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Revisión

Effectiveness of nutritional interventions on behavioral symptomatology of autism spectrum disorder: a systematic review

Efectividad de las intervenciones nutricionales en la sintomatología conductual del trastorno del espectro autista: revisión sistemática

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Abstract

Introduction: the main treatment for people with autism spectrum disorder (ASD) corresponds to cognitive behavioral therapy in conjunction with pharmacotherapy. Together they seek to attenuate the behavioral symptoms of these patients, as well as to increase their social functionality. However, other strategies have become popular to achieve the same goal of classical treatment. Particularly, nutritional interventions are positioned above others, and it is necessary to investigate their effectiveness, considering that children with ASD present a marked food selectivity, as well as gastrointestinal alterations.

Objective: to evaluate the effectiveness of nutritional interventions in the behavioral symptomatology of infants with ASD.

Methods: a systematic search was carried out in the Scopus and PubMed databases, in Spanish and English. The filters of clinical studies and original articles were used, choosing only nutritional interventions in children under 19 years of age and who had at least 4 weeks of intervention.

Results: evidence was found on gluten- and casein-free diets, ketogenic diet, omega-3 supplementation, prebiotics/probiotics, and vitamins/minerals presenting positive results in most of the articles analyzed; however, the heterogeneity presented requires a greater body of evidence to promote its use.

Conclusion: the five types of nutritional interventions evaluated show varied evidence that does not allow defining the degree of effectiveness between one or the other in terms of behavioral improvements in the population with ASD.

Keywords:

Autism spectrum disorder. Diet therapy. Dietary supplements. Ketogenic diet. Gluten-free diet.

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Resumen

Introducción: el principal tratamiento para las personas con trastorno del espectro autista (TEA) corresponde a la terapia cognitivo conductual en conjunto con farmacoterapia. En conjunto buscan atenuar la sintomatología conductual de estos pacientes, así como aumentar su funcionalidad social. Sin embargo, otras estrategias se han tornado populares para conseguir el mismo objetivo del tratamiento clásico. Particularmente, las intervenciones nutricionales se posicionan por sobre otras y es necesario investigar su efectividad, considerando que los infantes con TEA presentan una marcada selectividad alimentaria, así como alteraciones gastrointestinales.

Objetivo: evaluar la efectividad de las intervenciones nutricionales en la sintomatología conductual de infantes con TEA.

Método: se realizó una búsqueda sistemática en las bases de datos de Scopus y PubMed, en español e inglés. Se utilizaron los filtros de estudios clínicos y artículos originales, eligiendo solo intervenciones nutricionales en menores de 19 años y que tuvieran al menos 4 semanas de intervención.

Resultados: se encontró evidencia sobre las dietas libres de gluten y caseína, la dieta cetogénica, la suplementación de omega-3, los prebióticos/probióticos y las vitaminas/minerales, presentando resultados positivos en la mayoría de los artículos analizados; sin embargo, la heterogeneidad presentada exige un mayor cuerpo de evidencia para promover su utilización.

Conclusión: los cinco tipos de intervenciones nutricionales evaluadas muestran evidencia variada que no permite definir el grado de efectividad entre una u otra en términos de mejoras conductuales en la población con TEA.

Palabras clave:

Trastorno del espectro autista. Dietoterapia. Suplementos dietéticos. Dieta cetogénica. Dieta sin gluten.

INTRODUCTION

According to the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5), autism spectrum disorder (ASD) is categorized as a neurodevelopmental disorder characterized by affecting communication and behavior, mainly in children (1). Its prevalence according to the World Health Organization (WHO) is 1 in 160 children (2), while data from the Autism and Developmental Disabilities Monitoring Network (ADDM) in the United States indicates that the figure is 1 in 59 children, and 4.3 times more prevalent in boys than girls (3).

Manifestations vary depending on the severity of the condition, developmental level, and chronological age of the patient, and these symptoms typically present from early childhood (4). The symptomatology limits daily functioning, impairing social interaction with repetitive and restrictive behavior patterns. This disorder frequently presents a high comorbidity, since 63-96 % of these children present with anxiety and/or depression; 20-50 % with intellectual disability, 12-26 % with epilepsy; 51 % with motor disorders, 50-80 % with insomnia, and 9-91 % with gastrointestinal problems such as chronic constipation, diarrhea and abdominal pain. Along these lines, 75 % of children with ASD present problems related to eating, including food selectivity based on texture, color or temperature; rituals around the presentation of food and compulsive consumption, affecting the proper functioning of the gastrointestinal system (5,6).

