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REVIEW ARTICLE

Alimentary Management via Food Supplements for Young Children with Autism: A Review

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This is a revised and updated version of an article originally published in the discontinued Early Years Research (EYR) journal, without a Digital Object Identifier (DOI). EYR were published by the same scholarly association of The Asian Educational Therapist (AET). As part of the journal's transition to a formal digital editorial management system in 2025, it has now been digitally archived by AET with a new DOI for better preservation, discoverability and citation tracking. This article underwent a second peer review to ensure its content reflects current and contemporary practice in the field, with revisions updated by the authors. Readers are advised to cite the new version with the DOI.
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ABSTRACT

The primary traits of autism spectrum disorder (ASD) consist of the inability to socialize, communicate and use imagination, and/or manifestations of stereotypical behavior. A disruption in the development of an autistic brain has been widely accepted in explaining the neurodevelopmental causes linked to ASD, but the association between the brain and the condition remains unclear. In this regard, a majority of young children with ASD have been observed to manifest gastrointestinal (GI) problems with a rise in intestinal permeability contributing to the pathogenesis of severity of ASD symptoms. GI abnormalities, given their reported prevalence and correlation with the severity of key ASD related behavioral abnormalities and the development of autism related endophenotypes (e.g., immune dysregulation, hyperserotonemia, and metabolic dysfunction) are of particular interest in this paper. This review discusses the GI pathologies seen in ASD individuals and the association of particular GI conditions with known deficiencies in vitamins and minerals. With emerging evidence for a gut-brain connection in ASD, vitamins and minerals have been widely used in nutritional or dietary treatment for ASD.

Keywords: *Autism Spectrum Disorder, Mineral, Nutritional Deficiency, Treatment, Vitamin*

1. INTRODUCTION

Autism spectrum disorder (ASD) is traditionally defined by the triad of impairments, a term first introduced by Lorna Gladys Wing (b.1928–d.2014) and Judith Gould, describing: (i) impaired communication, (ii) impaired social skills, and (iii) restricted and repetitive patterns of behavior (Wing & Gould, 1979). Garcia (2021) similarly defines the triad as (i) difficulty in communication or language, (ii) social and emotional deficits, and (iii) cognitive inflexibility, reflecting the everyday challenges faced by individuals with ASD. Cashin and team (2009) note that the "actual triad of impairment is static and ubiquitous unlike the variable and fluctuating behavioral manifestation…central to all diagnosis that together makes up the autism spectrum" (p. 189), and further extend it to the behavioral "real triad of impairment."

With the DSM-5, the triad has been replaced by a dyad of impairments: (A) deficits in social communication and interaction, and (B) restrictive, repetitive patterns of behavior, while also recognizing sensory issues (hyper- or hypo-reactivity to stimuli or unusual interests) within the behavioral category (APA, 2013). Additionally, the DSM-5 incorporates criteria from the Behavior Assessment System for Children-Third Edition (BASC-3) (Reynolds & Kamphaus, 2015; Zhou et al., 2022), emphasizing early developmental onset, clinically significant impairment, and differentiation from intellectual disability (Zhou et al., 2022). A severity scale (Levels 1–3) based on the support required for daily functioning is also included (Camulli & Goh, 2018).

Beyond the core diagnostic features of ASD, increasing attention has been directed toward associated physiological and metabolic factors that may influence the manifestation and management of ASD symptoms, particularly among young children. This paper aims to examine the role of nutritional and dietary deficiencies in young children with autism spectrum disorder (ASD), with particular attention to gastrointestinal dysfunction and the potential therapeutic use of vitamin and mineral food supplements in the alimentary management (AM) of ASD-related symptoms. The authors of this paper have defined term "alimentary management" referring to the application of targeted dietary interventions, which include vitamins, minerals, and other nutritional supplements, to support physiological, gastrointestinal, and behavioral functioning in individuals with ASD.

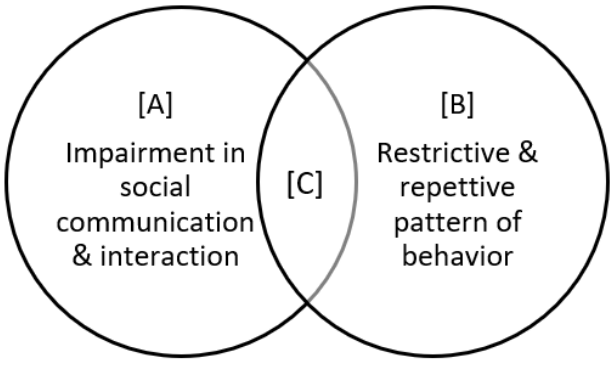


Figure 1. DSM-5 Diagnostic Criteria for ASD

2. CAUSES OF AUTISM SPECTRUM DISORDER (ASD)

Being a heterogeneous condition, ASD is not autism per se but a wide range of varieties or subtypes and specific subtypes. The cause of ASD is not one but many. Nobody knows exactly what causes

autism, whose term was first coined by Paul Eugen Bleuler (b.1857-d.1939) in his 1911 book on schizophrenia (Bleuler, 1911/1950). Bleuler (1911/1950) used autism to describe a signature characteristic of adults with what was then known as dementia praecox (a group of schizophrenias) – "a severe mental illness: a state of insulation from reality so complete that it excluded other human beings" (p. 63).

