

Review

Dietary interventions for autism spectrum disorder: An updated systematic review of human studies

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ABSTRACT

Autism is a complex spectrum of disorders (ASD) with genetic, epigenetic, autoimmune, oxidative stress, and environmental aetiologies. Treatment of ASD using dietary approaches is a promising strategy, especially owing to its safety and availability. Our study critically analysed the roles and efficacy of antioxidants, probiotics, prebiotics, camel milk and vitamin D. This systematic review provides an updated synopsis of human studies that investigated therapeutic benefits of these dietary interventions in autism. A total of 943 papers were identified out of which 21 articles were included in the systematic review. The selected studies investigated the impact of 5 different dietary supplementations in ASD symptoms and behaviours. These agents include; antioxidants/polyphenolic compounds, probiotics, prebiotics, camel milk and vitamin D. From the results of the present review, antioxidants/polyphenolic compounds decreased the levels of inflammatory cytokines and improved behavioural symptoms. Probiotics improved behavioural and GI symptoms as well as restored gut microbiota equilibrium. Prebiotics decreased levels of inflammatory cytokines, improved behavioural and GI symptoms and improved gut microbiota. Vitamin D improved behavioural symptoms and offered protective effects against neurotoxicity. Camel milk reduced inflammatory responses and oxidative stress. Given the chronic nature as well as early onset of ASD, dietary supplements become useful to complement nutritional deficiencies in children with ASD. Key benefits of these agents stem from their ability to target multiple physiological areas via the gut brain-axis while they are devoid of potential harmful or aggravating effects on ASD patients. The evidence collated in this review propose that dietary intervention may provide a new platform for the management of autism.

KEYWORDS: Autism spectrum disorder (ASD), dietary intervention, gut microbiota, public health.

Introduction

Autism spectrum disorder (ASD) is a complex developmental disorder characterized by a wide array of symptoms such as impaired verbal skills, social withdrawal, repetitive behavior, insistence to routines, and abnormal response to sensory stimuli.^{1,2} ASD is associated with a spectrum of metabolic, mitochondrial, immune, inflam-

matory, and behavioral anomalies involving different parts of the body that appear in the first years of life and continue throughout the lifespan of the patient.³ The disease condition generally manifests in the first 3 years of life. It is estimated that 1 out of every 88 children is diagnosed with an autism spectrum disorder.^{4,5} Although ASD is regarded to be heritable with complex genetic heterogeneity,⁶ growing evidence indicates that the to-

tal fraction of ASD ascribable to genetic inheritance may only be 30–40%.⁷ Out of the remaining 60–70%, about half have different kinds of polymorphisms and the other half have de novo mutations with little or no similarities. These findings suggest that factors of non-genetic origin may play important roles in the aetiology of ASD.⁸

A growing evidence shows that the gut-brain axis plays a key role in the pathogenesis of ASD.^{9,10} The gut-brain axis is regarded as a bidirectional pathway of communication between the gut and the brain.¹⁰ The gut microbiota modulates brain function via the neuroendocrine, neuro-immune and autonomic nervous systems and through microbiological toxin production.^{11,12} Cases of altered gut microbiome have been found in children with autism, a condition known as dysbiosis.^{13–15} Dysbiosis is characterized by an imbalance between beneficial microorganisms and pathogenic microorganisms resident in the gut.¹⁵ Gut dysbiosis also results in systemic inflammation and neuro-inflammation which subsequently impair brain functions (Gut-Brain Axis).¹⁰ In addition, children with ASD exhibit picky eating habits and food selectivity which can result in nutritional deficiencies.^{16–18}

While some studies have highlighted some level of efficacy of elimination diets in autism, certain leading systematic reviews remain doubtful about their effectiveness.^{19–21} Examples include the gluten-free and casein-free (GFCF) diets on children with autism. The use of GFCF diets is based on the framework of the “opioid excess theory”, the disorder symptoms that are comparable to the behavioural effects of opiate which hypothesizes that certain food proteins such as gluten and casein can be metabolized into opioid peptides. These peptides might subsequently enter the blood stream and act upon the central nervous system. Therefore, a diet with minimal proteins (gluten-free and casein-free) was highlighted to ameliorate the behavioural symptoms of children with autism.²¹ Another nutritional strategy-ketogenic diet (KD), which is a high fat diet that forces the body to use fat as a fuel source was also proposed for ASD.¹⁶ However, KD has been associated with adverse events such as constipation, increased serum cholesterol, hemolytic anemia, decreased serum protein, as well as vomiting and dehydration which may worsen ASD symptoms.²²

On the other hand, recent evidence indicates that supplementation with certain dietary agents is beneficial in reducing the severity of ASD symptoms, as well as in improving behavioural anomalies in children with autism.^{2,4,23,24} Some of these agents such as antioxidants (flavonoids, polyphenols), probiotics, prebiotics, vitamin D, and camel milk, contribute to overall protection

against oxidative stress, exert a neuroprotective effect, strengthen intestinal barrier, decrease GI symptoms and inflammation and also improve gut microbiota.^{25–30} These agents come out as safer alternatives to elimination and ketogenic diets because of their ability to target multiple physiological areas via the gut brain-axis and are devoid of potential harmful or aggravating effects on ASD patients. Even though the therapeutic evidence of dietary interventions and their mechanisms of actions are very new, they provide a promising platform for designing future treatments for alleviating ASD symptoms. This systematic review provides an updated synopsis of dietary interventions in autism to evaluate their therapeutic efficacy and beneficial effects.

Material and Method

Information sources and search strategy

Relevant studies were identified from scientific databases such as PubMed, Google scholar, and Scopus. This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.³¹ Using the keywords: (“probiotics” OR “prebiotics” OR “polyphenols” OR “antioxidants” OR “camel milk” OR “vitamin D” OR “dietary interventions”) in (“autism” OR “ASD”), (“gut-brain axis” AND “autism”). Titles and abstracts were screened to select articles of interest. For relevant abstracts, full articles were obtained and reviewed. A backward search was done from which the reference lists of retrieved results were screened.

Inclusion and Exclusion Criteria

The present systematic review identified studies that evaluated dietary interventions in autism. As recommended by the PRISMA guidelines and graphically illustrated in figure 1, the study selection was performed using the procedure composed of four main steps: identification, screening, eligibility and inclusion. Articles were included if they met the following criteria: (1) Studies involving dietary interventions in humans, (2) articles that provided sufficient data, including dietary agents, study/experimental design, sample size, study population, duration of study and clinical findings. Articles were excluded for the following reasons: (1) articles that were not published in English language, (2) articles had no focus on dietary interventions in autism, (3) articles were not original research, (4) articles reported *in vitro* data, (5) articles reported animal studies, (6) articles without full texts. No limits were applied to the year of study.

