HHS Public Access

Author manuscript

*Adolesc Psychiatry (Hilversum)*. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

*Adolesc Psychiatry (Hilversum)*. 2015 ; 5(2): 84–95. doi:10.2174/2210676605021504301549 37.

# Non-Pharmacological Treatments for ADHD in Youth

**Anup Sharma**[1,*], **Patricia L. Gerbarg**[2], and **Richard P. Brown**[3]

[1]University of Pennsylvania School of Medicine, USA

[2]New York Medical College, USA

[3]Columbia University College of Physicians and Surgeons, USA

## Abstract

**Background—**Complementary and alternative medicine (CAM) in psychiatry or integrative psychiatry covers a wide range of biological, psychological and mind-body treatments that enhance standard medical practices and patient outcomes. While CAM approaches are popular amongst patients in their practice as well as in self-report because of their ease of use, health professionals have received limited education in these interventions and often are unaware of their patients' use of CAM treatments.

**Method—**This overview highlights evidence-based CAM treatments for attention deficit hyperactivity disorder (ADHD) including dietary interventions, phytomedicines, mind-body practices and neurofeedback.

**Results—**While conventional treatments are the mainstays for ADHD, there are a large number of available treatments that can be used to enhance treatment response.

**Conclusion—**With improved education and further scientific and clinical research, validated integrative treatments will provide more effective, lower risk and lower cost care for patients with ADHD.

### Keywords

Complementary and alternative medicine; ADHD; diet; herbs; melatonin; nootrophics; yoga; breathing practices; meditation; neurofeedback

## INTRODUCTION

Complementary and alternative medicine (CAM) includes a wide range of biological, psychological and mind-body treatments that are used to enhance standard medical practices and thereby improve patient outcomes. Integrative Psychiatry (IP), a form of CAM, "seeks to enrich mainstream mental health care with valuable treatments from global healing traditions as well as from modern laboratories in related fields" (Muskin, Gerbarg, & Brown,

*Address correspondence to this author at the Department of Psychiatry, University of Pennsylvania School of Medicine, 3535 Market Street, 2nd floor, Philadelphia, PA 19104, USA; Tel: 215-746-7234; Fax: 215-573-5668; anup.sharma2@uphs.upenn.edu.

**CONFLICT OF INTEREST**

Drs. Brown and Gerbarg: co-developed the Breath-Body-Mind program and receive occasional financial remuneration for teaching it.

2013). Many patients with mental health disorders utilize these modalities, often without physician supervision (Elkins *et al.*, 2005; Kessler *et al.*, 2001). A 2000–2001 survey of adolescents diagnosed with ADHD or depression that was conducted at five community mental health clinics found that 15% of patients had taken herbal supplements within the past year and 20% over their lifetime (Cala, Crismon, & Baumgartner, 2003). Another study found that 54% of parents used CAM to treat their child's attentional deficit hyperactivity disorder (ADHD), while only 11% had reported their use of complementary and alternative treatments to their child's physician (Chan, Rappaport & Kemper, 2003). More than 90% of parents of children with ADHD hope to see more research on CAM conducted (Huang, Seshadri, Matthews, & Ostfeld, 2013). Understanding the growing evidence supporting the efficacy of certain CAM therapies will prepare clinicians to best advise patients when discussing integrative treatments.

Among the many available CAM treatments, a subset has been studied for efficacy in ADHD. This overview highlights evidence-based treatments, including dietary interventions, phytomedicines, mind-body practices and neurofeedback. Although behavioral therapies are an important treatment modality, because of space limitations they are not discussed in this review. For some treatments, there exists supporting evidence from animal studies and preliminary clinical trials. As for many other treatments, larger randomized controlled studies are necessary. Still, considering the favorable risk/benefit profile of many CAM treatments, clinicians should consider offering their patients complimentary interventions, particularly for patients who have experienced limited success or side effects with standard pharmaceutical treatments, or for those individuals who are averse to prescription medications for reasons such as concerns about their short- and long-term effects.

## DIETARY INTERVENTIONS FOR ADHD

The role of diet as a contributor or modulator of ADHD symptomatology remains controversial (Millichap & Yee, 2012). In the Raine Study, a cohort of approximately 2800 Australian children were followed from birth to age 14 to determine whether certain dietary patterns were associated with ADHD. Adolescents with a high score for a "Western" dietary pattern were more likely to have been diagnosed with ADHD (odds ratio [OR] = 2.24, 95% confidence interval [CI] = 1.33, 3.80) even after adjusting for potential confounders. In contrast, those with a high score for a "Healthy" dietary pattern were less likely to have an ADHD diagnosis (Howard *et al.*, 2011). While this study was the first to correlate the Western diet with ADHD, no conclusions regarding causality could be reached given its cross-sectional design. Dietary strategies evaluated in ADHD include elimination of synthetic food additives, sensitizing food allergens or sugar. Dietary supplementation studies in ADHD include the use of vitamins, minerals, omega-3 and omega-6 fatty acids, amino acids and natural metabolites.

## MINIMIZING RISKS

In 1994, the Dietary Supplement Health and Education Act (DSHEA) defined the term "dietary supplement" to include herbs, vitamins, minerals and amino acids. Unlike most modern drugs, herbal and other dietary supplements are not subject to an FDA approval

process. The FDA is responsible for post-marketing activities including monitoring of adverse events (Feucht & Patel, 2011). Few herbs relevant to psychiatric practice have clinically significant medication interactions. Nevertheless, risks for herb-drug interactions (HDIs) can be minimized by monitoring for side effects and obtaining serum levels of medications that have a narrow therapeutic window, for example insulin, warfarin, digoxin, immunosuppressants in transplant cases, antiretroviral drugs, and chemotherapy agents (Gerbarg & Brown, 2013; Gerbarg & Brown, in press).

The safety and efficacy of any product, whether a prescription drug or a supplement, depends upon its quality. This is especially true for herbs because the quality and potency can be affected by numerous factors including the growing conditions, time of harvest, processing, stability of constituents and testing for contaminants (Brown, Gerbarg, & Muskin, 2009; Gerbarg & Brown, 2013, Gerbarg & Brown, in press). Physicians may wish to visit websites such as www.herbalgram.org, www.fda.gov/medwatch, www.consumerlab.com, www.supplementwatch.com, www.drugs.com that provide results of impartial evaluations of many supplements and identify high-quality brands. Although these sites do not present every aspect of product quality, they do cover important characteristics of herbal products, vitamins and nutrients, such as the percentage of active ingredient and purity.

## ELIMINATION DIETS

The hypothesis that synthetic food additives could induce hyperkinetic behavior was introduced in the 1970's by Feingold (1975) who proposed that petroleum-based additives, including synthetic colors, flavors and preservatives as well as foods that contain natural salicylates could induce neurologic damage and trigger hyperactivity, as well as other behavioral problems. Consequently, a program was created to test whether removal of these additives from the diet could improve symptoms of ADHD. Among the food dyes that the Feingold program eliminates are Red 40 (Allura red AC), Yellow 5 (tartrazine), and Yellow 6 (sunset yellow). These three additives account for 90% of food dyes certified by the FDA each year and are commonly found in candies, cereals, desserts and other child-oriented foods. In addition, the Feingold diet eliminates artificial flavorings (e.g. vanillin), artificial fat preservatives (BHA, BHT, TBHQ) and natural salicylates.

Over the past three decades, studies of elimination diets for ADHD symptoms have shown mixed results. An early meta-analysis of Feingold diet studies found minimal clinical efficacy for hyperactivity (Kavale & Forness, 1983). Interest was again rekindled when a later study found a significant association between synthetic food colorings and parent-rated ADHD symptoms (Schab & Trinh, 2004). A 2011 qualitative review found that a subgroup of children diagnosed with ADHD may be sensitive to these additives and could benefit from a restricted diet (Stevens, Kuczek, Burgess, Hurt & Arnold, 2011). A meta-analysis including only double-blind, placebo-controlled randomized trials approximated that 33% of children with ADHD may respond clinically to dietary interventions, though only 8% have symptoms related to synthetic food colors (Nigg, Lewis, Edinger & Falk, 2012). Another meta-analysis found that when data from blinded assessments were segregated and analyzed apart from proximal unblinded assessments, the effect sizes of elimination diets on ADHD

symptoms declined (standardized mean difference [SMD] 1.48 to 0.51), and remained modest for artificial food color exclusions (SMD 0.34 to 0.42) (Sonuga-Barke *et al.*, 2013).

