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Review

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Review

Investigating the Impact of Nutrition and Oxidative Stress on Attention Deficit Hyperactivity Disorder

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Abstract: Attention deficit hyperactivity disorder (ADHD) is the most common childhood-onset neurodevelopmental disorder characterized by difficulty maintaining attention, impulsivity and hyperactivity. Although the cause of this disorder is still unclear, recent studies state that heredity is important in the development of ADHD. This is linked to a few comorbidities: depression, criminal behavior and anxiety. Although genetic factors play a major role in the pathogenesis of ADHD, there are also non-genetic factors, one of which would be oxidative stress (OS) that are associated with ADHD. OS is implicated in the pathogenesis of ADHD, through lower levels of antioxidant enzymes such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), as well as a lower total antioxidant status (TOS) compared to control groups. Moreover, there is a close bidirectional connection between the nervous system and the intestinal microbiota, and the communication between the two systems is carried out through the gut-brain axis (GBA). A thorough review of diet, OS implications, mechanism of action, pharmacokinetics, and drug-drug interactions are reviewed here, with a special focus on treatment in adults with comorbid conditions.

Keywords: ADHD; oxidative stress; diet; gut-brain axis; gut microbiota

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1. Introduction

Attention deficit hyperactivity disorder is one of the most common neuropsychiatric disorders affecting up to 4% of adults. ADHD presents symptoms that are often severe during childhood, evolving in direct proportion with advancing age [1]. Being responsible for increasing the risk of other psychiatric disorders, addictions, and accidents [2], some researchers analyzed the risk factors involved in the pathogenesis of ADHD [3]. Psychostimulant and non-psychostimulant drugs are used to treat this condition. Although both are effective, psychostimulant drugs have greater efficacy over a shorter period [4].

Recently, researchers have focused on the contribution of OS to the pathophysiology of ADHD [5,6]. OS is a biological condition that can produce considerable amounts of oxidants or low levels of antioxidants [7]. OS can damage lipids, proteins, and DNA, altering the signal and gene expression, inhibiting protein activity, and causing apoptosis [8]. Moreover, reactive oxygen species (ROS) are

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molecules derived from oxygen, including free radicals and non-radical compounds, which act as oxidants or can be easily transformed into free radicals [8]. These reactive molecules can degrade carbohydrates, proteins, lipids, and nucleic acids [9]. Low levels of ROS are necessary for normal cellular function, while excess ROS can damage cells [10].

However, different types of antioxidants protect the body's cells, some of them having the property of crossing the blood-brain barrier, which allows them to protect nerve cells [10]. CAT, SOD and GPx are some examples of antioxidant enzymes, along with vitamins C, E and A [10].

Recent research places particular importance on the diet, specifically on micronutrients such as vitamin (B, D), minerals: zinc (Zn), magnesium (Mg), copper (Cu), selenium (Se), iron (Fe) and polyunsaturated fatty acids (PUFA) due to the role of attention deficit hyperactivity disorder [11,12]. Micronutrient deficiency plays a role in the pathophysiology of ADHD, an example can be Fe deficiency, because in the brain, Fe acts as an essential cofactor of tyrosine hydroxylase in the synthesis but also the metabolism of catecholamines, being involved in oxygen transport and myelination [13]. Although supplementation with certain micronutrients has been shown to be significant in reducing ADHD symptoms, taking them in very high doses can lead to the risk of adverse effects. Thus, in 2020, Lange, investigated the side effects that vitamin E supplementation has, showing an increased risk of prostate carcinoma, and long-term supplementation with ω-3 PUFAs (Omega-3 polyunsaturated fatty acids) can be associated with serious adverse effects [11].

