scale: decrease in symptoms.
Mazahery, et al. 2017 (59)	n=117 2.5 a 8 years	Administration of vitamin D, omega-3 or both.	Improved social awareness and social communicative functioning.
Doaei, et al. 2021 (64)	n=54 5-15 years	Administration of omega-3 and placebo.	Improvement of stereotyped behavior and social communication.
Yui K, et al. 2012 (66)	n=13	Administration of triglycerides enriched with ARA and olive oil placebo.	Positive effect on treatment patients and improvement against social isolation.
Amminger G, et al. 2007 (67)	n=13 5-17 years	Administration of omega-3 fatty acids.	Improvements in hyperactivity and stereotyped behaviors.
Voigt R, et al. 2014 (64)	n=48	Administration of DHA or placebo	According to BASC scale: improvement in functional communication.

BITSEA: Brief Infant Toddler Social Emotional Assessment
ASD: Autism Spectrum Disorder
BASC: Behavior Assesment System for Children

DISCUSSION

It has been possible to demonstrate the metabolic mechanisms and studies that support the effect of the nutrients studied in improving the symptoms of children with ASD. Probiotics, due to their action to improve the symptoms of children with ASD and relief gastrointestinal disturbances, constitute a good treatment alternative.

It has also been shown that probiotics, by accompanying other established therapies, improve their effectiveness, finally achieving better adherence to treatment. Although it is true that a metabolic pathway involved in the alteration of the "brain-gut axis" has been proposed [11-18], research should be carried out to specifically understand how certain brain regions are affected, causing the behaviors associated with patients with ASD. It is suggested that more research with a larger number of participants should also be carried out to achieve a better assessment of the evidence of effects.

Likewise, the importance of vitamins B6, B9 and B12 should be highlighted, since they contribute to the improvement in the symptoms of patients with ASD, mainly in their neurobehavioral development, due to the important changes in the improvement of language [24-31], also highlighting the synergy that some of these vitamins have with other nutrients such as magnesium.

Vitamin C supplements reduce brain inflammation, improving pathological behavior problems in people with ASD, by reducing mitochondrial dysfunction, oxidative stress and its dopaminergic action. It is important to mention that vitamin C is particularly effective in reducing oxidative damage, when used together with vitamin E [34-38]. When there is a deficiency of vitamin C, neurons show a decrease in their growth and activity, increased susceptibility to oxidative damage, leading to the growth of dystrophic or corkscrew hairs, gingival hyperplasia and weakening of the blood vessel walls.

It has been shown that the association between gluten-free and casein-free diet in patients with ASD promotes the improvement of cognitive symptoms, gastrointestinal tract, intestinal permeability and hypersensitivity [45-49]. It also causes an improvement in social behavior and communication. The time of intake of diets without gluten and/or casein, of at least 6 months, is sufficient to observe its effects, showing an improvement in symptoms.

The intake of omega 3 has as a result, in patients with ASD, an increase in the words produced and the use of combined gestures, as well as an improvement in social motivation, awareness and social communicative functioning [53-59]. It also has a positive effect on stereotyped behavior and hyperactivity.

CONCLUSIÓN

In children with ASD, taking probiotics could improve behavior and achieve greater adherence to other treatments. Including vitamins B6, B9 and B12 improves both behavioral behavior as well as language. Vitamin C supplements have been implicated in improvements in behavior problems. A diet low in gluten and/or casein causes a slight change in gastrointestinal symptoms, but there is still not enough scientific evidence for its use. The consumption of omega 3 has beneficial effects on signs and symptoms such as lethargy, stereotyped behavior, hyperactivity, communication and social motivation.

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REFERENCES

1. Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. Transl Pediatr. 2020; 9(1):55-65. DOI: 10.21037/tp.2019.09.09

2. Liu Y, Liong M, Ella Y, Huang H, Peng W, Cheng Y, et al. Effects of Lactobacillus plantarum PS128 on Children with Autism Spectrum Disorder in Taiwan: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients. 2019; 11(4): 820. DOI: 10.3390/nu11040820

3. MINSA. El 81% de personas tratadas por autismo en Perú son varones [Internet]. 2019 [citado 2021 Nov 15]. Disponible en: https://www.gob.pe/institucion/minsa/noticias/27103-el-81-de-personas-tratadas-por-autismo-en-peru-son-varones