Treatment is aimed at minimizing central abnormalities and associated impairments, along with maximizing functional independence. Facilitating learning and the acquisition of adaptation skills will be promoted; along with eliminating, minimizing, or preventing problem behaviors. Cognitive-behavioral interventions are the most used treatments and with the best results in the core behaviors of ASD. It has been observed in different studies that early, intensive and specific interventions for each child have a better clinical evolution, as well as the incorporation of a multidisciplinary team that includes the participation of parents (7,8). At the same time, the active collaboration of the tutors has promoted their organization for the good of their children, generating instances where complementary therapies to cognitive-behavioral interventions or classic pharmacological treatment are considered. In these contexts, alternative interventions have emerged with popularity that attract a lot of attention from parents since they could be beneficial in the universe of children with ASD, such as naturalistic therapies, massages, chiropractic, acupuncture, equine therapy, yoga, music therapy and dietary treatments (9,10).

Regarding the latter, restrictive strategies and supplementation of different nutrients stand out, however, their effects are under discussion due to the lack of randomized clinical studies carried out, together with the inconsistency of the physiological mechanisms involved (11). In view of this, the present review aims to evaluate the effectiveness and the mechanisms involved in nutritional interventions in the mitigation of behavioral symptoms in children and adolescents with ASD.

METHODS

The bibliographic search was carried out in the PUBMED and SCOPUS databases by two researchers who worked independently, where the following terms were considered: “dieta”, “nutrientes”, “trastorno del espectro autista”, “diet”, “nutrients” and “Autism Spectrum Disorder”. Boolean operators AND-OR were used, forming the following search algorithms: 1) Diet OR Nutrients AND Autism Spectrum Disorder; 2) Nutrients AND Autism Spectrum Disorder; 3) Diet AND Autism Spectrum Disorder; 4) Diet OR Nutrients AND Spectrum Disorder Autistic; 5) Nutrients AND Autism Spectrum Disorder; and 6) Diet AND Autism Spectrum Disorder. The search was limited to the last 5 years (2016-2020), a filter was used by type of study (Clinical Trial for PubMed and Articles for Scopus) and studies in English and Spanish were considered. Was considered clinical trials in humans under 19 years diagnosed with autism spectrum disorder, with interventions lasting at least 4 weeks, and which included assessment of specific behaviours before and after the intervention. Reviews were excluded.

RESULTS

A total of 865 studies were identified in the 2 databases used, of which only 16 were considered (Fig. 1). From the selected articles, 5 types of dietary interventions were identified have been proposed for the treatment of ASD; gluten and casein free exclusion diet, ketogenic diet, supplementation of: polyunsaturated fatty acids, probiotics/prebiotics, vitamins and minerals.

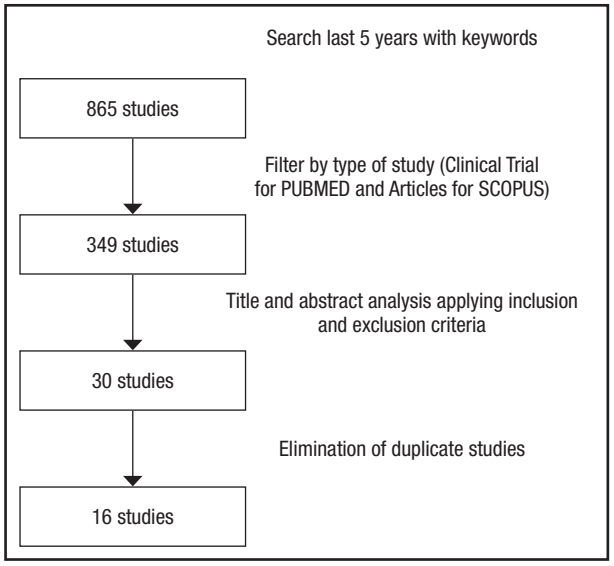

Figure 1.
Flow diagram of the literature search.

GLUTEN/CASEIN-FREE DIET

This strategy is based on "The Opioid Excess Theory", which postulates that the flow of proteins of large molecular size due to greater intestinal permeability generates alterations in the immune response and in the central nervous system (CNS) through activation of opioid receptors (12). The aforementioned permeability would be predisposed in patients with ASD due to a deregulation in the expression of genes related to the pore-forming components (CLDN-1, OCLN and TRIC) and barrier (CLDN-2, CLDN-10 and CLDN-15), allowing alterations derived from casein and gluten. In the degradation of the former, β-casomorphin-7 (β-CM7) is obtained, which acts as an agonist of the μ-opioid receptor (MOR), with respect to gluten; exorphins such as A4, A5, B4 and B537, which interact with the δ-opioid receptor in the CNS, modulating the morphine-serotonin system (13). The aforementioned pathway would generate alterations in brain functions because the excess of the aforementioned peptides evokes negative effects on attention, brain maturation, social communication and learning. In this sense, the dietary restriction of the aforementioned components would prevent the over-activation of this pathway.