On the other hand, the gut microbiome plays an important role in ADHD, its composition and function being also associated with other mental disorders. Communication between the gut microbiome and the brain is bidirectional and is achieved through the gut-brain axis [11,14]. The brain and gut function as interdependent units, the gut microbiota produces metabolites (serotonin), having a function in neuronal function, and the brain sends signals (dopamine) to the gut that directly or indirectly affect the gut microbiota [15]. Disturbances of the intestinal microbiome are correlated with several conditions such as: irritable bowel syndrome, cardiovascular diseases, immune disorders, obesity, inflammatory bowel disease [15–17]. In the absence of a healthy microbiome, some bacteria such as Clostridium difficile proliferate, leading to gastrointestinal disorders such as diarrhea [18]. In this review, we will focus on the function of OS as a factor in the pathophysiology of ADHD, the influence of diet on treatment, and their connection to the gut microbiome.

2. ADHD

Attention deficit hyperactivity disorder is a prevalent neuropsychiatric disorder that is diagnosed based on persistent developmental levels of hyperactivity, inattention, and impulsivity [19,20]. ADHD occurs together with other psychiatric disorders such as depression, anxiety, bipolar disorder, autism spectrum disorders, conduct disorder, eating disorders, but also substance use disorders [21]. Although it is a hereditary disorder (76%), some environmental factors such as severe institutional deprivation, prenatal risk factors, play a role in the pathogenesis of ADHD [3]. Moreover, maternal stress but also the administration of acetaminophen during pregnancy are environmental factors that can trigger changes in the maternal gut microbiota, potentially affecting fetal brain development [22].

This disorder has a prevalence of 5% in children between the ages of 4 and 17 years, and many diagnosed children go on to have problems with education or other mental illnesses in adolescence [23]. In 2022, a prevalence of approximately 7% was reported in children and adolescents [12].

Children with ADHD show a higher frequency of learning, language, motor, cognitive and mental health disorders, however, the symptoms and signs of ADHD differ in different periods of childhood [24]. Children with ADHD who do not follow treatment are at greater risk of dropping out of school and abusing drugs and alcohol [25]. Also, lack of treatment in childhood can result in a much higher risk of experiencing additional mental health difficulties in adulthood [25].

Even if ADHD is diagnosed in childhood, it persists into adulthood [26], with a prevalence of 3.2% in adult women. Usually, women with ADHD who did not show symptoms in childhood, discover their disorder after one of their children is diagnosed with the disorder. Women are twice as likely to have ADHD as men [27].

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Although the causes of ADHD are not completely known, the treatment of this disorder includes psychostimulants [20,27], such as methylphenidate (MPH), dexmethylphenidate, dextroamphetamine, mixed amphetamine salts, pemoline and modafinil [27], but also other non-psychostimulant drugs such as atomoxetine and bupropion [27,28]. The most well-known psychostimulant drugs used for ADHD are MPH and amphetamine (Figure 1), which improve symptoms by blocking the presynaptic dopamine and norepinephrine transporters and increasing catecholaminergic transmission in the striatum, prefrontal cortex, and hippocampus. In the case of non-psychostimulant treatment, this includes atomoxetine which inhibits the transport of norepinephrine [5].

Figure 1. Treatment used for ADHD.

In adults, ADHD treatment aims to improve symptoms but also manage comorbidity. Compared to the treatment of children, the treatment of adults differs, for example, in France, MPH is the only stimulant that treats this disorder, but unfortunately there is no authorization for its use in adults [1,29]. Although the treatment is associated with short-term side effects, such as decreased appetite, anxiety [12,30], sleep problems [31] at the same time, there are long-term effects such as affecting bone health [32]. MPH can induce OS by increasing reactive nitrogen and oxygen species that can alter antioxidant defense mechanisms that may or may not involve enzymes [33,34].

Recent studies confirm the use of probiotics and prebiotics as a therapeutic method in psychiatric disorders, including ADHD [12,35]. Probiotics are live microorganisms found in fermented foods or nutritional supplements [36]. Various research on the brains of animal models of depression and stress show that probiotic treatment could regulate the composition of the gut microbiota and enhance the peripheral levels of the precursor serotonin and tryptophan [36,37]. Moreover, probiotics act by regulating the immune system, restoring intestinal balance and supporting the integrity of the intestinal barrier [35].

