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Therapeutic Diet against Autism - a critical review

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ABSTRACT

The treatment of Autism Spectrum Disorder (ASD) is a multifaceted challenge that necessitates a multidimensional approach. Genetic factors underlie susceptibility and symptomatology in ASD, emphasizing the importance of individualized interventions. Behavioral insights have uncovered intricate connections between diet and ASD behaviours, elucidating the potential for tailored nutritional strategies. The interplay between diet, nutrition, and ASD is complex. The therapeutic strategies are encompassing promising avenues and managing by marine ascidian-derived compounds, nutrigenomics, coenzyme Q10 supplementation, and the role of physical activity. Epigenetic approaches offer further promise, as dietary modifications may influence gene expression patterns. The future of ASD treatment lies in a comprehensive, evidence-based and individualized approach, with therapeutic diets at the forefront as a potential means of enhancing clinical management and improving the overall quality of life for individuals affected by ASD. The dynamic nature of this evolving field holds great potential for advancing our understanding of ASD and optimizing therapeutic strategies.

KEYWORDS

Autism spectrum disorder, Diet, Genetic, Influences, Management, Nutrition, Therapeutic strategies.

1. Introduction

Autism Spectrum Disorder (ASD) is an impaired neurodevelopmental, heterogeneous condition with multifactorial aetiology and variable symptom presentations associated with difficulties in communication and interaction along with restricted, repetitive behaviours (Marlborough et al., 2021). Emerging evidence suggests that nutritional factors may play a role in influencing ASD symptoms and contributing to the overall management of the disorder. Recent research has explored the potential benefits of specific diets, micronutrient supplementation, and nutritional Interventions as complementary approaches to traditional therapeutic strategies (Alam et al., 2023). ASD's complex aetiology involves a combination of genetic (as represented in figure no. 1) and environmental factors. Genetic influences, including de novo mutations, copy number variations, and common variants, contribute to approximately 50% of ASD cases, with a hereditary component. Siblings in affected families face a higher ASD risk, reflecting a genetic predisposition. Mutations in genes related to synaptogenesis and conditions like fragile X syndrome are associated with ASD. Specific chromosomal regions, such as 2q, 7q, 15q, and 16p, contain ASD-related genes. Inborn metabolic errors and genes linked to cerebellar development, the GABA system, and serotonin transport may also play a role (Marlborough et al., 2021). Environmental factors, prenatal drug exposure, autoimmune disorders, infections, and diet contribute to ASD by affecting gut and immune function. The interplay between genetic susceptibility and environmental factors determines ASD severity, warranting further investigation for effective treatments (Essa & Qoronfleh., 2020).

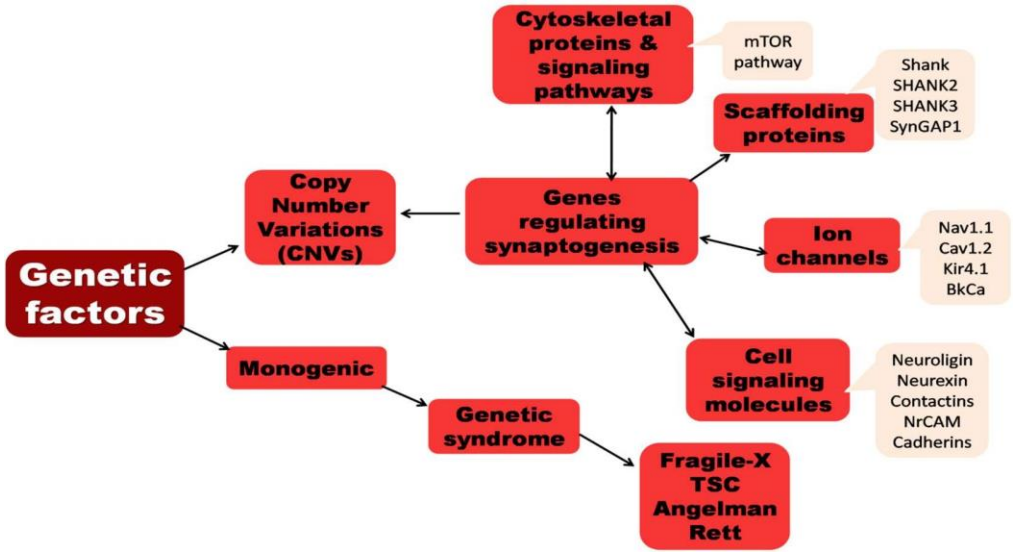

Figure 1. Diagrammatic representation of classification of different genetic factors associated with autism spectrum disorder (ASD) and cellular and metabolic pathways. *(The illustration is demonstrating the specific genes that are responsible for the development of ASD associated phenotypic behaviours and changes among autistic children. Na_v 1.1-sodium channel type 1. Ca_v 1.2-voltage dependent L-type Ca^{2+} channel, Kir4.1, and $BKCa^{2+}$-potassium channels; Source:* ***Essa &Qoronfleh, 2020****).*

The neuropathogenesis of Autism Spectrum Disorder (ASD) is a multifaceted and evolving field of study, characterised by intricate interactions among genetic, neurobiological, and environmental factors. Genetic research has identified a complex interplay of genetic variants and mutations, often affecting synaptic function and neural connectivity, contributing to the core features of ASD (Kirkovski et al., 2023). Neurobiological investigations reveal alterations in neural connectivity and the emergence of neuroinflammatory processes, potentially impacting brain development and function. Furthermore, emerging insights into epigenetic regulation suggest that environmental influences can shape gene expression patterns, further influencing the aetiology of ASD. This complex amalgamation of factors underscores the need for ongoing research to unravel the neuropathogenesis of ASD (Parlatini et al., 2023), ultimately facilitating the development of targeted interventions and therapies for affected individuals. ASD is a problem with the missing heritability, leading to increased focus on environmental factors instead.

Proposed risk factors include air pollution, pesticides, socio-economic factors, and maternal health during pregnancy. Epigenetics, a growing field, explores how external factors influence the genome and contribute to ASD (Genovese & Butler, 2023). Core ASD features, like impaired social communication and repetitive behaviours, are associated with genetic variations affecting brain development and neural connectivity. Understanding the interplay between genetics, epigenetics, and environmental factors is crucial for advancing ASD comprehension and guiding targeted interventions (Bhandari et al., 2020). The relationship between the factors is described in figure no. 2 (Sivamaruthi et al., 2020).