Regarding the studies with casein and gluten exclusion diets (Table I), five studies were found with populations that vary in: sample size, origin, age group, timing of the intervention and symptom assessment scales. When evaluating the smaller studies (6 and 8 weeks) (14,15), a gluten-free diet (GFD) was considered in the Iranian and Polish population, obtaining improvements in stereotyped behavior, communication and social interaction, as well as in the scores of the instruments: ADO-2, SCQ and ASRS, respectively. Regarding interventions that con-

Table I. Clinical trials of gluten-free/casein-free diet

Reference	Participants	Intervention	Results	Evaluation Scale
Ghalichi et al. 2016	n = 76 Iranian schoolchildren	6 weeks GFD	Significant decrease in stereotyped behavior ($p < 0.001$) and social interaction ($p < 0.001$)	ADI-R GARS-2
Hyman et al. 2016	n = 14 US preschoolers	30 weeks GFCFD	No significant findings	Conner Scale RLRS
Hafid et al. 2018	n = 30 Moroccan schoolchildren	48 weeks GFCFD	No significant findings	CARS
Gonzalez-Domenech et al. 2020	n = 29 Spanish schoolchildren	48 weeks GFCFD	No significant findings	ABC ATEC
Piwowarczyk et al. 2020	n = 58 Polish preschoolers and schoolchildren	8 weeks GFD	No significant findings	ADOS-2 ASRS SCQ

ABC: Aberrant Behavior Scale; ADI -R: Autism Diagnostic Interview; ADOS-2: observation scale for autism; ASRS: Autism Spectrum Classification; ATEC: Autism Treatment Checklist; CARS: Childhood Autism Rating Scale; GARS-2: Gilliam Autism Rating Scale; GFCFD: gluten-free and casein-free diet; GFD: gluten-free diet; RLRS: Ritvo-Freeman Real Life Rating Scale; SQC: Social Communication Questionnaire.

sider both the GFD and the Casein-Free Diet (CFD), 12-month interventions are observed in children under 18 years of age, obtaining improvements in the symptomatology appreciated by the CARS and ABC post-intervention psychometric tools (16,17). Regarding the same strategy, but with a greater extension of intervention, no significant findings were found in behavioral symptomatology as measured from the Conner Scale and the Ritvo-Freeman Scale (18). It is important to mention that, in the latter, sample size was considerably smaller and the average age of the infants considered did not exceed 4 years.

KETOGENIC DIET

The interest in using this regimen derives from its use in refractory epilepsy, prescribed when conventional treatments are not effective (19). It is postulated that restricting carbohydrates in the diet directly alters neuronal metabolism through the use of ketone bodies as an alternative energy substrate for the CNS. This would promote improvements in activities such as socialization and the regulation of repetitive behaviors, reported at the preclinical level (20). Effects would derive from the regulation of mitochondrial function and reduction of inflammation at the level of neuronal tissue. Another important aspect of this regimen consists of the high intake of triglycerides, which play an essential role at the level of the mitochondrial membrane, an organelle that precisely would present dysfunction in children with ASD (20).

The only study that considered the inclusion and exclusion criteria was a 3-month clinical trial conducted in Honolulu, United States (21). The intervention used a gluten-free ketogenic diet with the addition of medium-chain triglycerides (MCT). The distribution consisted of 20 % of the total caloric value of MCT, consumption of 20-25 g/day of carbohydrates, and double the recommendations for protein per day established by the RDA (Recommended Dietary Allowances). A decrease was observed in the total score for the ADOS-2 scale, improvements in the score for the imitation item, body use and fear/nervousness for the CARS-2 scale. In addition, parents also reported improvements in eye contact, concentration, and hyperactivity.

SUPPLEMENTATION OF POLYUNSATURATED FATTY ACIDS

The role of polyunsaturated fatty acids (PUFA) has been studied in different biological processes, such as cell signaling, anti-inflammatory properties, neuroprotection and antioxidant activity. Its deficit in the body is associated with defects in development and behavior according to preclinical evidence in different species and models. From this it is postulated that dietary interventions based on PUFA supplementation would provide benefits at the CNS level, providing clinical improvements in patients suffering from mental disorders and/or neurodegenerative diseases (22).

Regarding the mechanisms involved, different studies consider that the consumption of PUFAs such as docosahexaenoic acid (DHA) and arachidonic acid (AA) are involved in signal transduction and neurogenesis at the hippocampal level, playing an important role in the regulation of the structural plasticity of the CNS. Specifically by the development and elongation of neurites, inducing tissue growth through cytoskeleton activity, together with the expansion of neuronal membranes due to the modulation of vesicular fusion (23) (Fig. 2).

Specifically in children with ASD, EPA and DHA supplementation is associated with the formation and maintenance of white and gray matter, central structures that are precisely impaired in this type of patient (24). On the other hand, the consumption of DHA in murine models has been shown to efficiently regulate the glutaminergic system, which has less activity in the brains of subjects with ASD, which is aligned with anxious symptoms and memory deficits (25).