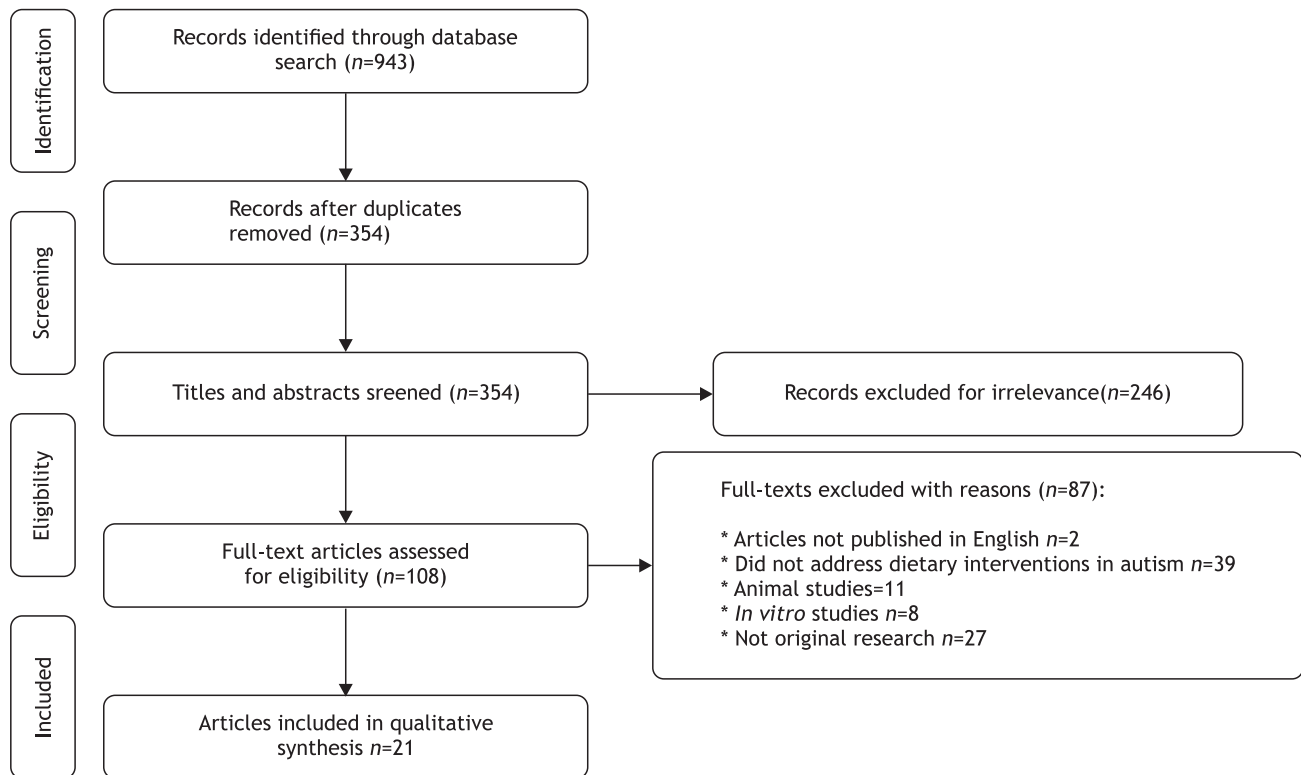


Figure 1. PRISMA flow diagram summarizing search study and selection process.

Study quality assessment

We used the Cochrane collaboration's tool for risk of bias assessment³² to evaluate whether the authors took adequate steps to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. The judgment was grouped into low, high or unclear risk of bias.³²

Results and Discussions

As shown in figure 1, a total of 943 articles were identified from the initial search, and duplicates were removed ($n=589$). Following title and abstract screening, 246 articles were excluded, while the remaining 108 articles were reviewed in detail. Based on our review, 87 additional publications were excluded due to the following reasons: 27 articles did not contain original research; 39 articles had no focus on dietary interventions; 11 articles reported only animal studies; 8 articles reported *in vitro* studies; 2 articles were not published in English language. A total of 21 articles were included in the review (table 1). While 8 articles examined the use of probiotics,^{33–40} 6 articles investigated antioxidants/polyphenolics,^{41–46} 2 articles examined the use of pre-

iotics-only regimen^{47,48} and 3 articles investigated camel milk.^{49–51} Furthermore, 1 article examined vitamin D3²⁹ and 1 article examined a combined probiotic + prebiotic regimen.⁵²

The data obtained from the assessment of the study quality of the included studies are shown in figures 2 and 3. While 9 studies^{36,41,44,45,48–52} showed unclear risks of performance bias, 3 studies^{36,44,52} showed unclear risks of selection bias and two studies^{33,45} showed high risk of selection bias. The risk of other biases in the included studies are unclear.

Generally, there was 100% low risk of attrition and reporting bias in the selected studies

Dietary interventions in autism

Antioxidants/Polyphenolics

Antioxidant-containing foods may offer promising therapeutic benefits in autism.⁵³ Studies have suggested that supplementation with antioxidants (such as polyphenolics, flavonoids) ameliorates symptoms of autism,^{54,55} but the evidence is not sufficient to recommend an antioxidant-based therapeutic practice for autism.

Recent findings have shown that dietary polyphenols are metabolized by gut microbiota resulting in metabo-

Table 1. Summary of human studies that investigated dietary interventions in autism.