4. Christensen D, Braun K, Baio J, Bilder D, Charles J, Constantino J, et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. MMWR Surveill Summ. 2018; 65(13):1-23. DOI: 10.15585/mmwr.ss6513a1

5. Santocchi E, Guiducci L, Fulceri F, Billeci L, Buzzigoli E, Apicella F, et al. Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters. BMC Psychiatry. 2016; 16:183. DOI: 10.1186/s12888-016-0887-5

6. Santocchi E , Guiducci L , Prosperi M, Calderoni S, Gaggini M, Apicella F, et al. Effects of Probiotic Supplementation on Gastrointestinal, Sensory and Core Symptoms in Autism Spectrum Disorders: A Randomized Controlled Trial. Front Psychiatry. 2020; 11: 550 - 593. DOI: 10.3389/fpsyt.2020.550593

7. Belardo A, Gevi F, Zolla L. The concomitant lower concentrations of vitamins B6, B9 and B12 may cause methylation deficien y in autistic children. J Nutr Biochem. 2019; 70:38-46. DOI: 10.1016/j.jnutbio.2019.04.004

8. Núñez P. Nutrición y trastornos del espectro autista. Universidad de Sevilla, Facultad de Farmacia. 2020.

9. Veselinović A, Petrović S, Žikić, V, Subotić M, Jakovljević V, Jeremić N, et al. Neuroinfammation in Autism and Supplementation Based on Omega-3 Polyunsaturated Fatty Acids: A Narrative Review. Medicina(Kaunas). 2021; 57(9):893. DOI: 10.3390/medicina57090893

10. El-Rashidy O, El-Baz F, El-Gendy Y, Khalaf R, Reda D, Saad K. Ketogenic diet versus gluten free casein free diet in autistic children: a case-control study. Metab Brain Dis. 2017; 32: 1935–194. DOI: 10.1007/s11011-017-0088-z

11. Fulceri F, Morelli M, Santocchi E, Cena H, Del Bianco T, Narzisi A, et al. Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. Dig Liver Dis. 2016;48(3):248–54. 48(3):248-54. DOI: 10.1016/j.dld.2015.11.026

12. Dinan T, Cryan J. Gut microbiota: a missing link in psychiatry. World Psychiatry. 2020; 19(1):111–112. DOI: 10.1002/wps.20726.

13. Holzer P, Farzi A. Neuropeptides and the Microbiota-Gut-Brain Axis. Adv Exp Med Biol. 2014; 817: 195–219. DOI: 10.1007/978-1-4939-0897-4_9

14. Srikantha P, Mohajeri H. The Possible Role of the Microbiota-Gut-Brain-Axis in Autism Spectrum Disorder. Int. J. Mol. Sci. 2019; 20(9): 2115. DOI: 10.3390/ijms20092115

15. Michielan A, D'Incà R. Intestinal Permeability in Infammatory Bowel Disease: Pathogenesis, Clinical Evaluation, and Therapy of Leaky Gut. Mediators of inflammation. 2016; 2015: 628157. DOI: 10.1155/2015/628157

16. Niu M, Li Q, Zhang J, Wen F, Dang W, Duan G, et al. Characterization of Intestinal Microbiota and Probiotics Treatment in Children With Autism Spectrum Disorders in China. Front Neurol. 2019; 10: 1084. DOI: 10.3389/fneur.2019.01084

17. Muhle R, Reed H, Stratigos K, Veenstra J. The emerging clinical neuroscience of autism spectrum disorder: A review. JAMA Psychiatry. 2018; 75(5):514-523. DOI: 10.1001/jamapsychiatry.2017.4685

18. Doron S, Snydman D. Risk and Safety of Probiotics. Clinical Infectious Diseases. 2016; 60(2):129–134. DOI: 10.1093/cid/civ085

19. Borriello S, Hammes W, Holzapfel W, Marteau P, Schrezenmeir J, Vaara M, et al. Safety of Probiotics That Contain Lactobacilli or Bifidoba teria. Clinical Infectious Diseases. 2003; 36(6): 775–780. DOI: 10.1086/368080

20. Liu D, Zeng L, Yan Z. The mechanisms and safety of probiotics against toxigenic clostridium difficile. Expert Review of Anti-infective Therapy. 2020; 18(10): 967-975. DOI: 10.1080/14787210.2020.1778464