When analyzing the results of the clinical trials found (Table II) various behavioral benefits are observed in most of the interventions; however, they do not coincide in any improved behavior (26-29). It could be suggested that fatty acid supplementation would be beneficial in general, but there are antecedents that have not been declared in all the studies; as the basal states of essential fatty acids, which could be the cause of improvement if these were in deficit before the intervention. Another important aspect that must be considered is that in the only study where significant behavioral improvements were not observed, it was in the trial where the intervention did not consider the addition of fat-soluble vitamins in parallel to PUFAs, suggesting important actions for this group of vitamins.

PREBIOTIC/PROBIOTIC SUPPLEMENTATION

The gut-brain axis is considered as the dynamic formed by the enteric and central nervous system, responsible for improving the response to stress and modulating the behavior of the individual. This is influenced by the bidirectional communication between both systems, together with the homeostasis exerted by the gastrointestinal, immune and neuronal systems. Although various anatomical areas are involved, the leading role is played by the gut microbiota (GM), which is made up of more than a thousand bacterial species confined to the human intestinal tract, forming a reservoir of essential metabolites for various host functions (30). The GM begins its conformation at the time of delivery, evolving in diversity and concentration according to the diet, environment and use of antibiotics to which the individual is exposed. This confers population diversity independent of the genetics of the host, providing a greater explanation of the environmental influence on humans, since the metabolites derived from GM act in all the systems mentioned above (31). One of the best strategies for its restoration and care is based on the use of prebiotic or probiotic formulas (32). The former consists of non-digestible fibers that are highly fermentable by intestinal bacteria, resulting in short-chain fatty acids (SCFA) from their metabolism, which have neuropeptide-like properties.

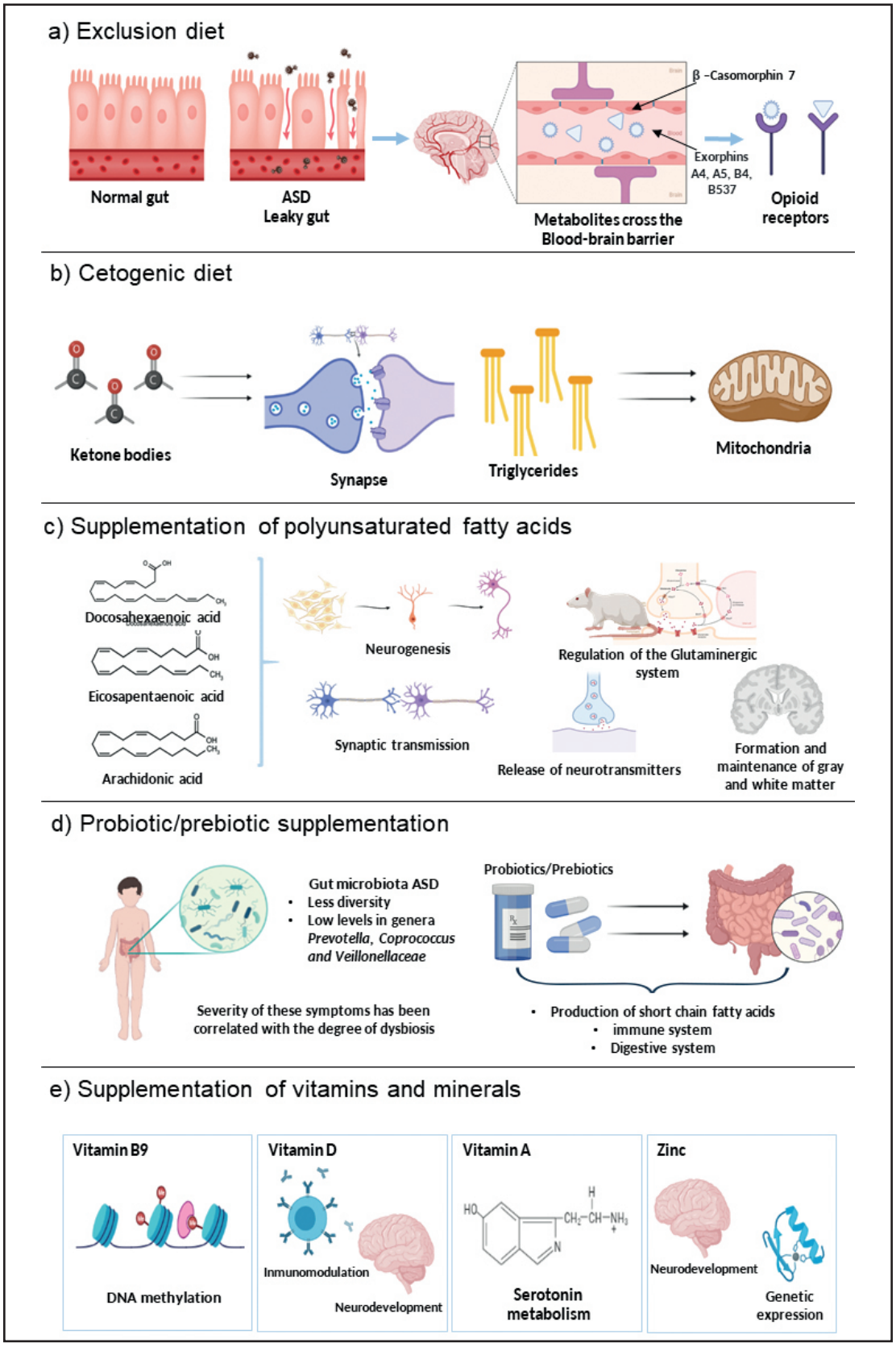

Figure 2.

