Progress in Neuro-Psychopharmacology & Biological Psychiatry 34 (2010) 76–80

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Ginkgo biloba for Attention-Deficit/Hyperactivity Disorder in children and adolescents: A double blind, randomized controlled trial

Bahman Salehi [a], Reza Imani [b], Mohammad Reza Mohammadi [b], Jalil Fallah [b], Mohammad Mohammadi [b], Ahmad Ghanizadeh [c], Ali Akbar Tasviechi [b], Ardalan Vossoughi [b], Shams-Ali Rezazadeh [d], Shahin Akhondzadeh [b,*]

[a] *Department of Psychiatry, Arak University of Medical Sciences, Arak, Iran*
[b] *Psychiatric Research Centre, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Research Center for Psychiatry and Behavioral Sciences, Shiraz University of Medical Sciences, Hafez Hospital, Shiraz, Iran*
[d] *Institute of Medicinal Plants (ACECR), Tehran, Iran*

ARTICLE INFO

Article history:
Received 25 July 2009
Received in revised form 28 September 2009
Accepted 29 September 2009
Available online 5 October 2009

Keywords:
Attention-Deficit/Hyperactivity Disorder
Clinical trial
Ginkgo biloba
Methylphenidate

ABSTRACT

Background: Although stimulants are highly effective in controlling the symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD), some children will not respond to, or are intolerant of stimulants. Thus, the desire for safe and effective nonstimulant medications has risen during the past several years. *Ginkgo biloba* has been suggested in the treatment of dementia and memory impairment. We hypothesized that *G. biloba* would be beneficial for treatment of ADHD, and this could be evaluated in a double blind, randomized, parallel group comparison of *G. biloba* (Ginko T.D.™ Tolidaru, Iran) and methylphenidate.

Methods: Fifty outpatients (39 boys and 11 girls) with a DSM-IV-TR diagnosis of ADHD were study population of this trial. Subjects were recruited from an outpatient child and adolescent clinic for a 6 week double blind, randomized clinical trial. All study subjects were randomly assigned to receive treatment using tablet of Ginko T.D.™ at a dose of 80–120 mg/day depending on weight (80 mg/day for <30 kg and 120 mg/day for >30 kg) (group 1) or methylphenidate at a dose of 20–30 mg/day depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg (group 2) for a 6 week double blind, randomized clinical trial. The principal measure of outcome was the Teacher and Parent ADHD Rating Scale- IV. Patients were assessed at baseline and at 21 and 42 days after the medication started.

Results: Significant differences were observed between the two groups on the Parent and Teacher Rating Scale scores. The changes at the endpoint compared to baseline were: −6.52 ± 11.43 (mean ± S.D.) and −15.92 ± 11.44 (mean ± S.D.) for Ginko T.D.™ and methyphenidate, respectively for Parent ADHD Rating Scale. The changes at the endpoint compared to baseline were: −0.84 ± 6.79 (mean ± S.D.) and −14.04 ± 8.67 (mean ± S.D.) for Ginko T.D.™ and methyphenidate, respectively for Teacher ADHD Rating Scale.

The difference between the Ginko T.D.™ and methylphenidate groups in the frequency of side effects was not significant except for decreased appetite, headache and insomnia that were observed more frequently in the methylphenidate group.

Conclusion: The results of this study suggest that administration of *G. biloba* was less effective than methylphenidate in the treatment of ADHD.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common neurobehavioural disorder of childhood. The incidence of ADHD is 5–10% in children and the symptoms are known to persist into adulthood in 10–60% of cases (Mohammadi and Akhondzadeh, 2007). Psychostimulant medications continue to be a primary treatment modality for children with ADHD (Cormier, 2008; Dopheide and Pliszka, 2009). Although the etiology of ADHD is not fully understood, potent drugs are being employed for its medical management while safe and effective alternatives are being neglected (Noorbala and Akhondzadeh, 2006; Mohammadi and Akhondzadeh, 2007; Cormier, 2008; Dopheide and Pliszka, 2009). Neurochemical studies suggest alterations in catecholaminergic — mainly dopaminergic and noradrenergic-transmitter functions markedly contribute to the symptoms of ADHD (Cormier, 2008). The symptoms of ADHD are significantly ameliorated by agents that specifically influence

Abbreviation: ADHD-RS, Attention-Deficit/Hyperactivity Disorder Rating Scale; DSM, Diagnosis and Statistical Manual of Mental Disorders.