Much later in 1943, Leo Kanner (b.1894-d.1981) used the term early infantile autism to describe the condition. A year later, Han Asperger (b.1906-d.1980) published a paper on some atypical neurological disorder resembling autism, which was named Asperger Syndrome (Asperger,1944) after him. Still very little was known about ASD until the last few decades when more research has been carried out to study the enigmatic condition. Even today, there is a great deal of ASD that remains unknown, despite recent studies that have identified dozens of genes associated with the condition by studying so-called de novo mutations, i.e., newly arising changes to the genome found in children but not their parents (Alvarez, 2018; also see An et al., 2018, for more detail). To date, most de novo mutations linked to ASD have been found in protein-coding genes, but there are also autism-associated mutations in non-coding regions of the genome that have yet to be identified (Alvarez, 2018). This constitutes the *unknowable unknown* (D'Souza & Renner, 2014) domain that requires "deep knowledge and specific focus of research *that* may limit *our* perspective" (words in italic are the authors' addition; D'Souza & Renner, 2014, p. 39) in the vast field of autism research.

This unknowable unknown in the current knowledge of ASD has been termed as "biological dark matter" (BDM; Ross, 2016), an informal term to describe an unclassified or poorly understood genetic material, which, in turn, may refer to genetic material produced by unclassified microbes. The term BDM can also be extended to include an un-isolated microbe, whose existence can only be inferred from the genetic material that it produces. In fact, some of the genetic material may not come under the three existing domains of life: bacteria, archaea and eukaryote. Hence, there is a possibility of a fourth domain of life may yet to be discovered (Lopez et al., 2015; Wu et al., 2011). However, the current tools that are used to investigate strongly interacting species and folded proteins are still not advanced enough to image, detect and understand the BDM and its working (Ross, 2016). This means better and more advanced investigative tools are urgently needed now and in the future.

Because the disorder is so complex and no two individuals with autism are exactly alike, there are probably many causes for autism. It is also likely that there is not a single cause for autism, but rather that it results from a combination of causes. Researchers (e.g., Amaral, 2017; Jick & Kaye, 2003; Ratajczak, 2011) in the field of autism are still investigating a wide range of possible varied causes of or contributors to ASD. These causes include the following: genetic mutations (Gaugler et al., 2014; Pinto et al., 2010), epigenetic interference (from the environment) (Hallmayer et al., 2011; Landrigan, 2010), hormonal disturbance (Berbel et al., 2014; Xie, 2021), gastrointestinal and/or metabolic dysfunctions (Frye et al., 2015; Madra et al., 2020), nutritional and dietary deficiencies (Herndon et al., 2009; Levy et al., 2007), breakdown in neurological connections (Wass, 2011; Zikopoulos & Barbas, 2013), and anomalous brain development (Chia et al., 2017; Courchesne et al., 2004), and the list can be endless with more new hypotheses being proposed each year.

The main focus of this paper lies in the nutritional and/or dietary deficiencies in young children with ASD. The authors of this paper acknowledge that research on dietary supplements for treating individuals with autism spectrum disorder (ASD) has been limited to small-scale studies (Adams et al., 2022; Marinov et al., 2025; Serafim et al, 2025), involving short-duration randomized controlled trials, open-label trials, case series, and pilot studies, which examine agents, e.g., multivitamins, omega-3 fatty acids, melatonin, probiotics, and targeted micronutrients. Often these studies involve small sample sizes, heterogeneous participant characteristics, variable outcome measures, and inconsistent dosing regimens, making it difficult to draw definitive conclusions about efficacy or safety across the ASD population.

As young children, as well as adults, with ASD may display significant abnormal or impaired metabolic or biochemical processes, vitamins and/or minerals have been recommended and are most widely used nutritional or dietary treatment for ASD. As such, high doses of **vitamin (e.g.,** Vitamin A, Vitamin B6, Vitamin B12, Vitamin C) (Indika et al., 2023) **and/or minerals** (e.g., magnesium and zinc) (Meguid et al., 2024) as well as other food supplements, such as Omega-3 fatty acids and Vitamin E (Businaro, 2022) and dimethylglycine (DMG) (Dhanjal et al., 2022) may have been used to correct for this condition.