Associated mechanisms of reported interventions.

Table II. Clinical trials of polyunsaturated fatty acid supplementation

Reference	Participants	Intervention	Results	Evaluation Scale
Ooy et al. 2015	n = 41 Singaporean schoolchildren and adolescents	12 weeks 1 g/day EPA + DHA + Vit E in two doses	Significant improvements in social awareness (p = 0.01), social communication (p = 0.001), social cognition (p = 0.001), social motivation (p = 0.01), stereotyped and repetitive behaviors (p = 0.001), and score total on SRS scale (p = 0.001)	CBCL SRS
Parellada et al. 2017	n = 60 Spanish schoolchildren and adolescents	8 weeks * 2 weeks off EPA + DHA + Vit E and according to age	No significant findings	CGI SRS
Mazahery et al. 2019	n = 73 New Zealand preschoolers and schoolchildren	48 weeks 722 mg DHA + Vit D3 2000 IU/day	Irritability and hyperactivity scores showed a significant effect of time (p < 0.001). The positive response rate was 63 % (p = 0.02), 74 % (p = 0.003), and 53 % (p = 0.11) in the VID, OM, and VIDOM groups, respectively, compared to 25 % (4/16) in the placebo group. Analysis of scores revealed an effect of OM (p = 0.03)	ABC

ABC: Aberrant Behavior Scale; CBCL: Child Behavior Checklist; CGI: Clinical Global Impression; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; SRS: Social Responsiveness Scale.

On the other hand, probiotics consist of live microorganisms that, consumed in adequate amounts by the host, confer health benefits, according to the establishment of the ingested strains in the GM of the individual. As a whole, both formulas could exert synergistic benefits, understanding that one increases the amount of bacteria, and the other increases the substrates necessary for their metabolism, survival and production of SCFA (33).

Regarding the composition of human GM, particular species of the genera *Bifidobaterium*, *Akkermansia* and *Lactobacillus* have been found to be beneficial to health and are included in many probiotic formulations. On the contrary, the presence of other genera such as *Bacteroides* and *Ruminococcus* are associated with negative health diagnoses. In this line, the central microbial diversity and the ratio of *Firmicutes* to *Bacteroidetes* have been proposed as general indicators of health (34). When comparing autistic children with controls, changes in the composition of *Firmicutes*, *Bacteriodetes*, *Actinobacteria* and *Proteobacteria* are detected. In turn, a less diverse microbial community has been reported in the gut of children with autism, specifically with a decrease in *Prevotella*, *Coprococcus*, and *Veillonellaceae*. Studies have even managed to correlate autistic symptomatology with reduced species diversity. Other differences in individuals with ASD include the overgrowth of species of the *Clostridium* genus, linked to the presence of gastrointestinal symptoms such as chronic constipation, diarrhea and abdominal pain. Low levels of *Bifidobacteria* have also been detected, which has anti-inflammatory effects, therefore, its reduction would alter the function of the intestinal barrier (35). In short, patients with ASD present a specific intestinal dysbiosis, and its restoration could reduce the gastrointestinal systems and obtain behavioral improvements.

Regarding the 3 clinical trials considered in the search (Table III), specific differences were found between the sample sizes considered, as well as the interventions used. A 10-week study in a US population used galactooligosaccharides, obtaining a decrease in antisocial symptomatology in 26 children with autism from the Autism Treatment Checklist (ATEC); however, similar results were not obtained in the EQ-SQ and SCAS-P (36). Regarding the use of probiotic formulas, two interventions with *Bifidobacterium* were found in the American and Taiwanese population, respectively. In the case of the eastern population, the treatment lasted only one month; however, it consider more than 70 children and pre-adolescents. Although symptom scores were reduced in quite a few categories on four different scales, none of the decreases were statistically significant (37). Moreover, when the intervention lasts longer, show significant improvements in irritability, stereotyped behaviors and hyperactivity (38). However, sample size is quite limited and the composition of the baseline GM is not analyzed.

VITAMINS AND MINERALS SUPPLEMENTATION

Regarding this area, 3 clinical trials were found that reported the supplementation of vitamins A, B9 and D as an intervention, together with another report on zinc (Table IV). Among the arguments to recommend the use of these micronutrients, the role that B complex vitamins can play in maintaining CNS functions stands out (39). Vitamin B9, for example, has antioxidant potential, a capacity that is precisely reduced in patients with ASD.

