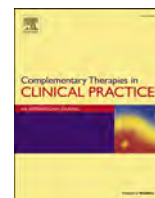




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Ginkgo biloba in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. A randomized, placebo-controlled, trial

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A B S T R A C T

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Ginkgo biloba

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Objective: To evaluate the efficacy of *Ginkgo biloba* as a complementary therapy for attention-deficit/hyperactivity disorder (ADHD).**Methods:** Children and adolescents with ADHD received methylphenidate (20–30 mg/day) plus either *G. biloba* (80–120 mg/day) or placebo for 6 weeks. Parent and teacher forms of the ADHD Rating Scale-IV (ADHD-RS-IV) were completed at baseline, week 2, and week 6. Treatment response was defined as 27% improvement from baseline in the ADHD-RS-IV.**Results:** Compared with placebo, more reduction was observed with *G. biloba* regarding ADHD-RS-IV parent rating inattention score (-7.74 ± 1.94 vs. -5.34 ± 1.85 , $P < 0.001$) and total score (-13.1 ± 3.36 vs. -10.2 ± 3.01 , $P = 0.001$) as well as teacher rating inattention score (-7.29 ± 1.90 vs. -5.96 ± 1.52 , $P = 0.004$). Response rate was higher with *G. biloba* compared with placebo based on parent rating (93.5% vs. 58.6%, $P = 0.002$).**Conclusions:** The *G. biloba* is an effective complementary treatment for ADHD. Further studies with longer treatment duration are warranted in this regard. IRCT2014111519958N1.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders in children. Symptoms are persistent and mainly include inattention, hyperactivity, and impulsivity [1]. The estimated worldwide prevalence of ADHD is about 5.3% in children and adolescents of the general population [2]. This disorder significantly impairs the academic and psychosocial functioning of the child [3–5] and results in high global burden [6].

Management of ADHD consists of both pharmacological and behavioral interventions [7]. Stimulants such as methylphenidate and non-stimulants such as atomoxetine (selective norepinephrine-reuptake inhibitor) are recommended by the current practice guidelines for the treatment of ADHD [7]. However, up to 30% of the patients have no satisfactorily response to these drugs, must avoid stimulant therapy, or may not tolerate drugs' common side effects such as appetite loss and sleep problems [8]. Accordingly, a large number of families use complementary or alternative medicines (CAM) for treatment of their children with ADHD. Common applied CAM methods include vitamins, minerals, and dietary modifications and supplements [9]. Although families report beneficial effects of a number of these CAM methods, there is lack of well-designed studies in this regard.

Herbal therapy is a common used CAM method in the treatment of ADHD [9]. Proposed mechanisms of action for the applied herbs include increasing serotonin level, central stimulating, antidepressant, and anxiolytic effects, and improving cognitive

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performance [10]. However, limited controlled trials are conducted on the efficacy of herbal medicines in the treatment of ADHD. Although a number of herbs are reported to be beneficial, clear conclusion could not be made due to limited number of studies and methodological inadequacies [11].

Ginkgo biloba (Ginkgoaceae; Maidenhair tree) is a native plant of China which has been used for centuries in Traditional Chinese Medicine. Seeds and leaves of the plant are used for therapeutic purposes. The known and main active ingredients of the plant are flavone glycosides and terpene lactones [12]. Clinical studies have evaluated the efficacy of *G. biloba* extracts for a variety of disorders such as anxiety and depression [13], Alzheimer's disease and dementias [14], memory impairment [15], and cerebral insufficiency [16]. Animal studies have shown that *G. biloba* increases central dopaminergic activity [17] which is implicated in the pathophysiology of ADHD [18]. Considering its effects on cognitive functions as well as safety and tolerability, *G. biloba* is an attractive herbal medicine to be investigated in the treatment of ADHD.

A number of open-label trials have reported beneficial effects of *G. biloba* for the treatment of ADHD in children [19–21]. In contrast, the randomized controlled trial conducted by Salehi et al. [22] found no efficacy for *G. biloba* as a monotherapy when compared with methylphenidate. However, it is not clear if *G. biloba* is effective as a complementary method in treatment of ADHD. Therefore, we aimed to evaluate the efficacy of *G. biloba* as a complementary therapy to methylphenidate in treatment of ADHD in children and adolescents. We hypothesized that combined treatment of *G. biloba* and methylphenidate is superior to methylphenidate alone in reducing symptoms of ADHD.

