Potential Impact of a Nutritional Factor on Attention-Deficit/Hyperactivity Disorder Using Amaranth

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder increasing in prevalence. The core features of this disorder include developmentally inappropriate levels of inattention, impulsivity, distractibility, and motoric overactivity. There is enough research evidence that help patients with ADHD in order to get real benefits with protein, polyunsaturated fatty acids, essential amino acids, vitamin D, zinc, ferritin, and magnesium. These nutrients have important roles in neurologic function, including involvement in neurotransmitter synthesis. The aim of this work is to present a product from amaranth seed extract in a powder form that treats ADHD disorder and has been approved by the Federal Committee for Protection from Sanitary Risks in Mexico. The product has been tested by several hundred Mexican children and adolescents with ADHD.

Keywords: Attention-Deficit; Hyperactivity Disorder; Natural product; Amaranth Extract; Diagnosis

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity and impulsivity and has a pooled prevalence rate of about 2.5% in the adult population [1,2]. The symptoms are often severe and may cause serious difficulties in the daily life of affected individuals [3]. The disorder often coexists with other neuropsychiatric disorders like depression and bipolar disorder, with which it also shares symptoms [4,5]. The aetiology of ADHD is complex and is most likely explained by the combined impact of many environmental and genetic factors [6,7]. In a recent study on ADHD and its relation to low birth weight, it was suggested that genetic variants in the kynurenine pathway might contribute to ADHD symptom severity [8].

The kynurenine pathway constitutes the major route for catabolism of the essential amino acid tryptophan [9]. More than 90% of tryptophan is catabolised to kynurenine, mainly in the liver by the tryptophan specific enzyme tryptophan 2,3-dioxygenase (TDO), but also in lungs, kidneys, spleen, placenta and blood by the enzyme indole 2,3-dioxygenase (IDO) [10]. In the brain, the catabolism of tryptophan to kynurenine is driven by TDO and IDO located in astrocytes and microglia [10].

ADHD often coexists with other neuropsychiatric disorders that have been associated with altered levels of metabolites of the kynurenine pathway, such as major depression and bipolar disorder [4,5]. Furthermore, known environmental risk factors for ADHD,
such as preeclampsia, postnatal infection and malnutrition, may involve abnormal tryptophan catabolism [11,12]. Neuropsychological deficits, for example in executive functioning, are often found in ADHD [13], and are thought to be related to a hypofunctional dopamine system [14]. Tryptophan metabolites can modulate several neurotransmitter systems, including dopaminergic transmission [10]. Moreover, in addition to kynurenine, tryptophan is also the precursor of serotonin (5-hydroxy-tryptamine, 5-HT), a neurotransmitter that has been suggested as an important agent in several neuropsychiatric disorders including ADHD [15].

Childhood neurodevelopmental and psychiatric disorders are known to be complex conditions of multifactorial aetiology, involving both genetic and environmental determinants. There is a rapidly growing awareness that mental symptoms and psychiatric disorders are linked to nutrition [16].

Food intake affects brain development and function in all age groups, starting from the phase in utero in terms of cognitive processes, mood, and brain performance. Accordingly, nutritional deficiencies can result in a vast array of age-dependent clinical symptoms, which affect the function of the central nervous system. A good nutrition can have a particularly strong effect on the developing brain between weeks 24 and 42 of gestation, during which several neurologic processes, including synapse formation and myelination build upon one another [17].

The central effect of nutrient deficiency or suppletionation is dependent on the requirement of the central nervous system for nutrient in specific metabolic pathways and structural components. A specific nutrient may promote normal brain development at one time point and be toxic at another. Furthermore, different concentrations of nutrients may be required during development. Concentrations of several nutrients are tightly regulated (e.g. iron) with aberrant brain development ensuing from both a deficiency and an excess. Important nutrients during late fetal and early neonatal life include protein, zinc, iron, copper, choline, and polyunsaturated fatty acids (PUFA) [17].

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are early onset neurodevelopmental disorders that may persist into adulthood. Both ASD and ADHD are umbrella terms that cover heterogeneity behavioral abnormalities. ADHD is characterized by inattentive, hyperactive and impulsive behavior, whereas the key symptoms of ASD include social deficits, communication deficits and stereotypical behavior [18,19]. Despite the differences in the core behavioral symptoms between ASD and ADHD, there are indications for an overlap between the disorders. Indeed, research indicates that these disorders are highly comorbid [20-22]. Although the etiology of ASD and ADHD remains largely unknown, a complex interaction of genetic and environmental factors is thought to contribute to the development of ASD and ADHD [20,23,24]. One of the potential environmental risk factors for neurodevelopmental disorders is diet [25].