Table III. Clinical trials of probiotic/prebiotic supplementation

Reference	Participants	Intervention	Results	Evaluation Scale
Sanctuary et al. 2019	n = 8 US preschoolers and schoolchildren	12 weeks 0.15 g/lb of weight/day BCP *B. infantis*	In the BCP group, there was a significant reduction in irritability ($p = 0.003$), stereotypy ($p = 0.006$), hyperactivity ($p = 0.007$), and total scores ($p = 0.006$), along with a trend toward a significant reduction in lethargy ($p = 0.076$) on the ABC scale. The combined treatment demonstrated a significant reduction only in lethargy ($p = 0.0499$)	ABC ABAS-II RBS-R
Grimaldi et al. 2018	n = 26 US schoolchildren and adolescents	10 weeks GOS + GFCFD	The results of the social skills scale of the AQ questionnaire ($p < 0.05$) and improvements in antisocial behavior of the ATEC questionnaire ($p = 0.05$)	AQ ATEC EQ-SQ SCAS-P
Wenn Liu et al. 2019	n = 71 Taiwanese schoolchildren and adolescents	4 weeks 425 +/- 25 mg *B. fragilis* (PS128)	Exploratory analyses showed that reduced total scores ($p = 0.01$), hyperactivity and impulsivity ($p = 0.04$), and opposition and defiance ($p = 0.045$) were observed over four weeks in the PS128 group on SNAP-IV	ABC CBCL CGI SNAP-IV SRS

ABC: Aberrant Behavior Scale; ABAS-II: Adaptive Behavior Assessment; AQ: Autism Spectrum Quotient; ATEC: Autism Treatment Evaluation Checklist; BCP: bovine colostrum product; CBCL: Child Behavior Checklist; CGI: Clinical Global Impression; EQ-SQ: Empathy/Systemizing Quotient; GFCFD: gluten-free and casein-free diet; GOS: galactooligosaccharide; RBS-R: Repetitive Behavior Scale-Revised; SCAS-P: Spence Children's Anxiety Scale for Parents; SNAP-IV: Swanson, Nolan, and Pelham ADHD Rating Scale; SRS: Social Responsiveness Scale.

Table IV. Clinical trials of vitamins/minerals supplementation

Reference	Participants	Intervention	Results	Evaluation Scale
Caihong et al. 2016	n = 43 Chinese schoolchildren and preschoolers	12 weeks 800 mcg/day of folic acid in 2 doses + structured education TEACCH	No significant findings in supplementation independently	ABC ATEC CARS PEP-3
Minguo et al. 2018	n = 65 Chinese schoolchildren	24 weeks 200.000 IU of vitamin A in a single dose	Improvements in relation to people ($p = 0.0255$), emotional response ($p = 0.0270$), body use ($p = 0.0374$), adaptation to change ($p = 0.0345$), taste, smell and tact ($p = 0.0426$), anxiety ($p = 0.0446$), verbal and nonverbal communication ($p = 0.0450$), general impression ($p = 0.0169$), and total score ($p = 0.0141$) on CARS scale	ABC CARS CGI
Saad et al. 2015	n = 83 Egyptian preschoolers and schoolchildren	12 weeks 300 IU/kg up to 5000 IU/ day of calciferol	Improvement in irritability ($p = 0.021$), lethargy/social withdrawal ($p = 0.028$), hyperactivity ($p = 0.01$), and stereotypic behavior ($p = 0.04$) on the ABC scale. Improvement in social, emotional and imitation response ($p < 0.001$), body and object use ($p = 0.01$), visual response ($p = 0.003$), general impression and total score ($p < 0.001$) on the CARS scale	ABC CARS
Megid et al. 2019	n = 30 Egyptian preschoolers and schoolchildren	12 weeks 15-20 mg/kg/day of zinc	Improvement in locomotor score ($p < 0.0001$) and object control score ($p = 0.0004$) on the TGMD-2 scale	CARS MDGT-2

ABC: Aberrant Behavior Scale; CARS: Childhood Autism Rating Scale; ATEC: Autism Treatment Evaluation Checklist; PEP-3: Third Edition Psychoeducational Profile; CGI: Clinical Global Impression; MDGT-2: Test of Gross Motor Development version 2.