Genetic polymorphisms could explain differences in ADHD symptoms and the response to food additives. Polymorphisms of genes that regulate CNS dopamine levels, such as the dopamine transporter gene (DAT1), are associated with childhood ADHD (Gizer, Ficks, & Waldman, 2009). Polymorphisms in the histamine degradation gene (HNMT) result in impaired clearance of histamine which is released following a challenge with food additives (Murdoch, Lessof, Pollock & Young, 1987; Preuss *et al.*, 1998). In a double blind, randomized placebo controlled study, children with ADHD with specific HNMT or DAT1 polymorphisms experienced worsening clinical symptoms when challenged with food additives compared to children lacking these polymorphisms. These findings provide a genetic link between histamine risk alleles and ADHD symptoms following exposure to food additives. The short term exposure to additives is one limitation of this study (Stevenson *et al.*, 2010). Additional randomized controlled trials with genomic data are needed to better understand the effects of elimination diets on ADHD.

Considering that artificial food additives have no nutritional value and may exacerbate hyperactivity, parents and physicians may opt to do a trial by excluding these ingredients from the child's diet for a three-month period. The use of objective assessments may help evaluate if an elimination diet was beneficial or not. Assessing the effects of these elimination diets can be challenging because it is particularly difficult to control adolescents' food intake. Sample foods known to have additives include lemonade, flavored yogurt, bakery items, beverages, macaroni & cheese, candy, sodas, popsicles and colored vitamins. Parents can preferentially buy foods labeled "no artificial colorings or preservatives" and educate their adolescents on why additives are not good. Parents wishing to implement an elimination diet will need diligence, patience and guidance from physicians and dieticians.

## DIETARY SUPPLEMENTATION

### Minerals

Children with ADHD are at risk for nutrient deficiencies. Hyperactivity and inattention can interfere with the ability to sit and consume regular meals. Furthermore, stimulant medications can suppress appetite. The lack of a balanced diet, poor nutrient absorption due to medical conditions, co-morbid conditions such as anemia or restless leg syndrome (RLS) and country of origin should be considered when screening for mineral deficiencies in children with ADHD. Certain regions of the world are more prone to mineral deficiencies than others. There is evidence that ADHD is associated with low mineral levels in children living in Poland, Turkey, Israel, Canada and the United States (Kiddie, Weiss, Kitts, Levy-Milne & Wasell, 2010). The impact of supplementation of mineral cofactors is being studied to determine their impact on ADHD symptoms, especially in children with micronutrient deficiencies. (For an overview of the use of nutrients in mental health care see Akhondzadeh, Gerbarg, & Brown, 2013).

### Iron

Iron imbalances have been associated with neurological diseases including ADHD (Jellen, Beard, & Jones 2009). Iron is an essential cofactor in the endogenous synthesis of monoaminergic neurotransmitters implicated in the pathogenesis of ADHD. Iron-deficient mice exhibit decreased striatal densities of D1 and D2 receptors (Erikson, Jones, Hess, Zhang, & Beard, 2001) and the dopamine transporter (DAT) (Erickson, Jones, & Beard, 2000) suggesting that iron is not only important for dopamine synthesis but also downstream dopaminergic receptor activity. In addition, mice that lack the DAT are phenotypically hyperactive (Gainetdinov *et al.*, 1999). Studies show a correlation between low levels of serum ferritin and ADHD symptoms (Konofal, Lecendreux, Arnulf, & Mouren, 2004). In a controlled study of 23 children (ages 5–8 years) with low serum ferritin, iron supplementation (80mg/day) improved ADHD symptoms (Konofal *et al.*, 2008). Another study showed that low serum ferritin not only correlated with baseline ADHD symptoms, but also with the dose of amphetamines required for clinical improvement (Calarge, Farmer, DiSilvestro, & Arnold, 2010). Iron deficiency can cause restless leg 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 cofactor zinc has also been implicated in regulating dopamine and norepinephrine neurotransmission (Lepping & Huber, 2010). In clinical studies performed in the Middle East, zinc supplementation significantly improved ADHD symptoms compared to placebo. For example, a 12 week controlled study of 400 children with ADHD living in Turkey found that zinc sulfate (40mg/day) significantly improved ADHD symptoms compared to placebo (Bilici *et al.*, 2004). 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 (Arnold *et al.*, 2005). 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 (Arnold *et al.*, 2011); 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.

### Polyunsaturated Fatty Acids (PUFAS)

Omega-3 fatty acid deficiencies have been found in boys with ADHD (Antalis *et al.*, 2006). Omega-3 and omega-6 fatty acids are polyunsaturated fatty acids that maintain membrane fluidity (Simopoulos, 1991); serve as substrates in the biosynthesis of inflammatory eicosanoids (Simopoulos, 2002a; b); modulate dopaminergic neurotransmission (Chalon, 2006; Dervola *et al.*, 2012; Baumgartner *et al.*, 2012), 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 (Simopoulos, 2002a; b). 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. (Bloch & Qawasmi, 2011). 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 (standardized mean difference [SMD] = 0.17, 95% CI= 0.01–0.34) (Sonuga-Barke *et al.*, 2013).

A supervised trial of PUFA supplementation may be appropriate for certain children as a complementary treatment for ADHD. The daily use of a purified fish oil supplement has become more appealing due to concerns about contaminants such as mercury and polychlorinated biphenyls (PCBs) in fish. Essential fatty acid supplements have variable concentrations of omega-3 and omega-6 fatty acids. Most American diets contain excess omega-6 fatty acids. Based on clinical studies, a dose of 600–1000mg/day of omega-3 (with 2:1 ratio of EPA to DHA) is likely to be most effective (Antalis *et al.*, 2006).

## Phytomedicines and Nootropics for ADHD

For thousands of years, phytomedicine, the use of plants for healing, has been an integral part of traditional health systems worldwide (Aggarwal, Sundaram, Malani, & Ichikawa, 2007; Lai & Roy 2004). Bioactive compounds can be found in flowers, leaves, stem, roots, seed and berries. Hundreds of modern drugs were derived from plants (Fabricant & Farnsworth, 2001). In many cases, single active constituents have been used. However, whole plant extracts may contain bioactive compounds with synergistic and/or polyvalent properties such that more than one compound contributes to the clinical effect (Sarris, Panossian, Schweitzer, Stough, & Scholey, 2011; Panossian Hamm, Kadioglu, Wikman, & Efferth, 2013). Although scientific studies have shown that certain plant compounds improve attention and learning, only a few studies have been conducted with patients who have ADHD. While more data is needed, recent evidence and clinical experience indicates that certain herbs are beneficial as complementary and integrative treatments for ADHD.

## Rhodiola Rosea

*Rhodiola Rosea* (Golden Root, Arctic Root), an herb with a long history in traditional medicine, is one of the most extensively studied herbs. It belongs to a group of plants called adaptogens, named after its capacity to protect organisms from numerous kinds of stressors —environmental, chemical, infectious, hypoxic, toxic, and others (Panossian *et al.*, 2010; Brown & Gerbarg, 2004). *R. rosea* grows in extremely cold environments at high altitudes above 8,000 feet in the crevices of mountain rocks in the Arctic regions of Canada, Europe

and the former Soviet Union. In order to fulfill increasing demand of this rare herb, widespread cultivation is developing in many of these regions. There are over twenty different species of the genus Rhodiola, many of which grow in the same regions and thus can be confused with the species *R. rosea*. While frequently used in traditional systems, there has been a marked increase in research and clinical interest in this herb over the last 10 years. High-performance liquid chromatography (HPLC) analysis of the root of *R. rosea* reveals hundreds of bioactive compounds including essential oils, fats, sterols, organic acids and phenolics (Panossian *et al.*, 2010).

Dopamine and norepinephrine levels are deficient in cases of ADHD. In vitro, studies of *R. rosea* extract suggest that one of its mechanisms of activity is stimulation of the reticular activating system and elevation in levels of the neurotransmitters dopamine, serotonin and norephinephrine. (Petkov *et al.*, 1986; Stancheva & Mosharrof, 1987; van Diermen, Marston, Bravo, Reist, Carrupt & Hostettman, 2009). Furthermore, *R. rosea* helps balance the stress-response system by preventing excessive release of stress hormones like cortisol (Panossian *et al.*, 2010). Salidroside, an important neuroprotective constituent of *R. rosea* blocks apoptosis in rat neuronal cells (Cai *et al.* 2008), attenuates glutamate-induced apoptosis in primary hippocampal neurons (Chen *et al.* 2008), protects neuronal PC12 cells against amyloid peptide cytotoxicity (Jang *et al.* 2003) and protects human cortical cells against oxidative injury (Palumbo, Occhiuto, Spadaro, & Circosta, 2012). *R. rosea* extracts alone, salidroside, and a combination of *R. rosea, Schizandra chinensis*, and *Eleutherococcus senticosus* (Adapt232, Swedish Herbal Institute) exhibit metabolic and transcriptional effects on mediators of the stress response, homeostasis, energy metabolism, and the neuroendocrine-immune system (Panossian *et al.*, 2013). While hundreds of pharmacological studies have been performed on *R. Rosea* extract and components, which particular bioactive components mediate specific therapeutic effects continues to be investigated.