Nutrition has an impact on neurodevelopment, cognition, and behavior, and could therefore play an important role in neurodevelopmental disorders [26,27]. This insight, together with the lack of effective treatments for core ASD symptoms and the concerns about the safety of pharmacological treatments in ADHD [28], have led to increasing research into the efficacy of nutrition-related interventions as additional or alternative (non-pharmacological) treatments for these disorders. The dietary interventions that have been subjected to clinical trials include various forms of elimination diets and supplementation interventions [29,30]. In this review, we provide an overview of the literature with regard to the most common forms of elimination diets and their efficacy in ADHD and ASD. Furthermore, we discuss the potential mechanisms of elimination diets’ effects in both ADHD and ASD. Finally, we conclude with the practical implications and future directions into the investigation of elimination diets’ efficacy in the treatment of these early onset neurodevelopmental disorders.

Kanarek., et al. [31] found that the currently incomplete understanding of the etiology of ADHD, coupled with the problems associated with drug treatments, has led researchers and parents to search for definitive causes and alternative treatments of the disorder. Results of these searches indicate that dietary variables may contribute to the development of ADHD [32,33]. For example, hyperactivity and inattention are common symptoms associated with marginal zinc, iron, and magnesium deficiencies [34-36] and significant negative cor-
relations have been observed between both serum ferritin and zinc levels and parental reports of hyperactive behaviors [37]. Moreover, in some children, intake of supplements containing these micronutrients can reduce hyperactive behavior [34-37]. Additionally, recent work suggests that diets containing low levels of omega-3 polyunsaturated fatty acids can predispose children to ADHD, and that the use of supplements containing omega-3-polyunsaturated acids can ameliorate symptoms of hyperactivity in some children [38-41]. For the past 40 years, however, the most enduring and controversial issue with respect to diet and ADHD is the possible role of food additives/dyes in the development of the disorder [31].

In 2012, Ibrahim, et al. [42] wrote that the developmental disorders (DDs) are important leading cause of disability in developed countries and also in the United States. DDs are a group of individual conditions that result from abnormal nervous system development and cause altered function. They can begin at any time from prenatal to 22 years of age and the disability usually presents itself throughout a person's lifetime. Down syndrome, autism, neural tube defects, schizophrenia, cretinism, and attention-deficit hyperactivity disorder are among the most common DDs that currently plague numerous countries and have varying incidence rates. Their occurrence may be partially attributable to the lack of certain dietary nutrients. Notably, essential vitamins, minerals, and ω-3 fatty acids are often deficient in the general population of America and developed countries and are exceptionally deficient in patients suffering from mental disorders. Typically, most of these disorders are treated with prescription drugs, but many of these drugs cause unwanted side effects.

Therefore, psychiatrists recommend alternative or complementary nutritional remedies to overcome the adverse effects of those drugs. Studies have shown that daily supplements of vital nutrients, such as those containing amino acids, often effectively reduce symptoms of these patients, because they are converted into neurotransmitters that alleviate depression and other mental disorders. The aim of this article is to discuss the role of dietary imbalances in the incidence of attention-deficit hyperactivity disorder (ADHD) and to emphasize which dietary supplements can aid in the treatment of this mental disorder.

Typically, most of the diseases are treated with the prescribed drugs (conventional therapy), but many of these prescribed drugs cause unwanted side effects. Therefore, recently, remedies of natural origin that have potential therapeutic effects but with no side effects are recommended to be used in the majority of diseases with or without pharmacological drugs. The most commonly used remedies are essential amino acids, unsaturated fatty acids, vitamins, minerals, and some herbs.

Results and Discussion

The Role of Nutrition on Attention-Deficit/Hyperactivity Disorder (ADHD)

In 2016, Erlichman, et al. [43] indicate that in the United States, ADHD is one of the most common neurodevelopmental disorders of childhood. Surveys of complementary and alternative medicine (CAM) use in pediatric ADHD suggest that nearly 25% use these therapies, with biological based treatments such as dietary modification and supplementation is the most frequently used [44]. Dietary supplementation studies in ADHD include the use of essential amino acids, omega-3 and omega-6 fatty acids, vitamins, minerals, and natural metabolites.