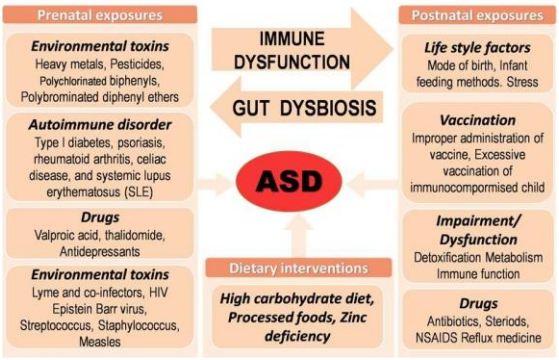

Figure 2.: Representation of the complex relationship among different environmental factors associated contributing towards the exposure and severity of Autism Spectrum Disorder or ASD-related issues (Source: **Sivamaruthi et al., 2020**)

1.1. Maternal prenatal exposure interplay

Studies on maternal diet and Autism Spectrum Disorder (ASD) suggests potential protective factors like folate and vitamin D, with emerging evidence for other nutrients. Modifying maternal diet during pregnancy could impact ASD disability (Bird et al., 2017). Various maternal prenatal exposure factors have been studied in relation to Autism Spectrum Disorder (ASD). These factors encompass a range of environmental and lifestyle elements that a pregnant mother may encounter during her pregnancy. Here are some notable maternal prenatal exposure factors associated with ASD are mentioned below (Essa & Qoronfleh, 2020; Zhong et al., 2020)

- Air Pollution: Exposure to air pollutants during pregnancy, such as particulate matter (PM), nitrogen dioxide (NO2), and heavy metals, has been linked to an increased risk of ASD in offspring (Essa & Qoronfleh, 2020).
- Pesticides: Maternal exposure to pesticides, especially organophosphates and pyrethroids, during pregnancy has been associated with an elevated risk of ASD in several studies (Essa & Qoronfleh, 2020).
- Maternal Diet and Nutrition: Certain nutritional factors, including low folate intake, obesity, and diabetes during pregnancy, have been suggested as potential risk factors for ASD (Essa &Qoronfleh., 2020; Zhong et al., 2020).
- Psychosocial and Socioeconomic Factors: Maternal stress, anxiety, depression, and low socioeconomic status during pregnancy have been linked to an increased risk of ASD in some studies (Essa &Qoronfleh., 2020).
- Medications and Supplements: The use of certain medications and supplements during pregnancy, such as valproic acid and selective serotonin reuptake inhibitors (SSRIs), has been investigated for their potential association with ASD risk (Zhong et al., 2020).
- Maternal Infections and Immune Responses: Maternal infections during pregnancy, as well as immune responses and inflammation, have been examined for their potential role in ASD development
- Metabolic Conditions: Conditions like maternal obesity and gestational diabetes have been explored as potential risk factors for ASD (Zhong et al., 2020).

1.2. Challenges of autistic children-association of comorbidities, behavioural insights

The challenges faced by autistic children are multifaceted and encompass a range of comorbidities and behavioural insights. Comorbidities, such as attention deficit hyperactivity disorder (ADHD), anxiety,

and gastrointestinal issues, frequently co-occur with autism, complicating diagnosis and treatment, have highlighted the prevalence of these comorbid conditions in autistic children (Yan et al., 2023). Moreover, behavioural insights have revealed the diverse and unique needs of autistic individuals, emphasising the importance of individualised support and interventions. have advanced our understanding of the behavioural profiles of autistic children and underscored the need for tailored approaches to address their challenges (Patton et al., 2020). In light of these complexities, addressing the challenges of autistic children necessitates a holistic and multidisciplinary approach that takes into account comorbidities, behavioural nuances, and individualised care strategies (Frye et al., 2022).

2. **Therapeutic nutrition - managing symptoms of Autism spectrum disorders**

Therapeutic nutrition for managing Autism Spectrum Disorders (ASD) shows promising results in treating autism. The effects of nutrient-rich diets on ASD symptoms, revealing improvements in behaviour and communication (Adams et al., 2019). Children with Autism Spectrum Disorder (ASD) often have parents who are more attentive to their dietary needs. However, studies indicate inadequate intake of essential nutrients, including vitamins A, B1, B12, D, and folate, as well as calcium, magnesium, potassium, iodine, omega-3, omega-6, linoleic acid, and α-linolenic acid in children with ASD (Indika et al., 2023). Notably, deficiencies in vitamin D and calcium affect bone health, and vitamin B12 deficiency is common in children with ASD (Schiavi et al., 2022). Metabolic and nutritional differences between children with ASD and healthy children include elevated biomarkers of oxidative stress and vitamin deficiencies, with compromised energy transport, suffusion, and detoxification capacity, some of which correlate with ASD severity. Age-related trends show increased risk of overweight and obesity in children aged 2-5 with ASD, while those aged 5-11 are more likely to be underweight. It is crucial to address these nutritional disparities to support the overall health of children with ASD (Essa &Qoronfleh, 2020).

2.1. Macronutrients (Carbohydrate, protein, fat)

Macronutrients, such as carbohydrates, proteins, and fats, are fundamental components of the diet and have vital implications in the context of Autism Spectrum Disorder (ASD) treatment and management. The intake of these macronutrients in children with ASD has been a subject of investigation, revealing variations in dietary patterns (Qishawi et al., 2023). While some studies report no significant differences in macronutrient intake between children with ASD and their typically developing counterparts, others

suggest that children with ASD may have insufficient energy, carbohydrate, protein, and fat intake. These variations could be attributed to factors like selective nutritional behaviours and intestinal permeability commonly observed in individuals with ASD (Adams et al., 2019; Indika et al., 2023). Protein is also necessary to regulate several channels at cellular level. Difficulties and alteration among the protein channels can lead several psychiatric diseased conditions as described in the table no. 1 later.