Dietary agent	Study design	Sample size (n)	Study population	Study duration	Findings	References
Camel Milk	Randomized controlled trial	60	2-12-year-old children with ASD (Saudi Arabia)	2 weeks	Significantly (p<0.5) increased levels of glutathione, superoxide dismutase, and myeloperoxidase; improved autistic behaviour detected by Childhood Autism Rating Scale (CARS)	Al-Ayadhi and Elamin 201351
Camel milk	Randomized controlled trial	65	2-12-year-old children with ASD (Saudi Arabia)	2 weeks	Improvements were detected by CARS, Social Responsiveness Scale (SRS) and Autism Treatment Evaluation Checklist (ATEC) scales, following 2 weeks of camel milk consumption, but not in the placebo group	Al-Ayadhi et al. 201549
Camel milk	Randomized controlled trial	45	2-12-year-old children with ASD (Saudi Arabia)	2 weeks	Camel milk significantly improved clinical symptoms (CARS score) of autism and decreased serum level of thymus and activation-regulated chemokine (TARC) in autistic children	Bashir and Al-Ayadhi 201450
Antioxidants - (Luteolin + quercetin) containing dietary formulation	Open-label controlled trial	40	4–10-year-old children with ASD (Greece)	26 weeks	Decreased levels of inflammatory cytokines (IL-6 and TNF); improvements in overall behaviour in patients and reduction in ASD symptoms and	Tsilioni et al. 201542
Antioxidants (Flavonoid and Luteolin)	Open-label controlled trial	50	4–10-year-old children with ASD (Greece)	26 weeks	Improvement in overall behavior as indicated by a reduction in ABC (Aberrant Behaviour checklist) scores	Taliou et al. 201346
Antioxidants (Sulforaphane derived from broccoli sprouts)	Randomized controlled trial	44	13–27-year-old young men with moderate to severe ASD (US)	4-18 weeks	Significant decrease (improvement of behaviour) in ABC (p<0.001) and SRS scores (p=0.017) and improvement in social interaction	Singh et al. 201443
Avmacol®, a sulforaphane-producing dietary supplement	Open-label controlled trial	15	5–22-year-old children/young adults with ASD(USA)	12 weeks	Improvements (decreases) in mean scores of SRS and ABC over the study period; Identification of urinary metabolites associated with clinical improvements in participants	Bent et al. 201844
High antioxidant cacao	Pilot study	17	4–17-year-old children with ASD (USA)	4 weeks	Significant improvements on ABC-2 subscales of irritability (p=0.03); social withdrawal (p=0.01); stereotypic behaviour (p=0.05); hyperactivity/noncompliance (p=0.04); inappropriate speech (p=0.05). Significant improvements on the ASRS subscales of social/communication (p=0.04), abnormal behaviours (p=0.003), self-regulation (p=0.02).	Sadek et al. 201845
Antioxidants (Cysteine-Rich Whey Protein (CRWP))	Randomized controlled trial	46	3–5-year-old children with ASD (USA)	3 months	CRWP nutritional intervention significantly improved behaviours associated with ASD as well as glutathione levels	Castejon et al., 202141

Continues

Table 1. Continued.

Dietary agent	Study design	Sample size (n)	Study population	Study duration	Findings	References
Probiotics (<i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosus</i> , <i>Bifidobacteria longum</i>)	Open-label controlled trial	30	5–9-year-old children with ASD (Egypt)	3 months	Enhanced levels of <i>Bifidobacteria</i> in stool samples, Behavioral improvement, Improved GI symptoms following assessment with using a six-item GI Severity Index (6-GSI) questionnaire and Autism Treatment Evaluation Checklist (ATEC)	Shaaban et al 201834
Probiotics (3 strains of <i>Lactobacillus</i> , 2 strains of <i>Bifidobacteria</i> , 1 strain of <i>Streptococcus</i>)	Open-label controlled trial	29	2–9-year-old children with ASD (Slovakia)	4 months	Probiotic supplementation normalized bacterial balance in fecal microbiota in children with ASD	Tomova et al 201535
Probiotics (VISBIOME) (8 probiotic species of <i>Lactobacillus</i> and <i>Bifidobacterium</i>)	Randomized controlled trial	13	3–12-year-old children with ASD (USA)	8 weeks	A parent-selected target symptom showed significant improvement in GI complaints with probiotic supplementation compared with placebo (p=0.02)	Arnold et al 201936
Probiotics (<i>Lactobacillus plantarum</i> PS128)	Randomized controlled trial	80	7–15-year-old children with ASD (Taiwan)	28 days	PS128 ameliorated opposition/defiance behaviours; Improved behavioural symptoms compared to placebo	Liu et al 201937
Probiotics (<i>Lactobacillus plantarum</i> PS128)	Open-label controlled trial	131	45–127-month-old children with ASD (Italy)	6 months	Improved attention, improved communication skills, improved personal autonomies	Mensi et al 202133
Probiotics Vivomixx® oor Visbiome® (<i>Streptococcus thermophilus</i> , <i>Bifidobacterium breve</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium infantis</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus para-casei</i> , <i>Lactobacillus delbrueckii</i> subsp. <i>Bulgaricus</i>)	Randomized controlled trial	85	18–72 months old children with ASD (Italy)	6 months	Improvements in GI symptoms, adaptive functioning, and sensory profiles compared with placebo	Sanocchi et al 202038
Probiotics + prebiotics (<i>Bifidobacterium infantis</i>) + colostrum supplement (bovine colostrum product)	Randomized controlled trial	8	2–11-year-old children with ASD (USA)	12 weeks	<ul style="list-style-type: none"> – Reduced frequency of GI symptoms in both BCP and BCP only+ <i>B. infantis</i> group – Improved intestinal microflora profile and reduced behavioral abnormalities with combination therapy 	Sanctuary et al 201952
Probiotics (<i>Lactobacillus plantarum</i> WCFS1)	Randomized controlled trial	22	4–16-year-old children with ASD (UK)	12 weeks	<ul style="list-style-type: none"> – Increased <i>Lactobacilli</i> and <i>enterococci</i> counts and significantly reduced <i>Clostridium</i> cluster counts compared to placebo – Significant improvements in TBPS (Total Behaviour Problem Score) 	Parracho et al 201040

Continues

Table 1. Continued.

Dietary agent	Study design	Sample size (n)	Study population	Study duration	Findings	References
Probiotics (<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus delbrueckii</i> , <i>Bifidobacteria longum</i> , <i>Bifidobacteria bifidum</i>)	Open-label controlled trial	33	3–16-year-old children with ASD (USA)	21 days	Improved behavioural symptoms Improved GI symptoms (constipation and diarrhea)	West et al 201339
Prebiotics (<i>Bimuno</i> ® galactooligosaccharide (B-GOS®))	Randomized controlled trial	30	4–11-year-old children with ASD (UK)	6 weeks	<ul style="list-style-type: none"> – Improved ant-social behaviour – Enhanced gut microbiota – Reduced gastrointestinal (GI) discomfort 	Grimaldi et al 201847
Prebiotics (partially hydrolyzed guar gum)	Randomized controlled trial	13	4–9-year-old children with ASD (Japan)	2 months	<ul style="list-style-type: none"> – Decreased behavioural irritability – Improved gut microbiota – Relieved constipation and gut dysbiosis symptoms – Decreased concentrations of inflammatory cytokines (IL-1b, IL-6 and TNF-α) 	Inoue et al 201948
Vitamin D3	Case-controlled cross-sectional study	122	3–9-year-old children with ASD (Egypt)	3 months	Improved behavioural outcome (Improved CARS and ABC scores)	Saad et al. 201629

lites that are more bioactive as well as possessing more antioxidant capacity than the native form.^{27,56–58} The gut microflora break down polyphenols into metabolites that are readily absorbed from the intestine and transported via the blood to the brain where the metabolites exert biological activities.⁵⁹