Essential Amino acids

The amino acids tryptophan, tyrosine, phenylalanine, and methionine are often helpful in treating many mood disorders [45]. Tryptophan is a precursor of serotonin and is usually converted into serotonin when taken alone on an empty stomach. So, tryptophan can induce sleep or tranquility. In cases of serotonin deficiencies, serotonin levels can be restored by tryptophan leading to diminished depression [46]. Tyrosine is not an essential amino acid, because it can be made from the amino acid phenylalanine. Tyrosine and its precursor phenylalanine are converted into dopamine and norepinephrine [47]. Dietary supplements that contain tyrosine and/or phenylalanine lead to alertness. Methionine combines with Adenosine triphosphate (ATP) to produce S-Adenosyl methionine (SAM), which facilitates the production of neurotransmitters in the brain [48]. In addition, SAM is essential for the biosynthesis of phospholipids and for gene expression as it regulates chromatin function.
Polyunsaturated Fatty Acids (PUFAS)

Omega-3 fatty acid deficiencies have been found in boys with ADHD [49]. Omega-3 and omega-6 fatty acids are polyunsaturated fatty acids that maintain membrane fluidity [50]; serve as substrates in the biosynthesis of inflammatory eicosanoids [51,52]; modulate dopaminergic neurotransmission [53,54] and support other cellular functions. There are three omega-3 fatty acids relevant to human physiology: eicosapentanoic acid (EPA), docosahexanoic acid (DHA), and alpha-linolenic acid (ALA). The two omega-6 fatty acids are arachidonic acid (AA) and gamma-linolenic acid (GLA). Essential PU-FAs cannot be synthesized endogenously and must be derived from dietary sources.

The high ratio of omega-6/omega-3 fatty acids commonly found in western diets is believed to play a role in chronic inflammatory diseases [51,52]. Supplementation with Omega-3 fatty acids or a combination of omega 3/6 fatty acids can improve symptoms of ADHD. One meta-analysis of 10 trials involving 699 participants found a small but significant overall improvement in ADHD with omega-3 fatty acid supplementation (standardized mean difference [SMD] = 0.31, confidence interval [CI] = 0.16 - 0.4, p~.0001) with similar results for both inattentive and hyperactivity symptoms. Higher doses of EPA were significantly associated with reduction of ADHD symptoms [55]. Another meta-analysis found that when data from blinded assessments were segregated from proximal un-blinded assessments, the effect sizes of free fatty acid supplementation on ADHD symptoms remained statistically significant [56].

Vitamins

Supplementation of vitamins E, B6, and B12 to hyperactive children (7 - 13 years) for 14 weeks showed a good response regarding increased concentration, reduced fatigability, headache, and an improvement from nocturnal enuresis. This means that each of these vitamins had a role in improving the accompanied symptoms in hyperactive children [57]. Vitamin B12 is necessary for the formation of nerve sheaths, and its deficiency may cause nervousness, neuritis, numbness, and poor memory. Stampfer, et al. [58] reported that vitamin E supplementation protects biological membranes such as those found in the nerves and muscles and is used successfully in the therapy of progressive neuromuscular diseases. Parry and Bredesen [59] reported that vitamin B6 helps to maintain the balance of sodium and potassium and thus regulates the body fluids and promotes normal function of the nervous and musculoskeletal systems.

In addition to its regulation of calcium and phosphorous in the intestine and stimulation of bone cell mineralization, vitamin D is a neuroactive steroid that has been shown in both animal and human studies to be important for normal brain development [60,61]. Vitamin D receptors and enzymes are located in neuronal cells of the substantia nigra, hippocampus, hypothalamus, prefrontal cortex, and cingulated gyrus; many of these regions have also been shown to have abnormalities in ADHD [62]. There is data to suggest that Vitamin D deficiency during development has deleterious effects on the dopamine system and, in animal models, vitamin D has been shown to be associated with the production of tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis [63]. Vitamin D may exert its neurological effects through various mechanisms. In animal models, it has been shown that vitamin D is an important factor for the differentiation of developing brain cells, is involved in axonal growth, can increase antioxidants such as glutathione and therefore protect against oxidative stress, and can regulate various neurotrophic factors such as nerve growth factor. Although largely cross-sectional in design, there have been studies demonstrating an association between low vitamin D levels with schizophrenia, depression, and Alzheimer’s Disease [63].