3. VITAMINS AND MINERALS FOR AUTISM TREATMENT

Vitamins and minerals are among the most frequently used nutritional interventions in the management of autism spectrum disorder (ASD) in both children and adults (Adams, 2015; Adams & Holloway, 2004; Zhou et al., 2013). Their widespread use reflects a growing interest in biological and metabolic factors that may contribute to ASD symptomatology, particularly those involving oxidative stress, immune dysregulation, and gastrointestinal dysfunction. According to the curriculum of the Autism Case Training (ACT) program (Hyman et al., 2020), vitamin and dietary supplements including probiotics (Sivamaruthi et al., 2020) alongside exercise-based therapies, are commonly applied as complementary approaches to ASD management. However, while these interventions are frequently used in clinical and community settings, the empirical evidence supporting their effectiveness remains heterogeneous and, in many cases, inconclusive (Sathe et al., 2017; Monteiro et al., 2020).

In nutritional or dietary treatment frameworks for children with ASD, a range of vitamins and minerals have been proposed as therapeutic agents based on their presumed roles in neurological functioning, immune regulation, or antioxidant defense (Farrell et al., 2011). Nevertheless, most of these interventions are supported by varying levels of evidence, ranging from small randomized trials to theoretical or biochemical rationales. The following supplements are commonly cited in the literature:

3.1 Carnosine, Vitamin E, and Zinc (Zn)

These compounds are often administered together because of their antioxidant properties and their potential role in supporting the production of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Chez et al., 2002). Antioxidant supplementation has been hypothesized to mitigate oxidative stress, which has been reported to be elevated in individuals with ASD. However, clinical findings remain inconsistent, and excessive intake may lead to adverse effects such as irritability or hyperactivity. More recent systematic reviews have suggested that although antioxidant supplementation shows theoretical promise, large-scale randomized trials are still lacking (Frustaci et al., 2012; Monteiro et al., 2020).

3.2 Dimethylglycine (DMG)

DMG has been proposed as a supplement that may reduce inflammation and enhance immune function. The theoretical basis for its use lies in its role in methylation pathways and metabolic regulation. However, empirical evidence remains limited. Early studies failed to demonstrate consistent improvements in core ASD symptoms, and more recent analyses continue to emphasize the need for well-controlled clinical trials before therapeutic claims can be substantiated (Lin et al., 2016; Sathe et al., 2017).

3.3 Melatonin

Melatonin is one of the more extensively studied supplements in ASD populations and is commonly prescribed to address sleep disturbances, particularly difficulties in sleep onset and maintenance (Malow et al., 2021; Melke et al., 2008; Rossignol & Frye, 2014). Recent meta-analyses indicate that melatonin

supplementation can significantly improve sleep latency and duration in children with ASD, although its effects on core behavioral symptoms remain indirect (Cortesi et al., 2012; Malow et al., 2021).

3.4 Omega-3 Fatty Acids

Omega-3 fatty acids have been investigated for their potential neuroprotective and anti-inflammatory properties. Early studies suggested that these fatty acids might improve cognitive and behavioral functioning in neurodevelopmental disorders (Amminger et al., 2007). However, subsequent randomized controlled trials have produced mixed findings, with several systematic reviews concluding that evidence for significant improvement in core ASD symptoms is weak or inconsistent (Monteiro et al., 2020; Jiang et al., 2023). Moreover, excessive intake may increase the risk of bleeding, particularly when combined with anticoagulant medications.

3.5 Probiotics

Probiotics are used in the context of the “gut–brain axis” hypothesis, which posits that alterations in gut microbiota may influence neurological and behavioral functioning in ASD. Probiotic supplementation aims to restore microbial balance and alleviate gastrointestinal symptoms, which are common among individuals with ASD (Navarro et al., 2016). Although emerging studies have shown modest improvements in gastrointestinal symptoms and some behavioral outcomes, the evidence remains preliminary and highly variable across studies (Sivamaruthi et al., 2020; Iglesias-Vázquez et al., 2020).

3.6 Vitamin A (Cod Liver Oil)

Vitamin A supplementation has been proposed to support immune functioning and visual health. Some recent studies have also explored its potential influence on neural development and gut barrier integrity (Lai et al., 2021). However, vitamin A has a narrow therapeutic window, and excessive intake may result in hepatotoxicity or increased intracranial pressure, highlighting the importance of medical supervision.

3.7 Vitamin B6 (Pyridoxine) and Magnesium (Mg)

Vitamin B6 and magnesium have historically been used together in ASD interventions based on the hypothesis that they may enhance neurotransmitter synthesis and improve neuronal functioning (Nye & Brice, 2005). Although early clinical studies suggested modest behavioral improvements, subsequent systematic reviews have concluded that the evidence remains limited and methodologically weak (Sathe et al., 2017; Monteiro et al, 2020). Furthermore, excessive intake of vitamin B6 can lead to peripheral neuropathy, while magnesium toxicity may occur at high doses.

