Chapter 16

Updates on the Use of Natural Treatments for Attention-Deficit Hyperactivity Disorder (ADHD)

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood characterized by the three core symptoms of hyperactivity, impulsiveness, and sustained inattention. While the etiology of ADHD remains unknown, several studies suggest ADHD pathophysiology to involve frontal network abnormality and dysregulation of catecholaminergic and dopaminergic functions. Stimulants, which are structurally similar to endogenous catecholamines, are the most commonly prescribed drugs for treatment of ADHD, but are classified as Schedule II based on the Controlled Substances Act due to high likelihood for diversion and abuse. Non-stimulant medications, as well as antidepressants, have also been used in ADHD treatment but have been found to be inferior to stimulant interventions and to cause intolerable side effects. The search for safer yet effective ADHD treatments led to a growing interest in natural medicines and a host of other complementary and alternative treatments for ADHD. While the use of these therapies is well documented, not much is known about their safety and efficacy. In this chapter, we describe current evidence-based complementary and alternative therapies for ADHD, focusing on nutritional and botanical agents, and provide details on the performance of these agents in clinical trials. Here, we discuss the rationale for the use of natural products for ADHD, mention the potential mechanisms of action of these treatments, and highlight safety and efficacy issues associated with the use of these treatments. In conclusion, we give an exhaustive update on the use of nutritional and botanical medicines as complementary and alternative ADHD therapies for ADHD, which

could potentially provide important information on the efficacy and safety of these types of interventions.

Keywords: ADHD, natural, herbal, botanical, nutritional

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder of childhood, characterized by the three core symptoms of hyperactivity, impulsivity, and inattention [1]. Diagnosis of ADHD has been on the rise since it was recognized as a specific disorder in the 1970s. Currently, the worldwide prevalence rate of ADHD is approximately 5%, making it the most common psychiatric disorder among children [2]. In addition, although most frequently diagnosed during childhood, ADHD may affect an individual throughout life [3]. Given its serious academic, social, and familial consequences, along with the risk of incurring comorbid conditions and later substance abuse, it is imperative to develop efficacious treatments for ADHD [4].

2. Treatment of ADHD: An overview

Numerous treatment strategies for ADHD have been implemented over the years. Conventional treatment usually includes a pharmaceutical and a non-pharmacological intervention such as behavioral/psychosocial approaches. We describe in the following text some of the widely used pharmacological and non-pharmacological ADHD treatments as well as safety and efficacy and issues or limitations associated with the use of these interventions.

2.1. Pharmacological interventions

ADHD has been associated with dysfunctions in catecholaminergic function in the brain [5]. The fact that medications that increase brain catecholamine levels have been shown to alleviate ADHD symptoms provided solid support for the use of pharmacological treatments for ADHD [5]. Drugs used in managing ADHD are classified as stimulant and non-stimulant medications. Stimulant or psychostimulant drugs are the most common pharmacological intervention for ADHD [6, 7]. These drugs (e.g., methylphenidate and dextroamphetamine) are structurally similar to endogenous catecholamines. They work by increasing extracellular dopamine and norepinephrine levels in order to restore the dysregulated neurotransmitter balance in the brain of ADHD patients [5]. Methylphenidate (Ritalin® or Concerta®) is the most prescribed and used psychostimulant accounting for around 70% of ADHD patients who are under stimulant treatment [6, 8, 9].

Non-stimulant medications such as the norepinephrine specific reuptake inhibitor, atomoxetine, as well as antidepressants such as imipramine, phenelzine, and bupropion have also been

used in the treatment of ADHD [9, 10]. Similar to psychostimulants, these drugs act by increasing catecholamine levels in the brain, thus correcting the perceived neurotransmitter imbalance. However, non-stimulants have been found to be inferior to stimulant drugs on efficacy endpoints [6, 10].

Although pharmacological interventions generally improve ADHD symptoms for most children, as many as 20–30% of children either do not respond to these drugs or are unable to tolerate them due to the wide range of side/adverse effects they may produce [11, 12]. Common side effects associated with stimulant use are decreased appetite, insomnia, and headache [11]. Other side effects such as motor tics, abdominal pain, irritability, nausea, and fatigue have also been reported [9, 13]. For this reason, some parents are unwilling to medicate their children with stimulants due to concerns about the safety and risks associated with the long-term use. In addition, stimulants also have a high likelihood for diversion and abuse, and are classified as Schedule II based on the Controlled Substances Act. This is a major concern since ADHD has also been associated with increased risk of substance use disorder [14].

2.2. Non-pharmacological interventions

A variety of non-pharmacological interventions is available for treating ADHD. These treatment strategies can either be used alone or in combination with pharmacological therapy [13]. Behavioral therapy, also known as behavioral modification, is one of the most common, effective, and accepted non-pharmacological treatment for ADHD. This therapy, which typically involves reinforcing desired behaviors through rewards and praise and decreasing problem behaviors by setting limits and consequences, has shown great promise particularly in youth and adults with ADHD [15, 16]. Another form of behavioral therapy is social skills training. This is conducted in a group setting where a therapist or a teacher demonstrates appropriate social behaviors and then encourages patients to repeat and practice those behaviors [16, 17]. Other potential approaches include memory training through the use of computer software (Cogmed), electroencephalography biofeedback or neurofeedback, exercise, yoga, meditation, acupuncture, and green space [12, 18, 19]. As these therapies are not widely available, only a few patients can benefit from the effects of behavioral therapy. Despite the fact that these interventions are easy to implement, time demands, the need of a professional therapist, and participation by family members and teachers also limit the use of behavioral ADHD treatments.

