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Ginkgo biloba as an adjunct to methylphenidate in the treatment of attention deficit hyperactivity disorder in children: review of articles

Paria Hebrani(MD), Fatemeh Behdani(MD)*, Hoda Jalayer(MD)

Psychiatry and Behavioral Sciences Research Center, Ibn-e-sina Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Attention-deficit/hyperactivity disorder is one of the most common psychiatric disorders in childhood. The medications which inhibit the reuptake of noradrenline and dopamine including psychostimulants such as methylphenidate and dextroamphetamine and non-stimulating pre-frontal cortex noradrenaline reuptake inhibitor such as atomoxetine, are the standard treatment of ADHD. Adverse effects of stimulants have been reported in thirty percent of patients with attention-deficit/ hyperactivity disorder. More than fifty percent of the parents of these children have tried one or more complementary or alternative medicines including vitamins in their children. Ginkgo biloba has been described to be effective for various neuropsychiatric symptoms. It was assumed that ginkgo biloba might improve some symptoms of attention deficit disorder as well. Nevertheless, no systematic study reported a possible efficacy of ginkgo biloba in attention deficit disorder. This review article evaluates the available evidence on the efficacy of ginkgo biloba medication in Attention-deficit/hyperactivity disorder children to present an appropriate guidance for this common child disorder.

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Introduction

The incidence rate of attention deficit hyperactivity disorder (ADHD) in children of school aged has grown since 1970(1). The prevalence rate of ADHD is estimated 3% to 12% of school-aged children(2,3). In Mashhad, Iran, it is estimated that it affects 12.3% of preschool age children(4). Fifty percent of these children may suffer from ADHD symptoms for the rest of their lives(5).

Based on the Diagnostic and Statistical Manual of Mental Disorders criteria, fourth edition (DSM – IV), it is a neurological condition that involves problems with inattention and hyperactivity-impulsivity that are developmentally inconsistent with the age of the child. Children should display symptoms at least in two settings for six months. There must be a clear evidence of interference with the development of the appropriate social, academic or occupational functioning (home and school)(6).

Attention deficit disorder (ADD) is characterized by distractibility, restlessness and irritability. Inattention interferes with learning while the problems of restlessness and irritability affect behavior. Associated oppositionality, argumentativeness and low frustration tolerance make it more problematic. Learning disabilities and aggressive conduct disorder are common in this

***Corresponding author:** Fatemeh Behdani.
Psychiatry and Behavioral Sciences Research Center, Ibn-e-sina Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
E-mail: Behdanif@mums.ac.ir
Tel: 051-37112722

population, which disrupt their duties at home and at school (7). Depression and anxiety, irritability and explosiveness, substance abuse and antisocial behavior also occur as a consequence or comorbid disorder (8,9).

Literature review

ADHD is a multifactorial disease. Research has focused on genetic and environmental risk factors, structural and physiologic alterations in brain function. Twin studies have estimated the heritability of ADHD to be 0.76 (3) Hebrani showed that boys and girls did not differ in the familial risk factors that mediated ADHD and the familial aggregation of ADHD in the relatives of ADHD proband(10). However, ADHD is associated with the comorbid disorders, the pattern of these conditions is not influenced by the proband's gender (11).

Genetic studies have focused on dopamine receptors. Dopamine D4 receptor is found in the frontal subcortical networks and its function has disturbed in individuals who have ADHD (12).

Dopamine and norepinephrine neural pathways are supposed to be the likely sites of pathophysiologic dysfunction of ADHD. Animal studies have shown that the dysregulation of these pathways exhibited symptoms similar to ADHD(3,13).

Stimulants block the reuptake of noradrenergic neurotransmitters and enhance their release(13).

Imaging studies have indicated the different activity of the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, dorsal anterior cingulate cortex and striatum (caudate and putamen). The dorsal anterior cingulated cortex has an important role in attention, motor control and reward-based decision-making. Striatum is the location of the dopamine transporter binding and dopaminergic abnormalities (14,15).

Dysfunction of the neural circuitry within prefrontal cortex has two potential theories; maturational lag or developmental deviation (16-19).

A lag in developmental maturation represents that normal maturing of the prefrontal cortex is delayed. Based on severity of the symptoms, it may gradually match the maturation level of normal peers (8). Developmental deviation has been found in electroencephalograph (EEG) studies. The symptoms of ADHD and cognitive disturbance may improve as maturation continues (20).

Research has shown the attribution of harmful exposure to the fetus/child in the prenatal, perinatal, postnatal and early childhood phases as the causes of ADHD (21).

Exposure to alcohol, tobacco and lead during prenatal may increase the risk of ADHD (22).