3. Oxidative Stress in ADHD

In recent years, more and more studies have reported the influence that OS has on neuropsychiatric disorders, but its mode of action is still unclear [9]. OS shows higher levels in people with ADHD, thus, in children with this disorder, higher levels of malondialdehyde MDA were recorded compared to controls [5]. In numerous randomized, double-blind, placebo-controlled trials, participants with ADHD were found to have lower total oxidant status (TOS) [38,39].

Thus, among the main antioxidants that have been associated with ADHD are glutathione peroxidase [40], catalase [41], superoxide dismutase [42], antioxidant glutathione (GSH) [8], γ-linolenic acid (GLA) [43], melatonin [44], total antioxidant capacity (TAC) [45], glutathione-S-transferase (GST) [46]. There are also other antioxidants known as markers of OS: lipid peroxidation products (LPO) [41], plasma levels of advanced oxidation protein product (AOPP) [41], nitrites + nitrates (Nox) [41], glutathione reductase activity (GRd) [41], total thiols [7], MDA [47], TOS [39] and total antioxidant status (TAS) [39].

GPx is an antioxidant enzyme with a role in combating OS and maintaining redox balance [48]. In a study conducted on 35 ADHD patients from Gazi University Faculty of Medicine, Child and Adolescent Psychiatry Clinic and 35 healthy control patients, a lower level of plasma GPx was reported in ADHD patients compared to the group healthy. Another important enzyme is CAT having a role in the metabolism of H2O2 and reactive nitrogen species [49]. In this case, the activity of the CAT enzyme in plasma was higher than in the case of controls [40,41], and in saliva and serum it showed lower values [45,50]. Also, another study reported a low level of GPx and CAT [46], however, there are also studies in which its values were not significant [41].

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Both in plasma (Table 1) [42,46] and in studies using rat brain [51–53] both reported low levels of SOD, but there are also studies that reported insignificant values [40]. Also, low levels of LPO [41], TAS [38,54,55] and of GST [46], and increased in the case of GSH [8], GLA [43] and GRd [41].

Table 1. Oxidative stress biomarkers from different biological samples and the levels compared to the control.

Sample	Antioxidants	Level compared to control/treatment	Reference
Plasma	GPx	lower	[40]
			[46]
		activity did not change	[41]
	CAT	activity was higher	[40,41]
		lower	[46]
	SOD	not significantly	[42,46]
		lower	[42,46]
	TAS	lower	[38,54,55]
	GSH	high	[8]
	GLA	high	[43]
	LPO	lower	[41]
	AOPP		
	NOx		
	GRd	high	
	total thiols	lower	[7]
	GST	lower	[46]
Serum	SOD1	significantly lower	[56]
	Melatonin	high	[44]
	TAC	lower	[45]
	CAT		
	GSH		
	MDA		
	MDA	high	[47]
		lower	[57]
Saliva	CAT	lower	[50]
Rat brain homogenates-Tx MPH	SOD	lower	[51,58]
	CAT	lower	[51]
	GSH	lower	[58]
	GPx		
Rat brain homogenates	GSH	lower	[53]
	SOD		
	CAT		
	GPx		
not specified	TOS	significantly higher	[39]
	TAS	lower than in the control group	

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AOPP - advanced oxidation protein product plasma levels; CAT - catalase; GLA - acid γ-linolenic; GPx - glutathione peroxidase; GRd - glutathione reductase activity; GSH - antioxidant glutathione; GST - glutathione-S-transferase; LPO - products of lipid peroxidation; MDA - malondialdehyde; NOx - nitrite + nitrate levels; SOD - superoxide dismutase; TAS - total antioxidant status; SOD1 – superoxide dismutase 1; TAC - total antioxidant capacity; TOS - total oxidant status.