Over the years, there has been much interest and controversy on the importance of food and diet and its potential role in ADHD and ADHD symptomatology [20]. Some food items have been shown to cause or worsen ADHD symptoms in children. The strategy, therefore, is to identify offensive food items and eliminate these items from the child's diet in order to prevent or minimize the occurrence of ADHD symptoms. This can be done by eliminating the particular food item (single-food elimination) or multiple food elements that are most commonly reported to cause ADHD symptoms. Common culprits include sugar, dairy products, junk foods, food additives, preservative, and others [18, 21]. Another dietary regimen that has been gaining support is the "oligoantigenic" or "few foods" diet, which entails strict removal of nearly all foods, except a limited number that have been proven to cause no problems or are

deemed "hypoallergenic" [18, 19, 21]. However, due to inadequate research on the efficacy of these regimens, employing dietary modifications to treat ADHD is still controversial. Furthermore, continued compliance and nutritional imbalances are causes of concern for dietary treatments.

3. Natural health products for ADHD

3.1. Rationale for the use of natural health products

In view of the safety and efficacy issues of current pharmacological interventions, and the desire for safer yet effective ADHD treatments, there has been a growing interest in natural health products (e.g., botanical/herbal medicines, vitamins, and minerals) and other complementary and alternative medicines for ADHD [12, 18, 19]. It has been estimated that more than 50% of parents of children with ADHD treat their child using one or more of these products [22-25]. Despite their growing popularity, physicians are still reluctant to recommend these products, as they question the efficacy of these treatments. Thus, only a few families disclose the use of these products to their child's physician [18, 24, 25]. Research is still underway to demonstrate the effectiveness of natural products in the treatment of ADHD. In the following sections, we describe some of the widely used natural medicines for ADHD, discuss the potential mechanism of action of these agents, and give updates on their performance in recent clinical research.

3.2. Updates on natural treatments for ADHD: evidence from clinical studies

3.2.1. Botanical agents

Botanical agents or herbal medicines are popular alternative treatment for ADHD, as they appeal to parents looking for a more "natural" treatment for their child [12, 18]. Certain botanical agents have shown promise in the treatment of ADHD in light of the findings of clinical trials [Table 1].

Herb	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
Pycnogenol	· Randomized, double-blind, placebo-controlled, study. · 61 children, 6-14 y/o with ADHD (n=44 pycnogenol vs. n=17 placebo).	Significant attenuation of hyperactivity and improvement of attention.	Increased production of nitric oxide that is involved in the regulation of norepinephrine and dopamine release and intake.	Mild side effects, such as a rise in slowness and gastric discomfort, were reported	Trebatická et al., 2006 [26]

Herb	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	· Pycnogenol (1 mg/kg/day) or placebo treatment for 4 weeks.				
	· Randomized, double-blind, placebo-controlled study. · 61 outpatient children, 6-14 y/o with ADHD (n= not specified Pycnogenol v. placebo) · Pycnogenol (1 mg/kg/day) or placebo treatment for 4 weeks	Improvement of attention, reduction of oxidative damage to DNA and normalization of the total antioxidant status.	Potent antioxidant properties.	No reported adverse effects.	Chovanová et al., 2006 [27]
	· Randomized, double-blind, placebo-controlled, crossover study. · 24 adults, 24-53 y/o with ADHD (n= not specified Pycnogenol vs. placebo vs. methylphenidate) · Duration of treatment is 3 weeks	Neither methylphenidate nor Pycnogenol outperformed the placebo control on any ADHD rating scale employed.			Tenenbaum et al., 2002 [30]
St. John's Wort *(Hypericum perforatum)*	· Randomized, placebo-controlled trial. · 3 adolescents, 14-16 y/o with ADHD (n=2 St. John's Wort v. n=1 placebo). · St. John's Wort (30 mg/day) or placebo treatment, for 4 weeks.	Improvement of hyperactivity, inattention and immaturity symptoms.	Inhibition of serotonin and norepinephrine reuptake.	No reported adverse effects.	Niederhofer H., 2010 [33]
	· Randomized, double-blind, placebo-controlled trial.	No significant improvement in ADHD symptoms.	Inhibit serotonin and norepinephrine reuptake	No reported adverse effects.	Weber et al., 2008 [34]

Herb	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	· 56 children, 6-17 y/o with ADHD (n=27 SJW v. n=27 placebo). · *H. perforatum* (300 mg) or placebo, 3 times a day for 8 weeks.				
Gingko Biloba	· Open clinical pilot study · 20 children with ADHD · Ginkgo (EGb 761®), 240 mg daily, was administered for 3 to 5 weeks.	Improvement of ADHD core symptoms.	Elevation of brain electrical activity, particularly in contingent negative variation (CNV) amplitude.	A very low rate of mild adverse effects occurred during the observation period.	Uebel-von Sanderslebe n et al., 2014 [36]
	· Randomized, double-blind controlled trial. · 50 children, 6-14 y/o with ADHD(n=25 Ginkgo biloba vs. n=25 methylphenidate) · *Gingko biloba* (80-120 mg/day) or methylphenidate (20-30 mg/day), for 16 weeks.	Gingko Biloba was less effective than methylphenidate in the treatment of ADHD.	Reverse inhibition of MAO-A and MAO-B.	Lesser side effects (headache, insomnia, and loss of appetite) than methylphenidate	Salehi et al., 2010 [35]
Gingko Biloba and Ginseng	· Open, pilot study. 36 children, 3-17 y/o with ADHD. · Combination of herbal product containing American ginseng extract, *Panax quinquefolium* (200 mg) and *Gingko Biloba* extract (50 mg), twice a day (empty stomach) for 4 weeks.	Improvement in various attributes (anxiety, social, hyperactive-impulsive) of ADHD.	Gingko Biloba can reverse the reduction of 5-HT_{IA2} and noradrenergic receptors. It also stimulates synaptic plasticity, increased blood glucose utilization, reduces lactate and pyruvate, increases dopamine and norepinephrine, and promotes nerve growth.	Five (14%) subjects reported adverse events (more emotional & more impulsive, more hyperactive and more aggressive, sweating, headache, tiredness), only 2 of which were considered related to the study medication.	Lyon M.R. et al., 2001 [37]