3.8 Vitamin B12 (Cobalamin) and Folinic Acid

Vitamin B12 injections combined with oral folinic acid have been investigated as a means of addressing abnormalities in methylation and antioxidant metabolism observed in some individuals with ASD (Al-Farsi et al., 2013; Moretti et al., 2005; Zhang et al., 2016). Several studies have reported improvements in biochemical markers such as glutathione levels, although behavioral outcomes remain variable. Recent clinical research continues to explore this intervention, particularly among subgroups of children with metabolic abnormalities (Frye et al., 2018).

3.9 Vitamin C (Ascorbic Acid)

Vitamin C has been examined for its potential to reduce stereotypic behaviors in individuals with ASD (Dolske et al., 1993). While some early findings suggested modest improvements, the evidence base remains limited, and excessive intake may result in nephrolithiasis or gastrointestinal disturbances.

From a biological perspective, vitamins and minerals are essential micronutrients that support normal physiological development. Vitamins are organic compounds synthesized by plants or animals, whereas minerals are inorganic elements derived from soil and water and absorbed through dietary sources. Adequate intake of both is necessary for healthy development in children as well as adults. Some proponents of plant-derived micronutrients argue that plant-based sources may enhance bioavailability due to the presence of co-nutrients that facilitate absorption (Gropper & Smith, 2020; Office of Dietary Supplements, 2026). Nevertheless, not all essential nutrients are available from plant sources. Nutrients such as vitamin B12, vitamin D3, creatine, carnosine, heme iron, DHA, and taurine are primarily derived from animal-based foods (Ramirez, 2020).

Within the context of ASD treatment, selected vitamins and minerals (including multivitamin and megavitamin therapies) have been widely used as dietary supplements (Adams, 2015; Adams & Holloway, 2004; Zhou et al., 2013). Golnik and Ireland (2009), cited in Adams (2015), reported that vitamin and mineral supplementation is recommended by approximately 49% of physicians treating children with autism. Despite this high rate of clinical recommendation, the therapeutic effectiveness of such interventions remains a subject of ongoing debate. For the purposes of this paper, the term alimentary management will be used to refer to the use of vitamin and mineral supplementation in ASD treatment.

Several biochemical studies have reported evidence of increased oxidative stress in children with ASD (El-Ansary et al., 2017; Frustaci et al., 2012; Jiang et al., 2023). Oxidative stress reflects an imbalance between free radical production and antioxidant defenses, which may contribute to neuronal dysfunction. Given that many vitamins and minerals function as antioxidants or cofactors in metabolic pathways, it has been suggested that children with ASD may have increased nutritional requirements or reduced levels of these micronutrients (Frustaci et al., 2012; Frye et al., 2018). Adams (2015), citing studies by James et al. (2004, 2006, 2009; see also Jiang et al., 2023), reported that children with ASD demonstrate increased oxidative stress, impaired methylation processes (characterized by decreased S-adenosylmethionine), and reduced glutathione levels compared with neurotypical children. These metabolic abnormalities have been interpreted as potential targets for nutritional interventions, although causal relationships have yet to be definitively established.

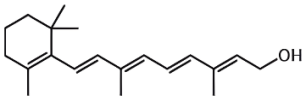
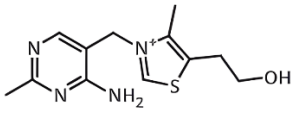
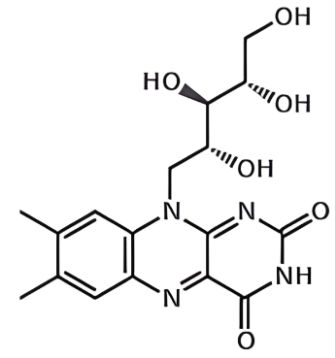
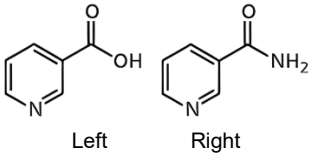
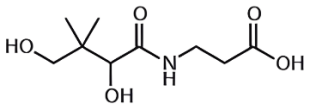
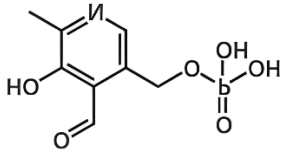
In response to these findings, Professor James B. Adams and colleagues at Arizona State University established the Autism Nutrition Research Center (ANRC) in 2014. The center developed nutritional guidelines intended to provide comprehensive dietary support for individuals with ASD (ANRC, 2020). One outcome of this initiative is the formulation known as ANRC Essentials, a multi-vitamin and mineral supplement containing more than thirty ingredients designed to address potential micronutrient deficiencies (Adams, 2015). The formulation includes relatively high doses of several vitamins, such as B-complex vitamins, vitamins C, D, and K, based on the hypothesis that individuals with ASD may require higher levels of certain nutrients than the general population.