4. Food Diet in ADHD

Dietary interventions can influence behavior but also mental health because supplementing or restricting some nutrients or some foods result in positive effects in improving ADHD symptoms [59]. Nutrition has an essential role in neuropsychiatric disorders, thus demonstrating that children with ADHD present micronutrient deficiencies [60]. For the normal development of the brain, a ratio of vitamins and minerals is necessary because their deficiencies can lead to the dysfunction of some brain regions that have a role in the pathogenesis of ADHD [61]. Following a diagnosis of ADHD, the National Institute for Health and Care Excellence in the United Kingdom recommends a balanced diet and nutrition along with regular exercise as drug treatment is not recommended for preschoolers [62]. Also, to reduce ADHD symptoms, the Mediterranean diet is recommended [63], which involves high consumption of saturated and monounsaturated fats and a high consumption of vegetables, fruits, legumes, cereals. Another diet model is the elimination diet which involves the elimination of food additives or food products that have a high degree of allergy. Their concept is based on the link between adverse reactions to certain foods and ADHD disorder [64].

More precisely, there are numerous studies demonstrating the potential role in neurodevelopmental disorders of micronutrients (Table 2) [65–67]. Mg is the most common cation with great physiological importance [68], being involved in the development and functioning of the brain [69]. It is prevalent mainly in plant foods (vegetables, legumes, grains, seeds and nuts), the consumption of which is recommended to reduce ADHD symptoms [70]. Mg deficiency can have common symptoms such as: aggression, fatigue, nervousness and attention deficit [71]. Magnesium supplementation also reduces ADHD symptoms in children [68]. Thus, in a study involving 148 boys aged 4 to 9 years, 44 of them with ADHD, 40 with autism spectrum disorder, and 32 patients with both ADHD and autism spectrum disorder, the authors observed that Mg levels depended on samples studied. Blood serum, urine and hair samples were analyzed and hair Mg is significantly reduced in children with ADHD compared to controls [60].

Table 2. Types of micronutrients and possible effects: focusing on oxidative stress and effects on the brain.

Microutrients	Types	Effects	Food	References
Minerals	Zn	It helps regulate gene expression, has antioxidant properties and can protect against macular degeneration caused by OS	Meat, seafood, fruits and vegetables, cereals, dairy, legumes, nuts	[72,73]
	Fe	An insufficient iron level can be a risk factor for death	It is found in two forms: heme iron, from meat and non-heme iron present in vegetables, legumes, cereals, nuts	[74]
	Mg	It crosses the blood-brain barrier and plays a key role in neuronal maturation and central nervous system function	Vegetables (spinach), pulses, cereals, fruits, nuts	[75,76]

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	Se	It functions as a cofactor of GPx enzymes that have a role in protecting against OS. It reduces lipid oxidation by catalyzing the reduction of peroxides	Vegetables, nuts, fish, grains, meat	[77,78]
Vitamins	B6	Role in neurotransmitter synthesis (gamma-aminobutyric acid, serotonin and dopamine) and stress reduction	Meat, dairy products, beans, nuts, potatoes and more fruits and vegetables	[79,80]
	B12	Essential for DNA function and metabolism. Vitamin B12 deficiency leads to an increase in the pro-inflammatory cytokine IL-6. Proinflammatory cytokines produce inflammation that increases ROS levels and can lead to OS	Meat, milk, eggs and fish	[81,82]
	D	Role in bone metabolism, brain function and regulates Ca. It can stimulate the activity and expression of GGT, which participates in the glutathione cycle between neurons and astrocytes. It increases the level of glutathione to protect neurons, so it can lead to the decrease of ROS	Sun exposure, fatty fish, dairy products, cereals, orange juice, eggs	[34,83]
Polyunsaturated fatty acids	ω-3 PUFAs	They can prevent chronic diseases, reduce lipoperoxidation levels, reduce the ratio of SOD/CAT enzymes. High doses of omega 3 fatty acids can trigger OS	Fish (mackerel, salmon), microalgae and some microorganisms	[84–86]

Ca – calcium; CAT - catalase; Fe – iron; GGT - gamma-glutamyl transpeptidase; GPx - glutathione peroxidase; IL-6 - interleukin-6; Mg – magnesium; OS – oxidative stress; ROS - reactive oxygen species; Se – selenium; SOD - superoxide dismutase; Zn – zinc; ω-3 PUFAs - Omega-3 polyunsaturated fatty acids.