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Herb	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
Ginseng	· Observational study · 18 children, 6-14 y/o with ADHD. · Korean red ginseng (1000 mg) twice a day, for 8 weeks.	Korean red ginseng improved inattentiveness in ADHD children.	Ginseng can boost dopamine and norepinephrine levels in the brain.	Some participants complained bad taste and a degree of repulsive feeling.	Lee et al., 2011 [38]
	· Randomized, double-blind, placebo-controlled clinical trial. · 70 children, 6-15 y/o with ADHD (n=33 Korean red ginseng v. n=37 placebo). · Korean red ginseng extract (1000 mg) and placebo, twice a day for 8 weeks.	Ginseng extract significantly improved the inattention/ hyperactivity symptoms of ADHD.	Ginseng can reduce the production of the adrenal corticosteroids, cortisol, and dehydroepiandrostero ne (DHEA).	No serious adverse reactions reported apart from loose stool by one patient from the Ginseng group.	Ko et al., 2014 [39]
Valerian *(Valeriana officinalis)*	· Double-blind, placebo-controlled pilot study. · 30 children, 5-11 y/o with ADHD (n=10 Valeriana officinalis mother tincture (VOMT) or n=10 3x potency of VOMT v. n=10 placebo, for 3 weeks)	Significant improvement in ADHD symptoms was found from VOMT or 3x potency group, in comparison to placebo	Valerian's main active compound, valerenic acid, inhibits the breakdown of GABA in the central nervous system, an action similar to that of benzodiazepine drugs.	No reported side/ adverse effects.	Razlog et al., 2011 [40]
Ningdong granule	· Randomized, double-blind, methylphenidate-controlled trial. · 72 children, 6-13 y/o with ADHD (n=36 Ningdong v. n=36 methylphenidate). · Ningdong (5 mg/kg/ day) vs methylphenidate (1	Similar to methylphenidate, Ningdong granule ameliorated ADHD symptoms.	Regulation of dopaminergic activity by increasing homovanillic acid content of in sera.	Hypersomnia was reported as Ningdong granule's side effects. Methylphenidate had more side effects than Ningdong granule.	Li et al., 2011 [41]

Herb	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	mf/kg/day), for 8 weeks.				
Bacopa *(Bacopa monniera)*	· Open-label study · 31 children, 6-12 y/o with ADHD. · Standardized *Bacopa monniera* extract (SBME) (225 mg/day), for 6 months.	SBME significantly reduced ADHD symptom; reduced scores in restlessness, impulsiveness, learning problems, impulsivity, and psychiatric problems.	Bacopa was shown to increase dopamine levels in the cortex. In addition, it also possesses neuroprotective, antioxidant, and memory-enhancing effects.	SBME was found to be safe and tolerable in children. Only mild gastrointestinal side effects (e.g. nausea) were observed in 3 subjects.	Dave et al., 2014 [42]

Table 1. Botanical agents for ADHD

3.2.1.1. Pycnogenol® (French maritime pine bark extract)

Pycnogenol® is a standardized extract from the bark of French maritime pine (*Pinus pinaster*). This extract was reported to have a rich store of phenolic acids, catechin, taxifolin, and procyanidins, each with diverse biological effects. A number of studies have suggested that Pycnogenol® may be beneficial for ADHD and its symptoms. Of note, a double-blind, placebo-controlled study of 61 children (ages 6–14 years old) found that Pycnogenol® (1mg/kg/day) ameliorated the symptoms of ADHD including reduced hyperactivity, increased attention, and improved visual-motor coordination [26]. Only mild side effects (a rise in slowness and gastric discomfort) were reported. These benefits of Pycnogenol® on ADHD symptoms were attributed to its ability to increase nitric oxide production. Nitric oxide plays a role in the regulation of norepinephrine and dopamine release and intake [26]. Another study (randomized, double-blind, placebo-controlled) also reported that Pycnogenol® administration (1 mg/kg/day) improves attention of ADHD children, coupled with reduction of oxidative damage to DNA and normalization of total antioxidant status [27]. The potent antioxidant properties of Pycnogenol® are thought to be beneficial to ADHD given the presumed role of oxidative stress in the etiology of this disorder [28]. Pycnogenol® was also shown to normalize urinary catecholamine concentration of children with ADHD [29] and is believed to act as a vasodilator improving cerebral blood flow to brain regions involved in ADHD [19]. Contrastingly, Tenenbaum *et al.* [30] reported that Pycnogenol® failed to produce treatment effects in adults (24–53 years old) with ADHD over a period of 3 weeks. However, it should be noted that in this study neither Pycnogenol® nor the positive control, methylphenidate, outperformed placebo on any ADHD rating scale [31]. In summary, Pycnogenol® is a promising botanical alternative for the management of ADHD and its symptoms; however, more studies are needed before it can be used as a stand-alone ADHD treatment.