Polyphenolic compounds act as natural antioxidants specifically due to their radical-scavenging properties (figure 4) which are linked to the number of free hydroxyl groups in their skeleton capable of donating H. to the oxidizing compound.⁶⁰ Polyphenolic compounds with multiple hydroxyl groups possess more potent radical scavenging properties than those with only one hydroxyl group.⁶¹

An imbalance between generation of reactive oxygen species (ROS) and their elimination especially by the antioxidant defence system in the body results in oxidative stress (figure 4). While oxidative stress-induced mechanisms are associated with the aetiology of ASD,^{62,63} disruptions in the antioxidant defence systems could lead to changes in neuronal structure and general brain function, inflammation and dysregulation of immune function.^{62,64} Interestingly, polyphenolic compounds act as natural antioxidants attributable to their free radical scavenging properties linked to their chemical structure.^{27,59}

Six articles that investigated antioxidants/polyphenolics were included in this review.^{41–46}

In an open-label clinical trial by Tsilioni et al, 4–10-year-old children with ASD in Greece were treated with Luteolin+quercetin-containing dietary formulation for 26 weeks.⁴² At the end of the treatment, a significant decrease in the mean serum IL-6 and TNF was observed ($p=0.036$ and $p=0.015$, respectively) compared with levels before treatment. Improvements in behavioural pattern of the participants were also noted after treatment.⁴² A randomized trial was conducted in 13–27 years old young men with moderate to severe ASD in the United States.⁴³ This was carried out for a period of 4–18 weeks using daily oral doses of sulforaphane (50–150 μmol). At the end of the treatment period, participants receiving sulforaphane showed significant decrease (improvement in behaviour) in ABC ($p<0.001$) and SRS scores ($p=0.017$). A significantly ($p=0.015–0.007$) greater number of participants that received sulforaphane demonstrated improvement in social interaction, verbal communication and abnormal behaviour.⁴³ Similarly, Bent et al. conducted an open-label study with sulforaphane supplements (Avmacol®) in 5–22 years old children/young adults with ASD in the United States.⁴⁴ Approximately 2.5 μmol glucoraphanin (GR)/lb (sulforaphane precursor) was administered for 12 weeks.

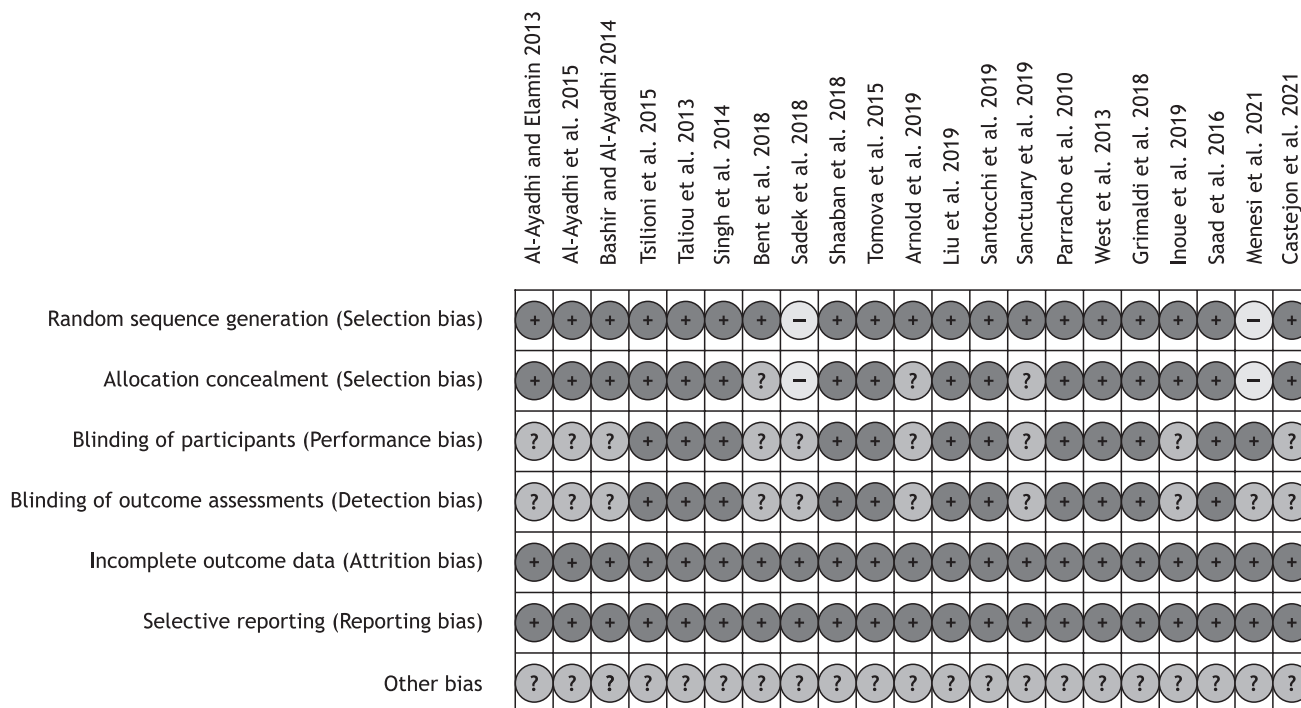


Figure 2. Summary of risk of bias of the included studies. Risk of bias for individual studies was determined using the Cochrane tool for assessment of risk of bias.

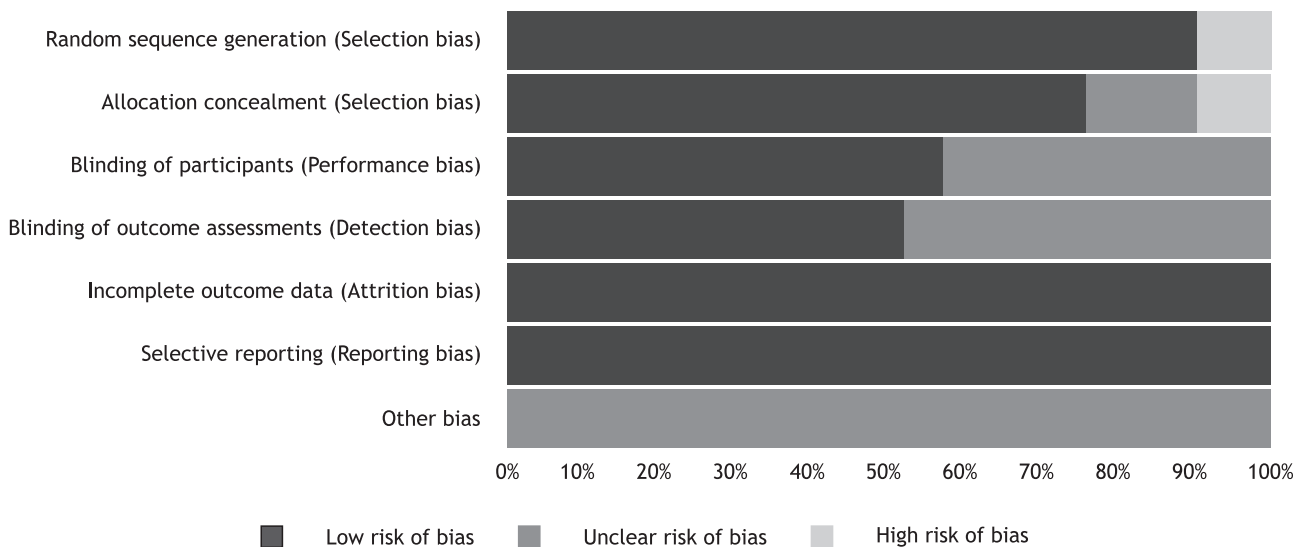


Figure 3. Risk of bias graph: summary of risk of bias is presented as percentage across all included studies