2. Materials and methods

2.1. Participants and study setting

This randomized, double-blinded, placebo-controlled, clinical trial was conducted on children and adolescents with ADHD referring to the Department of Child and Adolescent Psychiatry at the Noor University Hospital in Isfahan city (Iran) between September and December 2014. Inclusion criteria were a) age between 6 and 12 years, b) diagnosis of ADHD by a child and adolescent psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [23], and c) the Children's Global Assessment Scale (CGAS) score of <80 indicating decreased general function [24]. Exclusion criteria were any evidence of mental retardation ($IQ \leq 70$), type I bipolar disorder, psychosis, pervasive developmental disorders, organic brain disease, seizure, or cardiovascular disease. The study protocol was approved by the Ethics Committee of the Isfahan University of Medical Sciences and informed consent was obtained from parents. The study was registered at the Iranian Registry of Clinical trials (<http://www.irct.ir>; registration number: IRCT2014111519958N1).

2.2. Interventions

The herbal medicine used in this study was an extract of the *G. biloba* leaves standardized by flavonoid glycoside 24% and terpene lactone 6%. The solvents used in the extract are ethanol and water and the herbal-to-extract ratio is 4:1 (Ginko T.D.TM, Tolid-Daru Co., Tehran, Iran). After a two-week psychiatric drug free baseline period, participants were randomized into the *G. biloba* and placebo groups. All children were treated by methylphenidate (Ritalin®, NOVARTIS, Switzerland) with a total dose of 20 mg/day (10 mg/b.i.d) for those with body weight of <30 kg, and 30 mg/day (10 mg/t d s) for those >30 kg. Dosage was increased gradually by 10 mg/week up to the assigned total dose. Children in the *G. biloba*

group received enteric coated tablets of *G. biloba* with a total dose of 80 mg/day (40 mg/b.i.d) for those with body weight of <30 kg, and 120 mg/day (40 mg/t d s) for those >30 kg. Dosage was gradually increased by 40 mg/week up to the assigned total dose. This dosage regimen was determined according to previous studies [22]. Children in the placebo group received placebo tablets (School of Pharmacy, IUMS, Isfahan, Iran) which were filled with starch and lactose and identically sized and colored to match the *G. biloba* tablets. Participants consumed medicines for a total of 6 consecutive weeks and continued treatment with methylphenidate thereafter.

The study was designed as to be a randomized and double-blinded trial with two parallel arms. Randomization was done using the random allocation software producing a table with two alphabets which were randomly distributed among consecutive numbers [25]. Patients were consecutively entered into the study and were assigned an order number and received the intervention based on the allocation sequence. The randomization and allocation process was done by a psychologist who was not involved in participants' recruitment, treatment, or follow-up. The assignments were kept in sealed and opaque envelopes until the point of data analysis. Also, the outcome assessor was not aware about the study arms.

2.3. Measurements

All participants were visited and interviewed at baseline by a Child and Adolescent Psychiatrist (FSH). Physical examination was done and a standard 12-lead electrocardiogram was obtained to evaluate any evidence of cardiovascular disease. Parents were interviewed by a general psychiatrist (MR) to gather data on demographic characteristics, ADHD symptoms duration and severity, past medical and drug history, and global functioning of the child. Weight was measured using a single calibrated scale. Participants were visited again at 2 weeks and 6 weeks after medication to evaluate the following treatment outcomes.

2.3.1. The ADHD rating Scale-IV (ADHD-RS-IV), parent and teacher ratings

The ADHD-RS-IV is a widely applied instrument for the assessment and rating of the ADHD symptoms. It evaluates 18 symptoms of ADHD (defined by the DSM-IV-TR) and consists of two sub-scales including inattention and hyperactivity–impulsivity. Response to each item is graded from 0 (never) to 3 (always). The total score ranges from 0 to 27 for each sub-scale and from 0 to 54 for the total scale. The ADHD-RS-IV can be completed by teachers as well as by clinicians interviewing with the parents [26,27]. The validity and reliability of the ADHD-RS-IV is established and studies have indicated an appropriate responsiveness to treatments [26]. The ADHD-RS-IV was completed by parents (with interview) and teachers at baseline, and then at week 2 and week 6 after treatment.