In clinical trials, *R. rosea* has been studied as part of 11 RCTs evaluating its effects on mental health conditions, mental performance and physical performance in high school students, college students and military cadets. Studies have shown that *R. Rosea* can improve cognitive functions such as attention, accuracy and memory (Darbinyan *et al.*, 2000; Shevtsov *et al.*, 2003; Spasov, Mandrikov, & Mironova, 2000; Spasov, Wikman *et al.*, 2000), reduce mental fatigue (Olsson *et al.*, 2009) and exert anti-depressant effects (Darbinyan *et al.*, 2007). The extracts were well tolerated across studies, including in elderly patients without any reports of significant adverse effects. Additional studies are needed to further explore potential benefits in neuropsychiatric disorders such as ADHD.

*R. rosea* root extracts have inhibited CYP3A4 enzyme systems *in vitro* (Hellum *et al.*, 2010). However, subsequent studies have shown no significant effects on CYP3A4 isozymes in animal *in vivo* studies (Panossian, 2013). Furthermore, there have been no reports of significant herb-drug interactions (HDIs) in any human studies (Gerbarg & Brown, 2013; Brinker, 2010). Although *R. rosea* does not significantly affect metabolism of warfarin, it has a mild anti-platelet affect and may cause bruising, usually when taken in doses exceeding the recommended maximum dose (800 mg/day). Theoretically, this could increase the risk of bleeding in patients on warfarin or other anti-coagulant drugs. However, no cases

of increased bleeding due to *R. rosea* HDIs have been reported to date. This is in contrast to numerous studies and reports of *R. rosea* extract enhancing the benefits of medications, including chemotherapy agents (Brown & Gerbarg, 2004; Brown, Gerbarg, & Muskin, 2009; Gerbarg & Brown, 2013; Brinker, 2010).

Physician supervision is advised when using *R. rosea* as a sole or complementary treatment for ADHD. In milder cases, *R. rosea* has been used as a solo treatment. It can be mentally stimulating while also emotionally calming. When used as an adjunct to pharmacologic stimulants, *R. rosea* is generally well tolerated. For pediatric use, small doses can be made by dissolving a capsule form of dry root extract, for example, Rosavin (Ameriden International) containing 100mg *R. rosea*, in 8-ounces of any liquid, labeled, stored in the refrigerator, and administered in appropriate amounts with one ounce containing 12.5 mg of extract. *R. rosea* should be given in the morning on an empty stomach to maintain its effect throughout the course of the day. For children 8–12 years old, very small doses can be helpful in ameliorating symptoms of ADHD, particularly in cases in which increases in prescription stimulant doses are problematic. For children 12–18 years old, *R. rosea* can be started at 50mg/day and increased by 50mg every 5–7 days, up to a maximum of 500mg/day and as long as it is well tolerated. Doses above 600mg per day are not recommended as these dosages have not yet been adequately studied nor have they proven clinically useful (Brown & Gerbarg, 2012a; Brown, Gerbarg, & Muskin, 2009).

## Ginkgo Biloba

*Ginkgo Biloba*, extracted from the leaves of the maidenhair tree, has been used for centuries in traditional Chinese medicine to treat cognitive and memory impairments. The most studied standardized Ginkgo extract, EGb 761, contains hundreds of chemical constituents including 24% flavinoid glycosides, 6% terpenoids and 5–10% organic acids. The flavonoid and terpene fractions are believed to mediate bio-active properties.

Biological studies provide evidence that components of *G. Biloba* extract have anti-oxidant qualities (Ahlemeyer & Krieglstein, 2003; Smith & Luo, 2004; Wei *et al.*, 2000), anti-apoptotic functions (Ahlemeyer, Möwes, & Krieglstein, 1999; Defeudis, 2002), protect against mitochondrial dysfunction (Shi *et al.*, 2009), improve blood perfusion (Koltermann *et al.*, 2007) and decrease ischemia-reperfusion injury (Saleem, Zhuang, Biswal, Christern & Doré, 2008). Administration of the flavonoid and terpene fractions of *G. Biloba* in rats increased extracellular dopamine levels in the prefrontal cortex; an area deficient in this neurotransmitter in ADHD patients (Yoshitake, Yoshitake & Kehr, 2010). Although *in vitro* and animal studies indicate that Ginkgo extracts inhibits MAO activity (Fehske, Leuner & Muller, 2009; White, Scates & Cooper, 1996), human imaging studies following ginkgo treatment did not detect any change in MAO A or B levels (Ponto & Schultz, 2003). This could be explained by differences in dosing, which tend to be higher in animal studies than in human studies (Diamond & Bailey, 2013) or by differences in the metabolism of humans compared to that of rodents.

Given *G. Biloba* extract's neuroprotective activities, a number of studies have assessed its effects on cognitive functions in neuropsychiatric diseases. Meta-analyses indicate that Ginkgo significantly improved selective attention, fluid intelligence, memory, executive

function and processing speed compared to placebo (Diamond & Bailey, 2013). These cognitive domains are often impaired in ADHD patients. Initial studies of patients with dementia using heterogeneous methodologies found mixed results (Herrschaft *et al.*, 2012). In a small pilot study of adolescents (n = 6) with ADHD plus co-morbid disorders 200mg/ daily of EGb 761 significantly improved arousal, hyperactivity, anxiety, frustration tolerance and cognitive aspects of attentional processing (Niederhofer, 2010). Another 6 week randomized, double-blind, placebo controlled study of 50 children with ADHD compared 80–120mg of *G. Biloba* T.D. to 20–30mg of methylphenidate. Methylphenidate was far more effective than *G. Biloba* T.D. for ADHD (Salehi *et al.*, 2010). However, these results may be due to subtherapeutic doses and/or a less potent preparation called G. Biloba T.D. Additional RCTs using adequate doses of a preparation such as EGb 761 with an established record of efficacy in clinical trials are warranted.

Under physician supervision, *G. Biloba* can be used as a complementary treatment for patients with ADHD. It can be helpful for patients who are overly sensitive to and overly stimulated by prescription stimulants, *R. rosea* or other treatments. It can also reduce residual ADHD symptoms and be used concurrently with medications or other herbs. For example, in a four-week pilot study *G. biloba* combined with American Ginseng (*Panax Quinquefolium*) reduced symptoms in children with ADHD symptoms (Lyon *et al.*, 2001). Ginkgo rarely causes side effects, but when it does, these can be minimized by starting with lower doses and gradually increasing until therapeutic effects are attained while monitoring for side effects such as nausea, headaches and skin rashes. Caution is advised when administering Ginkgo to patients taking anticoagulants such as heparin, warfarin and aspirin, and its use should be discontinued two weeks prior to surgery.

### Neurohormones: Melatonin

Parents report sleep problems in 25–55% of ADHD patients (Corkum, Tannock & Moldofsky 1998). A meta-analysis including 16 clinical trials showed that children with ADHD are significantly more impaired in both subjective measures (bedtime resistance, sleep onset difficulties, morning awakening difficulties, etc) and objective measures (number of stage shifts/hrs sleep, apnea-hyponea index, etc) of sleep disturbances (Cortese, Faraone, Konofal, & Lecendreux, 2009). There are multiple causes of sleep problems associated with ADHD including side effects of stimulant medications, restless leg syndrome, sleep-disordered breathing, sleep onset insomnia, co-morbid psychiatric conditions and poor sleep hygiene. Patients with ADHD who have sleep problems need a diagnostic evaluation using clinical interviews, structured assessment tools and possibly sleep studies (Weiss & Salpekar, 2010). Whether common pathophysiological processes can explain both sleep problems and ADHD symptoms is an active area of investigation.

Melatonin is a natural hormone found in both plants and animals. In humans, it is secreted by the pineal gland in response to the 24-hour day-night cycle. Production of melatonin is inhibited by light and promoted in darkness. Once secreted, it binds to melatonin receptors in the suprachiasmatic nucleus of the hypothalamus resulting in reduced body temperature and sedation, possibly via increased GABAergic inhibitory effects (Bendz & Scates, 2010).