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3.2.1.2. St. John's wort (Hypericum perforatum)

St. John's wort is best known for its antidepressant effects. It is an alternative option for treating mild-to-moderate depression, even in children under the age of 12, with few side effects [18]. This herb was also demonstrated to have beneficial effects on other psychiatric disorders, including major depression, bipolar depression, obsessive-compulsive disorder, social phobia, and somatization disorder [32]. It has been suggested that the effects of St. John's wort may be related to its ability to inhibit the reuptake of serotonin, norepinephrine, and dopamine [33]. For this reason, the effect of St. John's wort was tested in a preliminary study in three ADHD patients (14–16 years old) and the result showed that St. John's wort improved ADHD symptoms [33]. In contrast, a much more rigorous (randomized, double-blind, placebo-controlled) trial reported that St. John's wort (300 mg/day) did not improve ADHD symptoms in 54 children (aged 6–17 years old), after 8 weeks of intervention [34]. Thus, the effects of St. John's wort on ADHD is still unclear, necessitating further studies.

3.2.1.3. Ginkgo biloba

Ginkgo biloba is a unique species of a tree native to East Asia. The memory enhancing effects of *G. biloba* has been extensively studied, and it is being utilized as an alternative treatment for memory impairment and dementia [35]. Some studies also reported that the ginkgo has beneficial effects on ADHD. Uebel-von Sandersleben *et al.* [36] reported that *G. biloba* (240 mg, daily) improved core symptoms of ADHD in children, following 3–5 weeks of treatment. *G. biloba* (50 mg) was also found to alleviate ADHD symptoms in children (36 kids, ages 3–17), when administered with ginseng (200 mg), over the course of 4 weeks [37]. In this study, minor side effects were observed (e.g., subjects became more emotional and more impulsive, more hyperactive and more aggressive, sweating, headache, tiredness) [37]. The beneficial effects of *G. biloba* on ADHD are attributed to its various activities such as (1) improvement of cerebrovascular blood flow that may help reduce hyperactivity due to lack of focus, (2) reversal of 5-HT1A and noradrenergic receptor reductions, and (3) inhibition of both MAO-A and MAO-B in the brain [35, 37]. However, a 6-week double-blind randomized controlled trial by Salehi *et al.* [35] found that *G. biloba* (80–120 mg/day) was less effective than methylphenidate in managing ADHD symptoms in a sample of 50 children.

3.2.1.4. Ginseng

Ginseng has been shown to improve ADHD symptoms [37]. Ginseng, both American (*Panax quinquefolius*) and Asian (*Panax ginseng*), is known to produce beneficial effects on the body. Ginseng species contain a class of phytochemicals called ginsenosides, which are known as potent antioxidants and exert neuroprotective properties [38, 39]. Ginsenosides have also been reported to boost levels of dopamine and norepinephrine in the brain. In this sense, ginseng may effectively alleviate symptoms of ADHD. Indeed, an observational clinical study showed that Korean red ginseng (KRG) (*Panax ginseng*), given at 1,000 mg, twice a day, for 8 weeks, improved inattentiveness in children (18 kids, ages 6–14) with ADHD [38]. In addition, a double-blind randomized placebo-controlled trial reported that 100 mg of KRG, taken twice a day, decreased inattention and hyperactivity scores of ADHD children (ages 6–15 years old),

after an 8-week treatment period [39]. Side effects associated with ginseng use included perspiration, headache, fatigue, and a degree of repulsive feeling experienced by patients due to the unique flavor of red ginseng [38]. Thus, ginseng has the potential to be used as a complementary and alternative therapy for ADHD, provided that its efficacy and safety issues are resolved.

3.2.1.5. Valerian (Valeriana officinalis)

Valerian is a perineal plant that is known to have sedative and antispasmodic effects. Valerian has been used as a treatment for insomnia, restlessness, and anxiety [12]. Its application in the management of ADHD has also been evaluated. In a double-blind, placebo-controlled, pilot study, it was shown that treatment with Valerian tincture for two weeks improved ADHD symptoms in children (30 kids) aged 5–11 years old [40]. The effects of Valerian are thought to be facilitated by the action of valerenic acid, one of its major components, on the gamma-aminobutyric acid $(GABA)_A$ receptor. Valerian is generally safe and its use on children ages 3–12 years is approved by the European Scientific Cooperative on Phytotherapy, provided that it is used under medical supervision [12, 18, 40]. Nevertheless, the use of valerian as an alternative treatment for ADHD is limited by the insufficient clinical evidence supporting its efficacy.

3.2.1.6. Ningdong

Ningdong granule (NDG) is a Chinese medicinal preparation that has been used for various medicinal purposes for many years now. As it showed therapeutic benefits in the treatment of Tourette syndrome [41], the effects of Ningdong were evaluated in ADHD patients. Accordingly, Li *et al.* [41] performed a randomized, methylphenidate-controlled, double-blinded trial, where 72 children with ADHD were given NDG (5 mg/kg/day) or methylphenidate (1 mg/kg/day) for 8 weeks. Results showed that NDG has equivalent effect to methylphenidate in improving ADHD symptoms, but with lesser side effects. They also reported that NDG was well tolerated by children with ADHD as revealed by blood, urine, and stool analysis, and renal and hepatic function assessments. Interestingly, levels of homovanillic acid, which is involved in the regulation of dopamine, in the sera increased in the NDG group without causing any change in dopamine concentration. Thus, the authors suggested that NDG is a promising, safe, and effective alternative therapy for ADHD. However, more research needs to be done before NDG can be used as an alternative ADHD treatment.

3.2.1.7. Bacopa (Bacopa monniera)

Bacopa also known as water hyssop or Brahmi is an Ayurvedic medicine that has been used for many centuries for its positive effects on memory, learning, and concentration. Preliminary studies have shown that Bacopa has benefits (i.e., improvement in memory and learning tasks) in children with ADHD [12]. These findings were supported by an open-label study demonstrating that Bacopa extract (225 mg/day), given for a period of 6 months, significantly alleviated the ADHD symptoms of 31 children, ages 6–12 years old [42]. The positive effects

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of Bacopa on ADHD are thought to be achieved via cholinesterase inhibition, dopamine regulation, neuroprotective, and/or antioxidant effects [12, 42]. Bacopa was well-tolerated by children, with only mild gastrointestinal side effects (nausea) reported [42]. Further studies (e.g., double-blind, randomized clinical trials) are necessary to verify the efficacy of this botanical agent as a therapy for ADHD.