2.3.2. Children's Global Assessment Scale

The CGAS is widely used by mental health professionals to measure general (psychosocial) functioning of children. It consists of ten categories of general functioning with scores ranging from 1–10 to 91–100; there are 10-score intervals between each category [24]. The CGAS was completed during an interview with parents at baseline and then at week 6 after treatment.

2.3.3. Side effects

Side effects were assessed by a psychiatrist at week 2 and week 6 after treatment.

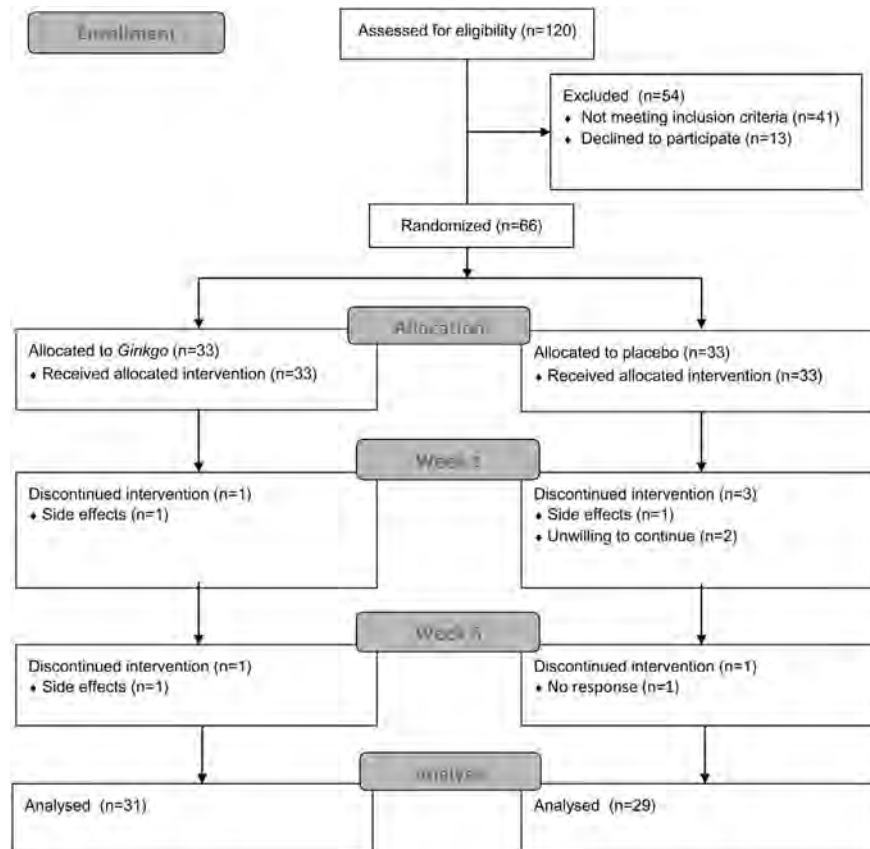


Fig. 1. Patients' flow diagram.

2.4. Data analyses

2.4.1. Primary and secondary outcomes

The study primary outcome was considered to be the amount of change in ADHD-RS-IV scores after medication [22]. Clinical treatment response has been variously defined by trials of ADHD as between 25% and 30% improvement from baseline in rating scales such as the ADHD-RS-IV [28]. We defined treatment response as at least 27% improvement from baseline in the ADHD-RS-IV total score based on a large multinational study on psychometric properties of this scale [26]. Secondary outcomes were considered as change in the global functioning as assessed by the CGSA, as well as the treatments' side effects.

2.4.2. Sample size calculation

We expected at least 3.3 score difference between the two study groups in change of the ADHD-RS-IV total score after treatment based on available data [22]. Considering type I error of 0.05, study power of 0.8, and about 10% drop-out rate, the sample size was calculated as 33 in each group.