Proteins are crucial for growth and development, and the source of protein, whether from vegetables or animals, requires further investigation. Camel milk, rich in protein and micronutrients, has shown potential benefits in improving ASD symptoms (Kandeel & El-Deeb, 2022). A study involving camel milk supplementation demonstrated significant improvements in behavioural assessments among children with ASD (Alam et al., 2023; Essa & Qoronfleh., 2020). In the case of fats, omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have garnered attention due to their potential role in mitigating ASD symptoms (Essa & Qoronfleh., 2020). Studies have reported lower levels of these essential fatty acids in children with ASD, and supplementation has shown promise in improving behaviour. Macronutrients play pivotal roles in the nutritional status and well-being of individuals with ASD. Adequate intake and balanced sources of carbohydrates, proteins, and fats are essential for overall health. The potential benefits of camel milk and omega-3 supplementation offer intriguing avenues for further exploration, but comprehensive studies are required to clarify their roles in personalised nutrition strategies for individuals with ASD (Schiavi et al., 2022; Nolan et al., 2022).

Table 1. Voltage-regulated Calcium channels and calcium channel subunits that are implicated in Autistic children [Source: Essa & Qoronfleh., 2020]

Sl. No.	Protein	Normal functions	Associated diseases
2.	CACNA2D3 (Voltage-regulated calcium channel, alpha 2/delta 3 subunit)	Accessory calcium channel subunit; regulates entry of Ca2+ into excitable cells	ASD
3.	CACNA2D4 (Voltage-regulated calcium channel, alpha 2/delta 4 subunit)	Accessory calcium channel subunit; regulates entry of Ca2+ into excitable cells	Gene deletion along with CACNAIC leads to ASD
4.	CACNAIC (Voltage-regulated L-type calcium channel, alpha IC subunit)	Regulates entry of Ca ions into excitable cells: muscle contraction, hormone/ neurotransmitter release, gene expression, cell cycle	Timothy syndrome, ASD, psychiatric diseases

5.	CACNAID (Voltage-regulated calcium channel, alpha ID subunit)	High-voltage activated, long-lasting Sinoatrial node calcium activity	Sinoatrial syndrome, ASD, psychiatric diseases
6.	CACNAIE (Voltage-regulated R-type calcium channel, alpha IE subunit0	High-voltage activated, rapidly inactivating	ASD, psychiatric diseases
7.	CACNAIF (Voltage-regulated L-type calcium channel, alpha IF subunit)	Regulates entry of Ca2+ into excitable cells: muscle contraction, hormone/ congenital neurotransmitter release, gene expression, cell cycle	ASD and X-linked stationary night blindness
8.	CACNAIG (Voltage-regulated T-type calcium channel, alpha 1G subunit)	Regulates entry of Ca into excitable cells: muscle contraction, hormone/ neurotransmitter release, gene expression, cell cycle	ASD; intellectual disability; juvenile myoclonic epilepsy
9.	CACNAIH (Voltage-regulated T-type calcium channel, alpha 1H subunit)	Regulates neuronal and cardiac pacemaker activity	Familial autism; childhood absence epilepsy
10.	CACNAII (Voltage-regulated T-type calcium channel, alpha 11 subunit)	Characterized by a slower activation and inactivation compared to other ASD T-channels	Possibly implicated ASD
11.	CACNB2 (Accessory calcium channel beta-2 subunit)	Contributes to the function of calcium channels. Modulates voltage dependence of activation and inactivation and controls trafficking of the calcium channel family	ASD, psychiatric diseases

2.2. Micronutrients

Micronutrients, such as vitamins and minerals, play essential roles in various biological processes, including brain development and function. Research has examined the influence of these micronutrients on ASD or Autism Spectrum Disorder (Essa & Qoronfleh, 2020). Here are some key micronutrients and their potential influences on ASD -

- Vitamin D: Vitamin D is crucial for bone health, immune function, and neurodevelopment. Low maternal vitamin D levels during pregnancy have been associated with an increased risk of ASD in offspring. Furthermore, vitamin D supplementation has shown potential benefits in improving ASD symptoms (Vinkhuyzen et al., 2018).
- Folate (Vitamin B9): Folate is essential for DNA synthesis and methylation processes in the brain. Studies have suggested that maternal folate intake may influence the risk of ASD in offspring (Essa & Qoronfleh, 2020), with inadequate folate intake during pregnancy associated with a higher risk

(Ahmad et al., 2022; Sachdeva et al., 2022).

- Vitamin B12: Vitamin B12 plays a role in neurological function, and deficiencies have been linked to developmental delays and cognitive impairments. Some research suggests that vitamin B12 deficiency may be more prevalent in children with ASD (Sachdeva et al., 2022).
- Omega-3 Fatty Acids: Omega-3 fatty acids, found in fish oil, have anti-inflammatory properties and support brain health. Supplementation with omega-3 fatty acids has been investigated for its potential in improving social and communication skills in individuals with ASD (Essa & Qoronfleh, 2020).
- Zinc: Zinc is essential for various physiological processes, including brain function. Studies have reported differences in zinc levels in individuals with ASD. Zinc supplementation has been explored as a potential intervention for improving certain ASD symptoms (Feng et al., 2023).
- Iron: Iron is critical for cognitive development and oxygen transport. Some research has indicated differences in iron metabolism in individuals with ASD. Iron supplementation has been considered to address deficiencies in children with ASD (De Giacomo et al., 2022).
- Magnesium: Magnesium plays a role in neurotransmitter function and may influence behaviour. Some studies have suggested that magnesium supplementation may help reduce hyperactivity and improve attention in children with ASD (Sachdeva et al., 2022; Alam et al., 2023).
- Selenium: Selenium is an antioxidant mineral that supports brain health. Research has examined selenium levels in individuals with ASD, although findings have been mixed (Triana et al., 2023).

2.3. Functional foods - for supplementation

Recent research in the field of Autism Spectrum Disorder (ASD) has underscored the potential of supplementation and various functional foods as interventions to ameliorate ASD symptoms (Alam et al., 2023). The potential therapeutic implications of various functional foods rich in specific bioactive compounds. Plant based foods contain phytochemicals and those polyphenolic compounds act as antioxidant and anti-inflammatory substances, and may have a positive impact on ASD-related behaviours by modulating neuroinflammatory responses (Essa & Qoronfleh, 2020). On the other hand,addressing the need for safe and effective medications in autism management has led to the exploration of

plant-based natural products with therapeutic potential. When used alongside conventional rehabilitation and training programmes, these natural compounds can ameliorate core symptoms with minimal side effects (Adam et al., 2022).