3.2.2. Nutritional medicines/supplements

Studies have shown that certain vitamins and minerals may also play a role in the pathology of ADHD. Accordingly, a multitude of vitamins, minerals, and other nutritional supplements have been proposed as complementary and alternative treatment for ADHD [Table 2].

Supplement	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
Vitamin B6 and Magnesium	· Open study · 76 children (40 ADHD children & 36 healthy children) · All children were given a magnesium-vitamin B6 (Mg-B6) regimen (6 mg/kg/d Mg, 0.6 mg/kg/d vit-B6) for 8 weeks.	Mg-B6 treatment significantly attenuated hyperactivity and aggressiveness. School attention was also improved.	Vitamin B6 facilitates the production of the serotonin. Magnesium has been shown to be a non-specific inhibitor of calcium channels, and could act as NMDA channel inhibitor. In the same way, it could also influence catecholamine signaling in the brain.	No reported side effects	Mousain-Bosc et al., (2006) [43]
Zinc	· Randomized, double-blind, parallel-group placebo-controlled · 400 children 6-14 y/o (n=202 zinc vs. n=198 placebo) · 150 mg zinc sulfate or 150 mg sucrose (placebo) daily for 12 weeks	Zinc sulfate was better than placebo in decreasing hyperactivity, impulsivity and improving socialization, but not inattention.	Deficiency in zinc is suggested to play a role in hyperactivity, concentration impairment and delay of cognitive development.	No serious side effects reported. However, metallic taste was a common complaint.	Bilici M et al., (2004) [47]
	· Randomized, double-blind, placebo-control · 44 children, 5-11 y/o (n=22 methylphenidate	Significantly greater treatment effects were observed in zinc sulfate with	Zinc regulates dopamine function, indirectly, through its action on melatonin.	Nausea and metallic taste were frequent complaints from	Akhondzadeh et al., (2004) [46]

Supplement	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	+zinc vs. n=22 methylphenidate +placebo) · Methylphenidate 1mg/kg/day; 55 mg/day zinc sulfate; sucrose (placebo) 55 mg, for 6 weeks	methylphenidate over placebo with methylphenidate.		the participants. Overall, it was well tolerated.	
	· Randomized, double-blind, placebo-controlled, pilot trial · 52 children 6-14 y/o (n=20 Zinc_1 or n=8 Zinc_2 v. n=24 placebo) · Zinc_1 15 mg/day (once a day) or Zinc_2 30 mg/day (twice a day) or placebo (8 weeks); amphetamine 5-15 mg/ daily (based on the weight) · Duration of experiment was 13 weeks (8 weeks controlled + 5 weeks amphetamine add-on)	No appreciable difference between both dosages of zinc and placebo The addition of amphetamine to zinc supplementation did not alter the result.	Zinc is an important cofactor in the metabolism of relevant to neurotransmitters, prostaglandins, and melatonin and indirectly affects dopamine metabolism. Specific to ADHD, the dopamine transporter has a zinc building site that blocks transport.	1 patient reported gastrointestinal discomfort.	Arnold L et al., (2011) [48]
Iron	·Randomized, double-blind, placebo-controlled, pilot trial · 23 children with low serum ferritin level (<30 ng/mL) 5-8 y/o (n=18 iron vs. n=5 placebo) · 80 mg ferrous sulfate tablets or placebo once daily in the morning for 12 weeks	Iron supplementation significantly improved hyperactive/ impulsive and inattentive symptoms of ADHD.	Iron is a co-factor in the synthesis of both norepinephrine and dopamine. Iron deficiency was also strongly suggested to correlate with ADHD and restless leg syndrome.	Minor side effects were reported, such as nausea, constipation, and abdominal pain.	Konofal E et al., (2008) [49]

Supplement	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	· Randomized, double-blind, placebo-controlled · Initially, 41 children participated but were reduced to 29 children due to side effects, 8-12 y/o (n=15 HUFA v. n=14 placebo) · *Highly unsaturated fatty acid (HUFA) supplement (*daily doses: EPA 186 mg, DHA 480 mg, γ-linolenic acid 96 mg, vitamin E 60 IU, *cis*-linoleic acid 864 mg, AA 42 mg and thyme oil 8 mg) or olive oil (placebo), for 12 weeks	HUFA supplementation significantly attenuated ADHD-related symptoms.	HUFA can profoundly influence signal transduction.	A digestive upset and difficulty of swallowing were the only documented complaints.	Ricahrdson and Puri B. (2002) [53]
Essential fatty acid supplement	· Open-label, proof-of-efficacy pilot study · 9 children 8-16 y/o · 16.2 g EPA/DHA concentrates per day. The dosage was adjusted dependent on the ratio of arachidonic acid (AA) to EPA in the isolated plasma phospholipids at four weeks	High dose of EPA/DHA supplement improved ADHD-related symptoms	Children with ADHD were found to have low levels of LC PUFAs, including AA, EPA and DHA in the plasma phospholipids, as well as high ratio of AA to EPA.	One participant reported of loose stools while taking 30 ml of the liquid of EPA/DHA concentrate per day.	Sorgi P et al., (2007) [52]
	· Randomized, double-blind, cross-over, placebo-controlled · 132 children (104 completers) 7-12 y/o (n=36 PUFAs v. n= 41 PUFA + micronutrients v. n=27 placebo)	Significant treatment effects were found for parents rating of ADHD symptoms in both PUFA treatment groups compared to placebo.	PUFAs are key components all cellular and intracellular membranes or phospholipids, where they perform vital structural and chemical functions	No reported adverse effects.	Sinn N and Bryan J, (2007) [55]