* Corresponding author. Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran 13337, Iran. Tel.: +98 21 88281866; fax: +98 21 55419113.
E-mail address: s.akhond@neda.net (S. Akhondzadeh).

0278-5846/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2009.09.026

these neurotransmitter systems (Curatolo et al., 2009). Approximately 70% of the children treated with stimulants show improvement in the primary ADHD symptoms and in co-morbidity such as conduct disorder, although the benefits may not hold beyond two years (Noorbala and Akhondzadeh, 2006). Despite the well-established efficacy and safety of stimulants for ADHD, alternative medicines are still needed for several reasons (Richard et al., 2003). About 30% of children and adolescents with ADHD may not respond to stimulants or may be unable to tolerate potential adverse events such as decreased appetite, mood lability and sleep disturbances (Mohammadi and Akhondzadeh, 2007). Although stimulants do not increase risk for later substance abuse in ADHD, concerns have been raised about special prescription rules, and a potential for abuse by persons other than the ADHD subjects (Mohammadi and Akhondzadeh, 2007). Herbal medicines have been shown to ameliorate ADHD related behaviors (Akhondzadeh et al., 2005). For example, a recent study showed that *Passiflora incarnata* may be a novel therapeutic agent for the treatment of attention deficit hyperactivity disorder. In addition, a tolerable side effect profile may be considered as one of the advantages of *Passiflora* in the treatment of attention deficit hyperactivity disorder (Akhondzadeh et al., 2005). *Ginkgo biloba* has been suggested in the treatment of dementia and memory impairment (Canter and Ernst, 2007; Birks and Grimley Evans, 2009). Nevertheless, a recent systematic review has concluded that there is no convincing evidence that *G. biloba* has a positive effect on any aspect of cognitive performance in healthy people (Canter and Ernst, 2007). In addition, some studies suggest *G. biloba* in the treatment of ADHD, especially in children who are primarily inattentive (Lyon et al., 2001; Frei, 2002). Ginkgo improves cerebrovascular blood flow and may help to reduce hyperactivity due to boredom and lack of focus (Lyon et al., 2001; Ponto and Schultz, 2003). Ginkgo extract has been shown to affect several central neurotransmitter systems (Nathan, 2000); it has been shown to reverse the reduction in 5-HT_{1A} receptors and noradrenergic receptors in the aged rat (Huguet and Tarrade, 1992; Winter and Timineri, 1999). It was demonstrated that ginkgo extract produces reversible inhibition of both MAO-A and MAO-B in the brain (White et al., 1996). This mechanism may underlie the anxiolytic and mild antidepressant effects of ginkgo extract, and it may contribute to the improvement in the symptoms of ADHD (Ponto and Schultz, 2003). The action of *G. biloba* was investigated in 50 hyperactive children aged from 2 to 13 years. It was found that *G. biloba* had a greater effect on excitability, frustration tolerance and mood than methylphenidate (Lyon et al., 2001). Although many medicinal plants textbooks refer to efficacy of *G. biloba* in the treatment of ADHD, there is no enough evidence-based documents so far (Akhondzadeh, 2007). In addition, the Lyon study was an open label trial (Lyon et al., 2001). Therefore, we hypothesized that *G. biloba* would be beneficial for treatment of ADHD, and this could be evaluated in a double blind, randomized, parallel group comparison of *G. biloba* (Ginko T.D.™ Tolidaru, Iran) and methylphenidate.

2. Methods

2.1. Trial setting

This was a six-week, parallel group, randomized clinical trial undertaken in an outpatient child and adolescent clinic at Roozbeh Psychiatric Hospital in Tehran, Iran during April 2007–May 2009.