- Luteolin's Neuroinflammatory Control: Luteolin, a natural flavonoid, plays a vital role in autism management by regulating neuroinflammation (Zhang et al., 2023). It reduces the activation of microglia, immune cells in the central nervous system, which is associated with autism. By inhibiting excess production of glial fibrillary acidic protein (GFAP) and phosphorylated transcription factor STAT3, luteolin helps mitigate inflammation (Savino et al., 2023). This mechanism is crucial as autism often involves neuroinflammation. Luteolin's ability to reduce inflammatory markers and improve social behaviours in autistic individuals makes it an important candidate for autism treatment (Essa & Qoronfleh, 2020).
- Green Tea Extract's Antioxidant Défense: Green tea extract, rich in antioxidants, contributes to autism treatment by countering oxidative stress. Oxidative stress is a known factor in autism development, characterised by increased lipid peroxidation and altered antioxidant enzyme activity. The extract's antioxidants help protect cells from damage, reducing the risk of neurodevelopmental complications (Savino et al., 2023). By addressing oxidative stress, green tea extract offers a valuable avenue for managing autism, with potential benefits for overall health (Essa & Qoronfleh, 2020; Saadat et al., 2023).
- Piperine's Neural Protection: Piperine, a major alkaloid found in black and long pepper, is gaining attention in autism treatment due to its neural protection mechanisms. It activates ion channels in nerve cells, protecting against cell damage from excessive glutamate release. This action helps maintain neuronal viability and function. Piperine also exhibits antioxidative effects and enhances memory and cognition. Its ability to mitigate oxidative stress, improve memory, and offer neuroprotection positions piperine as a valuable candidate for addressing autism's neural aspects (Essa & Qoronfleh, 2020).
- Curcumin's Multifaceted Action: Curcumin, the primary curcuminoid in turmeric, offers a multifaceted approach to autism management. It has anti-inflammatory properties and can cross the blood-brain barrier, making it effective in reducing neuroinflammation. Curcumin also regulates oxidative stress, mitochondrial function, and protein aggregation, all

factors associated with autism (Mushtaq et al., 2023). Moreover, it enhances synaptic plasticity, potentially improving cognitive function. While clinical studies are ongoing, curcumin's diverse mechanisms and potential to reduce inflammatory markers make it an important component in exploring autism treatments (Essa & Qoronfleh, 2020).

- Cannabinoids' Immune Modulation: Cannabinoids like Cannabidiol (CBD) and Cannabidivarin (CBDV) have shown promise in autism treatment by modulating the immune system and providing antioxidant defence. They regulate immune responses, suppress inflammatory processes, and offer neuroprotection with minimal side effects. In autism, where immune dysfunction is often observed, these cannabinoids hold potential for improving symptoms and enhancing overall well-being. Their mechanisms offer an alternative to traditional medications with fewer adverse effects (de Camargo et al., 2022; Essa & Qoronfleh, 2020).
- Ginkgo biloba Extract's Neuroprotection: Ginkgo biloba extract, particularly EGb 761, plays a vital role in autism treatment by offering neuroprotection. Its flavone glycosides and terpene lactones protect against neurodegenerative conditions (Singh et al., 2019). Observational studies have shown improvements in behaviour and symptoms in autistic individuals. By reducing behavioural irritability, hyperactivity, and enhancing cognitive function, this extract offers potential as an adjunct to conventional treatments like risperidone. Although more research is needed, its neuroprotective mechanisms make it a promising candidate for autism management (Essa & Qoronfleh, 2020).
- Probiotics for Autism Spectrum Disorders: Probiotics, live microorganisms that confer health benefits when consumed in adequate amounts, have garnered interest for their potential to ameliorate symptoms associated with autism spectrum disorders (ASD). Mechanistically, probiotics exert their influence by modulating the gut microbiota composition (elaborating the specific stain of probiotic and regulated outcomes in the table no. 2) and promoting a balanced microbial community (Alam et al., 2023). Disruptions in the gut microbiome, often observed in individuals with ASD, are believed to contribute to gastrointestinal symptoms and potentially impact behavioural and cognitive aspects of the condition. Probiotics can help restore gut microbiota equilibrium, reduce inflammation, and improve gut barrier

function. This restoration of gut health may contribute to the management of ASD symptoms, particularly those linked to gastrointestinal distress (He et al., 2023).

Table 2.: Evidence based study outcomes from several tested probiotic stains and documentation for their observed impact on ASD [Source: **Alam et al., 2023**].

Sl. No.	Probiotic strains	Outcomes
1.	*Bacteriocides fragilis*	Improvement in social behaviour and cognition deficits in children with FXS
2.	*Bifidobacteria (B. longum, B.infantis), lactobacilli (L. acidophilus,L. delbrueckii subsp. L. bulgaris and L. plantarum) and Streptococcus salivaris subsp. thermophilus*	Reduction of gastrointestinal disturbances and neurobehavioral symptoms in ASD
3.	Bifidobacteria and Lactobacilli	Improvement in ASD-related behaviours by reducing glutamate with increased glutamate ex-citotoxicity
4.	Bifidobacterium infantis in combination with a prebiotic Bovine Colostrum Product (BCP)	Decrease in the frequency of specific gastrointestinal symptoms. Diminished occurrence of atypical behaviours. Lower levels of IL-13 and TNF-alpha.
5.	General probiotics	Better school performance and dietary choices.
6.	*Lactobacillus acidophilus*	Reduced D/L-arabinitol linked to carb and mineral absorption issues in ASD.
7.	*Lactobacillus acidophilus, Lactobacillus rhamnosus and Bifidobacterium*	Probiotics enhanced ASD behaviours and GI symptoms in kids.
8.	*Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterialongum*	ASD severity improved with significant gains in language, communication, sociability, sensory or cognition, and overall health and behaviour; along with improved GI issues.
9.	Lactobacillus plantarum WCFS1	Enhanced anti-social behaviour, anxiety, and communication issues in ASD kids.
10.	*Lactobacillus reuteri*	Reduced antisocial behaviour in male Shank3 KO and less repetitive behaviour in both male and female Shank3 mouse model.
11.	Probiotic and oxytocin combination therapy	Enhanced key ASD behaviours, decreased gut flora issues.

12.	*Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. bulgaricus*	Electroencephalogram or EEG shows improved brain activity balance in ASD kids, along with changes in serum and fecal markers like lipopolysaccharide, leptin, TNF, IL-6, PAI-1, and calprotectin.