Supplement	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	· Six PUFA capsules 400 mg fish oil and 100 mg evening primrose oil or six palm oil (placebo) capsules a day, for 15 weeks	Single crossover (placebo to PUFA) for another 15 weeks reiterated these results. No additional effects from micronutrients are noted.	Other nutrients and vitamins are involved in the PUFA role of synthesizing prostaglandins, chemicals with important biological roles in brain function		
	· Randomized, one-way cross-over, placebo-controlled (Phase 1 double-blind; phase 2 single blind) · 7-12 y/o Phase 1- 132 children with ADHD (n= not specified) PUFA vs. PUFA+ multivitamins/ minerals vs. placebo, for 15 weeks · Phase 2- 109 ADHD children (n=not specified) all children were given PUFA+ multivitamins/minerals for another 15 weeks · Six active or six placebo capsules per day	After 15 weeks, improvements from the PUFA group in their ability to switch and control attention compared to the placebo group. Similar observation from the placebo group after taking PUFA supplement from weeks 16-30. No significant improvements in other cognitive measures, or with additional micronutrient supplementation	PUFA have been associated with dopamine activity in the frontal lobes of the brain.	Slight nausea was reported in two patients and one report episodes of nose bleeding.	Sinn N, Bryan J, and Wilson C, (2008) [57]
	· Randomized, double-blind, single-center, placebo-controlled (15 weeks) (phase 1) followed by an open-label extension (15 weeks) (phase 2) · Phase 1- 200 children 6-13 y/o	Omega-3 supplement significantly attenuated hyperactivity/ impulsivity, as well as mood/behavior dysregulation.	Omega3 LC-PUFA has been linked to brain and central nervous system functioning, and a deficiency in Omega3 fatty acids in rats and monkeys is associated with behavioral, sensory,	No major adverse effects documented apart from gastrointestinal discomfort, atopic dermatitis, hyperactivity, tics, nausea, elevated	Manor I et al., (2012) [56]

Supplement	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	· 2 capsules phosphatidylserine (PS)-Omega 3 (300 mg of PS and 120 mg of EPA + DHA) or 2 capsules filled with cellulose (placebo) 2 times/day. · Phase 2 – · 150 children all participants received two capsules of PS-Omega3 daily which provided 150 mg of PS and 60 mg of EPA + DHA	Sustained efficacy were noted who continued to received PS-Omega 3 in the open-label extension	and neurological dysfunction.	serum glutamic oxaloacetic transaminase (SGOT) and tantrum episodes	
	· Randomized, double-blind, placebo-controlled · 78 children 7-13 y/o (n=39 EFA supplement v. n=39 placebo Vitamin C.) · EFA capsule (240 mg of linoleic acid (LA), 60 mg of a-linolenic acid (ALA), 95 mg of mineral oil, and 5 mg of a-tocopherol (as an antioxidant) 2 times/day or Vit. C (500 mg ascorbic acid) 2 times/day, for 7 weeks	Although both interventions ameliorated some ADHD symptoms, no significant differences were found between the groups.	Essential fatty acids (EFA) are needed for normal sensory, cognitive, and motor function	Well tolerated and no adverse effects were reported.	Raz R, Carasso RL, Yehuda S (2009) [58]
	· Randomized, double-blind, placebo-controlled · 50 children 6-13 y/o (n=25 LC-Polyunsaturated fatty	No apparent benefit was noted for the PUFA supplementation for the ADHD symptoms	PUFA supplement contains DHA. DHA is thought to reflect the proportion of FA in the brain, and a decrease of the former in the blood might mediate	Well tolerated and no adverse effects were reported.	Stevens L et al., (2003) [54]

Supplement	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	acids (PUFAs) v. n=25 placebo olive oil · 8 capsules of PUFA or placebo a day, for 4 months		the abnormal neuronal signaling that results in aberrant behaviors.		
	· Randomized, double-blind, placebo-controlled · 54 children 6-12 y/o (n=27 Docosahexaenoic acid (DHA) v. n=27 placebo) · 345 mg of DHA per day (n=32) or a placebo capsule (n =31) for 4 months	DHA supplementation did not significantly improve in any objective or subjective measure of ADHD symptoms.	There is a direct relationship between plasma phospholipid DHA content and metabolism of serotonin and dopamine within the central nervous system DHA and other polyunsaturated fatty acids may influence synaptic functions through effects on membrane structures.	Well tolerated and no adverse effects were reported.	Voigt et al., (2001) [60]
	· Randomized, double-blind, placebo-controlled · 40 children with ADHD 6-12 y/o (n=20 docosahexaenoic acid (DHA) v. n=20 placebo) · DHA group took fermented soybean milk (600 mg DHA/125 ml, 3/week), bread rolls (300 mg DHA/ 45 g, 2/ week) and steamed bread (600 mg DHA/60 g, 2/week) or placebo foods containing olive oil instead of DHA-rich fish oil for 2 weeks.	DHA supplementation did not improve ADHD-related symptoms.	Levels of DHA was significantly lower in the serum phospholipid fraction in hyperactive children	No serious side effects were reported in the study.	Hirayama S, Hamazaki T, and Terasawa K (2004) [59]