Additional components of the formulation include methylated folate (methyl-tetrahydrofolate) rather than folic acid, which is considered more metabolically compatible for some individuals with ASD (James et al., 2004; Jiang et al., 2023). The supplement also contains methylsulfonylmethane (MSM), which serves as a source of sulfate that may be deficient in some individuals with ASD (Adams et al., 2011a), as well as low-dose lithium, included at levels comparable to typical dietary intake rather than pharmacological doses. While preliminary studies have reported improvements in nutritional status and some behavioral outcomes following supplementation, further independent randomized controlled trials are required to

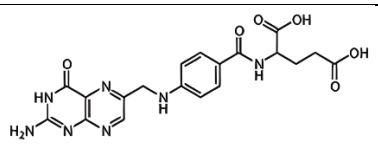
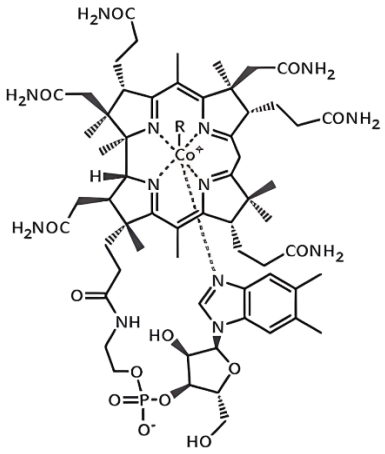
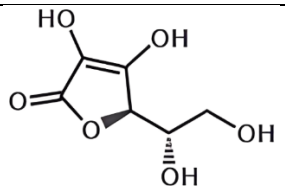
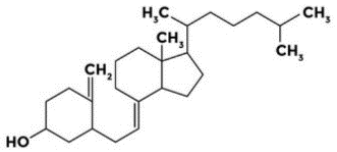
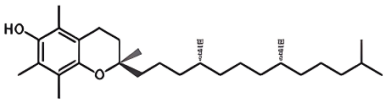
confirm the efficacy and safety of such comprehensive micronutrient interventions (Adams et al., 2018; Monteiro et al., 2020).

Table 1 shows a list of selected vitamins (with ANRC-recommended dosages) that have been used in the alimentary management of ASD (with cited studies): Vitamins A (Lai et al., 2021; Liu et al., 2017), B1 (Lonsdale, 2004; Smart et al., 2019), B2 (Kałużna-Czaplińska et al., 2011), B3 (Willyard, 2021), B5 (Melillo, 2013), B6 (Kałużna-Czaplińska et al., 2011; Martineau et al., 1985), B9 (Nuttall, 2017), B12 (Pineles et al., 2010; Zhang et al., 2018), C (McGinnis, 2004; Rafee, Burrell & Cederna-Meko, 2019), D3 (Cannell, 2017; Feng et al., 2017) and E (Daniells, 2009; Morris & Agin, 2009) … in addition to several minerals such as calcium, choline, copper, iron, lithium, magnesium, manganese, potassium, selenium, and zinc, to name some of them here.

Table 1. Essential Roles of Selected Vitamins used in Alimentary Management of ASD

Vitamin	Chemical Structure	Essential Role
Vitamin A (Retinol) Recommended dosage: 8000 IU (ANRC, 2014)[1]		• Essential for vision • Strengthening of immunity • Keeping skin & connective tissues healthy
Vitamin B1 (Thiamin) Recommended dosage: 30mg (ANRC, 2014)		• Keeping nerves & muscle tissues healthy • Processing of carbohydrates $(CH_2O)_n$ & some proteins
Vitamin B2 (Riboflavin) Recommended dosage: 40mg (ANRC, 2014)		• Essential for body growth • Production of erythrocytes • **Keeping the eyes healthy** • Processing of carbohydrates $(CH_2O)_n$
Vitamin B3 (Niacin: on the left - Nicotinic Acid; & on the right - Nicotineamide) Recommended dosage: 50mg (ANRC, 2014)	 Left Right	• Essential for digestion & keeps digestive system healthy • Processing of carbohydrates $(CH_2O)_n$
Vitamin B5 (Pantothenic Acid) Recommended dosage: 30mg (ANRC, 2014)		• Production of erythrocytes • Processing of carbohydrates $(CH_2O)_n$ • Keeping the digestive system healthy
Vitamin B6 (Pyridoxal Phosphate) Recommended dosage: 20mg (ANRC, 2014)		• Essential for making neurochemicals • Essential for normal brain function • Production of erythrocytes • Production of granulocytes or immune system cells

[1] Formulation of ANRC Essentials (2014) as cited in Table 2 (Adams, 2015, p. 2378).