Studies indicated that the diet such as consuming certain additives or food preservatives may exacerbate ADHD symptoms (5).

Treatment of ADHD

Treatment of ADHD is multidimensional. Conventional treatment include pharmacological and behavioral therapies and psychoeducational treatment. The drugs which inhibit the reuptake of noradrenline and dopamine such as psychostimulants including methylphenidate and dextroamphetamine and non-stimulating pre-frontal cortex noradrenaline reuptake inhibitor such as atomoxetine, are the standard treatment of ADHD(23).

Studies have shown a positive effect of reboxetine, selective serotonin reuptake inhibitors (SSRIs), in the treatment of ADHD symptoms(24).

SSRIs and other antidepressants are proposed with varying degrees of success. Adverse effects of stimulants have been reported in 30% of ADHD patients including anorexia, weight loss, abdominal pains, sleep disturbances, headaches, irritability, depressed mood and appetite (25-29) with some reports of stimulant induced psychosis (30).

Increasing apprehension regarding stimulant medication and the ramifications of its use on children, has led to the investigation and acknowledgment of alternative therapeutic medications (31). More than 50% of parents of children diagnosed with ADHD have tried one or more Complementary or Alternative Medicines (CAMs) including vitamins in their children (31,32).

Studies have been conducted about the effect of omega-3 and omega -6 supplements to improve ADHD symptoms. However, the results have been inconsistent and there were many contradictions. Behdani showed that the augmentation of omega-3 did not have a priority to placebo(33).

Herbs such as ginkgo biloba, matricaria chamomilla, humulus lupulus, valeriana officinalis, passiflora incarnata and melissa officinalis have been reported to have some possible benefits on the treatment of ADD (34). Ginkgo biloba has been described to be effective in various neuropsychiatric symptoms(35). Thus, it was assumed that ginkgo biloba might improve some symptoms of ADD. No systematic study reported a possible efficacy of ginkgo biloba in ADD.

Ginkgo biloba

Researches have shown that ginkgo biloba possesses neurotrophic potential. Thus, it has neuroprotective effects on animal and human models(36,37). Rats undergoing traumatic motor nerve damage showed more rapid reinnervation under the influence of ginkgo extract compared to the untreated controls (38).

European and recent North American trial (39) have been shown that ginkgo has significant cog-

nition-enhancing or neurotropic effects. It might indicate that ginko has a positive effect on the memory enhancement and cognitive performance in subjects with dementia(40). Furthermore, Gginkgo has shown to significantly improve the memory and other cognitive functions in healthy adults (41). Ginkgo extract has shown to affect several central neurotransmitter systems and reverse the reduction in 5-hydroxy triptophan 1A receptors (42) and noradrenergic receptors in the aged rat (43). Recently, it was demonstrated that ginkgo extract produced the reversible inhibition of both monoamino oxidase A and monoamino oxidase B in the brain (44). This mechanism might underlie the anxiolytic and mild antidepressant effects of ginkgo extract, which might contribute to the improvement in the symptoms of ADHD.

Ginkgo as a complementary or alternative medicine therapy for ADHD

The action of ginkgo biloba was investigated by lyon et al. (2001) in 50 hyperactive children aged from 2 to 13 years. They found that ginkgo biloba had a greater effect on excitability, frustration tolerance and mood compared to methylphenidate (44).

In Salehi`s double blind, randomized clinical trial (2010), the administration of ginkgo biloba was less effective than methylphenidate in the treatment of ADHD. They studied fifty ADHD patients (39 boys and 11 girls). Participants received Ginko T.D ™ at a dose of 80–120 mg/day (group 1) or methylphenidate at a dose of 20–30 mg/day (group 2) for a 6-week period (45).

Niederhofer et al. (2010) administered ginkgo biloba as an herbal alternative in six psychiatric outpatients diagnosed with ADD. During the treatment with ginkgo biloba, the patients' mean scores improved significantly in overall and especially in hyperactivity, inattention and immaturity factors. This preliminary study indicated that ginkgo biloba might be a beneficial and useful treatment of ADD with minimal side effects (46).

Conclusion

Although many medicinal plant textbooks referred to the efficacy of ginkgo biloba in the treatment of ADHD, there was no enough evidence-based documents so far. Moreover, there are controversial results about the efficacy of ginkgo biloba.

Further researches should investigate the effect of ginkgo biloba in the treatment of ADHD. This could be evaluated in a double blind, controlled and randomized trials more efficiently. For example, the comparison of augmentation of ginkgo biloba in one group and the methylphenidate (Ritalin) administration in placebo group might have different responses.

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Conflict of Interest

The authors declare no conflict of interest.

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