Supplement	Methods	Results	Proposed mechanism of action	Safety and efficacy	Reference
	· Randomized, double-blind placebo-controlled, parallel, and multicenter · 51 children(ADHD and Fragile X syndrome) 6-13 y/o (n=24 ALC v. n=27 placebo) · Acetyl-L-Carnitine (20-50 mg/kg/day) 500 mg 2 times/day or placebo for 52 weeks	Acetyl-L-Carnitine significantly ameliorated the symptoms of ADHD over placebo on Clinical Global Impressions (CGI) parental rating, but not on CGI teacher's rating.	Acetyl-L-Carnitine was found to improve learning and attenuate the hyperactivity in a rat model of neonatal anoxia	Safe and tolerable with no side effects reported	Torrioli et al., (2008) [62]
Acetyl-L-Carnitine	· Multi-site parallel-group double-blind randomized pilot trial · 112 children 5-12 y/o (n=53 Acetyl-L-Carnitine v. n=59 placebo) · ALC in weight-based doses from 500 to 1500 mg 2 times/day or placebo for 16 weeks	No significant treatment effects to overall ADHD rating outcome. Superiority of Acetyl-L-Carnitine over placebo in the inattentive subtype	Acetyl-L-Carnitine exerts mild M3 muscarinic receptor agonism in rats, simulating acetylcholine release. The compound significantly increases glutamatergic receptor binding and protects against age-related reductions in the GABA/benzodiazepine receptor binding capacity	Safe and tolerable with no side effects reported	Arnold L et al., (2007) [63]

Table 2. Nutritional medicines/supplements for ADHD

3.3. Vitamins

Vitamins have been considered as an adjunct or alternative treatment for ADHD, although no studies have systemically evaluated their effects in ADHD patients. The use of vitamins for ADHD has been based on the finding that multivitamin supplements improved concentration and attention in children without ADHD [18]. In particular, Vitamin B6 (0.6 mg/kg/day) combined with magnesium (6 mg/kg/day) improved clinical symptoms of children with ADHD following an 8-week treatment period [43]. ADHD symptoms returned a few weeks after treatment was stopped. The beneficial effect of vitamin B6 on ADHD has been attributed to its ability to facilitate the production of the catecholamine, serotonin [12, 44]. In addition,

despite not directly addressing ADHD symptoms, vitamin or multivitamin supplementation can provide additional benefits for children with ADHD, who usually have poor dietary habits [18]. Caution must be exercised, however, with the use of large doses of vitamins, existing as megavitamins or megadoses, especially in young patients, considering the limited evidence to support the efficacy of vitamins in improving ADHD symptoms [18]. Double-blind, randomized, clinical studies are needed to substantiate the use of vitamins for the treatment of ADHD.

3.4. Minerals

Mineral supplementation has also been proposed to be an alternative intervention for ADHD. Mineral deficiencies have also been implicated in the etiology ADHD, and thus mineral supplementation may be useful to correct the underlying mineral deficiency and possibly control ADHD symptoms. In addition, minerals are cofactors in the synthesis, uptake, and breakdown of important neurotransmitters, also implicated to play crucial roles in ADHD symptomatology [19, 45].

Of the mineral supplements, zinc may have been the most studied and have received much support as an adjunct treatment for ADHD [19]. Low levels of zinc have been associated with deficits in several cognitive functions including information processing [19, 46]. Thus, zinc supplementation may have beneficial effects on cognition and related processes. In a 12-week, double-blind study, children supplemented with 150 mg of zinc sulfate showed reductions in hyperactivity, impulsivity, and impaired socialization [47]. Akhondzadeh *et al.* [46] also reported that zinc sulfate augmented the effect of methylphenidate in alleviating ADHD symptoms in children. Zinc is generally well-tolerated with only minor side effects reported (e.g., gastrointestinal discomforts and metallic taste). However, Arnold [48] showed negligible clinical effects of zinc supplementation in ADHD patients. These discrepant results are possibly due to differences in underlying nutritional status, genetic factors, and/or dosages of zinc used in different studies [18]. More elaborate and comprehensive clinical studies are required to solve these discrepancies.

Another mineral that has received special attention and has been evaluated in clinical trials for ADHD treatment is iron. Previous studies showed that children with iron-deficiency anemia also displayed attentional deficits [45]. Iron is a co-factor in the synthesis of both norepinephrine and dopamine [11, 19]. A randomized, double-blind, placebo-controlled study found that iron supplementation improved ADHD symptoms in children (23 kids, 5–8 years old) [49]. However, in the absence of anemia, iron supplementation in children with ADHD did not produce consistent behavioral improvements [19, 45].

Magnesium was also shown to improve ADHD symptoms. Magnesium is involved in neurotransmitter synthesis, and some studies have even associated magnesium deficiencies with ADHD [50]. Indeed, supplementation of magnesium and vitamin B6 in ADHD children improved ADHD symptoms [43].

Altogether, these findings indicate that certain minerals may be helpful in the treatment of ADHD. However, caution must be practiced when using minerals because of potential health risks associated with intake of large dosages.

3.5. Essential fatty acids

In recent years, there has been a lot of interest on the benefits of essential fatty acid (EFA, e.g., omega-3, omega-6) supplementation in children with ADHD. EFA supplementation exerted modest effects on alleviating the symptoms of ADHD [51, 52]. Richardson and Puri [53] reported that high-dose supplementation of EFA (fish oil; 8–16 g) improved behavior and inattention and reduced hyperactivity and defiance in children with ADHD. Another report also indicated better attention and behavioral improvement in children receiving combined omega-3 and omega-6 supplementation [54]. Similarly, Sinn and Bryan [55] reported significant improvement in ADHD symptoms (parent-rated behavior and attentional tasks) in children given EFA for 15 weeks, versus the placebo-treated group. Of note, other investigators have reported selective improvement (parent-reported benefits for restless-hyperactive symptoms in the absence of teacher-reported effects) of ADHD symptoms in subjects after EFA supplementation [56, 57]. While the exact mechanism EFAs in ADHD is not yet established, the efficacy of EFAs may be attributed to its effects on brain development (e.g., cell growth, neural signaling, and effects on gene expression) [18, 51]. It has also been postulated that increased EFA levels in cellular membranes impact dopaminergic and serotonergic activity [19, 51].