2.2. Participants

Male and female subjects, ages 6 to 14 years included 50 outpatients (39 boys and 11 girls) with a DSM-IV-TR diagnosis of ADHD were study population of this trial. At screening, investigators conducted a psychiatric evaluation with the DSM-IV-TR criteria for ADHD and the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview and performed a complete medical history and physical examination (American Psychiatric Association, 2000; Ghanizadeh et al., 2006). Additional inclusion criteria included total and/or subscale scores on Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) School Version at least 1.5 standard deviations above norms for patient's age and gender (DuPaul et al., 1998). The patients were recruited from the outpatient child and adolescent clinic at Roozbeh Psychiatric Hospital. The diagnosis of ADHD was confirmed by a child and adolescent psychiatrist before participants were initiated into the study. All patients had combined subtype of ADHD and were newly diagnosed. Parents were carefully interviewed and asked to rate the severity of the DSM-IV-TR ADHD symptoms that their children displayed at home. Children were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders (DSM-IV axis I); any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation (I.Q.<70). In addition, patients were excluded if they had a clinically significant chronic medical condition, including organic brain disorder, seizures and, current abuse or dependence on drugs within 6 months. Additional exclusion criteria were hypertension, hypotension. To participate, parents and children had to be willing to comply with all requirements of the study. After a description of the procedures and purpose of the study, written informed consent was obtained from each patient's parent or guardian. Informed consent was received before the administration of any study procedure or dispensing of study medication in accordance with the ethical standards of the investigative site's institutional review board and with the Helsinki declaration of 1975, as revised in 2000. The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant No: 5404). This trial is registered with the Iranian Clinical Trials Registry (IRCT138711151556N6).

2.3. Study design

Patients underwent a standard clinical assessment comprised of a psychiatric evaluation, a structured diagnostic interview, a medical history and an electrocardiogram (ECG). Patients were randomized to receive tablet of *G. biloba* (Ginko T.D.™ Tolidaru, Iran) or methylphenidate in a 1:1 ratio using a computer-generated code. Both tablets were encapsulated and were identical. The assignments were kept in sealed, opaque envelopes until the point of analysis of data. The randomization and allocation process was done by the pharmacist at the Roozbeh Hospital. All study subjects were randomly assigned to receive treatment using tablet of Ginko T.D.™ at a dose of 80–120 mg/day depending on weight (80 mg/day for <30 kg and 120 mg/day for >30 kg (group 1) or methylphenidate at a dose of 20–30 mg/day depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg (group 2) for a 6 week double blind, randomized clinical trial.

Each tablet of Ginko T.D.™ contains 40 mg dried extract of *G. biloba*. Ginko T.D.™ was titrated up during the trial according to the following schedule: week 1: 40 mg/day; week 2: 80 mg/day (one capsule of Ginko T.D.™ in the morning and one capsule of Ginko T.D.™ at midday) and week 3: 120 mg/day for children >30 kg (one capsule of Ginko T.D.™ in the morning, one capsule of Ginko T.D.™ at midday and one capsule of Ginko T.D.™ at 16.00). Methylphenidate was titrated up during the trial according to the following schedule: week 1: 10 mg/day (5 mg in the morning and 5 mg at midday); week 2: 20 mg/day (10 mg in the morning and 10 mg at midday) and week 3: 30 mg/day for children > 30 kg (10 mg in the morning, 10 mg at midday and 10 mg at 16.00). In this schedule, drugs were blindly administered during titration. Throughout the study the person who administrated the medications, the rater and the patients along with their parents were blind to group assignments. The principal measure of outcome was the Parent and Teacher ADHD Rating Scale-IV that has been used extensively in Iran in school-age children and provides valid measures of behavioral abnormality and attention (DuPaul et al., 1998; Akhondzadeh et al., 2003,

2004; Mohammadi and Akhondzadeh, 2007; Amiri et al., 2008; Kahbazi et al., 2009). ADHD-RS-IV is an instrument that assesses the 18 symptoms of ADHD as defined in the DSM-IV-TR according to a 4-point Likert scale. The mean decrease in ADHD -RS-IV score from baseline was used as the main outcome measure of response of ADHD treatment. Patients were assessed at baseline and 21 and 42 days after the medication started. Side effects were systematically recorded throughout the study and were assessed using a checklist that comprises 20 side effects including psychic, neurologic, autonomic and other side effects, administered by a child psychiatrist on days 7, 21and 42. Two patients dropped out from the Ginko T.D.™ group and two from the methylphenidate group due to lost to follow up (lack of collaboration of parents), leaving 46 patients who completed the trial. Hematology tests were collected at baseline and weeks 2, 4 and 6; serum chemistry and urinalysis were evaluated at baseline and week 6; body weight and vital sign were measured at baseline and weeks 1, 2, 4, and 6; and 12-lead electrocardiogram and physical examinations were evaluated at baseline and week 6.