Vitamin B9 (Folic Acid) Recommended dosage: not provided		• Essential for growing tissues • Essential for brain function & mental health • Production of DNA & RNA
Vitamin B12 (Cobalamin) Recommended dosage: 600mcg (ANRC, 2014)		• Essential for health of nervous system • Production of erythrocytes • Production of DNA & RNA
Vitamin C (Ascorbic Acid) Recommended dosage: 500mg (ANRC, 2014)		• Essential for healthy immune system • Production of collagen needed for making connective tissues • Absorption of non-heme iron • Wound healing • Protective effects against many cancers
Vitamin D3 (Cholecalciferol) Recommended dosage: 1500 IU		• Beneficial to mood, heart health & weight loss • Absorption of calcium (Ca) & phosphorus (P) • Strengthening of bones • Keeping immune system healthy
Vitamin E (Alpha-Tocopherol) Recommended dosage: 100mg		• As an antioxidant to help prevention of damage to cells • Production of erythrocytes • Preventive role in cancer

According to Bjørklund et al. (2019), "[I]nsufficient intake of vitamins and minerals through poor food habit has been considered as one of the main contributing factors to numerous child health problems such as anemia, scurvy, hypothyroidism, rickets, and so on due to lack of iron, vitamin C, iodine, and Vitamin D, respectively" (p. 374). The same has been also observed in children with ASD, especially in vitamin deficiency, resulting in challenging issues (weak digestion capacity, poor absorption, abnormal or impaired metabolic or biochemical processes) such that high doses of vitamins B1, B2, B3, B5, B6, B12, C, and D become critical for children with ASD (Adams, 2015; Bjørklund et al., 2019) and are best included in their alimentary management. For instance, vitamins B2 and B6 are essential in helping to decrease dicarboxylic acids ($HO_2C(CH_2)_nCO_2H$) level in the urine of children with ASD (Kałużna-Czaplińska et al., 2011).

Duvall et al. (2013) also reported of a case of a child with severe ASD who displayed limp, tachypnea, cough, hypoxin and tachycardia-induced pulmonary hypertension due to inadequate levels of vitamins B1, B6, B12 and D, and also undetected Vitamin C level. In another instance, DeSoto (2016) hypothesized and reported the supportive role of Vitamin K in neural development as earlier studies (e.g., Adams et al., 2011b; Johnson et al., 2008) found that children with ASD frequently suffered from Vitamin K deficiency more than neurotypical children, and Hyman et al. (2012) recommended for

inclusion of Vitamin K in nutrient supplement for children with ASD. Table 2 below provides a summary of selected studies supporting the inclusion of selected vitamins in the alimentary management for children with ASD.

Table 2. Selected Vitamin for Inclusion in Alimentary Management of ASD

Vitamins (Selected)	Studies supporting the inclusion of vitamins in the alimentary management for children with ASD
Vitamin A	• Increase in the oxytocin level via the CD38 process pathway[2] in individuals with ASD (Riebold et al., 2011) leads to significant increase in brain activity and social abilities (Gordon et al., 2013)
Vitamin B1	• Improves symptoms of children with ASD (Lonsdale, Shamberger, & Audhya, 2002) • Essential in apoptotic factors, neurotransmitter system and oxidative stress; impacts positively on basic myelin protein glycogen synthetase kinase-3β, alpha-1 antitrypsin, and glyoxalase 1 (Khanh vinh quốc Lương & Lan Thi Hoàng Nguyễn, 2013)
Vitamin B2	• Supplementation of Vitamin B2 helps Vitamin B6 and magnesium to reduce excretion of urinary dicarboxylic acids in autistic children and increase excretion of carboxylic acids is related to excessive bacterial overgrowth, which has been related to ASD resulting in an impairment in the gut-brain axis (Gątarek et al., 2020; Kałużna-Czaplińska, Socha, & Rynkowski, 2011)
Vitamin B3	• Vitamin B3 (niacin) is required in folate metabolism; abnormalities in folate metabolism have been linked to ASD (Frye, Slattery, & Quadros, 2017)
Vitamin B6	• Vitamin B6 and magnesium (with Vitamin B2 supplementation) help to reduce excretion of urinary dicarboxylic acids in autistic children, increase excretion of carboxylic acids related to excessive bacterial activity in the gut (called bacterial overgrowth known to associate with ASD) which is an impairment in the gut-brain axis (Gątarek et al., 2020; Kałużna-Czaplińska, Socha, & Rynkowski, 2011)
Vitamin B12	• Essential for brain or cognitive development (Hendren et al., 2016; Morris et al., 2007) • Better management of depression and anger (Fraguas et al., 2006; Fava & Mischoulon, 2009)
Vitamin C	• E**ssential** for a healthy immune system in which some children with ASD are suffering due to V**itamin C** deficiency (Rafee, Burrell, & Cederna-Meko, 2019) • Supplementation of Vitamin C contributes to a reduction in the stereotypical behaviors such as rocking, flapping hands, and pacing seen in children with ASD (Dolske et al., 1993), but further research is needed
Vitamin D3	• Essential for neurodevelopment and gene regulation (Kittana et al., 2022) • Reduction in the risk of ASD (Saad et al., 2018; vinh quốc Lu'o'ng & Nguyễn, 2013) • Strengthening of strengthen bone and teeth formation in babies (Bowles, 2017)
Vitamin E	• Essential for combating inflammation and oxidative stress observed in children with ASD (Pangrazzi, Balasco, & Bozzi, 2020) • Combination of omega-3 fatty acids and vitamin E may improve speech in autistic children with verbal disorders (Morris & Agin, 2009) • Combination of omega-3 fatty acids and Vitamin E may improve behavior in children with neurodevelopmental disorders such as ASD (Gumpricht & Rockway, 2014)
Vitamin K	• Essential for neural development in young children (Adams et al., 2011b; DeSoto, 2016); Hyman et al., 2012)