Zn is also associated with ADHD [87], having a role in the production of melatonin, which is necessary for dopamine metabolism [88]. The main food sources of Zn are: poultry, red meat, seafood, nuts, seeds. Consumption is recommended because Zn has antioxidant properties and can protect against OS [70,72,73]. Children with ADHD have a much lower serum Zn level [89]. In 2020, Robberecht, et al. observed lower Zn levels in hair and nails in children with ADHD [68]. Another study demonstrated that 6 to 10 weeks of Zn and Fe supplementation improved ADHD symptoms [90].

Another important micronutrient is Fe known for its role in basic brain function [91]. As a cofactor of tyrosine hydroxylase, its deficiency leads to lower dopamine production, resulting in increased ADHD symptoms, affecting behavior [68]. Fe supplementation shows clinical utility in patients with ADHD [92]. In the etiology of ADHD, Fe deficiency is one of the basic nutritional factors, with a role in the basic functions of the brain, myelination, the development of

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oligodendrocytes and the synthesis of neurotransmitters [93]. However, there are other micronutrients with a role in reducing ADHD symptoms, among them are Se, Cu, the latter, having. Se is found in foods such as: vegetables, fish and meat. It functions as a cofactor of GPx enzymes that have a role in protecting against OS [77,78], and the high Cu/Zn ratio may contribute to the risk of ADHD [68].

Vitamins are organic compounds obtained through diet, with the exception of vitamin D which is synthesized by exposing the skin to the sun [94]. Thus, in addition to exposing the skin to the sun, there are also some foods, such as: fish, dairy products, cereals, orange juice and eggs [34,83]. Vitamin D deficiency has been associated with neurodevelopmental disorders, including attention deficit hyperactivity disorder, and its deficiency affects the expression of synaptic proteins [95]. On the other hand, vitamin B6 is found in meat, dairy products, nuts, fruits and vegetables [80], and vitamin B12 in meat, milk, eggs and fish [79]. Lower levels of B vitamins: B2, B6, B9, B12 were significantly associated with ADHD. Vitamin B12 is involved in catalyzing the conversion of homocysteine into methionine, through methionine synthase, an essential reaction in the nucleotide synthesis process [94]. Both vitamin B6, B12 and vitamin D have a role in reducing OS [34,79–83].

At the same time, deficiencies of some unsaturated fatty acids may contribute to ADHD [96]. PUFA are essential for normal neurotransmitter function [97]. ω-3 PUFAs are found in fish, microalgae and some microorganisms and have the role of reducing the ratio of SOD/CAT enzymes [84–86]. Supplementation with Omega-3 fatty acids can improve ADHD symptoms [63] and the ratio of ω-3 to ω-6 PUFA can be much more effective [98]. More specifically, fish oil supplementation is the most promising dietary intervention

Regarding diet as an option for ADHD, it mainly consists of dietary supplements with minerals, vitamins and PUFA (Table 3) [12]. Because sugar, sweets, artificial food colors, and preservatives are associated with ADHD symptoms [99,100], some authors recommend eating fruits, vegetables, fish, and other foods high in PUFA and other micronutrients to protect against OS and reduce the risk of ADHD [12]. Mg is mainly found in plant foods (vegetables, legumes, grains, seeds and nuts), their consumption is recommended to reduce ADHD symptoms. Also, Zn is found in food sources such as: poultry, red meat, seafood, nuts, seeds [70].