21. Sato K, Why is vitamin B6 effective in alleviating the symptoms of autism?. Medical Hypotheses. 2018; 115:103-106. DOI: 10.1016/j.mehy.2018.04.007

22. Obara T, Ishikuro M, Tamiya G, Ueki M, Yamanaka C, Mizuno S, et al. Potential identification of vitamin B6 responsiveness in autism spectrum disorder utilizing phenotype variables and machine learning methods. ScientificReports. 2018; 8:14840. DOI:10.1038/s41598-018-33110-w

23. Altun H, Kurutas E, Sahin N, Güngör O, Findikli E. The Levels of Vitamin D, Vitamin D Receptor, Homocysteine and Complex B Vitamin in Children with Autism Spectrum Disorders. Clin Psychopharmacol Neurosci. 2018; 16(4): 383–390. DOI: 10.9758/cpn.2018.16.4.383

24. Khan F, Rahman M, Akhter S, Momen A, Raihan S. Vitamin B6 and Magnesium on Neurobehavioral Status of Autism Spectrum Disorder: A Randomized, Double-Blind, Placebo Controlled Study. 2021; 32(1):12-18. DOI: 10.3329/bjm.v32i1.51089.

25. Rossignol D, Frye R. The Effectiveness of Cobalamin (B12) Treatment for Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. J Pers Med. 2021; 11:784. DOI:10.3390/jpm11080784

26. Madra M, Ringel R, Margolis K. Gastrointestinal Issues and autism spectrum disorder. Child Adolesc Psychiatr Clin N Am. 2020; 29(3):501–513. DOI: 10.1016/j.chc.2020.02.005

27. Bjørklund G, Waly M, Al-Farsi Y, Saad K, Dadar M, Rahman M, et al. The Role of Vitamins in Autism Spectrum Disorder: What Do We Know?. J Mol Neurosci. 2019; 67, 373–387. DOI:10.1007/s12031-018-1237-5

28. Zhang Y, Hodgson N, Trivedi M, Abdolmaleky H, Fournier M, Cuenod M, et al. Decreased Brain Levels of Vitamin B12 in Aging, Autism and Schizophrenia. Autism and Schizophrenia. PLoS ONE. 2016; 11(1): e0146797. DOI: 10.1371/journal.pone.0146797

29. Raghavan R, Riley A, Volk H, Caruso D, Hironaka L, Sices L, et al, Maternal Multivitamin Intake, Plasma Folate and Vitamin B12 Levels and Autism Spectrum Disorder Risk in Offspring. Paediatr Perinat Epidemiol. 2017; (32)1:100-111. DOI:10.1111/ppe.12414.

30. Zhang Z, Yu L, Li S, Liu J. Association Study of Polymorphisms in Genes Relevant to Vitamin B12 and Folate Metabolism with Childhood Autism Spectrum Disorder in a Han Chinese Population. Med Sci Monit. 2018; 24:370–376. DOI: 10.12659/MSM.905567

31. Belardo A, Gevi F, Zolla L. The concomitant lower concentrations of vitamins B6, B9 and B12 may cause methylation deficiency in autistic children. J Nutr Biochem. 2019; 70:38-46. DOI: 10.1016/j.jnutbio.2019.04.004

32. Núñez P. Nutrición y trastornos del espectro autista.Universidad de Sevilla.Facultad de Farmacia. 2020

33. Pangrazzi L, Balasco L, Bozzi Y. Oxidative Stress and Immune System Dysfunction in Autism Spectrum Disorders. Int J Mol Sci. 2020 May 6;21(9):3293. DOI: 10.3390/ijms21093293

34. Karhu E, Zukerman R, Eshraghi R, Mittal J, Deth R, Castejon A et al. Nutritional interventions for autism spectrum disorder. Nutr Rev. 2020 Jul 1;78(7):515-531. DOI: 10.1093/nutrit/nuz092

35. Pangrazzi L, Balasco L, Bozzi Y. Natural Antioxidants: A Novel Therapeutic Approach to Autism Spectrum Disorders? Antioxidants (Basel). 2020 Nov 26;9(12):1186. DOI: 10.3390/antiox9121186