Chronic sleep onset insomnia can account for one third to one half of the cases of sleep disturbances among children with ADHD (Bendtz *et al.* 2010). These children with insomnia show both a delayed sleep phase as well as delayed secretion of melatonin compared with ADHD children without chronic insomnia (van der Heijden, Smits, van Someren, & Gunning, 2005). This suggests that ADHD patients with chronic insomnia may benefit from a trial of melatonin to promote sleep onset. In a four week double-blind, randomized, placebo-controlled study of 105 children (ages 6–12) with sleep onset insomnia and ADHD, those given melatonin showed significant improvements in sleep latency (p=.01) and sleep efficiency (p=.01) (van der Heijden, Smits, van Someren, Ridderinkhof & Gunning, 2007). A 3 year follow-up study of these children found that 65% continued to use melatonin every evening and 12% used it occasionally. Long term melatonin treatment was determined to be an effective treatment for sleep onset problems in 88% of cases. Temporal discontinuation of treatment resulted in delayed onset of sleep in 92% of children. While melatonin supplementation did not affect behavioral or mood symptoms after four weeks of use, parents reported improvements in both behavior (71%) and mood (61%) in the follow-up study. No adverse effects or safety concerns were noted (Hoebert, van der Heijden, van Geijlswijk & Smits, 2009). Thus, melatonin can be used as a complementary treatment for patients with ADHD and sleep onset insomnia. Melatonin, available as an over-the-counter supplement since 1993, causes few side effects (headache, dizziness, nausea, fatigue) and lacks a “hangover” effect unlike other sleep agents. Its use in patients with severe neurological deficits and epilepsy is controversial (Feucht & Patel, 2011). Use of melatonin products with proven efficacy in clinical trials and evaluated for potency and purity is advisable. Melatonin is available in tablet, capsule, liquid and sublingual forms. Dosing starts at 0.3–1mg with a final dose range of 1 to 3mg for children weighing 100 pounds (40 kg) or less and 3–6 mg for those over 100 pounds (40 kg). Melatonin comes in a fast-release formulation for sleep onset problems, slow-release for sleep maintenance, and a combination of both formulations.

## Racetams

Nootrophic are a diverse group of drugs, supplements and nutraceuticals that enhance cognitive functions. The term was coined after the discovery of piracetam, the first member of a class of compounds called racetams, which contribute to multiple neurophysiological actions. For example, piracetam is a positive allosteric modulator of AMPA receptors (Copani *et al.*, 1992; O’Neill & Witkin, 2007). AMPA receptors are ionotropic glutamate receptors involved in excitatory neurotransmission, learning and memory (Ahmed & Oswald, 2010). Racetams have also been implicated in neuroprotection, the release of brain-derived neurotrophic factor (BDNF), long-term potentiation, enhanced connectivity, and other potentially cognitive enhancing processes (Wu *et al.*, 2004). A significant percentage of children with ADHD also have learning disabilities or language impairments. These children with co-morbid conditions perform worse on measures of cognitive function and academic achievement (Cohen *et al.*, 2000; Jonsdottir, Bouma, Sergeant, & Scherder, 2005). Clinically, the racetams such as piracetam, aniracetam and pramiracetam have been found to be helpful in treating these impairments. A randomized, double-blind, placebo controlled study of 225 children with dyslexia (ages 7–12) found that administration of 3,600mg/day of piracetam resulted in significant improvements in reading and comprehension. The

improvements were evident after 12 weeks and remained throughout the full 36 weeks of the trial. There were no adverse reactions to piracetam (Wilsher *et al.*, 1987). Additional studies are needed to extend these findings to children diagnosed with ADHD and dyslexia.

Under physician supervision, racetams can be used as a complementary treatment for patients with ADHD who have co-morbid learning or language-related disabilities. Based on the authors' clinical experience, pramiracetam tends to be more calming, whereas aniracetam is more stimulating. For aniracetam, 750mg twice a day can be particularly effective, well-tolerated and unlikely to cause agitation or other side effects. Additional trials for children with ADHD and learning or language disabilities would be worthwhile.

## Mind-Body Practices for ADHD

Mind-body practices constitute a large and diverse group of mental and physical practices including yoga, tai chi, qi gong, meditation, and paced breathing, as well as many others. While there are plenty of unique mind-body practices, only a few have been studied in ADHD. This section focuses on those that have are evidence-based and have been found to be clinically helpful to patients with ADHD (For a more extensive discussion see Brown & Gerbarg, 2012b).

Patients with ADHD and co-morbid conditions such as conduct disorder (CD) and oppositional defiant disorder (ODD) can demonstrate detrimental externalizing behaviors such as physical aggression, bullying, defiance, theft and vandalism. Hyperactive/impulsive patients have a number of structural and functional abnormalities in the central nervous system (Castellanos *et al.*, 2003; Durston *et al.*, 2003; Valera, Faraone, Murray, & Seidman, 2007) and the peripheral nervous system (Scarpa & Raine, 1997; Crowell *et al.*, 2006). These include imbalances in autonomic nervous system (ANS) activity associated with symptoms of impulsivity, hyperactivity, emotional reactivity and aggressiveness (Beauchaine, Gatze-Kopp, & Mead, 2007). Using cardiac physiological markers, autonomic nervous system activity was compared in children with either hyperactive/impulsive ADHD, aggressive CD or control adolescents. Those with ADHD or CD showed reduced vagal parasympathetic activity, which has been associated with impaired emotional regulatory control. These children also had lower thresholds for fight-flight reactions and when challenged with a videotaped conflict demonstrated increased vagal parasympathetic withdrawal compared to controls. (Beauchaine, Katkin, Strassberg, & Snarr, 2001, Beauchaine *et al.*, 2013). A number of mind-body systems such as yoga postures, breathing techniques and meditation have been found to modulate autonomic nervous system activity (Bernardi, Porta, Gabutti, Spicuzza, & Sleight, 2001; Brown & Gerbarg, 2005; Raghuraj, Ramakrishnan, Nagendra & Telles, 1998; Telles, Gaur, & Balkrishna, 2009). Balancing the ANS and correcting such abnormalities may explain many of the beneficial effects of mind-body practices in patients with ADHD (Brown & Gerbarg 2012b, Brown, Gerbarg, & Muench, 2013). Using cardiac markers of ANS activity in a small study of 11 healthy yoga practitioners versus 11 matched healthy non-yoga practitioners, yoga practice induced significantly higher parasympathetic nervous system activity compared to a walking control intervention (Khattab, Khattab, Ortak, Richardt, & Bonnemeier 2007).

Mind-body practices can also affect neurotransmitter levels. For example, a Mass Resonance Spectroscopy (MRS) study revealed that thalamic GABA levels increased immediately after yoga sessions (Streeter *et al.*, 2007) and over a 12 week period of yoga practice (Streeter *et al.*, 2010).

Structural anatomic changes associated with mind-body practices are being studied. In small studies, cortical regions associated with attention, interoception, and auditory and visual processing were thicker in long-term meditators than in matched controls (Lazar *et al.*, 2005). Following an 8 week mindfulness-based stress reduction program, increases in gray matter were observed in areas involved in learning, memory and emotion regulation (Hölzel *et al.*, 2011).

## Yoga

A preliminary randomized controlled trial assessing the effects of a multi-component, yoga-based program on adolescents (age 17–18) compared to a physical education control group found that the yoga treatment group showed significantly improved measures of mood and anxiety (Noggle, Steiner, Minami, & Khalsa, 2012). A study of another multi-component, yoga program with 445 adolescents (ages 14–18) found that the yoga treatment group showed significantly reduced measures of impulsivity as compared to the control group (Ghahremani *et al.*, 2013).

Two randomized clinical trials have looked at the effects of yoga specifically on children and adolescents with ADHD. In a small randomized controlled study, 19 boys (ages 8–13) with hyperactive/impulsive ADHD stabilized on pharmacotherapy were randomized to a 20 session yoga program or to a control group comprising interactive games. The yoga group, but not the control group, showed significant improvements on the five subscales of the Conners' Parents Rating Scales (CPRS). For the yoga group, the degree of improvement on the Conners' Teacher Rating Scales (CTRS) correlated with the number of sessions. However, neither group showed statistically significant scores rated by teachers. The study was limited by a small sample size and by differences in assessment conditions between parents and teachers (Jensen & Kenny, 2004). In another randomized controlled study, 19 children with ADHD (ages 8–13) were assigned to either a yoga program (twenty weekly 1 hour yoga group) or a conventional program of motor exercises for 34 weeks. The yoga training was superior for all outcome measures of an ADHD rating scale for parents and teachers. The small sample size, attendance variability and exclusion of children with co-morbid behavioral conditions were among the limitations of this study (Haffner, Roos, Goldstein, Parzer, &Resch, 2006). Neither study reported any safety problems or adverse effects in the yoga treatment group. A recent review gave a Grade B for current evidence supporting the use of yoga as an adjunct to pharmacotherapy in children with ADHD (Balasubramaniam, Telles, & Doraiswamy, 2013).