2.4.3. Statistical analyses

Data were analyzed using the SPSS software version 16.0 (SPSS Inc., Chicago IL, USA). Data are reported as mean $\pm$ standard deviation (SD) or number (%). Normal distribution of quantitative data was checked with the Kolmogorov–Smirnov Test. Comparisons between the two groups were done with the Independent Sample t-Test, Mann–Whitney U Test, and Chi-Square (or Fisher's Exact) Test. Repeated measure analysis was done to test the trend of changes in study outcome variables over the study period. A P-value of <0.05 (two-tailed) was considered as statistically

significant in all analyses. Confidence intervals (CI) are also reported where relevant.

3. Results

3.1. Participant characteristics

A total of 120 children with ADHD were evaluated during the study period from which 79 cases were eligible for the study.

Table 1

Comparison of demographic data and baseline disease characteristics between the two study groups.

	Ginkgo n = 31	Placebo n = 29	P-value
Age, year	7.83 $\pm$ 1.21	8.41 $\pm$ 1.40	0.094 ^a
Male/Female	19(61.3)/12(38.7)	20(69)/9(31)	0.363 ^b
Weight, kg	23.06 $\pm$ 5.07	25.10 $\pm$ 6.26	0.170 ^a
Disease duration			
New case	22 (71)	19 (65.5)	0.430 ^b
1–2 years	9 (29)	10 (35.5)	
Baseline CGAS	62.5 $\pm$ 6.8	63.1 $\pm$ 6.0	0.824 ^c
Dosage of <i>G. biloba</i>			
80 mg/day	3 (9.6)	5 (17.2)	0.316 ^b
120 mg/day	28 (90.3)	24 (82.7)	
Dosage of methylphenidate			
20 mg/day	3 (9.6)	5 (17.2)	0.316 ^b
30 mg/day	28 (90.3)	24 (82.7)	

Data are presented as mean $\pm$ standard deviation, number (%).

ADHD: attention deficit hyperactivity disorder, CGAS: Children's Global Assessment Scale.

^a Independent Sample t-Test.

^b Fisher's Exact Test.

^c Mann–Whitney U Test.

Table 2
Comparison of the ADHD parent rating scores between the two study groups.

Variable	Group	Baseline	Week 2	Week 6	Time	Treatment	Time × treatment
Inattention	Ginkgo	21.32 ± 4.38	16.06 ± 3.96	13.58 ± 3.86	F = 707.09 P ^b < 0.001	F = 0.11 P ^b = 0.734	F = 23.72 P ^b < 0.001
	Placebo	19.68 ± 4.89	15.82 ± 4.60	14.34 ± 4.03			
	P ^a	0.178	0.831	0.457			
Hyperactivity–impulsivity	Ginkgo	16.93 ± 6.06	12.93 ± 4.89	11.54 ± 4.42	F = 254.42 P ^b < 0.001	F = 0.06 P ^b = 0.799	F = 0.66 P ^b = 0.417
	Placebo	16.24 ± 5.68	12.82 ± 4.59	11.37 ± 4.11			
	P ^a	0.650	0.930	0.879			
Total score	Ginkgo	38.25 ± 8.35	29.00 ± 6.44	25.12 ± 5.82	F = 796.38 P ^b < 0.001	F = 0.18 P ^b = 0.669	F = 12.48 P ^b = 0.001
	Placebo	35.93 ± 6.60	28.65 ± 5.55	25.72 ± 5.09			
	P ^a	0.238	0.826	0.676			

^a Independent Sample t-Test for comparing means between the two groups.
^b ANOVA repeated measures test for assessing time effect, treatment effect, and interaction between time and treatment.

Finally, 66 patients were equally randomized into the *G. biloba* and placebo groups. Six patients dropped-out of the study after starting medication (Fig. 1). Those who discontinued the study were not different from others regarding age, gender, weight, and baseline CGAS or ADHD scores (all P values >0.05). Demographic data and disease characteristics of the patients who completed the study are summarized in Table 1. There was no significant difference between the two study arms in demographic data or baseline disease characteristics (all P values >0.05).