2.4. Statistical analysis

A two-way repeated measures analysis of variance (time- treatment interaction) was used. The two groups (Ginko T.D.™ and methylphenidate) as a between-subjects factor (group) and the three measurements during treatment as the within-subjects factor (time) were considered. This was done for Parent and Teacher ADHD Rating Scale scores. In addition, a one-way repeated measures analysis of variance with a two-tailed post-hoc Tukey mean comparison test were performed on the change in Parent and Teacher ADHD Rating Scale scores from baseline. Results are presented as mean ± SD. differences and were considered significant with $P \leq 0.05$. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was performed. To consider, $\alpha = 0.05$, $\beta = 0.2$, the final difference between the two groups at least score of 5 on the Teacher and Parent ADHD Rating Scale, S = 6 and power = 0.8, the sample size was calculated at least 23 in each group. Intention to treat (ITT) analysis with the last observation carried forward (LOCF) procedure was performed.

3. Results

No significant differences were identified between patients randomly assigned to the Group 1 or 2 conditions with regard to basic demographic data including age, gender and ethnicity (Table 1).

3.1. Parent ADHD Rating Scale

The mean ± SD. scores of the two groups are shown in Fig. 1 (total Score) and Table 2 (subscales). There were no significant differences between two groups at Day 0 (baseline) on the Parent ADHD Rating Scale (total score) ($t = 0.01$, $df = 48$, $P = 0.98$). The difference between the two groups was significant as indicated by the effect of group, the between-subjects factor ($F = 4.16$, $df = 1$, $P = 0.047$) (total score). The time/treatment interaction was significant (groups by time interaction, $F = 6.20$, $df = 1.53$, $P = 0.006$) (total score). In the methylphenidate group, post hoc comparisons of the baseline Parent ADHD Rating Scale scores with the scores at Day 42 by means of the Tukey procedure revealed significant decreases from baseline ($P < 0.001$). The differences between the two protocols were significant at the endpoint ($t = 2.91$, $df = 48$, $P = 0.005$). This difference was significant either for Inattentive or for Hyperactive/Impulsive subscales (Table 2). The changes at the endpoint compared to baseline were: −6.52 ± 11.43 (mean ± S.D.) and −15.92 ± 11.44 (mean ± S.D.) for Ginko T.D.™ and methyphenidate, respectively (total score).

A significant difference was observed on the reduction of scores of the Parent ADHD Rating Scale at Week 6 compared to baseline in the two groups ($t = 2.90$, $df = 48$, $P = 0.005$) (total score). There was a significant difference between two groups in terms of the percentage of responders (those with at least 40% decreases in Parent ADHD Rating Scale score between baseline and treatment end) (Ginko T.D.™: 32%, 8 of 25, and methylphenidate: 88%, 22 of 25).

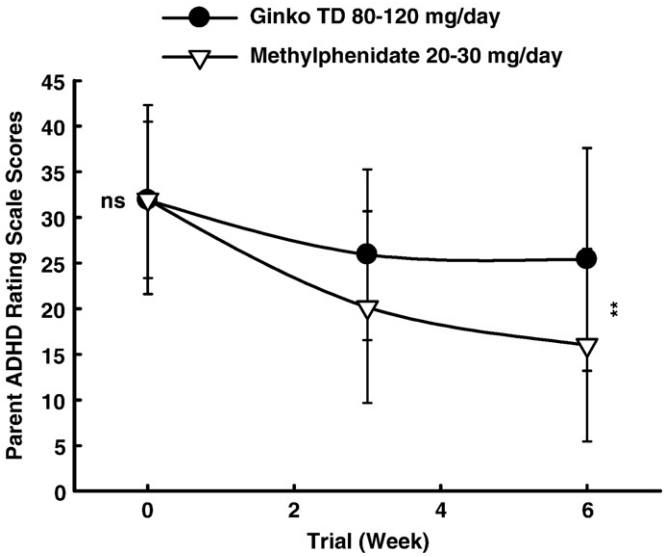

Fig. 1. Mean ± SD. scores of two groups on the Parent ADHD Rating Scale-IV. ns = non-significant and **<0.01.