36. Rafee Y, Burrell K, Cederna-Meko C. Lessons in early identification and treatment from a case of disabling vitamin C deficiency in a child with autism spectrum disorder. Int J Psychiatry Med. 2019 Jan;54(1):64-73. DOI: 10.1177/0091217418791443

37. Adams J, Bhargava A, Coleman D, Frye R, Rossignol D. Ratings of the Effectiveness of Nutraceuticals for Autism Spectrum Disorders: Results of a National Survey. J Pers Med. 2021 Aug 31;11(9):878. DOI: 10.3390/jpm11090878

38. Bjørklund G, Waly M, Al-Farsi Y, Saad K, Dadar M, Rahman M et al. The Role of Vitamins in Autism Spectrum Disorder: What Do We Know? J Mol Neurosci. 2019 Mar;67(3):373-387. DOI: 10.1007/s12031-018-1237-5

39. Loyacono N, Sanz M, Gerbi M, Martinez L. Gastrointestinal, nutritional, endocrine, and microbiota conditions in autism spectrum disorder. Arch Argent Pediatr. 2020; 118(3): 271-277. DOI:10.5546/aap.2020.eng.e271

40. Baspinar B, Yardimci H. Gluten-Free Casein-Free Diet for Autism Spectrum Disorders: Can It Be Effective in Solving Behavioural and Gastrointestinal Problems? Eurasian J Med. 2020; 52(3):292-7. DOI: 10.5152/eurasianjmed.2020.19230

41. Ristori M, Quagliariello A, Reddel S, Ianiro G, Vicari S, Gasbarrini A, et al. Autism, Gastrointestinal Symptoms and Modulation of Gut Microbiota by Nutritional Interventions. Nutrients. 2019;11(11). DOI: 10.3390/nu11112812

42. Wang Y, Lebwohl B, Mehta R, Cao Y, Green P, Grodstein F, et al. Long-term Intake of Gluten and Cognitive Function Among US Women. JAMA. 2021; 4(5): e2113020. DOI:10.1001/jama network open.2021.13020

43. Biesiekierski J. What is gluten?. Journal of gastroenterology and hepatology. 2017; 32 (1): 78–81. DOI: 10.1111/jgh.13703

44. Shewry P. What Is Gluten-Why Is It Special?. Frontiers in nutrition. 2019; 6(101). DOI: 10.3389/fnut.2019.00101

45. Niland B, Cash B. Health Benefits and Adverse Effects of a Gluten-Free Diet in Non-Celiac Disease Patients. Gastroenterology & Hepatology. 2018; 14(2): 82–91.

46. Cejudo C, Losada A. Influencia de la nutrición biológica en niños con Trastorno del Espectro Autista residentes del Partido de San Miguel en la Provincia de Buenos Aires. Revista Neuronum. 2020; 7(1): 278-295.

47. Marí S, Llopis A, Zazpe I, Marí A, Suárez M. Nutritional Impact of a Gluten-Free Casein-Free Diet in Children with Autism Spectrum Disorder. J Autism Dev Disord. 2016;46(2):673-84. DOI: 10.1007/s10803-015-2582-7

48. Hartman R, Patel D. Dietary Approaches to the Management of Autism Spectrum Disorders. En: Essa MM, Qoronfleh MW, editores. Personalized Food Intervention and Therapy for Autism Spectrum Disorder Management. Advances in Neurobiology. 2020; 24:547-71. DOI: 10.1007/978-3-030-30402-7_19.

49. Rodríguez L. Dieta sin gluten en autismo [Tesis doctoral] Valladolid: Universidad de Valladolid; 2021 Disponible en: https://uvadoc.uva.es/bitstream/handle/10324/48209/TFG-M-N2386.pdf?sequence=1

50. Bozzatello P, Brignolo E, De Grandi E, Bellino S. Supplementation with omega-3 fatty acids in psychiatric disorders: A review of literature data. J Clin Med. 2016;5(8):67. DOI: 10.3390/jcm5080067.

51. Agostoni C, Nobile M, Ciappolino V, Delvecchio G, Tesei A, Turolo S, et al. The role of omega-3 fatty acids in developmental psychopathology: A systematic review on early psychosis, autism, and ADHD. Int J Mol Sci. 2017;18(12):2608. DOI: 10.3390/ijms18122608.