Besides vitamins, minerals (e.g., calcium, magnesium and zinc) have also been found to play an essential role in the alimentary management of children (as well as adults) with ASD (Babaknejad et al., 2016). According to Babaknejad et al. (2016), "[I]n comparison with healthy individuals, autistic patients, have different levels of trace elements like copper, magnesium, and zinc (Dufault et al., 2009; Morris & Agin, 2009)" (p. 2). A trace element (also known as minor element) is a chemical element whose concentration is very low (i.e., a trace amount) (Bhattacharya, Misra, & Hussain, 2016). These elements can be placed under two categories; (i) essential and (ii) non-essential. It is the former that are required for important physiological and biochemical processes in both plants and animals. They "have been proven to influence the brain neurotransmitter metabolism significantly" (Babaknejad et al., 2016, p. 2). Not only do trace elements play a role in biological processes, they also function as catalysts engaging in oxidation and reduction mechanisms (see Wada, 2004, for detail).

[2] "**CD38** (cluster of differentiation 38) is encoded by the **CD38** gene. It acts as an enzyme in several cellular reactions involved in calcium (Ca2+) mobilization and signaling" (Kelly, 2019, para. 7).

According to the late Professor Bell Freedman (b.1950-d.2015) of Dalhousie University, Halifax, in Canada, "[T]race elements that are most often associated with **environmental toxicity** are the heavy metals cadmium, chromium, cobalt, copper, iron, lead, mercury, nickel, silver, tin, and zinc, as well as the lighter elements aluminum, arsenic, and selenium. Some cases of elemental pollution are natural in origin" (Freedman, 2018, p. 426). In fact, toxic elements (e.g., lead and mercury) and deficiency of nutrients as well as trace elements are known as environmental factors that appear as "one cause of those epigenetic changes in wild and laboratory animals" (Leitch, 2021, para. 6) and Kelley et al. (2021, p.) have warned that humans are not immune to the effect of harmful environmental chemicals.

Among the several important trace elements in cell signaling, zinc (Zn) "plays a vital role in enzyme function, nucleic acid metabolism, growth, and finally cellular repair, most importantly in pregnant women and newborns" (Babaknejad et al., 2016, p. 2). Zn deficiency (especially when measuring Zn levels in the plasma, hair, and nails) has been found high in children diagnosed with ASD (Faber et al., 2009) and it constitutes a major factor in the etiology of behavioral and mood disturbances (Sayehmiri et al., 2015, p. 2). Zn also plays a role in immune system functioning (Prasad 1995), protein synthesis (Prasad 1995), wound healing (Heyneman 1996), DNA synthesis (IOM/FNB 2001), and cell division (Prasad 1995). In addition, according to Prasad et al. (1997), Zn is required for proper sense of taste (gustatory) and smell (olfactory), which can be determined via the administration of the Sensory Profile (Dunn, 1999).

Another important trace element is copper (Cu). Bjørklund (2013) reported that a disturbance in the copper (Cu) and zinc (Zn) metabolism is found in children with ASD in the following ways: (i) Zinc deficiency; (ii) excess Cu levels; and (iii) low Zn/Cu ratio; these issues of Zn/Cu imbalance are common in children diagnosed with an ASD. Given the importance of Zn/Cu metabolism for healthy neurological functioning and detoxification of heavy metals (including Hg), Faber et al. (2009) argued that these two trace elements may contribute in the pathogenesis of ASD.

Another essential trace mineral is iron (Fe), a constituent of hemoglobin and myoglobin that plays a vital role in the transport of oxygen (O_2) in the body. Iron deficiency (ID), with or without anemia, can impair cognition and affect and is associated with developmental slowing in infants and mood changes and poor concentration in children with ASD (Latif et al., 2002). Although studies done on the association between ID parameters and clinical symptoms of ASD have been sporadic, high prevalence of iron deficiency (ID) and iron deficiency anemia (IDA) has been reported in children with ASD (Bilgiç et al., 2010; Dosman et al., 2006; Latif et al., 2002). However, a recent study done by Gunes, Ekinci and Celik (2017) found the hemoglobin levels of children with ASD were lower than neurotypical children and argued that it was not sufficient to result in anemia. They postulated that the IDA in children with ASD might be associated with intellectual disability instead of ASD symptom severity.