Fasting urinary metabolites as well as measures of behaviour (ABC and SRS) were evaluated at the start and at the end of the study. Mean scores of both ABC and SRS showed improvements (decreases) over the study period. Urinary metabolites associated with clinical improvements in participants were identified.⁴⁴

A pilot study reported by Sadek et al revealed that administration of high antioxidant cacao for 4 weeks significantly improved behaviours of children with ASD.⁴⁵

Participants received 16 g per day of dark chocolate. ABC and ASRS (Autism Spectrum Rating Scale) were completed at baseline, end of 2nd and 4th week. Results obtained revealed significant improvements in the behavioural measures.⁴⁵ In Greece, Taliou and colleagues supplemented flavonoid and luteolin in 4-10-year-old children with autism for 26 weeks.⁴⁶ Results obtained from that study revealed improvement in general behaviour as shown by a reduction in ABC scores.⁴⁶

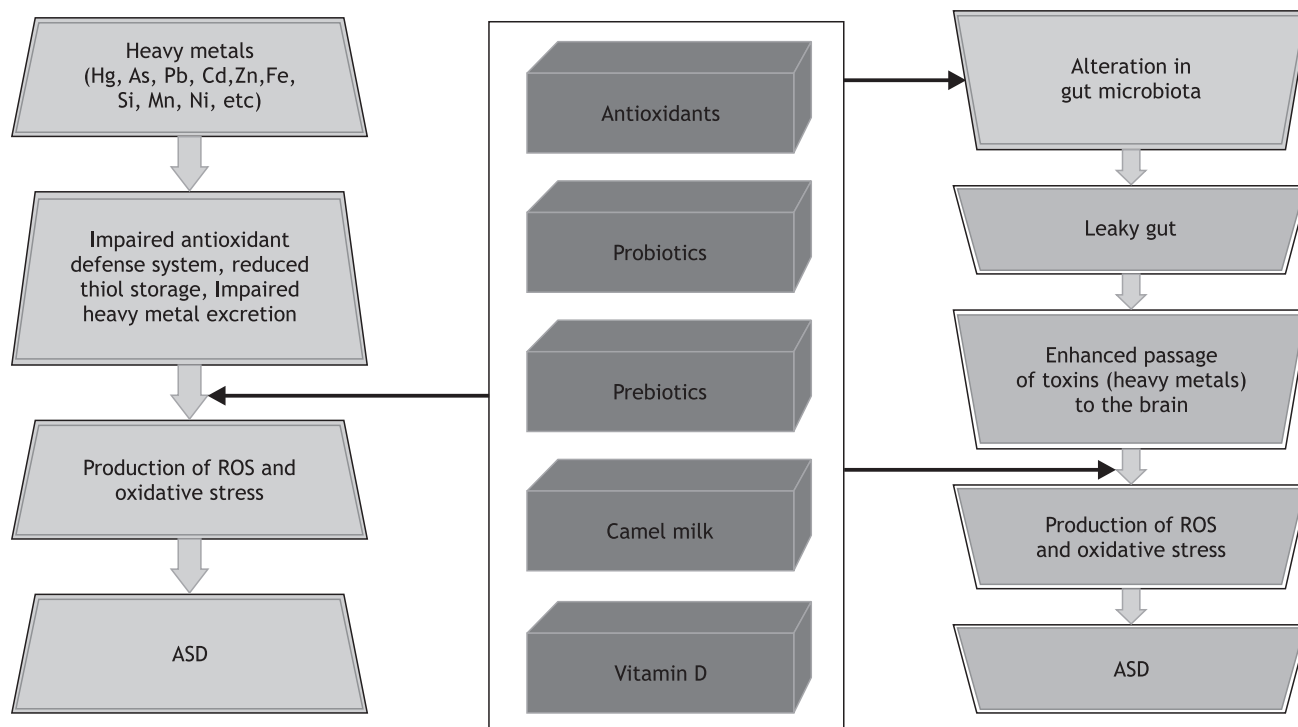


Figure 4. Interconnections between ASD and the possible mechanisms/beneficial effects of dietary agents.

Castejon et al, performed a 3 months' study to probe the effectiveness of Cysteine-Rich Whey Protein (CRWP) intervention in children with ASD and to ascertain whether improvements in intracellular glutathione (reduced and oxidized) correlated with behavioural changes.⁴¹ Findings from that study demonstrated that intervention with CRWP significantly improved both glutathione levels and abnormal behaviours associated with ASD.⁴¹

Probiotics

Probiotics are live microorganisms which have the capacity to maintain or restore the microbiota balance in the intestinal tract when consumed in adequate amounts.⁶⁵ Probiotics consist of bacteria that are identical to those that naturally inhabit the human gut. These bacteria are basically of two groups -Lactobacillus and Bifidobacterium spp.⁶⁵

Imbalance in gut microbiota or dysbiosis has been implicated in the pathogenesis of ASD.^{59,66} Several pieces of evidence have indicated that the gut microbiota composition of patients with autism differed significantly in comparison to healthy controls.⁶⁷⁻⁷¹ Such disruptions in the gut microbiome may predispose an individual to altered gut motility and secretion, resulting in diarrhoea or constipation, which are common symptoms reported in patients with autism.⁷² Dysbiosis occurs majorly due to an altered integrity of the intestinal barrier which

enhances passage of toxins (produced by pathogenic bacteria) from the gut lumen to the brain ('leaky gut') (figure 5).¹⁴ These toxic molecules influence neurotransmitter function in the brain, resulting in abnormalities in behavioural patterns such as impaired socialization, decreased pain response, communication abnormalities and self-abusive or repetitive behaviours, delirium, confusion, which are core symptoms of ASD.⁷³ Interestingly, probiotics enhance gut microbiota equilibrium and enhance the integrity of the gut mucosa.²⁸