52. Cheng Y, Tseng P, Chen Y, Stubbs B, Yang W, Chen T, et al. Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: a meta-analysis of randomized controlled trials. Neuropsychiatr Dis Treat. 2017;13:2531–43. DOI: 10.2147/NDT.S147305

53. Nasir M, Bloch M. Trim the fat: the role of omega-3 fatty acids in psychopharmacology. Ther Adv Psychopharmacol. 2019;9. DOI: 10.1177/2045125319869791

54. Martins B, Bandarra N, Figueiredo M. The role of marine omega-3 in human neurodevelopment, including Autism Spectrum Disorders and Attention-Deficit/ yperactivity Disorder - a review. Crit Rev Food Sci Nutr. 2020;60(9):1431–46. DOI: 10.1080/10408398.2019.1573800

55. Veselinović A, Petrović S, Žikić V, Subotić M, Jakovljević V, Jeremić N, et al. Neuroinflammationin autism and supplementation based on omega-3 polyunsaturated fatty acids: A narrative review. Medicina (Kaunas). 2021;57(9):893. DOI: 10.3390/medicina57090893

56. Chang J, Su K. Nutritional neuroscience as mainstream of psychiatry: The evidence- based treatment guidelines for using omega-3 fatty acids as a new treatment for psychiatric disorders in children and adolescents. Clin Psychopharmacol Neurosci. 2020;18(4):469–83. DOI: 10.9758/cpn.2020.18.4.469

57. Martinat M, Rossitto M, Di Miceli M, Layé S. Perinatal dietary polyunsaturated fatty acids in brain development, role in neurodevelopmental disorders. Nutrients. 2021;13(4):1185. DOI: 10.3390/nu13041185

58. DiNicolantonio J, O'Keefe J. The importance of marine omega-3s for brain development and the prevention and treatment of behavior, mood, and other brain disorders. Nutrients. 2020;12(8):2333. DOI: 10.3390/nu12082333

59. Mazahery H, Stonehouse W, Delshad M, Kruger M, Conlon C, Beck K, et al. Relationship between long chain n-3 polyunsaturated fatty acids and Autism Spectrum Disorder: Systematic review and meta-analysis of case-control and randomised controlled trials. Nutrients. 2017;9(2):155. DOI: 10.3390/nu9020155

60. Sheppard K, Boone K, Gracious B, Klebano ffM, Rogers L, Rausch J, et al. Efecto de la suplementación con omega-3 y 6 sobre el lenguaje en niños prematuros que presentan síntomas del trastorno del espectro autista . J. Autismo Dev. Desorden. 2017; 47 :3358–3369. DOI: 10.1007/s10803-017-3249-3

61. Parellada M, Llorente C, Calvo R, Gutierrez S, Lázaro L, Graell M, et al. Ensayo aleatorizado de omega-3 para trastornos del espectro autista: Efecto sobre la composición y el comportamiento de la membrana celular. EUR. Neuropsicofarmaco. 2017; 27 :1319–1330. DOI: 10.1016/j.euroneuro.2017.08.426

62. Raine A, Ang R, Choy O, Hibbeln J, Ho R, Lim C, et al. Omega-3 (ω-3) e intervenciones de habilidades sociales para reacciones Agresión y problemas de comportamiento de externalización infantil: un ensayo factorial aleatorizado, estratificad , doble ciego, controlado con placebo. psicol. Medicina. 2019; 49 :335–344. DOI: 10.1017/S0033291718000983

63. Keim S, Gracious B, Boone K, Klebano ffM, Rogers L, Rausch J, et al. Ω-3 and ω-6 fatty acid supplementation may reduce autism symptoms based on parent report in preterm toddlers. J Nutr. 2018;148(2):227–35. DOI: 10.1093/jn/nxx047

64. Voigt R, Mellon M, Katusic S, Weaver A, Matern D, Mellon B, et al. Suplementación dietética de ácido docosahexaenoico en niños con autismo. J. Gastroenterol pediátrico. Nutr. 2014; 58:715–722. DOI: 10.1097/MPG.0000000000000260

65. Doaei S, Bourbour F, Teymoori Z, Jafari F, Kalantari N, Abbas N, et al. El efecto de la suplementación con ácidos grasos omega-3 en los trastornos sociales y conductuales de los niños con autismo: un ensayo clínico aleatorizado. Endocrinol pediátrico. Diabetes Metab. 2021; 27 :12–18. DOI: 10.5114/pedm.2020.101806