## Mindfulness

Mindfulness, a form of meditation, involves non-judgmental observation of the present moment (Ludwig & Kabat-Zinn, 2008). Mindfulness training for children and adolescents may be effective in the treatment of physiological, psychosocial and behavioral conditions

(Black, Milam, & Sussman, 2009). A small pilot study of an 8-week mindfulness training program for 10 adolescents (aged 11–15) with ADHD, showed reduction in attention and behavioral problems and improvements in executive function as reported by parents and tutors. However, at 16-week follow-up, reductions in problem behaviors and attention performance did not persist (van der Oord, Bogels, & Peijnenburg, 2012). A review of meditation treatments for ADHD was unable to draw any conclusions regarding the effectiveness of meditation therapy for ADHD given the limited number of studies and sample sizes (Krisanaprakornkit, Ngamjarus, Witoonchart, & Pyakhatkul, 2010). More trials are needed to assess the role of different meditation treatments on ADHD symptoms.

Considering that initial reports of mind-body practices such as yoga training demonstrate benefits in children with ADHD; physicians and parents may consider a trial of yoga as a complementary treatment. Parents should learn about the yoga programs available in their area and identify teachers with experience in working with children with special needs. Assuming no physical contraindications and depending on the frequency of classes, a trial of yoga for several weeks or a month may be needed before assessing results. Children who are too symptomatic to participate in a class may be referred for individual sessions to a yoga therapist. In addition, some schools may offer or be willing to offer yoga programs as part of their curriculum.

## Neurofeedback for ADHD

Neurofeedback (NF) utilizes real time electroencephalography (EEG) or hemoencephalography (HEG) recordings to allow patients to self-regulate and reinforce specific aspects of their own neuronal activity. The patient's recorded EEG or HEG activity is entered into a computerized training program which then feeds the information back to the patient by through visual cues on a monitor or acoustic cues such as radio carrier waves. These cues enable patients to self-regulate specific aspects of brain activity using the training program.

Various neurofeedback training programs have been utilized in patients with ADHD to regulate aspects of brain activity (Larsen & Sherlin, 2013). A subgroup of patients with ADHD has excessive theta activity and/or reduced beta activity both at rest and while performing tasks (Gevensleben *et al.*, 2014). In the theta/beta training protocol, patients learn to decrease EEG activity in the theta band (4–7 Hz) while increasing activity in the beta band (12–25 Hz). This corresponds to a relaxed yet attentive mental state. Sensorimotor rhythm training focuses on increasing activity in the mid-beta (12–15 Hz) band; an activity pattern associated with active concentration. In patients with ADHD, this training protocol has been used to improve sleeping problems and increase vigilance (Arns & Kenemans, 2012). Slow cortical potential (SCP) training involves the ability to self-regulate SCP activity. SCPs are EEG polarizations that reflect cortical excitability. When SCPs are shifted in the negative direction, cell assemblies have a lower threshold of excitation; when they are shifted in the positive direction, cell assemblies have a higher threshold of excitation (Leins *et al.*, 2007). Children with ADHD have reduced shifts in the negative direction suggesting an overall higher threshold for brain activation when mental activity is required. In such

cases, neurofeed-back aims to correct abnormal underlying SCP activity and cortical excitability.

Early studies on the effects of NF treatment in children with ADHD exhibited methodological limitations and mixed results. More recently, in a multicenter, randomized, controlled study of 102 children (ages 8–12) with untreated ADHD, the effect of neurofeedback training was compared to a computerized attention skill training program (Gevensleben *et al.*, 2009). NF training included a block of theta/beta training and a block of slow cortical potential training (36 sessions, 50 minutes per session). The NF group demonstrated statistically significant improvements in parent and teacher ratings of ADHD symptoms with medium effect sizes of 0.4–0.6. Only 8 children discontinued the study. A 6-month follow-up study of 61 patients showed sustained superior scores for the NF group compared to the control group with improvements in both core ADHD symptoms as well as in other functional domains. For theta/beta training, decrease of theta activity in the resting EEG was associated with an improvement in ADHD symptoms. Similarly, change in alpha activity predicted clinical improvement following SCP training. These results suggest specificity of treatment effects (Gevensleben *et al.*, 2010). Further studies using improved techniques and individualized treatments are expected.

Neurofeedback may be used as an alternative or complementary treatment for patients suffering from ADHD. While additional data is needed, patients who demonstrate increased theta or theta/beta ratios are more likely to benefit from treatment with NF. Moreover, NF is most effective for inattention and impulsivity (Sherlin *et al.*, 2011). In practice, children treat NF interventions as if they were computer games and they rarely result in side effects. Still, there are some individuals who are sensitive to treatment. Side effects may include headache, nausea, dizziness, sleepiness or agitation. Furthermore, frequent (1–3/week) and prolonged (2–12 months) treatments are often required and may not be covered by insurance. The International Society for Neurofeedback (www.isnr.org) provides information as well as training workshops and certification for practitioners.

## CONCLUSIONS

While conventional psychopharmacology and behavioral therapies are mainstays of ADHD treatment, more can be achieved when these standard treatments are integrated with complementary approaches. We have highlighted evidence-based alternative treatments shown to be particularly useful for ADHD. In addition, many promising approaches warrant further study. Interest in integrative psychiatry (IP) grows as practitioners discover a more diverse set of tools for helping their patients. While CAM approaches are popular amongst patients, health professionals have received limited education in these interventions and often are unaware of their patients' use of CAM treatments. Through education and with further rigorous research, validated integrative treatments will provide more effective, lower risk and lower cost care for patients with ADHD.

## Acknowledgments

Declared none.

## Biographies

**Anup Sharma, MD PhD** is a PGY4 resident in the Department of Psychiatry at the University of Pennsylvania School of Medicine.

**Patricia L. Gerbarg, MD** is an Assistant Clinical Professor of Psychiatry at New York Medical College.

**Richard P. Brown, MD** is an Associate Clinical Professor of Psychiatry at Columbia University College of Physicians and Surgeons, NY

## REFERENCES


Akhondzadeh S, Gerbarg PL, Brown RP. Nutrients for prevention and treatment of mental health disorders. Psychiatric Clinics of North America. 2013; 36:25–36. [PubMed: 23538074]

Aggarwal, BB.; Sundaram, C.; Malani, N.; Ichikawa, H. Curcumin: the Indian solid gold. In: Aggarwal, BB.; Surh, Y-J.; Shishodia, S., editors. The molecular targets and therapeutic uses of curcumin in health and disease. New York: Springer; 2007. p. 1-75.

Ahlemeyer B, Krieglstein J. Neuroprotective effects of Ginkgo biloba extract. Cellular and Molecular Life Sciences CMLS. 2003; 60:1779–1792. [PubMed: 14523543]

Ahlemeyer B, Möwes A, Krieglstein J. Inhibition of serum deprivation-and staurosporine-induced neuronal apoptosis by Ginkgo biloba extract and some of its constituents. European journal of pharmacology. 1999; 367:423–430. [PubMed: 10079019]

Ahmed AH, Oswald RE. Piracetam defines a new binding site for allosteric modulators of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. Journal of medicinal chemistry. 2010; 53:2197–2203. [PubMed: 20163115]

Antalis CJ, Stevens LJ, Campbell M, Pazdro R, Ericson K, Burgess JR. Omega-3 fatty acid status in attention-deficit/hyperactivity disorder. Prostaglandins, leukotrienes and essential fatty acids. 2006; 75:299–308.