- **Prebiotics for Autism Spectrum Disorders:** Prebiotics, non-digestible dietary compounds that promote the growth and activity of beneficial gut bacteria, offer another avenue for managing symptoms in autism spectrum disorders (ASD). Prebiotics function by providing nourishment for specific gut microbes, fostering their proliferation and metabolic activity. This can enhance the production of short-chain fatty acids (SCFAs), which are known to have anti-inflammatory properties and may influence brain function. Given the bidirectional gut- brain axis, modulating the gut microbiota through prebiotic supplementation may indirectly impact behavioural and cognitive aspects of ASD (Song et al., 2022). The prebiotic intervention increased SCFA production and mitigated repetitive behaviours in an ASD mouse model. Prebiotic therapy holds potential as a complementary approach to address gastrointestinal and behavioural aspects of ASD, but further investigation is needed to refine its application and efficacy (Alam et al., 2023).

3. **Dietary interventions - recent treatments for autistic children**

Behavioural factors, parents interference lead to nutritional challenges in children with Autism Spectrum Disorder (ASD), that encompass a range of gastrointestinal issues, food sensitivities, and nutrient deficiencies in the autistic children (Alam et al., 2023). These challenges can include constipation, diarrhoea, medication and nutritional adaptation difficulties, allergies, and eating behaviours etc (Wu et al., 2023). Deficiencies in essential minerals like zinc, iron, calcium, and vitamins such as methylcobalamin and niacin are common in individuals with ASD, partly due to gastrointestinal inflammation impacting nutrient absorption. Probiotic imbalances can also affect vitamin synthesis. Many ASD patients exhibit deficiencies in vitamins A, thiamine, pantothenic acid, and essential amino acids, among others (Akhalil et al., 2023). Different types of evidence based nutritional approaches are described below in table no. 3

Table 3.: Representation of different types of evidence based Nutritional Interventions in terms of managing symptoms of autism disorder and their observed results on autistic children [Source: Alam et al., 2023].

Sl. No.	Nutritional interventions	Outcomes
1.	Alpha-tocopherol	Diminished oxidative stress, behaviour issues, and learning deficits in FXS mice.
2.	Breast milk	Reduced incidence of autism in FXS
3.	Folinic acid	Enhanced social behaviour and cognitive deficits in kids with ASD.
4.	Ketogenic diet	Enhanced epilepsy, repetitive behavior, social skills, and learning in ASD mice. Improved social exploration and interactions in rodents. Also, reduced hyperactivity and seizures in the FXS mouse model.
5.	Lithium	Mood stabilizers in ASD reduced hyperactivity, antisocial behavior, and cognitive deficits in FXS mice.
6.	Omega-3 fatty acids	Enhanced social traits in ASD and FXS rats, plus improved emotional memory and reduced neuro-inflammation in FXS mice.
7.	Soy vs. casein-based infant formulas	Increased seizures, autism, GI problems and allergies in ASD and FXS populations with soy
8.	Soy vs. casein-based rodent diet	More seizures and weight gain from soy.
9.	Specific carbohydrate diet	Enhanced GI symptoms, behaviour, and nutrition in a child with FXS and ASD.
10.	Vitamin B12	Lowered metabolic issues, irritability, and aggression in kids with ASD.
11.	Vitamin B6+ magnesium (Mg)	Improved core symptoms of ASD
12.	Vitamin D and Omega-3 fatty acids	Lowered hyperactivity and irritability in autistic children.

3.1. Gluten-Free Diet (GFD):

The Gluten-Free Diet (GFD) is a dietary approach that involves the elimination of foods containing gluten, a protein found in wheat, barley, and rye. This diet has gained attention in the management of Autism Spectrum Disorder (ASD) based on the belief that some individuals with ASD may

have sensitivities or allergies to gluten (Saleem Khasawneh & Ayasrah, 2023). The rationale behind the GFD is rooted in the idea that gluten consumption can lead to gastrointestinal discomfort and exacerbate behavioural and communication challenges in individuals with ASD. Proponents of this diet aim to alleviate digestive issues and potentially improve ASD symptoms by removing gluten from the diet (Quan et al., 2020).

3.2. Casein-Free Diet (CFD):

The Casein-Free Diet (CFD) is a dietary intervention that involves the elimination of casein, a protein found in milk and dairy products, from an individual's diet. This approach has been explored in the context of Autism Spectrum Disorder (ASD) based on the hypothesis that some individuals with ASD may have sensitivities or allergies to casein (Quan et al., 2020), which could contribute to gastrointestinal discomfort and exacerbate behavioural and communication challenges (Hakim et al., 2023). Proponents of the CFD aim to alleviate these issues and potentially improve the overall well-being of individuals with ASD by removing casein-containing foods from their diets (Saleem Khasawneh & Ayasrah, 2023).

3.3. Gluten-Free Casein-Free (GFCF) Diet:

The Casein-Free Gluten-Free Diet (CFGFD) is a dietary approach used in the management of Autism Spectrum Disorder (ASD), combining the elimination of two specific proteins: casein and gluten (Barnhill et al., 2020; Hakim et al., 2023). Casein is found in dairy products, while gluten is present in wheat, barley, and rye. The rationale behind this diet is twofold. Firstly, it is based on the belief that some individuals with ASD may have sensitivities or allergies to both casein and gluten, leading to gastrointestinal discomfort and exacerbating behavioural and communication challenges. Secondly, proponents of the CFGFD suggest that removing these proteins from the diet can reduce inflammation and promote overall well-being in individuals with ASD (Obih et al., 2016; Barnhill et al., 2020).

3.4. Ketogenic Diet:

The ketogenic diet is a high-fat, low-carbohydrate diet. Some studies suggest that it may improve behaviours and cognitive function in individuals with ASD, possibly by altering brain metabolism and reducing oxidative stress (Akhalil et al., 2023). Recent studies have shed light on the potential link between a ketogenic diet and its impact on autism spectrum disorder (ASD). The ketogenic diet, characterised by its high-fat and low-carbohydrate composition, has garnered attention for its effects on neurological conditions. Study by El-Rashidy et al. (2021) demonstrated a modified ketogenic diet led to significant improvements in core autism symptoms, social behaviours, and cognitive functions

in children with ASD (El-Rashidy et al., 2021). Recent studies are indicating that the ketogenic diet might influence neurotransmitter balance and mitochondrial function, offering a potential mechanism for its positive effects on neurodevelopmental disorders like autism (Lim et al., 2022).