The proposed mechanism is related to its property of decreasing the redox state of glutathione, along with playing an important role in the regulation of epigenetic modifications by decreasing DNA methylation (40). Moreover, it has been reported that fat-soluble vitamin A is positioned as a key factor in the regulation of the synthesis of neurotransmitters such as serotonin (41), and that it is precisely deregulated in people with autism. Regarding vitamin D, it is considered a fundamental micronutrient in neurodevelopment and systemic inflammatory regulation, by mechanisms of gene regulation (42). Considering that patients with ASD present proinflammatory stages, cholecalciferol supplementation could attenuate the consequences derived from the aforementioned process. Finally, and regarding zinc, maintaining normal levels in the blood promotes benefits at the level of cognitive and motor development (43), being essential for impaired central functions in autistic symptomatology. Regarding specific results, a 12-week intervention in a Chinese population with 800 mcg/day of vitamin B9 managed to report benefits at the level of sociability, verbal and paraverbal aspects, receptive language, affective expression and communication, according to the parameters of different evaluation scales (44). Regarding supplementation in a larger sample size of a single dose of vitamin A (200,000 IU) and with evaluation six months later, improvements were also found at the affective, communicative, and emotional levels and the total score on the Autism Rating Scale (45). Along these same lines, in an Egyptian population improvements at the attitudinal and behavioral level were also reported when 300 IU/day of vitamin D were administered for 12 weeks (46). Moreover, and regarding minerals, with zinc supplementation (15-20 mg/kg/day) improvements were also achieved in the total CARS score, as well as in locomotor aspects (47).

DISCUSSION

Autism spectrum disorder is characterized by a specific alteration in the communication and behavior of the subjects who suffer from it, developing repetitive and restrictive behaviours. Among the recognized risk factors are hereditary antecedents, parental psychiatric history, fetal exposure to psychotropic drugs and insecticides, among others. Although its prevalence is low compared to other mental disorders, it has been increasing over the last century, affecting more than 60 million people in the world, according to the data presented in the Global Burden of Disease study published in 2016 (48). Along this line, and based on the enrollment data of schools with specific needs in the United States, a specific increase has been detected since 2000, when 1.2 cases were received for every 1000 enrolled, to 2010, where this figure rose to 5.2 cases per 1000 enrolled (49). Experts on the subject allude to the fact that the evolution of diagnostic criteria could explain the present phenomenon; however, speculations position environmental influence as responsible. Studies related to epigenetic modifications support this last premise, being consistent with the profound changes faced as modern society (50).

From this situation, complementary therapeutic strategies emerge that are positioned more and more in caregivers of children with autism, nutritional practices being one of the most used alternative treatments (51). The literature in this area has grown significantly in the last ten years, even suggesting that the maternal diet during pregnancy is a crucial factor in the etiopathogenesis of autism in their offspring (52). From another point of view, the quality of the diet of children with ASD plays an important role in their symptoms, especially considering the food selectivity towards some organoleptic qualities of food and culinary preparations (53). However, regarding specific strategies, there is no consensus that allows health professionals to openly recommend a dietary treatment.

Based on this, the present review aimed to critically analyze the articles published to date based on the different dietary interventions currently practiced in the target population. Restriction diets are popularly used, and consist of eliminating components such as gluten and casein, present in wheat and dairy products, respectively, from the diet. The results found show improvements in most of the studies considered, however, they are not far from control groups. In addition, the methodological heterogeneity does not allow taking a specific position in this regard, mainly due to the different types of intervention (period, strategy, population, etc.) as well as evaluation scales (psychometric for caregivers or medical interviews), preventing standardization and normalization of the results reported. This premise is in line with a recent meta-analysis published in this regard, which analyzed six studies including 143 participants, all with low to very low quality of evidence (54). Kellers et al. declared that this type of diet does not show any benefit in the symptomatology reported during consultation (95 % CI: -0.89, 0.27) or the functionality perceived by third parties (95 % CI: -5.92, 7.14). On the contrary, this could generate alterations at the gastrointestinal level (RR, 2.33) (95 % CI: 0.69, 7.90). Considering the biases, inconsistencies, and imprecision of the data, it is also not possible to ensure that there are no benefits for this type of strategy. In this line, it is necessary to improve the methodological quality of future randomized controlled trials to be carried out, based on the standardization of subjects considered for each study, together with the evaluation scales used before and after the intervention.

Regarding the restriction of carbohydrates in a ketogenic diet, positive metrics were evidenced in different evaluation instruments, highlighting the time and specificity of the only intervention analyzed. However, the sample size considered would not allow to conclude beyond the subjects who participated in the study. It is important to mention that preclinical publications (55) demonstrate an important body of evidence to theoretically support ketogenic diet (KD); however, clinical trials are still insufficient to consider a position on the subject.

One of the most critical points of this type of intervention corresponds to the period in which the regimen is prescribed, considering that the palatability offered by the foods allowed in the strategy are not the favorites for the pediatric population, and even less so in subjects with marked food selectivity (56).

In this sense, the reports that indicate the prescription of KD with periods of over 12 months correspond to individualized clinical cases. From this, it would be interesting to solve two important points in this matter, first, to develop randomized clinical trials to increase the number of studies and population considered, subsequently allowing the generation of meta-analyses that can offer a better answer to the present problem. Second, in parallel, consider the development of works that can ensure the benefits of the intervention over time, understanding that the follow-up of patients with ASD is not limited to months and above all due to the food selectivity characteristic of the condition, which can be further exacerbated with restrictive strategies.