From our review, 8 articles examined the use of probiotics in children with autism.³³⁻⁴⁰ Tomova et al. probed the GI microbiome composition and also examined the changes in the faecal microbiota, hormone and cytokine levels following probiotic administration in ASD children, their healthy siblings and control children.³⁵ Daily supplementation with three *Lactobacillus* strains, two *Bifidobacterium* strains and a *Streptococcus* strain for a period of 4 months decreased the level of *Desulfovibrio* spp., *Bifidobacteria* and also normalized the Bacteroidetes/Firmicutes ratio in the faeces of children with autism. The study showed that ASD severity has a positive correlation with the severity of GI dysfunctions in the subjects. The level of TNF- α was decreased following probiotic supplementation. Generally, probiotic supplementation altered gut microbiota composition in ASD children.³⁵

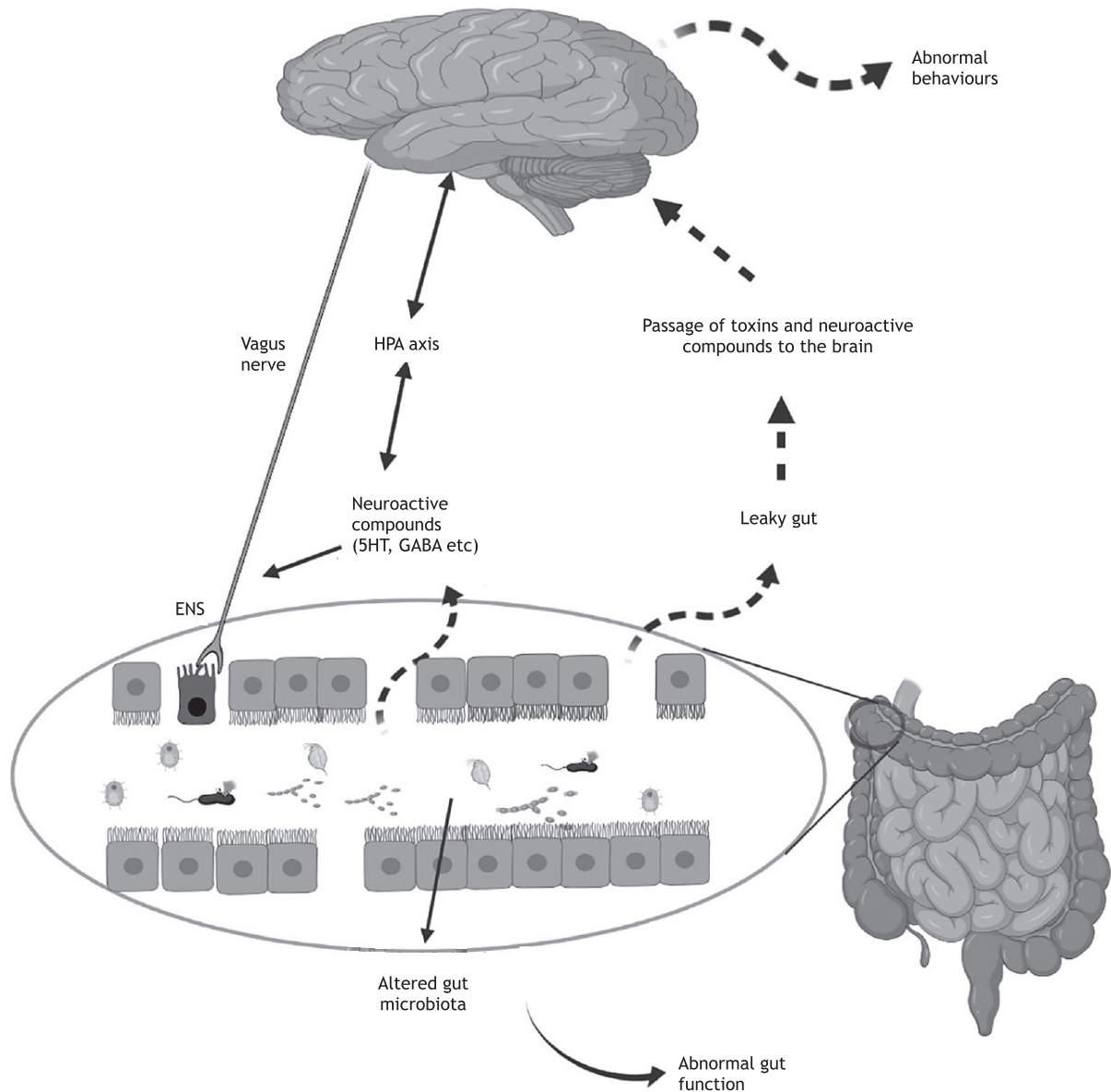


Figure 5. Relationships between the microbiota, gut brain axis and ASD: Toxins and neuroactive compounds (e. 5-HT and GABA) produced by certain microbiota can cross the “leaky gut” to affect brain function and induce abnormal behaviours. These neuroactive compounds can influence the HPA Axis directly and increase circulating levels of cortisol. Certain microbiota, metabolites produced and neuroactive compounds can activate enteric nervous system (ENS) and affect brain function via the vagus nerve.

In an open-label controlled trial, the supplementation of a mixture of 3 probiotic strains (*B. longum*, *L. rhamnosus*, *L. acidophilus* (100×10^6 CFU per gram; 5 g per day) for 3 months significantly altered the faecal microbiota (*Bifidobacteria* and *Lactobacilli*) of ASD children in Egypt.³⁴ The abdominal symptoms and the severity of the ASD, were quantified using a six-item GI Severity Index (6-GSI) questionnaire and Autism Treatment Evaluation Checklist (ATEC) respectively, before and after probiotics supplementation. These were found to be reduced in ASD children compared to baseline. The

study demonstrated that probiotic supplementation improves the behavioural pattern, gut microbiota and the abdominal discomforts in ASD children.³⁴ Arnold et al. investigated GI symptoms, and anxiety following VISBIOME® supplementation (mixture of 8 probiotic species, mostly *Lactobacillus* and *Bifidobacterium*) in an 8-week crossover trial separated by a 3-week washout. The study was carried out in 13 children with ASD aged 3–12 years. A parent-selected target symptom revealed significant improvement in GI complaints with probiotic supplementation compared to placebo ($p=0.02$).³⁶ A