3.5. Special Carbohydrate Diet (SCD): This dietrestricts complex carbohydrates. It is hypothesised to improve gut health and reduce inflammation, which may benefit individuals with ASD. However, more research is needed to establish its efficacy. This dietary approach is explored in Autism Spectrum Disorder (ASD) management, focusing on carbohydrates' impact on gastrointestinal health (Tosun & Mendes, 2023). This diet restricts complex carbohydrates and disaccharides to alleviate gastrointestinal issues and potentially ameliorate behavioural and ASD-related symptoms. It is based on the premise that some individuals with ASD may have gut microbiota imbalances, making it challenging to digest specific carbohydrates. By reducing complex carbohydrate intake, proponents aim to promote gut health, reduce inflammation, and positively influence behaviour. However, its efficacy varies among individuals, and strict adherence requires careful meal planning (Alam et al., 2023).

3.6. Feingold Diet:

The Feingold Diet, proposed by Dr. Benjamin Feingold, involves eliminating artificial additives, synthetic colourings, and salicylates from the diet of individuals with autism spectrum disorder (ASD). This dietary intervention aims to potentially alleviate hyperactivity, enhance attention span, and reduce behavioural issues in ASD (Akhalil et al., 2023).

3.7. Candida diet or Body Ecology Diet: The Body Ecology Diet has been explored as a potential intervention for autism spectrum disorder (ASD), although its efficacy remains a subject of scientific investigation. This dietary approach revolves around the premise that yeast overgrowth, particularly Candida albicans (Herman& Herman, 2022) in the gut can exacerbate ASD symptoms. The mechanism proposed is that an overgrowth of Candida may lead to increased gut permeability, allowing harmful substances to enter the bloodstream, potentially triggering immune responses and neurological symptoms associated with ASD. Proponents argue that by eliminating sugar, processed foods, and certain carbohydrates, this diet may reduce Candida overgrowth and improve gut health, thereby alleviating ASD symptoms. This diet mainly aims to control Candida overgrowth and promote gut health (Retnaningtyas et al., 2022; Essa & Qoronfleh., 2020).

3.8. Elimination Diets for Allergies: Some individuals with ASD have food allergies or sensitivities. Identifying and eliminating allergenic foods can improve symptoms in these cases. Allergy testing and dietary modifications should be done under medical supervision (Akhalil et al., 2023).

3.9. Mediterranean Diet:

The Mediterranean diet, rich in fruits, vegetables, whole grains, and healthy fats, has gained attention for its potential cognitive and neuroprotective benefits. Recent studies have explored its impact on children with ASD, highlighting potential positive effects on behaviour, communication, and social interactions (Essa & Qoronfleh, 2020). Although research in this area is evolving, the diet's mechanism of potential benefit lies in its anti-inflammatory and neuroprotective properties. The Mediterranean diet is rich in antioxidants and omega-3 fatty acids, which may help mitigate inflammation and oxidative stress—factors often associated with ASD. Additionally, its emphasis on a diverse range of nutrients could support overall health and potentially alleviate some ASD-related symptoms (Banerjee, 2023; Che et al., 2023).

3.10. Low FODMAP Diet:

The Low FODMAP Diet reduces the intake of fermentable carbohydrates known as FODMAPs, which include foods like certain grains, legumes, fruits, and dairy products. These carbohydrates are poorly absorbed in the small intestine and can lead to gastrointestinal discomfort, bloating, and altered gut microbiota composition. By minimising FODMAP consumption, the diet aims to alleviate gut-related symptoms and decrease the fermentation of carbohydrates in the gut (Bertuccioli et al., 2022). Gastrointestinal issues, such as abdominal pain and irregular bowel movements, are commonly reported in individuals with ASD. The Low FODMAP Diet may be beneficial in managing these gastrointestinal symptoms, potentially leading to increased comfort and improved overall well-being in individuals with ASD (Akhalil et al., 2023).

3.11. Low Oxalate Diet:

The Low Oxalate Diet restricts the intake of dietary oxalates, which are compounds found in various foods, particularly in certain vegetables, fruits, nuts, and grains. High oxalate levels in the diet can contribute to the formation of kidney stones and may also have implications for gut health. Kidney stones and gastrointestinal problems are not uncommon in individuals with ASD. By following a Low Oxalate Diet, the risk of kidney stone formation and potential gut-related symptoms related to oxalate intake can be minimised (Essa & Qoronfleh, 2020).

4. Futuristic approaches - prospects of Diet therapy for ASD

Emerging nutrition-based approaches for Autism Spectrum Disorder (ASD) treatment hold promise (Essa & Qoronfleh., 2020). Recent studies emphasise personalised strategies such as cofactor treatment to address micronutrient deficiencies associated with ASD. Nutrigenomics tailors' diets to an individual's genetic and metabolic profile. Phytochemicals exhibit neuroprotective potential, countering oxidative stress and inflammation implicated in ASD. Antioxidant-rich diets (Essa & Qoronfleh, 2020) and exercise (Karatay & Hulusi, 2023; Helsel et al., 2023), enhance cognitive function. Additionally, marine ascidians' bioactive compounds may modulate epigenetic mechanisms, addressing ASD-related gene dysregulation (Zhu et al., 2021; Dufault et al., 2023). These multifaceted approaches offer promise in improving the lives of individuals with ASD (Mousavinejad et al., 2018).

4.1. Altered Gut-Brain Axis and Microbiota

Alterations in gut microbiota composition have been observed in individuals with ASD. Recent research has investigated the potential link between gut dysbiosis and ASD symptoms, paving the way for studies exploring dietary interventions aimed at modulating the gut microbiome (Mehra et al., 2023). Studies have examined the effects of probiotics and prebiotics on gut microbiota diversity and behaviour in individuals with ASD. Recent research highlights the potential of these interventions in improving gastrointestinal symptoms and behaviour (He et al., 2023).

4.2. Nutrigenomics - Insight of gene and nutritional modifications

SHANK3 or ProSAP2 (SH3 and multiple ankyrin repeat domains 3) is a major gene involved in autism spectrum disorders. SHANK3 is a scaffolding protein that plays a crucial role in nerve cells such as cell-to-cell communication (Hamsa et al., 2023). They are also required for the formation and maturation of dendritic spines, which are involved in the transmission of nerve impulses. As abnormal SHANK3 was associated with cognitive deficits, including autism spectrum disorders, mutations in the SHANK3 gene cause autism spectrum disorders. SHANK3 also binds to neuroligins, which are essential for the formation of synapses. Autism spectrum disorder and cognitive disorders are also caused by mutations in the X-linked neuroligin 3 (NLGN3) and NLGN4 genes. Numerous studies have demonstrated that mutations in synaptic genes such as NLGN3 and NLGN4 also cause autism spectrum disorders (Moustafa et al., 2022). Supplemental zinc is advantageous against autism spectrum disorders. In addition to reversing the altered synaptic function, an increase in zinc intake reverses the effect of Autism spectrum disorder-related

behaviours. Consequently, foods containing zinc are effective in the treatment of autism spectrum disorders. Administration of proline rich foods such as broccoli, bell pepper, and soy protein also reduce autism spectrum disorder symptoms (Hamsa et al., 2023).