However, there are numerous studies (Table 3) confirming that micronutrient supplementation can improve symptoms of attention deficit hyperactivity disorder. In addition, supplementation with 150 mg Zn for 12 weeks had a positive result [46], while administration of a smaller amount (15 mg) for 13 weeks did not have a positive effect, and the researchers does not recommend this dose [46]. In another study involving 52 patients aged 7–14 years, 0.5–1 mg/kg/day of Zn was administered for 6 weeks alongside MPH treatment, this study, confirming the positive effect of Zn [89].

Table 3. Micronutrients supplementation in people with ADHD.

Supplements	Number of participants (n=)	Age (years)	Dose	Time	Result	References
Zn	400	9.61 ± 1.7	150 mg zinc sulfate	12 weeks	Positive effects on the symptoms of ADHD	[101]
	52	6 – 14	15 mg every morning or two times per day + amphetamine	13 weeks	it had no effect	[102]
	60	9.6 ± 1.70	0,5–1mg/kg/day methylphenidate + 10 mg Zn	6 weeks	Significantly improved attention	[89]

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Fe	23	5 – 8	80 mg/day ferrous sulfate	12 weeks	Improves ADHD symptoms in children with low serum ferritin levels	[103]
Mg	50	7 – 12	200 mg/day	6 months	Positive response to Mg supplementation	[104]
Vitamin D	96	9.76 ± 2.38	50,000 UI/week 25-hydroxy-vitamin D3	6 weeks	A positive effect on ADHD symptoms	[105]
	35	7 – 14	3000 IU/day 25-hydroxy-vitamin D3	12 weeks	may improve cognitive functions related to ADHD	[106]
Mg + Vitamin D	74	6 – 12	vitamin D (50.000 UI/week) + Mg supplements (6 mg/kg/day)	8 weeks	Reduced social problems and anxiety in children with ADHD	[107]
ω-3 PUFAs	40	8 – 14	10 g of full fat (80%) margarine daily enriched with either 650 mg of EPA/DHA	16 weeks	ω-3 PUFA supplementation may increase the performance of pharmacological treatments of ADHD	[108]

DHA - docosahexaenoic acid; EPA - eicosapentaenoic acid; Fe – iron; Mg – magnesium; n - number of participants; IU - International Units; Zn – zinc; ω-3 PUFAs - Omega-3 polyunsaturated fatty acids.

Another study of 23 participants aged 5–8 years confirmed that 80 mg/day of ferrous sulfate for 12 weeks improved ADHD symptoms in children with low serum ferritin [103]. Furthermore, supplementation with 200 mg/day of Mg for 6 months showed a positive effect on ADHD symptoms [104].

In another study, 74 participants were supplemented for 8 weeks with 50,000 IU/week of vitamin D and 6 mg/kg/day of magnesium supplements, the study, having a positive result, because vitamin D and magnesium supplementation at children with ADHD reduced behavioral problems, social problems and anxiety [107].

Vitamin D supplementation also improved ADHD symptoms [106,107], this fact being observed both in the study in which 96 patients were given 50,000 IU /week 25-hydroxy-vitamin D3 for 6 weeks [105], as well as in the study in which 35 patients aged between 7 and 14 participated who were administered 3000 IU/day 25 -hydroxy-vitamin D3 over a period of 12 weeks [106].

The effect of supplementation with ω-3 PUFA was tested on 40 patients aged between 8-14 years, who were given 10 g daily of margarine enriched with either 650 mg of eicosapentaenoic acid/ docosahexaenoic acid, for 16 weeks, and the result was positive [108].