Minerals

Iron (ferritin)

Iron imbalances have been associated with neurological diseases including ADHD [64]. Iron is an essential cofactor in the endogenous synthesis of monoaminergic neurotransmitters implicated in the pathogenesis of ADHD. In a controlled study of 23 children (ages 5 - 8 years) with low serum ferritin, iron supplementation (80mg/day) improved ADHD symptoms [65]. Another study showed that low serum ferritin (Ferritin is a marker of peripheral iron stores) and can be used to estimate body-iron store not only correlated with baseline ADHD symptoms, but also with the dose of amphetamines required for clinical improvement [66]. Iron deficiency can cause restless leg

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syndrome, easily mistaken as a symptom of ADHD in children. Serum ferritin levels should be checked in children with restless legs and in cases where there is reason to suspect a nutritional deficiency.

Zinc

The mineral co-factor zinc has also been implicated in regulating dopamine and norepinephrine neurotransmission [67]. In clinical studies performed in the Middle East, zinc supplementation significantly improved ADHD symptoms compared to placebo. For example, in a study performed in the United States, low serum zinc levels correlated with parent and teacher-rated scores of inattention, but not with the other core symptoms of hyperactivity and impulsivity [68]. A double blind study including 52 American children treated with either zinc glycinate or placebo for 8 weeks followed by 5 weeks of treatment with added d-amphetamine found that the clinical outcomes were equivocal with some measures favoring zinc and others favoring placebo [69]; however, a significantly lower dose of d-amphetamine was optimal for those receiving the zinc supplement (i.e. 37%) compared to those given placebo. Consequently, for ADHD patients residing in the United States, the clinical value of zinc supplementation remains to be determined.

Magnesium

Magnesium is involved in at least 300 enzymatic reactions, and required for fatty acid synthesis. It also plays a role in muscle relaxation, protein synthesis, and energy production. Muscles contain 27% of all the magnesium in the body and bones contain 60%. Dietary sources include: whole grains, nuts, legumes, seafood, and green vegetables [70]. In animal studies, magnesium has been shown to activate tyrosine hydroxylase, the rate-limiting step in dopamine synthesis. Magnesium also binds serotonin and dopamine to their receptors [71].

What is Amaranth Good for?

The historical evidence depicted that Amaranthus domestication and cultivation came into use about 8000 years ago in the Aztec, Mayan, and Incan civilizations. The most significant historical evidence supports that the amaranths was a staple food, called huahtli grown in Mexico during the Aztec civilization [72-74]. The Aztecs believed that it had magical properties which gave it strength. Due to this belief Amaranthus was used as a grain in religious practices, and was roughly equal to corn. But in the 1500s, the Spanish conquistadors prohibited the growing of Amaranthus to suppress the Aztec culture and religion which promoted its adoption and production in the other parts of world. At the present time only a limited amount of grain is being grown in México and used in the production of “alegria o happiness” in which amaranth is used in the form of popcorn to prepare a candy after it is mix with honey and for preparing a drink called atole.

Amaranth is tall - often six feet – with broad green leaves, bright red or gold flowers, and around 60 different species. The flowers are made up of miniscule, grain-like buds, this is why this plant often falls into the “grain” category. But amaranth is not technically a grain like oats, wheat, or rice. It's sometimes referred to as a “pseudo-cereal” because its nutritional profile is very similar.

Amaranth has a relatively high protein concentration between either 12.5% and 17.6%, according to Teutonico and Knorr (1985) [75]. Amaranth methionine content is around 0.226 g/100g total protein, whereas its lysine and tryptophan levels are about 0.747 and 0.181 g/100g total protein, respectively [76]. It is higher in minerals, such as calcium, iron, phosphorus, and carotenoids, than most vegetables.

Regarding dietary supplements, current evidence is scarce, yet promising. A case Report: Currently, in our laboratory we carried out a biotechnological procedure to make an amaranth extract in a powder form that treats ADHD. This formulation is called Focus-XP (Figure 1) and it has been approved by COFEPRIS or the Federal Committee for Protection from Sanitary Risks in Mexico. The product has been tested by several hundred Mexican children with ADHD and it has several advantages: people usually takes only 2 capsules that contain 100 mg each one; It takes only 20 minutes to treat ADHD; it does not cause any side effects; it’s a natural food ingredient; does not contain gluten nor lactose; and the price is affordable.