4.3. Epigenetic and Nutrition - Interplay of two vital factors

Epigenetics, a field of study examining heritable modifications to gene expression without altering DNA sequences, has emerged as a crucial player in understanding Autism Spectrum Disorder (ASD). Recent study conducted by Zhubi et al. (2021) has underscored the significance of DNA methylation patterns in ASD. Epigenetic modifications, like DNA methylation, histone alterations, and microRNA expression, can influence the expression of genes critical to neurodevelopment and synaptic function. Differential in DNA methylation in genes linked to synaptic transmission and neuronal signalling, suggesting their potential involvement in ASD pathogenesis (Zhubi et al., 2021). Furthermore, the interplay between environmental factors and epigenetic changes and those prenatal exposures to toxins or stress can influence the epigenome, potentially increasing susceptibility to ASD (Nguyen et al., 2020). This recognition of environmental influences on epigenetics emphasises the multifactorial nature of ASD aetiology (Bhandari et al., 2020).

By targeting specific epigenetic marks associated with gene dysregulation, researchers aim to develop novel interventions tailored to individuals with ASD. This approach holds promise for reversing or mitigating the impact of epigenetic alterations on gene expression and neural development (Zhu et al., 2021). Moreover, epigenetic markers may serve as valuable biomarkers for early diagnosis and the stratification of ASD subtypes, enabling personalised treatment approaches that consider the unique epigenetic profiles of individuals with ASD (Dufault et al., 2023). In sum, epigenetics offers a promising avenue for advancing our understanding of ASD and developing targeted interventions that could significantly improve the lives of those affected by this complex disorder. Epigenetic influences of food and nutrition on Autism Spectrum Disorder (ASD) involve the intricate interplay between an individual's dietary choices and the modification of gene expression through epigenetic mechanisms (Bastaki et al., 2020). One critical epigenetic process in this context is DNA methylation, which involves the addition of methyl groups to DNA molecules, potentially altering gene activity without changing the underlying DNA sequence. Research has shown that certain nutrients and dietary components can impact DNA methylation patterns,

which may be relevant to ASD. For example, folate, a B-vitamin found in various foods, serves as a methyl donor and plays a crucial role in DNA methylation. Studies have suggested that maternal folate intake during pregnancy can influence the epigenetic regulation of genes associated with neural development and potentially affect ASD risk in offspring (Zhu et al., 2021; Dufault et al., 2023). Additionally, dietary factors such as choline, betaine, and other methyl donors present in foods can also contribute to epigenetic modifications. For instance, they may influence the expression of genes related to synaptic plasticity, neurotransmitter regulation, and immune function—processes that are perturbed in individuals with ASD (Bastaki et al., 2020). Furthermore, omega-3 fatty acids, found in fatty fish and certain plant-based sources, have been investigated for their potential epigenetic effects in ASD (Bastaki et al., 2020). These essential fatty acids may modulate gene expression through histone modifications, another critical epigenetic mechanism, impacting neurodevelopment and inflammation (Zhu et al., 2021; Dufault et al., 2023).

4.4. Coenzyme Q10 treatment

Coenzyme Q10 (CoQ10), a crucial cellular energy co-factor and antioxidant, has garnered interest in Autism Spectrum Disorder (ASD) due to its role in mitochondrial function. Some studies have indicated potential CoQ10 deficiencies in individuals with ASD, linking it to mitochondrial dysfunction, which is implicated in the disorder (Mousavinejad et al., 2018). Preliminary research has explored CoQ10 supplementation for ASD, with mixed results; some individuals exhibited improvements in behaviour and communication. However, given the complex nature of ASD, CoQ10 should be considered as part of a broader, individualised approach to intervention, and further research is needed to clarify its specific role (Essa &Qoronfleh., 2020).

4.5. Physical activity for managing comorbid risk factors

Individuals with ASD often have early motor skill deficiencies, impacting activities like walking, swimming, and sports. Adolescents with ASD may struggle with coordination, balance, and social limitations, leading to reduced physical activity. These challenges, combined with sedentary behaviour and irregular eating, increase the risk of health problems, including a 49% higher risk of obesity compared to typically developing adolescents (Karatay & Hulusi, 2023; Helsel et al., 2023). Obesity in individuals with autism spectrum disorder (ASD) is associated with various health and psychosocial issues, including diabetes, cardiovascular risks, and depression. Physical activity plays a crucial role in mitigating ASD-related challenges, improving social, cognitive, and motor

skills, as well as academic performance. It enhances balance, coordination, speed, flexibility, and helps prevent obesity-related health problems by promoting metabolic health and enhancing overall well-being (Helsel et al., 2023)

4.6. Marine ascidians - Bioactive compounds to treat ASD

Marine ascidians, a unique group of marine invertebrates, have emerged as a subject of compelling scientific inquiry with the potential to revolutionise the future treatment landscape of Autism Spectrum Disorders (ASD). These compounds, including alkaloids and peptides, have demonstrated the ability to influence key