Arnold LE, Bozzolo H, Hollway J, Cook A, DiSilvestro RA, Bozzolo DR, Williams C. Serum zinc correlates with parent-and teacher-rated inattention in children with attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology. 2005; 15:628–636. [PubMed: 16190794]

Arnold LE, DiSilvestro RA, Bozzolo D, Bozzolo H, Crowl L, Fernandez S, Joseph E. Zinc for attention-deficit/hyperactivity disorder: placebo-controlled double-blind pilot trial alone and combined with amphetamine. Journal of child and adolescent psychopharmacology. 2011; 21:1–19. [PubMed: 21309695]

Arns M, Kenemans JL. Neurofeedback in ADHD and insomnia: Vigilance Stabilization through sleep spindles and circadian networks. Neuroscience and Biobehavioral Reviews. 2012; 44:183–194. [PubMed: 23099283]

Balasubramaniam M, Telles S, Doraiswamy PM. Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Frontiers in psychiatry. 2012; 3

Baumgartner J, Smuts CM, Malan L, Arnold M, Yee BK, Bianco LE, Zimmermann MB. Combined deficiency of iron and (n-3) fatty acids in male rats disrupts brain monoamine metabolism and produces greater memory deficits than iron deficiency or (n-3) fatty acid deficiency alone. The Journal of nutrition. 2012; 142:1463–1471. [PubMed: 22739379]

Beauchaine TP, Gatzke-Kopp L, Mead HK. Polyvagal theory and developmental psychopathology: Emotion dysregulation and conduct problems from preschool to adolescence. Biological psychology. 2007; 74:174–184. [PubMed: 17045726]

Beauchaine TP, Gatzke-Kopp L, Neuhaus E, Chipman J, Reid MJ, Webster-Stratton C. Sympathetic-and parasympathetic-linked cardiac function and prediction of externalizing behavior, emotion regulation, and prosocial behavior among preschoolers treated for ADHD. Journal of Consulting and Clinical Psychology. 2013; 81:481–493. [PubMed: 23544677]

Beauchaine TP, Katkin ES, Strassberg Z, Snarr J. Disinhibitory psychopathology in male adolescents: discriminating conduct disorder from attention-deficit/hyperactivity disorder through concurrent assessment of multiple autonomic states. Journal of Abnormal Psychology. 2001; 110:610–624. [PubMed: 11727950]

Bendz LM, Scates AC. Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. Annals of Pharmacotherapy. 2010; 44:185–191. [PubMed: 20028959]

Bernardi L, Porta C, Gabutti A, Spicuzza L, Sleight P. Modulatory effects of respiration. Autonomic neuroscience. 2001; 90:47–56. [PubMed: 11485292]

Bilici M, Yildirim F, Kandil S, Bekaroğlu M, Yildirmş S, Değer O, Aksu H. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2004; 28:181–190. [PubMed: 14687872]

Black DS, Milam J, Sussman S. Sitting-meditation interventions among youth: A review of treatment efficacy. Pediatrics. 2009; 124:e532–e541. [PubMed: 19706568]

Bloch MH, Qawasmi A. Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis. Journal of the American Academy of Child & Adolescent Psychiatry. 2011; 50:991–1000. [PubMed: 21961774]

Brinker, F. Herbal contraindications and drug interactions plus herbal adjuncts with medicines. 4th. Sandy, Oregon: Eclectic Medical Publications; 2010.

Brown RP, Gerbarg PL. Sudarshan kriya yogic breathing in the treatment of stress, anxiety, and depression: Part II-clinical applications and guidelines. Journal of Alternative & Complementary Medicine. 2005; 11:711–717. [PubMed: 16131297]

Brown, RP.; Gerbarg, PL. Non-drug treatments for ADHD: Options for kids, adults, and clinicians. New York: W.W. Norton & Company; 2012a.

Brown, RP.; Gerbarg, PL. The healing power of breath. (Book and CD set). NY: Shambhala Press; 2012b. 2012b

Brown, RP.; Gerbarg, PL.; Graham, B. The Rhodiola revolution. New York: Rodale Press, NY; 2004. 2004

Brown RP, Gerbarg PL, Muench F. Breathing practices for treatment of psychiatric and stress-related medical conditions. Psychiatric Clinics of North America. 2013; 36:121–140. [PubMed: 23538082]

Brown, RP.; Gerbarg, PL.; Muskin, PR. How to use herbs, nutrients, and yoga in mental health care. New York: W.W. Norton & Company; 2009.

Cai L, Wang H, Li Q, Qian Y, Yao W. Salidroside inhibits H2O2-induced apoptosis in PC 12 cells by preventing cytochrome c release and inactivating of caspase cascade. Acta biochimica et biophysica Sinica. 2008; 40:796–802. [PubMed: 18776992]

Cala S, Crismon ML, Baumgartner J. A survey of herbal use in children with attention-deficit—hyperactivity disorder or depression. Pharmacotherapy. 2003; 23:222–230. [PubMed: 12587812]

Calarge C, Farmer C, DiSilvestro R, Arnold LE. Serum ferritin and amphetamine response in youth with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology. 2010; 20:495–502. [PubMed: 21186968]

Castellanos FX, Sharp WS, Gottesman RF, Greenstein DK, Giedd JN, Rapoport JL. Anatomic brain abnormalities in monozygotic twins discordant for attention deficit hyperactivity disorder. American Journal of Psychiatry. 2003; 160:1693–1696. [PubMed: 12944348]

Chalon S. Omega-3 fatty acids and monoamine neurotransmission. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2006; 75:259–269.

Chan E, Rappaport LA, Kemper KJ. Complementary and alternative therapies in childhood attention and hyperactivity problems. Journal of Developmental & Behavioral Pediatrics. 2003; 24:4–8. [PubMed: 12584479]

Chen X, Liu J, Gu X, Ding F. Salidroside attenuates glutamate-induced apoptotic cell death in primary cultured hippocampal neurons of rats. Brain Research. 2008; 1238:189–198. [PubMed: 18680733]

Cohen NJ, Vallance DD, Barwick M, Im N, Menna R, Horodezky NB, Isaacson L. The interface between ADHD and language impairment: An examination of language, achievement, and

cognitive processing. Journal of Child Psychology and Psychiatry. 2000; 41:353–362. [PubMed: 10784082]

Copani A, Genazzani AA, Aleppo G, Casabona G, Canonico PL, Scapagnini U, Nicoletti F. Nootropic Drugs Positively Modulate α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid-Sensitive Glutamate Receptors in Neuronal Cultures. Journal of Neurochemistry. 1992; 58:1199–1204. [PubMed: 1372342]

Corkum P, Tannock R, Moldofsky H. Sleep disturbances in children with attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 1998; 37:637–646. [PubMed: 9628084]

Cortese S, Angriman M, Lecendreux M, Konofal E. Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. Expert Review of Neurotherapeutics. 2012; 12:1227–1240. [PubMed: 23082739]

Cortese S, Faraone SV, Konofal E, Lecendreux M. Sleep in children with attention-deficit/hyperactivity disorder: Meta-analysis of subjective and objective studies. Journal of the American Academy of Child and Adolescent Psychiatry. 2009; 48:894–908. [PubMed: 19625983]

Crowell SE, Beauchaine TP, Gatzke-Kopp L, Sylvers P, Mead H, Chipman-Chacon J. Autonomic correlates of attention-deficit/hyperactivity disorder and oppositional defiant disorder in preschool children. Journal of Abnormal Psychology. 2006; 115:174. [PubMed: 16492108]

Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. Rhodiola rosea in stress induced fatigue--a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine. 2000; 7:365–371. [PubMed: 11081987]

Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of Rhodiola rosea L extract SHR-5 in the treatment of mild to moderate depression. Nordic Journal of Psychiatry. 2007; 61:343–348. [PubMed: 17990195]

Defeudis FV. Bilobalide and neuroprotection. Pharmacological Research. 2002; 46:565–568. [PubMed: 12457632]

Dervola KS, Roberg BA, Wøien G, Bogen IL, Sandvik TH, Sagvolden T, Walaas SI. Marine omega-3 polyunsaturated fatty acids induce sex-specific changes in reinforcer-controlled behaviour and neurotransmitter metabolism in a spontaneously hypertensive rat model of ADHD. Behavioral and Brain Functions. 2012; 8:9081–1188.

Diamond BJ, Bailey MR. Ginkgo biloba: Indications, mechanisms, and safety. Psychiatric Clinics of North America. 2013; 36:73–83. [PubMed: 23538078]

Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, Casey BJ. Differential patterns of striatal activation in young children with and without ADHD. Biological Psychiatry. 2003; 53:871–878. [PubMed: 12742674]

Elkins G, Rajab MH, Marcus J. Complementary and alternative medicine use by psychiatric inpatients 1. Psychological Reports. 2005; 96:163–166. [PubMed: 15825920]

Erikson KM, Jones BC, Beard JL. Iron deficiency alters dopamine transporter functioning in rat striatum. The Journal of Nutrition. 2000; 130:2831–2837. [PubMed: 11053528]

Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Iron deficiency decreases dopamine D 1 and D 2 receptors in rat brain. Pharmacology Biochemistry and Behavior. 2001; 69:409–418.

Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environmental Health Perspectives. 2001; 109(Suppl 1):69. [PubMed: 11250806]

Fehske CJ, Leuner K, Müller WE. Ginkgo biloba extract (EGb761®) influences monoaminergic neurotransmission via inhibition of NE uptake, but not MAO activity after chronic treatment. Pharmacological Research. 2009; 60:68–73. [PubMed: 19427589]

Feingold BF. Hyperkinesis and learning disabilities linked to artificial food flavors and colors. American Journal of Nursing. 1975; 75:797–803. [PubMed: 1039267]

Feucht C, Patel DR. Herbal medicines in pediatric neuropsychiatry. Pediatric Clinics of North America. 2011; 58:33–54. [PubMed: 21281847]

Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG. Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science. 1999; 283:397–401. [PubMed: 9888856]

Gerbarg PL, Brown RP. Phytomedicines for prevention and treatment of mental health disorders. Psychiatric Clinics of North America. 2013; 36:37–47. [PubMed: 23538075]

Gerbarg, PL.; Brown, RP. Therapeutic nutrients and herbs. In: D'Addona, D.; Fogel, B.; Greenberg, D., editors. Psychiatric care of the medical patient. 4th. New York: Oxford University Press; (in press)

Gevensleben H, Holl B, Albrecht B, Schlamp D, Kratz O, Studer P, Heinrich H. Neurofeedback training in children with ADHD: 6-month follow-up of a randomised controlled trial. European Child & Adolescent Psychiatry. 2010; 19:715–724. [PubMed: 20499120]

Gevensleben H, Holl B, Albrecht B, Vogel C, Schlamp D, Kratz O, Heinrich H. Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. Journal of Child Psychology and Psychiatry. 2009; 50:780–789. [PubMed: 19207632]

Gevensleben H, Kleemeyer M, Rothenberger LG, Studer P, Flaig-Röhr A, Moll GH, Heinrich H. Neurofeedback in ADHD: Further pieces of the puzzle. Brain Topography. 2014; 27:20–32. [PubMed: 23563906]

Ghahremani DG, Oh EY, Dean AC, Mouzakis K, Wilson KD, London ED. Effects of the Youth Empowerment Seminar on impulsive behavior in adolescents. Journal of Adolescent Health. 2013; 53:139–141. [PubMed: 23601502]

Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: A meta-analytic review. Human Genetics. 2009; 126:51–90. [PubMed: 19506906]

Haffner J, Roos J, Goldstein N, Parzer P, Resch F. [The effectiveness of body-oriented methods of therapy in the treatment of attention-deficit hyperactivity disorder (ADHD): Results of a controlled pilot study]. Zeitschrift fur Kinder-und Jugendpsychiatrie und Psychotherapie. 2006; 34:37–47. [PubMed: 16485612]

Hellum BH, Tosse A, Hoybakk K, Thomsen M, Rohloff J, Georg Nilsen O. Potent in vitro inhibition of CYP3A4 and P-glycoprotein by Rhodiola rosea. Planta Medica. 2010; 76:331–338. [PubMed: 19790032]

Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: A randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. Journal of Psychiatric Research. 2012; 46:716–723. [PubMed: 22459264]

Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. Journal of Pineal Research. 2009; 47:1–7. [PubMed: 19486273]

Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, Lazar SW. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Research: Neuroimaging. 2011; 191:36–43. [PubMed: 21071182]

Howard AL, Robinson M, Smith GJ, Ambrosini GL, Piek JP, Oddy WH. ADHD is associated with a “Western” dietary pattern in adolescents. Journal of Attention Disorders. 2011; 15:403–411. [PubMed: 20631199]

Jang SI, Pae HO, Choi BM, Oh GS, Jeong S, Lee HJ, Chung HT. Salidroside from Rhodiola sachalinensis protects neuronal PC12 cells against cytotoxicity induced by amyloid-β. Immunopharmacology and Immunotoxicology. 2003; 25:295–304. [PubMed: 19180794]

Jellen LC, Beard JL, Jones BC. Systems genetics analysis of iron regulation in the brain. Biochimie. 2009; 91:1255–1259. [PubMed: 19393285]

Jensen PS, Kenny DT. The effects of yoga on the attention and behavior of boys with attention-deficit/hyperactivity disorder (ADHD). Journal of Attention Disorders. 2004; 7:205–216. [PubMed: 15487477]

Jonsdottir S, Bouma A, Sergeant JA, Scherder EJ. The impact of specific language impairment on working memory in children with ADHD combined subtype. Archives of Clinical Neuropsychology. 2005; 20:443–456. [PubMed: 15896559]

Kavale KA, Forness SR. Hyperactivity and diet treatment: A meta-analysis of the Feingold hypothesis. Journal of Learning Disabilities. 1983; 16:324–330. [PubMed: 6886553]

Kessler RC, Soukup J, Davis RB, Foster DF, Wilkey SA, Van Rompay MI, Eisenberg DM. The use of complementary and alternative therapies to treat anxiety and depression in the United States. American Journal of Psychiatry. 2001; 158:289–294. [PubMed: 11156813]

Khattab K, Khattab AA, Ortak J, Richardt G, Bonnemeier H. Iyengar yoga increases cardiac parasympathetic nervous modulation among healthy yoga practitioners. Evidence-Based Complementary and Alternative Medicine. 2007; 4:511–517. [PubMed: 18227919]

Kiddie JY, Weiss MD, Kitts DD, Levy-Milne R, Wasdell MB. Nutritional status of children with attention deficit hyperactivity disorder: a pilot study. International Journal of Pediatrics. 2010; 2010

Koltermann A, Hartkorn A, Koch E, Fürst R, Vollmar AM, Zahler S. Ginkgo biloba extract EGb® 761 increases endothelial nitric oxide production in vitro and in vivo. Cellular and Molecular Life Sciences. 2007; 64:1715–1722. [PubMed: 17497242]

Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention-deficit/hyperactivity disorder. Archives of Pediatrics & Adolescent Medicine. 2004; 158:1113–1115. [PubMed: 15583094]

Konofal E, Lecendreux M, Deron J, Marchand M, Cortese S, Zaïm M, Arnulf I. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatric Neurology. 2008; 38:20–26. [PubMed: 18054688]

Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N. Meditation therapies for attention-deficit/hyperactivity disorder (ADHD). Cochrane Database of Systematic Reviews. 2010; 6:CD006507. [PubMed: 20556767]

Lai PK, Roy J. Antimicrobial and chemopreventive properties of herbs and spices. Current Medicinal Chemistry. 2004; 11:1451–1460. [PubMed: 15180577]

Larsen S, Serlin L. Neurofeedback: An emerging technology for treating central nervous system dysregulation. Psychiatric Clinics of North America. 36:163–168. [PubMed: 23538085]

Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, Fischl B. Meditation experience is associated with increased cortical thickness. Neuroreport. 2005; 16:1893–1897. [PubMed: 16272874]

Leins U, Goth G, Hinterberger T, Klinger C, Rumpf N, Strehl U. Neurofeedback for children with ADHD: a comparison of SCP and Theta/Beta protocols. Applied Psychophysiology and Biofeedback. 2007; 32:73–88.

Lepping P, Huber M. Role of zinc in the pathogenesis of attention-deficit hyperactivity disorder. CNS drugs. 2010; 24:721–728. [PubMed: 20806985]

Ludwig DS, Kabat-Zinn J. Mindfulness in medicine. Journal of the American Medical Association. 2008; 300:1350–1352. [PubMed: 18799450]

Lyon MR, Cline JC, de Zepetnek JT, Shan JJ, Pang P, Ben-ishin C. Effect of the herbal extract combination Panax quinquefolium and Ginkgo biloba on attention-deficit hyperactivity disorder: a pilot study. Journal of Psychiatry and Neuroscience. 2001; 26:221–228. [PubMed: 11394191]

Millichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. Pediatrics. 2012; 129:330–337. [PubMed: 22232312]

Murdoch RD, Lessof MH, Pollock I, Young E. Effects of food additives on leukocyte histamine release in normal and urticaria subjects. Journal of the Royal College of Physicians of London. 1987; 21:251–256. [PubMed: 2445984]

Muskin PR, Gerbarg PL, Brown RP. Along roads less traveled: Complementary, alternative, and integrative treatments. Psychiatric Clinics of North America. 2013; 36(1):xiii–xv. [PubMed: 23538089]

Niederhofer H. Ginkgo biloba treating patients with attention-deficit disorder. Phytotherapy Research. 2010; 24:26–27. [PubMed: 19441138]

Nigg JT, Lewis K, Edinger T, Falk M. Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. Journal of the American Academy of Child and Adolescent Psychiatry. 2012; 51:86–97. [PubMed: 22176942]

Noggle JJ, Steiner NJ, Minami T, Khalsa SBS. Benefits of yoga for psychosocial well-being in a US high school curriculum: A preliminary randomized controlled trial. Journal of Developmental and Behavioral Pediatrics. 2012; 33:193–201. [PubMed: 22343481]

O'Neill MJ, Witkin JM. AMPA receptor potentiators: Application for depression and Parkinson's disease. Current Drug Targets. 2007; 8:603–620. [PubMed: 17504104]

Palumbo DR, Occhiuto F, Spadaro F, Circosta C. Rhodiola rosea extract protects human cortical neurons against glutamate and hydrogen peroxide-induced cell death through reduction in the accumulation of intracellular calcium. Phytotherapy Research. 2012; 26:878–883. [PubMed: 22086763]

Panossian AG. Adaptogens in mental and behavioral disorders. Psychiatric Clinics of North America. 2013; 36:49–64. [PubMed: 23538076]

Panossian A, Hamm R, Kadioglu O, Wikman G, Efferth T. Synergy and antagonism of active constituents of ADAPT-232 on transcriptional level of metabolic regulation of isolated neuroglial cells. Frontiers in Neuroscience. 2013; 7:16. [PubMed: 23430930]

Panossian A, Wikman G, Kaur P, Asea A. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. Phytomedicine. 2009; 16:617–622. [PubMed: 19188053]

Panossian A, Wikman G, Sarris J. Rosenroot (Rhodiola rosea): traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine. 2010; 17:481–493. [PubMed: 20378318]

Petkov VD, Yonkov D, Mosharoff A, Kambourova T, Alova L, Petkov VV, Todorov I. Effects of alcohol aqueous extract from Rhodiola rosea L. roots on learning and memory. Acta physiologica et pharmacologica Bulgarica. 1986; 12:3–16.