4-week, randomized controlled trial evaluated the effects of *Lactobacillus plantarum* PS128 (PS128) on boys with ASD, aged 7–15 in Taiwan. Following a 28-day period of PS128 supplementation, results obtained showed improved behavioural pattern as well as improved total score of SNAP-IV (Swanson, Nolan, and Pelham-IV-Taiwan version) compared with the placebo group.³⁷ Recently, a similar study was carried out by Mensi et al. investigating the effectiveness of *Lactobacillus plantarum* PS128 (PS128) in children with ASD.³³ In that study, patients supplemented with *Lactobacillus plantarum* (PS128) showed greater improvements and minimal side effects compared to patients that ingested other probiotics. Their data was consistent with results of earlier studies validating the therapeutic effects of *Lactobacillus plantarum* PS128 in Autism.³³

West and co-workers³⁹ probed the supplementation of probiotics in 3-16-year-old children with autism in the USA. Their data showed improved behavioural symptoms and improved GI symptoms (constipation and diarrhoea).³⁹ In the UK, Parracho et al⁴⁰ investigated the supplementation of probiotics in 4–16-year-old children with autism. Supplementation with *Lactobacillus plantarum* for 12 weeks produced a significantly reduced Clostridium cluster counts compared to placebo and enhanced Lactobacilli and enterococci counts compared to placebo. There was also a significant improvement in TBPS (Total Behaviour Problem Score).⁴⁰ Finally, Santocchi et al³⁸ evaluated the effects of probiotics in ASD in a randomized trial of 85 pre-schoolers in Italy. Data obtained demonstrated greater improvements in adaptive functioning, GI symptoms, and sensory profiles compared to placebo. This study suggests potentially beneficial effects of probiotics on core autism symptoms.³⁸

Prebiotics

Colonization of the gut by toxin-producing bacteria in the gut is associated with bowel problems in autism.⁷⁴ Prebiotics can enhance the growth of healthy bacteria and reduce the overgrowth of pathogenic *Clostridium difficile*.⁷⁵ Prebiotics are non-digestible dietary agents that modulate gut microbiota and are selectively utilized by beneficial microorganisms for growth within the host, thereby conferring health benefits to the host.⁷⁶ While probiotics (live microorganisms) can balance, or normalize gut microbiota, prebiotics inhibit the growth of pathogenic micro-organisms by nourishing beneficial micro-organisms. In essence, both prebiotics and probiotics work together to maintain healthy gut microbiota.⁷⁴ Non-digestible carbohydrates such as fructo-oligosaccharides, galacto-oligosaccharides and trans-ga-

lacto-oligosaccharides are common examples of prebiotics which modify the composition and function of gut microbiota.^{77,78} Beneficial gut micro-organisms ferment and degrade these non-digestible dietary substances and obtain energy for survival while influencing gut microbiota in the long run.^{77,79}

Studies have also indicated that prebiotics exert antioxidant and direct radical scavenging effects, thereby counteracting oxidative stress and the development of ROS-related diseases (figure 4).^{80,81} These effects are mediated by the action of short-chain fatty acids produced from their fermentation in the colon.⁸⁰ Prebiotics can also stimulate the activity of antioxidant enzymes Glutathione S- Transferases (GSTs) indicating possible antioxidant effects.⁸²

From our review, 2 studies examined the use of prebiotics-only regimen,^{47,48} while one RCT study investigated a combined probiotics+prebiotics regimen,⁵² respectively. Gremaldi and colleagues investigated the effect of exclusion diets and a 6-week Bimuno® galacto-oligosaccharide (B-GOS®) prebiotic intervention in 30 children with autism.⁴⁷ From this study, children on exclusion diets showed significantly lower incidence of abdominal pain and abnormal bowel movement, as well as decreased levels of *Bifidobacterium spp* and *Veillonellaceae* family, but higher levels of *Faecalibacterium prausnitzii* and *Bacteroides spp*. In addition, B-GOS® intervention resulted in improved anti-social behaviour, significant changes in gut microbiota, as well as pronounced changes in faecal and urine metabolites.⁴⁷ In another study, supplementation with partially hydrolyzed guar gum for 2 months in 4–9-year-old children with autism normalized gut microbiota and significantly increased defecation frequency per week.⁴⁸ In addition, the intervention significantly decreased levels of serum interleukin-1 β ($p < 0.05$) and tumor necrosis factor- α ($p = 0.07$), respectively. Behavioral irritability was also ameliorated as per ABC, Japanese Version.⁴⁸

Sanctuary et al⁵² used a combined regimen of probiotic and prebiotic [containing *Bifidobacterium infantis* + colostrum supplement (bovine colostrum product)] vs bovine colostrum product alone for 12 weeks in a randomized controlled trial. Results obtained revealed a reduction in the severity of GI symptoms and improved intestinal microflora profile as well as reduced behavioral abnormalities. These results were linked to a reduction in IL-13 and TNF- α production in some participants.⁵²

Camel milk

While low plasma levels of GSH (glutathione) and cysteine have been associated with autism, camel milk has been shown to enhance levels of GSH-Px (glutathione

peroxidase) and superoxide dismutase with an improvement in ASD clinical symptoms.⁴ The unique composition of camel milk makes it different from other ruminants' milk. Camel milk contains more minerals such as calcium, iron, magnesium, copper, zinc, potassium; and more vitamins (A, B2, E, C); less fat, less cholesterol, and less lactose, when compared to cow milk. While cow milk contains beta-lactoglobulin and beta-casein, these components are absent in camel milk.⁵¹ Due to the unique composition of camel milk, its use has been indicated to provide improvements in the behaviour of children with autism by increasing the levels of superoxide dismutase (SOD), myeloperoxidase (MPO), and plasma GSH, thereby reducing oxidative stress—a major component of autism's aetiology (figure 4).^{51,83} Camel milk also reduces oxidative stress via downregulation of mitogen-activated protein kinase (MAPK) signalling pathways.³⁰

In the present review, 3 studies^{49–51} sought to investigate the effects of camel milk on the clinical outcomes of autism and oxidative stress markers. Al-Ayadhi et al. investigated the effects of camel milk supplementation on oxidative stress parameters in children with autism.⁵¹ Findings from that study revealed significantly ($p < 0.5$) increased levels of glutathione, superoxide dismutase, and myeloperoxidase, as well as improved autistic behaviour validated by the Childhood Autism Rating Scale (CARS).⁵¹ A later study by the same authors probed the impacts of raw and boiled camel milk on the Childhood Autism Rating Scale (CARS) and oxidative stress biomarkers such as GSH, SOD, and MPO.⁴⁹ Participants aged between 2 to 12 years were randomized into 3 different groups: boiled camel milk, raw camel milk, cow milk (control) which received 500 mL milk products daily for 2 weeks. Significant reductions in the CARS and oxidative stress markers were noted following 2 weeks' consumption of raw and boiled camel milk compared to cow milk (control).⁴⁹ Lastly, Bashir and Al-Ayadhi⁵⁰ used a randomized trial to probe the impact of camel milk on the CARS assessment and serum levels of thymus and activation-regulated chemokine (TARC). Results obtained revealed that raw camel milk correlated with significant improvements in the CARS score compared with baseline, whereas, both raw and boiled camel milk correlated with significant decreases in TARC serum levels. Cow milk (control) did not produce any significant changes in these measurements.⁵⁰