Regarding supplementation strategies, essential fatty acids have historically been considered critical nutrients in psychiatric disorders, both in their diagnosis and in their etiopathogenesis (57). The evidence is clear in stating that they contribute significantly to the stabilization of different cell membranes and systemic inflammation, their deficiency being a risk factor for the deregulation of these processes. In this sense, autistic children consume a lower quantity of omega-3 fatty acids (SMD, -0.83 [95 % CI: -1.53 to -0.16]) than controls (58); even at blood level they present with lowest DHA (SMD, -2.14 [95 % CI: -3.22 to -1.07]; $p < 0.0001$), EPA (SMD, -0.72 [95 % CI: -1.25 to -0 .18], $p = 0.008$), and ARA (SMD, -0.83 [95 % CI: -1.48 to -0.17], $p = 0.01$) (25,58); therefore, supplementation with these nutrients could favor restoring their levels, thus their function at the level of neurogenesis and synapses, to translate into attitudinal improvements.

Regarding the studies analyzed in this review, the strategy offers positive results; however, in different parameters evaluated, they continue to be inconsistent among them. Literature is in line with what has been reported, confirming that in the intervened population (n = 104), compared to autistic controls without treatment, social interaction improved (SMD, -1.96 [95 % CI: -3.5 to -0.34]; $p = 0.02$), as did interests and repetitive and restricted behaviors (SMD, -1.08 [95 % CI: -2.17 to -0.01]; $p = 0.05$) (25), this being necessary to consider its recommendation. However, it is not yet clear if the reported benefits derive from the previous serum deficit, or specifically from the effects of these essential fatty acids intrinsically. Faced with this, it is necessary to replicate the trials by performing a pre-intervention measurement, or on the other hand, to standardize the subjects considered in the study. In the same way, it is important to set the dosage, it being recommended to establish the DRI according to age for EPA/DHA as a base, and from these figures offer different amounts to evaluate the effectiveness in a specific way.

Regarding strategies based on the modulation of the intestinal microbiota, the restoration of intestinal eubiosis has positioned itself with great relevance in novel strategies for the treatment of neurodevelopmental disorders (59). In the child population with autism (n = 493), the state of intestinal dysbiosis was already confirmed in 3 phyla and 7 different bacterial genera compared to controls (n = 404). Based on the principles of therapy through the modulation of the intestinal microbiota, the restoration of the deficit of the aforementioned microbial profiles could offer benefits at the CNS level, and from there, in altered behaviors. However, the included studies do not show promising results, unlike what happens with other CNS disorders (60). Although it is not possible to affirm that this strategy should be considered at present, there are reports that have reported the positive influence of the use of probiotics and prebiotics at the level of neurotransmitters in the autistic population (61), therefore, its constant evaluation is necessary. In addition, compared to non-dietary interventions, the projections in fecal transplants are even more promising, confirming their effectiveness in animal and human models (62-64). This suggests that the dosage or bacterial genera used are not adequate to promote the concrete restoration of GM. In this line, one of the critical considerations must aim to define the enterotypes of the population studied, and thus standardize the sample prior to the intervention. This would avoid confusion with other clinical and environmental variables that may be modulating the phenomenon.

Regarding the exclusive use of micronutrients, studies tend to be scarce and it is not possible to state a position on the matter. The largest body of evidence points to interventions aimed at treating prenatal care, where both observational and prospective multivitamin evidence fails to demonstrate a lower risk of ASD (65), being only favorable and considerable the use of 400 mcg of folic acid per day, as reported by a recent meta-analysis published this year (66). Regarding interventions in the population with the diagnosis already presented, one trial presented preliminary evidence that suggests considering folinic acid in future studies, since it found benefits at the level of inappropriate speech ($p = 0.04$), stereotypic behavior ($p = 0.03$), and hyperactivity ($p = 0.003$) versus controls (67). As for other vitamins, a meta-analysis that evaluated the effectiveness of vitamin D supplementation, considering 349 autistic subjects, was able to show slight but significant improvements in hyperactivity (-3.20; 95 % CI: [-6.06, -0.34]), being necessary to continue considering the present strategy (68).

CONCLUSIONS

The five types of dietary interventions included in this review show varied evidence that does not allow defining the degree of effectiveness between one or the other in terms of behavioral improvements in the population with ASD. Methodologically, the group in question corresponds to a population that is difficult to approach in clinical studies, considering the diversity of symptoms and clinical magnitude presented. On the other hand, the variability of psychometric instruments used in the studies makes it difficult to standardize the results obtained after the intervention. It is necessary that the body of evidence to be generated in the future considers the sample size, type and magnitude of the interventions, timing and cleaning periods, psychometric evaluation instruments and sociodemographic characteristics of the research subjects.

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