Ponto LLB, Schultz SK. Ginkgo biloba extract: review of CNS effects. Annals of Clinical Psychiatry. 2003; 15:109–119. [PubMed: 12938868]

Preuss CV, Wood TC, Szumlanski CL, Raftogianis RB, Otterness DM, Girard B, Weinshilboum RM. Human hista-mine N-methyltransferase pharmacogenetics: common genetic polymorphisms that alter activity. Molecular pharmacology. 1998; 53:708–717. [PubMed: 9547362]

Raghuraj P, Ramakrishnan AG, Nagendra HR, Telles S. Effect of two selected yogic breathing techniques on heart rate variability. Indian Journal of Physiology and Pharmacology. 1998; 42:467–472. [PubMed: 10874345]

Saleem S, Zhuang H, Biswal S, Christen Y, Doré S. Ginkgo biloba extract neuroprotective action is dependent on heme oxygenase 1 in ischemic reperfusion brain injury. Stroke. 2008; 39:3389–3396. [PubMed: 18845796]

Salehi B, Imani R, Mohammadi MR, Fallah J, Mohammadi M, Ghanizadeh A, Akhondzadeh S. Ginkgo biloba for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2010; 34:76–80. [PubMed: 19815048]

Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. European Neuropsychopharmacology. 2011; 21:841–860. [PubMed: 21601431]

Scarpa A, Raine A. Psychophysiology of anger and violent behavior. Psychiatric Clinics of North America. 1997; 20:375–394. [PubMed: 9196920]

Schab DW, Trinh NHT. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. Journal of Developmental and Behavioral Pediatrics. 2004; 25:423–434. [PubMed: 15613992]

Shevtsov VA, Zholus BI, Shervarly VI, Vol'skij VB, Korovin YP, Khristich MP, Wikman G. A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mental work. Phytomedicine. 2003; 10:95–105. [PubMed: 12725561]

Sherlin LH, Arns M, Lubar J, Heinrich H, Kerson C, Strehl U, Sterman MB. Neurofeedback and basic learning theory: implications for research and practice. Journal of Neurotherapy. 2011; 15:292–304.

Shi C, Zhao L, Zhu B, Li Q, Yew DT, Yao Z, Xu J. Protective effects of Ginkgo biloba extract (EGb761) and its constituents quercetin and ginkgolide B against β-amyloid peptide-induced toxicity in SH-SY5Y cells. Chemico-biological interactions. 2009; 181:115–123. [PubMed: 19464278]

Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. The American journal of clinical nutrition. 1991; 54:438–463. [PubMed: 1908631]

Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. Journal of the American College of Nutrition. 2002a; 21:495–505. [PubMed: 12480795]

Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomedicine & Pharmacotherapy. 2002b; 56:365–379. [PubMed: 12442909]

Smith JV, Luo Y. Studies on molecular mechanisms of Ginkgo biloba extract. Applied Microbiology and Biotechnology. 2004; 64:465–472. [PubMed: 14740187]

Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, Sergeant J. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. American Journal of Psychiatry. 2013; 170:275–289. [PubMed: 23360949]

Spasov AA, Wikman GK, Mandrikov VB, Mironova IA, Neumoin VV. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. Phytomedicine. 2000; 7:85–89. [PubMed: 10839209]

Spasov AA, Mandrikov VB, Mironova IA. [The effect of the preparation rodakson on the psychophysiological and physical adaptation of students to an academic load.]. Eksperimental'naia I Klinicheskaia Farmakologiia. 2000; 63:76–78.

Stancheva SL, Mosharrof A. Effect of the extract of rhodiola rosea L. on the content of the brain biogenic monoamines. Medecine Physiologie Comptes Rendus De L'Academie Bulgare Des Sciences. 1987; 40:85–87.

Stevens LJ, Kuczek T, Burgess JR, Hurt E, Arnold LE. Dietary sensitivities and ADHD symptoms: Thirty-five years of research. Clinical Pediatrics. 2011; 50:279–293. 0009922810384728. [PubMed: 21127082]

Stevenson J, Sonuga-Barke E, McCann D, Grimshaw K, Parker KM, Rose-Zerilli MJ, Warner JO. The role of histamine degradation gene polymorphisms in moderating the effects of food additives on children's ADHD symptoms. American Journal of Psychiatry. 2010; 167:1108–1115. [PubMed: 20551163]

Streeter CC, Jensen JE, Perlmutter RM, Cabral HJ, Tian H, Terhune DB, Renshaw PF. Yoga Asana sessions increase brain GABA levels: A pilot study. The Journal of Alternative and Complementary Medicine. 2007; 13:419–426. [PubMed: 17532734]

Streeter CC, Whitfield TH, Owen L, Rein T, Karri SK, Yakhkind A, Jensen JE. Effects of yoga versus walking on mood, anxiety, and brain GABA levels: a randomized controlled MRS study. The Journal of Alternative and Complementary Medicine. 2010; 16:1145–1152. [PubMed: 20722471]

Telles S, Gaur V, Balkrishna A. Effect of a yoga practice session and a yoga theory session on state anxiety 1. Perceptual and Motor Skills. 2009; 109:924–930. [PubMed: 20178291]

Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biological Psychiatry. 2007; 61:1361–1369. [PubMed: 16950217]

van der Heijden KB, Smits MG, van Someren EJ, Gunning WB. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. Chronobiology International. 2005; 22:559–570. [PubMed: 16076654]

van der Heijden KBV, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. Journal of the American Academy of Child and Adolescent Psychiatry. 2007; 46:233–241. [PubMed: 17242627]

van der Oord S, Bögels SM, Peijnenburg D. The effectiveness of mindfulness training for children with ADHD and mindful parenting for their parents. Journal of Child and Family Studies. 2012; 21:139–147. [PubMed: 22347788]

van Diermen D, Marston A, Bravo J, Reist M, Carrupt PA, Hostettmann K. Monoamine oxidase inhibition by Rhodiola rosea L. roots. Journal of Ethnopharmacology. 2009; 122:397–401. [PubMed: 19168123]

Wei T, Ni Y, Hou J, Chen C, Zhao B, Xin W. Hydrogen peroxide-induced oxidative damage and apoptosis in cerebellar granule cells: Protection by Ginkgo biloba extract. Pharmacological Research. 2000; 41:427–433. [PubMed: 10704267]

Weiss MD, Salpekar J. Sleep problems in the child with attention-deficit hyperactivity disorder. CNS Drugs. 2010; 24:811–828. [PubMed: 20839894]

White HL, Scates PW, Cooper BR. Extracts of Ginkgo biloba leaves inhibit monoamine oxidase. Life Sciences. 1996; 58:1315–1321. [PubMed: 8614288]

Wilsher CR, Bennett D, Chase CH, Conners CK, Diianni M, Feagans, Tallal P. Piracetam and dyslexia: effects on reading tests. Journal of Clinical Psychopharmacology. 1987; 7:230–237. [PubMed: 3305591]

Wu X, Zhu D, Jiang X, Okagaki P, Mearow K, Zhu G, Marini AM. AMPA protects cultured neurons against glutamate excitotoxicity through a phosphatidylinositol 3-kinase-dependent activation in extracellular signal-regulated kinase to upregulate BDNF gene expression. Journal of Neurochemistry. 2004; 90:807–818. [PubMed: 15287886]

Yoshitake T, Yoshitake S, Kehr J. The Ginkgo biloba extract EGb 761® and its main constituent flavonoids and ginkgolides increase extracellular dopamine levels in the rat prefrontal cortex. British Journal of Pharmacology. 2010; 159:659–668. [PubMed: 20105177]