Nevertheless, other studies have also reported no significant or very minimal effects of EFA treatment in ADHD patients vs. placebo-treated group. A randomized clinical trial reported that EFAs had minimal effects on ADHD symptoms [58]. Another study also did not find any benefit of two month EFA supplementation in subjects [59]. In addition, Voigt *et al.* [60] reported that four months of DHA supplementation (345 mg/day) did not decrease symptoms of ADHD. In one study, omega-3 fatty acid supplements have even been associated with worsening of inattention [19, 57].

In summary, although some studies have reported therapeutic benefits of EFA supplementation, the current evidence for EFA as a complementary and alternative medicine for ADHD is not yet established [61].

3.6. Amino acids

Amino acid supplements have also been considered as a complementary intervention for ADHD. These include acetyl-L-carnitine (ALC), GABA, glycine, L-theanine, L-tyrosine, taurine, 5-hydroxytryptophan (5-HTP), and s-adenosyl-L-methionine (SAMe) [12, 18]. However, research regarding amino acid supplementation for ADHD treatment in children has produced inconsistent data. Various risks have been reported with their use and only short-term benefits of the supplements have been found [18]. Most research in this field has focused on supplementation with ALC, an amino acid derivative. A randomized, double-blind placebo-controlled study reported that ALC supplementation significantly ameliorated the symptoms of ADHD in 51 children, aged 6–13 years old [62]. However, a double-blind, placebo-controlled clinical trial reported that ALC supplementation has no significant effect on the overall ADHD population (112 children, 5–12 years old) [63].

4. Emerging natural interventions for ADHD and other treatment options

4.1. Novel interventions: evidence from preclinical studies

4.1.1. Oroxylin A

Oroxylin A (5,7-dihydroxy-6-methoxyflavone) shows potential as a natural intervention for ADHD. Oroxylin A is a flavonoid isolated from the root of *Scutellaria baicalensis Georgi*, a herb commonly found in East Asia. It exerted antioxidant, anti-inflammatory, and anti-allergy activities, and produced memory-enhancing and neuroprotective effects. Studies showed that Oroxylin A in an antagonist of the γ-aminobutyric acid (GABA)-A receptor [64]. Preclinical studies have shown that Oroxylin A or its derivative (5,7-dihydroxy-6-methoxy-4'-phenoxy-flavone) improved ADHD-like behaviors of the spontaneously hypertensive rat, an animal model of ADHD [65, 66]. The beneficial effects of Oroxylin A are believed to be mediated via enhancement of dopamine neurotransmission. Studies are underway to determine the efficacy of oroxylin A in ADHD patients.

4.1.2. YY162

YY162 is pharmaceutical combination of terpenoid-strengthened *G. biloba* and ginsenoside Rg3 from ginseng. A recent study has shown that YY1612 attenuated ADHD-like conditions induced by Aroclor1254 in mice [67]. It also exerted neuroprotective effects with negligible behavioral side effects. These effects of YY162 were comparable to those produced by methylphenidate. The positive effects of YY162 on ADHD-like behavior are believed to be mediated through its antioxidant properties and its ability to positively modulate the dopamine and norepinephrine transporters. Studies on the effects YY162 in patients with ADHD would be invaluable to determine its worth as an ADHD medication.

4.2. Combination treatment and integrative approaches

Because ADHD is a multifactorial disorder, a multi-modal approach may prove effective in managing ADHD symptoms. A recent and growing trend in the management of ADHD is the combination of various ADHD treatment options (e.g., medication and behavioral therapies) also referred to as combination therapy, integrative, or multi-modal approach. Multi-modal approaches are highly recommended because it is believed to provide a more "holistic" and patient-specific approach.

Due to that fact that stimulants are the most widely used treatment for ADHD, most multi-modal approaches practiced or studied employed the use of a stimulant drug coupled with a behavioral/psychosocial therapy. In a landmark randomized clinical trial known as the Multimodal Treatment Study of Children with ADHD, it was shown that the combination behavioral and medication interventions was superior compared to the individual effects of its component [68]. However, this did not go uncontested because other large-scale and long-term clinical trials have reported contradicting results [4].

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Very few studies have evaluated the effects of medication and/or behavioral therapy combined with a nutritional/botanical component. Notably, Akhondzadeh *et al.* [46] performed a randomized, double-blind, trial evaluating the effects of zinc sulfate as an adjunct to methylphenidate. The result showed that the zinc enhanced the effects of methylphenidate in children (ages 5–11) with ADHD. This study stands as an example that natural products are very promising when used with other ADHD treatments.

5. Conclusion

There are a number of available treatment options for ADHD, however, some of them may pose risks to patients [18]. The botanical agents discussed in this study appear to be promising ADHD treatments considering their therapeutic effects and negligible negative side effects. Of the botanical agents reviewed, Pycnogenol is the most studied, widely supported, and promising ADHD treatment. Nutritional supplements are also generally considered safe, and among them, EFAs stand out as potential ADHD interventions. Although the use of natural medications for ADHD has been considered as a "safer" approach, natural products are still far from being called as standard ADHD treatments due to the lack of comprehensive and appropriately controlled clinical studies that interrogate both their efficacy and safety. Thus, more rigorous, appropriately designed clinical trials are required prior to establishing their worth as ADHD drugs.

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