3.2. Teacher ADHD Rating Scale

The mean ± SD. scores of two groups are shown in Fig. 2 (total score) and Table 2 (subscales). No significant differences were observed at

Table 1
Characteristics of the patients.

	Ginko T.D.™ group	Methylphenidate group
Girl	6	5
Boy	19	20
Age (mean ± SD)	9.12 ± 1.61 (year)	9.61 ± 2.26 (year)
Weight (mean ± SD)	30.70 ± 7.30 Kg	30.92 ± 9.21 Kg
Ethnicity	All Persian	All Persian

Table 2
ADHD Rating Scale-IV scores of study participants (inattentive and hyperactive/impulsive subscales).

	Ginkgo biloba	Ritalin	
Parent ADHD Rating Scale (inattentive)			*P*
Week 0	15.40 ± 4.25	15.11 ± 5.43	0.88
Week 3	12.02 ± 5.85	8.81 ± 5.26	0.04
Week 6	11.90 ± 8.45	7.00 ± 6.45	0.02
Teacher ADHD Rating Scale (inattentive)			
Week 0	12.02 ± 5.38	12.70 ± 5.92	0.67
Week 3	10.79 ± 5.43	9.22 ± 5.49	0.31
Week 6	11.04 ± 5.42	4.90 ± 3.33	0.0001
Parent ADHD Rating Scale (hyperactive/impulsive)			*P*
Week 0	16.52 ± 5.33	16.85 ± 6.24	0.84
Week 3	13.90 ± 6.12	11.35 ± 6.32	0.15
Week 6	13.50 ± 5.62	8.70 ± 5.42	0.003
Teacher ADHD Rating Scale (hyperactive/impulsive)			
Week 0	13.62 ± 6.72	14.10 ± 6.31	0.79
Week 3	12.97 ± 5.73	12.01 ± 5.61	0.55
Week 6	13.76 ± 6.63	6.78 ± 4.16	0.0001

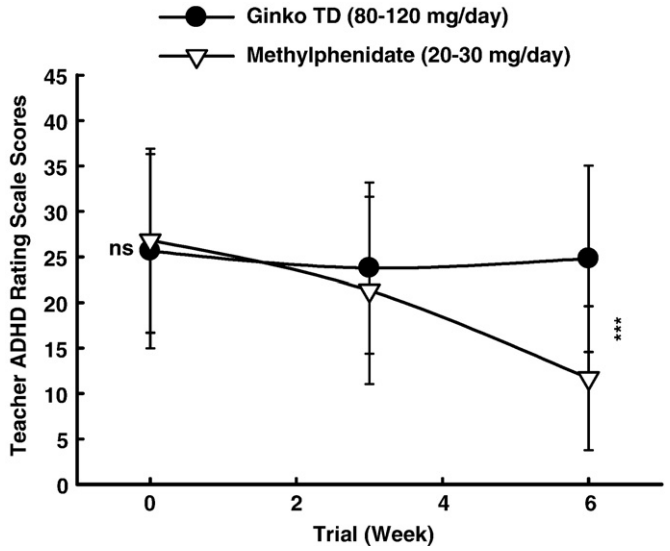

Fig. 2. Mean ± SD. scores of two groups on the Teacher ADHD Rating Scale-IV. ns = non-significant and ***<0.001.

baseline on the Teacher ADHD Rating Scale ($t = 0.39$, $df = 48$, $P = 0.69$) (total score). The difference between the two groups was significant as indicated by the effect of group, the between-subjects factor ($F = 4.03$, $df = 1$, $P = 0.05$) (total score). The time/treatment interaction was significant (groups by time interaction; Greenhouse–Geisser, $F = 18.37$, $df = 1.88$, $P = 0.0001$) (total score). In addition, a one-way repeated measures analysis of variance showed a significant effect of only the methylphenidate group on the Teacher ADHD Rating Scale scores. In the methylphenidate group post hoc comparisons of the baseline Teacher ADHD Rating Scale scores with the scores at Day 42 by means of the Tukey procedure revealed significant decreases from baseline. The differences between the two groups were significant at the endpoint ($t = 2.91$, $df = 48$, $P = 0.005$). This difference was significant either for Inattentive or for Hyperactive/Impulsive subscales (Table 2). The changes at the endpoint compared to baseline were: -0.84 ± 6.79 (mean ± S.D.) and -14.04 ± 8.67 (mean ± S.D.) for Ginko T.D.™ and methyphenidate, respectively (total score). A significant difference was observed on the reduction of scores of the Teacher ADHD Rating Scale at Week 6 compared to baseline in the two groups ($t = 5.991$, $df = 48$, $P = 0.0001$) (total score). There was a significant difference between two groups in terms of the percentage of responders (those with at least 40% decreases in Teacher ADHD Rating Scale score between baseline and treatment end) (Ginko T.D.™: 8%, 2 of 25, and methylphenidate: 64%, 16 of 25).