Selenium (Se), another trace mineral, is essential to good health. Se plays vital roles in DNA synthesis, thyroid hormone metabolism, reproduction, as well as protection from oxidative damage and infection (Ross et al., 2012). Its major dietary source can be found in plants, where its concentration generally reflects the concentration of the trace element in soils. However, some meats and seafood can also contribute dietary Se. Se is frequently used in the alimentary management of children with ASD, where the imbalance of Se is believed to cause the metabolic/psycho-metabolic disturbances. According to Skalny et al. (2018), "the mechanisms of the proposed Se neuroprotective effect in ASD may involve inhibition of oxidative stress, neuroinflammation, and microglia activation. In addition, synaptic dysfunction and gut-brain axis disturbances might be modified" (p. 193). However, more studies are needed to understand and highlight the mechanisms of the potential neuroprotective effects of Se in ASD as well as its efficiency in clinical trials. The efficiency of Se used in alimentary management of ASD remains unclear. "Moreover, data on the role of Se metabolism in ASD are insufficient and contradictory" (Skalny et al., 2018, p. 193).

Research on the use of dietary supplements in the treatment of ASD is limited by several methodological constraints that weaken conclusions and clinical applicability: e.g., small sample sizes, heterogeneous participant groups, short intervention durations, and inconsistent outcome measures, making comparisons across studies difficult and reduce statistical power (Amadi et al., 2022; He et al., 2023). Additionally, many existing trials do not use standardized, validated tools or long-term follow-up to assess sustained effects, and variability in supplement types, doses, and study designs further complicates synthesis of findings, underscoring the need for larger, rigorously controlled studies with well-defined protocols and objective outcomes (Amadi et al., 2022; He et al., 2023).

There are still many other minerals that are not discussed in this paper. Interested readers can always search in the Google Scholar for these papers on specific minerals, their key roles and how they can affect children with ASD.

4. CONCLUSION

Children with ASD are frequently reported by caregivers to exhibit food selectivity and restrictive eating patterns, placing them at heightened risk for nutritional deficiencies (Reynolds et al., 2012). Several studies have documented dietary insufficiencies in this population, particularly in the intake of iron, B vitamins, vitamins D and K, calcium, and zinc, affecting approximately one-third of children with ASD (Dosman et al., 2007; Herndon et al., 2009; Lindsay et al., 2006; Reynolds et al., 2012). These deficiencies may have far-reaching physiological and neurodevelopmental consequences.

Vitamins and minerals, whether provided through diet or supplements, can induce epigenetic modifications that influence gene expression through transcriptional and translational mechanisms (Bjørklund, 2013). The interaction of dietary nutrients with nuclear receptors can activate specific signaling pathways, ultimately modulating gene expression. For example, vitamin-specific receptors mediate distinct pathways that affect cellular functions: vitamin A serves as a substrate for the biosynthesis of retinoids essential for cell growth, differentiation, and vision (Amann et al., 2011). Its signaling pathway involves retinoid X receptor (RXR) heterodimerization with orphan receptors NGFI-B and NURR1. The downstream metabolites of retinol, namely all-trans and 9-cis retinoic acids, bind to these nuclear receptors to regulate target genes, illustrating a direct link between nutrient availability and gene expression (McGrane, 2007). While the detailed molecular mechanisms are beyond the scope of this paper, the biological significance is evident: recent research demonstrates that vitamin A deficiency increases the risk of gastrointestinal comorbidities and exacerbates core ASD symptoms (Cheng et al., 2021).

However, there remains the ‘dark matter’ (unknowable unknown) of the human genome that has limited the current understanding of ASD. This is what the authors of this paper have come to the other side of the learning journey as they cross the bridge of exploration, in this example, on Vitamin A and its effect on individuals with ASD. The food supplements will not be able to address the condition of ASD in its entirety. There are too many biological dark matter ‘particles’ in the present attempt to search for a probable solution using alimentary management via food supplements of the heterogeneous condition of ASD. Future research directions in the use of dietary supplements for autism spectrum disorder should prioritize rigorous study designs, including larger randomized controlled trials, to establish efficacy and safety. Additionally, studies should include culturally and geographically diverse samples to ensure findings are generalizable across different populations, and should systematically evaluate long-term outcomes, optimal dosing strategies, and potential interactions with medications or comorbid conditions.

Finally, when applying dietary supplements (e.g., mega-vitamin, essential minerals, and probiotics) in treating children with ASD, it should be undertaken with caution, as excessive or inappropriate intake may result in toxicity, adverse gastrointestinal or metabolic effects, and potential interactions with

prescribed medications. Hence, the authors want to reiterate that supplementation should be administered only under the supervision of qualified healthcare professionals to ensure appropriate dosage, safety, and monitoring of potential contraindications.

5. DISCLAIMER

The content of this paper is strictly for informational or educational purposes only, and does not substitute professional medical advice or consultations with healthcare professionals.

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7. COMPETING INTERESTS

The author has declared that no competing interests exist.

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10. DATA AVAILABILITY STATEMENT

Not applicable. No primary data were generated or analysed in this study.

11. ETHICS APPROVAL

Not applicable. This study did not require ethics approval.

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