Vitamin D

Reports have indicated that maternal vitamin D deficiency predisposes children to autism^{84,85} suggesting that supplementation with vitamin D may prove beneficial in ameliorating autism symptoms.⁸⁶ This evidence

is associated with neuro-protective effects of vitamin D, attributable to neuronal calcium regulation, anti-oxidative pathway, immunomodulation and detoxification.⁸⁷ Earlier studies have demonstrated that vitamin D upregulates the levels of glutathione in the brain.^{88,89} Besides being a potent antioxidant, glutathione scavenges oxidative products,^{90,91} protects nerve cells from toxins, and enhances conduction in the nerves critical to mental processing.⁹² Hence, it can be deduced that vitamin D plays important roles in the detoxification of the brain. All these mechanisms in conjunction with other factors may account for the neuroprotective effects of vitamin D and its ameliorative effects in autism.⁸⁶

In the present review, one cross-sectional study examined the impact of vitamin D in children with autism.²⁹ In that study, 57% of the patients had vitamin D deficiency, while 30% had vitamin D insufficiency. Results obtained from that study demonstrated significantly improved outcome (CARS and ABC) subscales that measured eye contact, behaviour, attention span and stereotype behaviour).²⁹

Limitations of the study

Some limitations were observed across the studies included in this review. Two studies lacked control groups,^{33,45} one study used a narrow age group and carried out work only in male children,⁴¹ while five studies^{36,44,45,48,52} used small sample sizes in their trials. These factors limit the generalizability of the results obtained from these studies; therefore, more robust randomized controlled trials (with sufficient group sizes) are required to validate and elaborate on findings. Secondly, we were not able to conduct quantitative analysis of current evidence due to significant heterogeneity in interventions and inconsistencies in outcome measures, hence we only performed qualitative review of the included studies. Lastly, Studies on dietary agents were typically short-term (<7 months) and provided limited evidence regarding the potential effects of these interventions.

Conclusion

The collated evidence in the present review indicate that dietary intervention may hold a promise in the management of autism. Dietary agents are generally available, accessible and considered safe because of their natural origin. The preliminary evidence is encouraging, however, given the limitations associated with these studies, the future direction will depend on larger, long-term and well-designed studies. Taken together, results from this study add to existing literature on the potential benefits and effectiveness of dietary interventions in improving symptoms associated with autism.

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Διατροφικές παρεμβάσεις για τη διαταραχή αυτιστικού φάσματος: Μία επικαιροποιημένη συστηματική ανασκόπηση των μελετών σε ανθρώπους

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ΠΕΡΙΛΗΨΗ

Ο αυτισμός είναι ένα σύνθετο φάσμα διαταραχών (ΔΑΦ) με αιτιολογία σχετιζόμενη με παράγοντες γενετικούς, επιγενετικούς, αυτοάνοσους, οξειδωτικού στρες και περιβαλλοντικούς. Η θεραπεία της ΔΑΦ με τη χρήση διατροφικών προσεγγίσεων είναι μια πολλά υποσχόμενη στρατηγική, ειδικά λόγω της ασφάλειας και της διαθεσιμότητάς της. Η μελέτη μας ανέλυσε κριτικά τους ρόλους και την αποτελεσματικότητα των αντιοξειδωτικών, των προβιοτικών, των πρεβιοτικών, του γάλακτος καμήλας και της βιταμίνης D. Αυτή η συστηματική ανασκόπηση παρέχει μια επικαιροποιημένη σύνοψη των μελετών σε ανθρώπους που διερεύνησαν τα θεραπευτικά οφέλη αυτών των διατροφικών παρεμβάσεων στον αυτισμό. Εντοπίστηκαν συνολικά 943 εργασίες από τις οποίες 21 άρθρα συμπεριλήφθηκαν στη συστηματική ανασκόπηση. Οι επιλεγμένες μελέτες διερεύνησαν την επίδραση 5 διαφορετικών συμπληρωμάτων διατροφής στα συμπτώματα και στις συμπεριφορές της ΔΑΦ. Αυτοί οι παράγοντες περιλαμβάνουν: αντιοξειδωτικά/πολυφαινολικές ενώσεις, προβιοτικά, πρεβιοτικά, γάλα καμήλας και βιταμίνη D. Από τα αποτελέσματα της παρούσας ανασκόπησης, οι αντιοξειδωτικές/πολυφαινολικές ενώσεις μείωσαν τα επίπεδα των φλεγμονωδών κυτοκινών και βελτίωσαν τα συμπτώματα συμπεριφοράς. Τα προβιοτικά βελτίωσαν τη συμπεριφορά και τα γαστρεντερικά συμπτώματα καθώς και αποκατέστησαν την ισορροπία μικροβιακής χλωρίδας του εντέρου. Τα πρεβιοτικά μείωσαν τα επίπεδα των φλεγμονωδών κυτοκινών, βελτίωσαν τη συμπεριφορά και τα γαστρεντερικά συμπτώματα καθώς και τη μικροβιακή χλωρίδα του εντέρου. Η βιταμίνη D βελτίωσε τα συμπτώματα συμπεριφοράς και προσέφερε προστατευτικά αποτελέσματα έναντι της νευροτοξικότητας. Το γάλα καμήλας μείωσε τις φλεγμονώδεις αντιδράσεις και το οξειδωτικό στρες. Δεδομένης της χρόνιας φύσης καθώς και της πρώιμης έναρξης των ΔΑΦ, τα συμπληρώματα διατροφής είναι χρήσιμα για τη συμπλήρωση των διατροφικών ελλείψεων σε παιδιά με ΔΑΦ. Τα βασικά οφέλη αυτών των παραγόντων προέρχονται από την ικανότητά τους να στοχεύουν πολλαπλές φυσιολογικές περιοχές μέσω του άξονα του εγκεφάλου του εντέρου, ενώ και στερούνται πιθανών επιβλαβών ή επιβαρυντικών επιδράσεων σε ασθενείς με ΔΑΦ. Τα στοιχεία που συγκεντρώθηκαν από αυτήν την ανασκόπηση υποδεικνύουν ότι η διατροφική παρέμβαση μπορεί παρέχει ένα νέο σύστημα για τη διαχείριση του αυτισμού.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Διαταραχή αυτιστικού φάσματος (ΔΑΦ), διατροφική παρέμβαση, μικροβιακή χλωρίδα εντέρου, δημόσια υγεία.