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The nutritional composition of Focus-XP is given in table 1.

<table>
<thead>
<tr>
<th>Components</th>
<th>Neutraceutical formulation in powder, value per 100g</th>
</tr>
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<tbody>
<tr>
<td>Energy</td>
<td>389.88 kcal/1637.50 kJ</td>
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<tr>
<td>Protein</td>
<td>44.00g</td>
</tr>
<tr>
<td>Lipids</td>
<td>4.52g</td>
</tr>
<tr>
<td>Of which:</td>
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<tr>
<td>Saturated fatty acids</td>
<td>1190 mg</td>
</tr>
<tr>
<td>Myristic acid</td>
<td>86.0 mg</td>
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<tr>
<td>Palmitic acid</td>
<td>948.5 mg</td>
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<tr>
<td>Stearic acid</td>
<td>174.7 mg</td>
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<tr>
<td>Arachidic acid</td>
<td>40.1 mg</td>
</tr>
<tr>
<td>Heptadecanoic acid</td>
<td>5.9 mg</td>
</tr>
<tr>
<td>Tricosanoic acid</td>
<td>12.2 mg</td>
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<tr>
<td>Unsaturated fatty acids</td>
<td>3330 mg</td>
</tr>
<tr>
<td>Myristoleic acid</td>
<td>3.6 mg</td>
</tr>
<tr>
<td>Palmitoleic acid</td>
<td>268.6 mg</td>
</tr>
<tr>
<td>Oleic acid (ω-9)</td>
<td>1105.5 mg</td>
</tr>
<tr>
<td>Linoleic acid (ω-6)</td>
<td>1937.6 mg</td>
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<tr>
<td>Alpha-linolenic acid (ω-3)</td>
<td>54.5 mg</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>200.2 mg</td>
</tr>
<tr>
<td>Total Carbohydrates</td>
<td>43.30g</td>
</tr>
<tr>
<td>of which, sugars</td>
<td>12.82g</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>2.14g</td>
</tr>
<tr>
<td>Humidity</td>
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</tr>
<tr>
<td>Ashes</td>
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<tr>
<td>Minerals</td>
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</tr>
<tr>
<td>Calcium</td>
<td>173.5 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>8.1 mg</td>
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<tr>
<td>Magnesium</td>
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<tr>
<td>Phosphorus</td>
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</tr>
<tr>
<td>Potassium</td>
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</tr>
<tr>
<td>Sodium</td>
<td>65.8 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>2.9 mg</td>
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<tr>
<td>Essential Amino acids</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>1.26g</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>1.89g</td>
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<tr>
<td>Leucine</td>
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</tr>
<tr>
<td>Lysine</td>
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<tr>
<td>Methionine</td>
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<tr>
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<tr>
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<tr>
<td>Tryptophan</td>
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<tr>
<td>Valine</td>
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Table 1: Nutritional composition of Focus-XP
Conclusions

Many symptoms of ADHD are addressed with behavioral therapy and medications; however, even with combined treatments, one-third of patients are still symptomatic. Currently there is no evidence to support supplementation as a mono-therapy for the treatment of ADHD, however, supplementation may improve medication response and overall well-being, especially in those with deficiencies. Although it is not definitively clear the percentage of children presenting with symptoms of ADHD who have nutrient deficiencies, the existing literature suggests that a subgroup of children with ADHD are at risk for nutrient deficiencies which may play a role in symptomology. In children presenting symptoms of ADHD, clinicians are encouraged to review the dietary history, consider risk factors for zinc, iron, magnesium, and vitamin D deficiency in appropriate manner.

Existing evidence suggests that nutrition, especially staple based foods, when part of a balanced pattern, contribute important protein, polyunsaturated fatty acids, minerals (zinc, iron, magnesium among others minerals), appropriate dietary fiber, vitamins, and antioxidants that can help mitigate or reduce the risk of ADHD. For ADHD, no one group of foods or dietary pattern seems to be a causal factor; but for this disorder unbalanced patterns increase the risk or symptoms.

The present report relates to a preparation of a formulation of principle assets of Amaranth comprising soluble proteins with a high content of essential amino acids, unsaturated fatty acids, a greater amount of minerals, and a low amount of carbohydrates obtained from an amaranth extract.

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None.

Conflict of Interest

Author declare no conflict of interest.

Bibliography


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