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5. ADHD vs Gut-Brain Axis

In the last decade, researchers have paid special attention to the link between gut microbiota and neurodevelopmental disorders, highlighting some potential correlations [37]. Communication between the gastrointestinal tract and the brain is achieved through the gut-brain axis. This bidirectional communication includes the brain, central nervous system, spinal cord, enteric nervous system, autonomic nervous system, and hypothalamic-pituitary-adrenal (HPA) axis. [109]. Thus, HPA plays a crucial role in maintaining body homeostasis and its regulation occurs mainly by changing cytokine secretion [35]. With the GBA, diet can exert its activity on ADHD, this communication system between the enteric nervous system and the central nervous system includes emotional and cognitive centers of the brain [110]. DNA sequencing can investigate the microbial composition and what role it plays in the pathogenesis of ADHD [110].

The gut microbiota consists of six major phyla: *Firmicutes*, *Bacteroides*, *Actinobacteria*, *Proteobacteria*, *Verrucobacteria* and *Fusobacteria* [22] that perform complex functions, including food and drug metabolism [37]. The gut microbiota has been linked to human metabolism, gut homeostasis, brain behavior and immune development [37]. Gut microbiota has been found to play a particular role in health and neuropsychiatric disorders, as it can affect mental health and brain activity. [111]. Gut microorganisms can influence central nervous system processes by regulating the immune system and via the vagus nerve [37]. The vagus nerve is considered a vital channel for two-way communication between the brain and gut, which can differentiate between pathogenic and non-pathogenic bacteria [64]. Microorganisms that are part of the intestinal microbiota participate in the food digestion process by secreting digestive enzymes and transforming complex nutrients into simple organic compounds. Another role that the gut microbiota fulfills is the synthesis of vitamins, especially those of the B complex [35].

Gut microorganisms produce various metabolites, such as short-chain fatty acids (SCFA). SCFA are considered the main class of biological products of the intestinal microbiota that can be obtained by fermentation of dietary fibers. Although the fermentation process of dietary fiber is essential in regulating the composition of the gut microbiota, SCFA can influence the health of the host from the cellular, tissue to organ level. Abnormalities in the production of these metabolites have been associated with ADHD symptoms [112].

The imbalance of intestinal microbiota, also known as dysbiosis, is caused by the growth of inflammatory microorganisms that can affect intestinal permeability, causing systemic inflammation through microbial translocation. In addition, dysbiosis can cause OS that affects neuronal cells and neurotransmitters related to ADHD [109]. In numerous investigations, researchers highlight the difference between the gut microbiome of ADHD patients and that of controls [110,113]. In a study evaluating the differences between the gut microbiome in ADHD patients and healthy controls, stool samples from 209 patients were analyzed, and it was found that there was a significant difference in the composition of the faecal microbiome in adult ADHD patients. compared to controls [113].

In another study in which the composition of the gut microbiota was analyzed, the authors found that drugs taken to treat ADHD can affect the gut microbiota. The most numerous genus of bacteria associated with ADHD symptoms is the genus *Coproccocus* [110]. On the other hand, in the study conducted by Aarts and colleagues in 2017, 96 participants were considered, 19 of them with ADHD and 77 healthy. The microbiome of people with ADHD was compared to the microbiome of humans by analyzing the 16S microbiome, and the result showed that the genus *Bifidobacterium* is much higher. [114]. In addition, in the study conducted by Sukmajaya et al. in 2021, a total of 49 bacterial taxa were differentiated between individuals with ADHD and healthy people, therefore, it is difficult to say which taxa differ the most in ADHD [109].

6. Conclusions

According to our analysis, further research is needed on the diagnosis of ADHD in adults. Although most studies focus on micronutrient supplementation in children and adolescents, a healthy diet is necessary to reduce ADHD symptoms. A healthy diet means eating fruits, vegetables, legumes and other foods rich in dietary fiber that play a role in maintaining a balanced microbiota.

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Other diets, such as the Mediterranean diet and the diet to eliminate certain foods that can cause side effects, have also been shown to improve ADHD symptoms. It is especially important to maintain a healthy microbiota to prevent the onset of neuropsychiatric disorders.

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