3.3. Clinical complications and side effects

A number of probable side effects were studied (Table 3). Ten side effects were observed over the trial that all of them were mild to moderate and tolerable. The difference between the Ginko T.D.™ and methylphenidate groups in the frequency of side effects was not significant except for decreased appetite, headache and insomnia that were observed more frequently in the methylphenidate group.

Table 3
Number of patients with side effects.

Complications	Ginko T.D.™	Methylphenidate	*P*
Abdominal pain	3 (12%)	5 (20%)	ns
nervousness	13 (52%)	19 (76%)	ns
Decreased appetite	5 (20%)	19 (76%)	0.0002
Sadness	2 (8%)	7 (28%)	ns
Insomnia	3 (12%)	12 (48%)	0.01
Weight loss	3 (12%)	8 (32%)	ns
Nausea	2 (8%)	4 (16%)	ns
Dry mouth	2 (8%)	4 16%	ns
Headaches	3 (12%)	13 (52%)	0.005
Anxiety	7 (28%)	9 (36%)	ns

4. Discussion

Stimulant pharmacotherapy has been used for many decades in the treatment of ADHD, in conjunction with psychosocial interventions such as parent training, contingency management, and social skills training (Mohammadi and Akhondzadeh, 2007). Although stimulants are highly effective in controlling the symptoms of ADHD, some children will not respond to, or are intolerant of stimulants. Thus, the desire for safe and effective nonstimulant medications has risen during the past several years (Banaschewski et al., 2004; Sawni, 2008). The results of this study suggest that administration of *G. biloba* has no comparable efficacy in comparison with methylphenidate in the treatment of ADHD. Nevertheless, in our study, those in the *G. biloba* group experienced fewer adverse events than the methylphenidate group in particular regarding insomnia, headaches and decreased appetite. This trial used similar enrollment criteria and the same rating scales as our previous trials to monitor improvement in symptoms over the course of the study. Our results are in contrast with the study of Lyon et al., who reported beneficial application of *G. biloba* in the treatment of thirty six children and adolescent with ADHD for 4 weeks in an open-label trial (Lyon et al., 2001). Nevertheless, they used a combination of *G. biloba* and American ginseng extract. In addition, our results are not in agreement with Frei's study that reported efficacy of *G. biloba* in the treatment of fifty children and adolescent with ADHD for 4 weeks based on Conners Global Index (Frei, 2002). It should be mentioned that the Lyon and Feri studies were both open label. Therefore, a controlled trial like the present study would be important (Lyon et al., 2001; Frei, 2002). This was a negative trial but what could be the value for our negative findings? There is no doubt, modern medicine needs to distinguish fact from fiction in herbal medicine and this can be achieved only through evidence based herbal medicine. The relatively short duration (6 weeks), small sample size of this trial and lack of placebo arm are limitations of this study. In conclusion, the results of this study do not support the application of *G. biloba* in the treatment of ADHD.

Acknowledgments

This study was Dr. Reza Imani's thesis toward the Iranian board of child psychiatry. This study was supported by a grant (grant number: 5404) from Tehran University of Medical Sciences to Prof. Shahin Akhondzadeh.