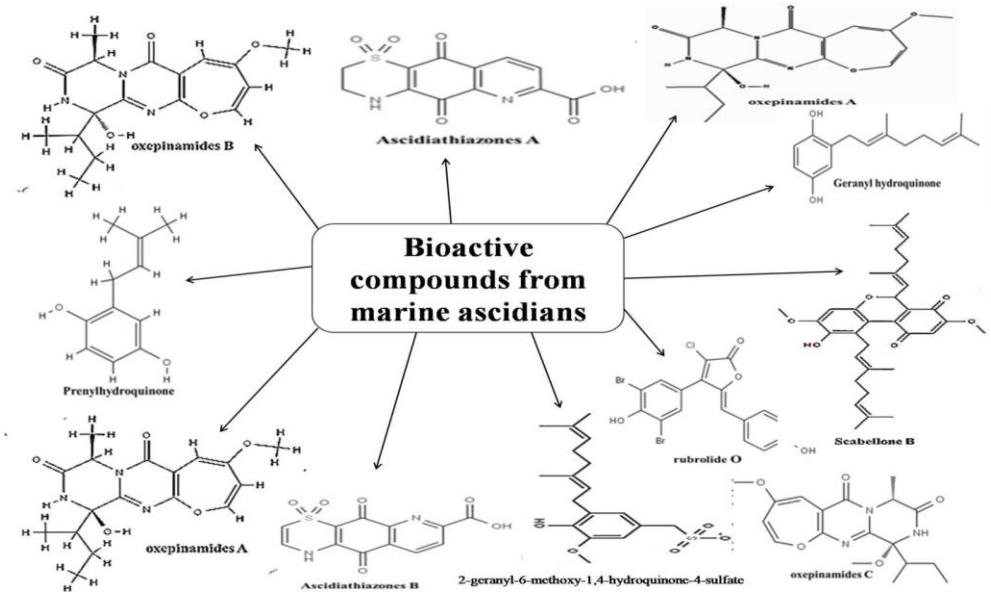

Figure 3. Representation of chemical structures of important marine ascidians derived bioactive compounds for effective management of Autism Spectrum Disorder or ASD (Source: Essa & Qoronfleh, 2020)

epigenetic processes such as DNA methylation and histone modifications. Here, in figure no. 3, some of the bioactive compounds from marine ascidians and their chemical structures are provided as well. The potential of marine ascidian-derived compounds to reverse aberrant DNA methylation patterns associated with ASD-linked genes, providing critical evidence of their capacity to modulate epigenetic mechanisms vital for neurodevelopment (Essa & Qoronfleh., 2020; Venkatesan et al., 2020). By targeting specific epigenetic marks linked to ASD-related gene dysregulation, these marine-derived compounds may offer novel treatment strategies capable of restoring normal gene expression patterns and ameliorating the neurodevelopmental challenges synonymous with ASD. As the scientific exploration of marine ascidians advances, it holds the promise of ushering in a new era

of therapeutic options that could profoundly enhance the lives of individuals on the autism spectrum (Venkatesan et al., 2020).

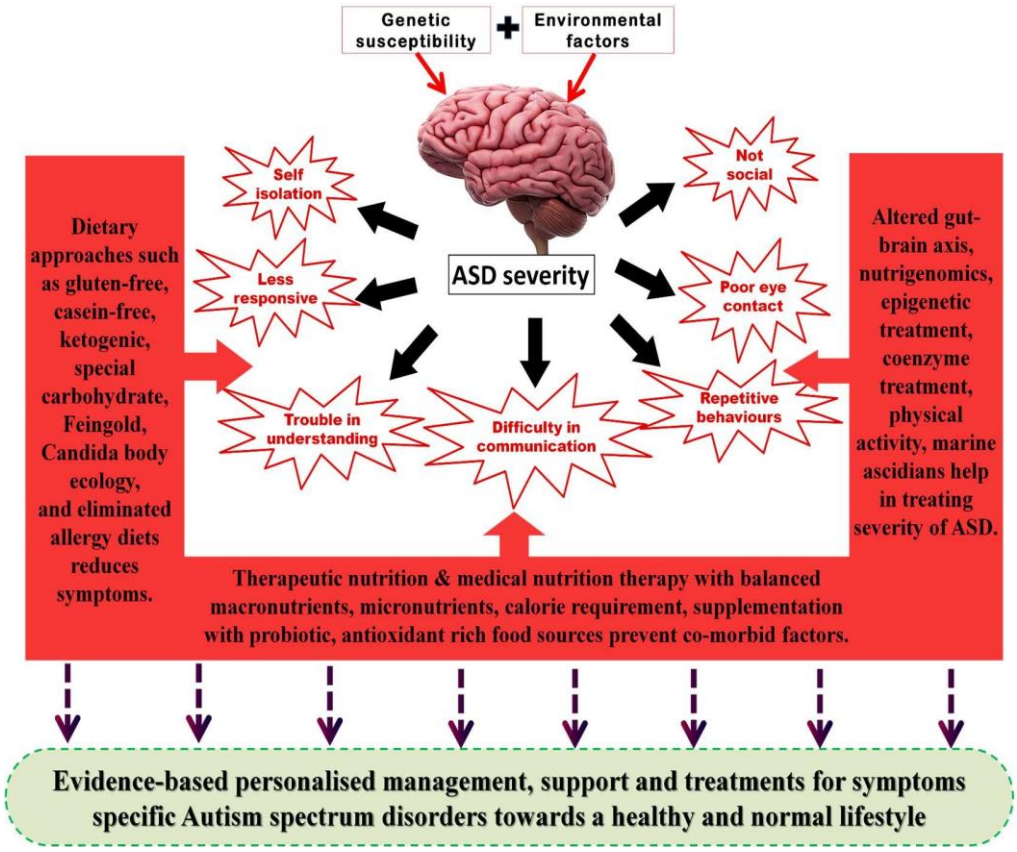

Figure 4. Schematic representation of therapeutic dietary and nutritional approaches against Autism Spectrum Disorder or ASD symptoms.

(The onset of the development of ASD regulated by different kinds of complex combinations of different risk factors like genetic or heritability, environmental contributors etc. This severity of autism like neurodevelopmental disorders and associated behaviours can be mitigated by evidence-based therapeutic nutrition and individualised approaches for betterment of the lifestyle management of autistic children.)

5. Conclusion

The heterogeneity of Autism Spectrum Disorder (ASD) demands individualised nutritional approaches for optimal outcomes. In summary, therapeutic nutrition presents a promising avenue for improving the management of Autism Spectrum Disorder (ASD). Recent research highlights the potential benefits of tailored nutritional interventions, addressing genetic, metabolic, and neurodevelopmental aspects of ASD. Dietary approaches are promisingly alleviating the symptoms and enhancing overall well-being, micronutrient supplementation, and considerations of gut-brain interactions, individual needs need to be addressed (as mentioned in figure no. 4).

A multidisciplinary, evidence-based approach, along with larger, well-designed trials, is crucial to establish stronger evidence and provide definitive recommendations for optimising therapeutic nutrition strategies for individuals with ASD. This evolving field holds the potential to significantly enhance the lives of individuals on the autism spectrum.

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