66. Yui K, Koshiba M, Nakamura S, Kobayashi Y. Effects of large doses of arachidonic acid added to docosahexaenoic acid on social impairment in individuals with autism spectrum disorders: a double-blind, placebo-controlled, randomized trial: A double-blind, placebo-controlled, randomized trial. J Clin Psychopharmacol. 2012;32(2):200–6. DOI: 10.1097/JCP.0b013e3182485791

67. Amminger G, Berger G, Schäfer M, Klier C, Friedrich M, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. Biol Psychiatry. 2007;61(4):551–3. DOI: 10.1007/s10803-010-1078-8

68. Kałużna J, Błaszczyk S. The level of arabinitol in autistic children after probiotic therapy. Nutrition. 2012; 28(2):124-126. DOI: 10.1016/j.nut.2011.08.002.

69. Sanctuary M, Kain J, Chen S, Kalanetra K, Lemay D, Rose D, et al. Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms. PLoS One. 2019; 14(1):e0210064. DOI: 10.1371/journal.pone.0210064

70. Shaaban S, El Gendy Y, Mehanna N, El-Senousy W, El-Feki H, Saad K, et al. The role of probiotics in children with autism spectrum disorder: A prospective, open-label study. Nutr Neurosci. 2018; 21(9):676-681. DOI: 10.1080/1028415X.2017.1347746

71. Tomova A, Husarova V, Lakatosova S, Bakos J, Vlkova B, Babinska K, et al. Gastrointestinal microbiota in children with autism in Slovakia. Physiol Behav. 2015; 138:179-187. DOI: 10.1016/j.physbeh.2014.10.033.

72. West R, Roberts E, Sichel L, Sichel J. Improvements in gastrointestinal symptoms among children with autism spectrum disorder receiving the Delpro® probiotic and immunomodulator formulation. J. Prob. Health. 2013; 1(1):1-6. DOI: 10.4172/2329-8901.1000102

73. Parracho H, Gibson G, Knott F, Bosscher D, Kleerebezem M, Mccartney A. A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. International Journal of Probiotics & Prebiotics. 2010; 5(2), 69-74.

74. Serrato K, Bazaldúa V, Garza G, Cuellar S, Márquez L, Sánchez M. Intervención nutricional con omega-3 en un grupo de pacientes con diagnóstico de Trastorno del Espectro Autista (TEA). Revista Salud Pública Y Nutrición. 2018; 17(4), 27–33. DOI: 10.29105/respyn17.4-3.

75. Hernández A, López L, Garza G, Cuellar S, Márquez L, Sánchez M. Impacto del bajo consumo de alimentos con gluten y caseína sobre síntomas gastrointestinales en niños de 3-12 años de edad con trastorno del espectro autista. Revista Salud Pública Y Nutrición. 2017; 16(3): 1–5. DOI: 10.29105/respyn16.3-1

76. González-Domenech P, Díaz F, García C. et al. Influence of a Combined Gluten-Free and Casein-Free Diet on Behavior Disorders in Children and Adolescents Diagnosed with Autism Spectrum Disorder: A 12-Month Follow-Up Clinical Trial. Journal Autism Dev Disord. 2020; 50: 935–948. DOI: 10.1007/s10803-019-04333-1

77. Ghalichi F, Ghaemmaghami J, Malek A, Ostadrahimi A. Effect of gluten free diet on gastrointestinal and behavioral indices for children with autism spectrum disorders: a randomized clinical trial. World Journal Pediatr. 2016; 12(4): 436-42. DOI: 10.1007/s12519-016-0040-z.

78. Hyman S, Stewart P, Foley J, Peck R, Morris D, Wang H, et al. The Gluten-Free/ Casein-Free Diet: A Double-Blind Challenge Trial in Children with Autism. Journal Autism Dev Disord. 2016; 46(1): 205-20. DOI: 10.1007/s10803-015-2564-9

79. Harris C, Card B. A pilot study to evaluate nutritional influences on gastrointestinal symptoms and behavior patterns in children with Autism Spectrum Disorder. Complement Ther Med. 2012; 20(6): 437-40. DOI: 10.1016/j.ctim.2012.08.004