References

Akhondzadeh S. Herbal medicine in the treatment of psychiatric and neurological disorders. In: L'Abate L, editor. Low-cost approaches to promote physical and mental health: theory research and practice. New York: Springer; 2007. p. 119–38.
Akhondzadeh S, Tavakolian R, Davari-Ashtiani R, Arabgol F, Amini H. Selegiline in the treatment of attention-deficit hyperactivity disorder in children: a double-blind and randomized trial. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:841–5.
Akhondzadeh S, Mohammadi MR, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial [ISRCTN64132371]. BMC Psychiatry 2004;8(4):9.
Akhondzadeh S, Mohammadi MR, Momeni F. *Passiflora incarnata* in the treatment of attention-deficit hyperactivity disorder in children and adolescents. Therapy 2005;2:609–14.
American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, DC: American Psychiatric Association; 2000. Text Revision.
Amiri S, Mohammadi MR, Mohammadi M, Nouroozinejad GH, Kahbazi M, Akhondzadeh S. Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:145–9.
Banaschewski T, Roessner V, Dittmann RW, Santosh PJ, Rothenberger A. Non-stimulant medications in the treatment of ADHD. Eur Child Adolesc Psychiatry 2004;13:102–16.

Birks J, Grimley Evans J. *Ginkgo biloba* for cognitive impairment and dementia. Cochrane Database Syst Rev 2009;21:CD003120.
Canter PH, Ernst E. *Ginkgo biloba* is not a smart drug: an updated systematic review of randomized clinical trials testing the nootropic effects of *G. biloba* extracts in healthy people. Hum Psychopharmacol 2007;22:265–78.
Cormier E. Attention deficit/hyperactivity disorder: a review and update. J Pediatr Nurs 2008;23:345–57.
Curatolo P, Paloscia C, D'Agati E, Moavero R, Pasini A. The neurobiology of attention deficit/hyperactivity disorder. Eur J Paediatr Neurol 2009;13:299–304.
Dopheide JA, Pliszka SR. Attention-deficit-hyperactivity disorder: an update. Pharmacotherapy 2009;29:656–79.
DuPaul G, Power T, Anastopoulos A, Reid R. ADHD Rating Scale-IV. New York: Guilford; 1998.
Frei H. *Ginkgo biloba* and attention deficit hyperactivity disorder in children: open study to investigate the efficacy and tolerability of a plant remedy. Schweiz Z Ganzheitsmed 2002;14:10–3.
Ghanizadeh A, Mohammadi MR, Yazdanshenas A. Psychometric properties of the Farsi translation of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. BMC Psychiatry 2006;15(6):10.
Huguet F, Tarrade T. Alpha-2-adrenoceptor changes during cerebral ageing. The effect of *Ginkgo biloba* extract. J Pharm Pharmacol 1992;44:24–7.
Kahbazi M, Ghoreishi A, Rahiminejad F, Mohammadi MR, Kamalipour A, Akhondzadeh S. A randomized, double-blind and placebo-controlled trial of modafinil in children and adolescents with attention deficit and hyperactivity disorder. Psychiatry Res 2009;168:234–7.
Lyon MR, Cline JC, Totosy de Zepetnek J, Shan JJ, Pang P, Benishin C. Effect of the herbal extract combination *Panax quinquefolium* and *Ginkgo biloba* on attention-deficit hyperactivity disorder: a pilot study. Psychiatry Neurosci 2001;26:221–8.
Mohammadi MR, Akhondzadeh S. Attention-deficit/hyperactivity disorder: etiology and pharmacotherapy. Exp Rev Neurotrapeutics 2007;7:195–201.
Nathan P. Can the cognitive enhancing effects of *Ginkgo biloba* be explained by its pharmacology? Med Hypotheses 2000;55:491–3.
Noorbala AA, Akhondzadeh S. Attention-deficit/hyperactivity disorder: etiology and pharmacotherapy. Arch Iranian Med 2006;9:374–80.
Ponto LL, Schultz SK. *Ginkgo biloba* extract: review of CNS effects. Ann Clin Psychiatry 2003;15:109–19.
Richard W, Root II, Robert J, Resnick J. An update on the diagnosis and treatment of Attention-Deficit/Hyperactivity Disorder in children. Prof Psychol Res Pract 2003;34:34–41.
Sawni A. Attention-deficit/hyperactivity disorder and complementary/alternative medicine. Adolesc Med State Art Rev 2008;19:313–26.
White H, Scates P, Cooper B. Extracts of *Ginkgo biloba* leaves inhibit monoamine oxidase. Life Sci 1996;58:1315–21.
Winter JC, Timineri D. The discriminative stimulus properties of EGb 761, an extract of *Ginkgo biloba*. Pharmacol Biochem Behav 1999;62:543–7.