3.2. Trend of changes in ADHD parent rating scores over the study

The parent rating scores of inattention and hyperactivity-impulsivity as well as the total score were significantly reduced in both groups over the study period (all P values <0.001), Table 2. There was a significant interaction between time × treatment for inattention, but the main effect of treatment was not significant (P = 0.734), Fig. 2. Interaction between time × treatment (P = 0.417) and main effect for treatment (P = 0.799) were not significant for hyperactivity-impulsivity, Fig. 3. There was significant interaction between time × treatment for the total score (P = 0.001), but the main effect of treatment was not significant (P = 0.669), Table 2.

3.3. Trend of changes in ADHD teacher rating scores over the study

The teacher rating scores of inattention and hyperactivity-impulsivity as well as the total score were significantly reduced in both groups over the study period (all P values <0.001), Table 3. There was an interaction between time × groups (P = 0.004) for inattention, but the main effect of treatment was not significant (P = 0.610), Fig. 4. Interaction between time × treatment and the main effect for treatment were not significant for hyperactivity-impulsivity (Fig. 5), nor for the total score (all P values >0.05), Table 3.

3.4. Comparison of study primary outcomes between the Ginkgo and placebo groups

Comparison of the amount of changes in the parent and teacher rating scores between the two study groups is summarized in Table 4. A significantly more reduction was observed with *G. biloba* compared with placebo regarding the parent rating score of inattention (mean difference [CI95%] = −2.39 [−1.41 to −3.38], P < 0.001). Also, the parent rating total score was significantly more reduced in the *G. biloba* group (mean difference [CI95%] = −2.92 [−1.26 to −4.57], P = 0.001). With regard to the teacher rating scores, a significantly more reduction was observed for inattention

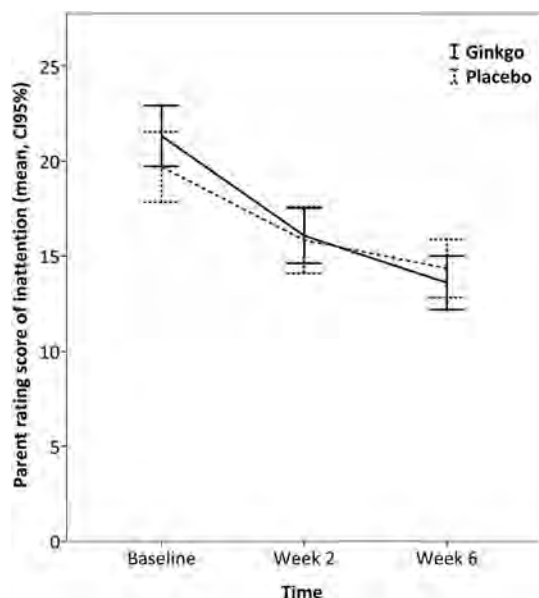


Fig. 2. Trend of changes in the parent rating score of inattention symptoms in the study groups over the study period.

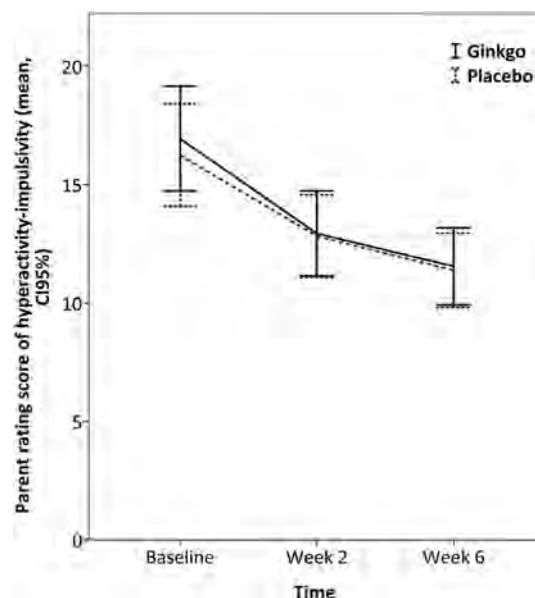


Fig. 3. Trend of changes in the parent rating score of hyperactivity–impulsivity symptoms in the study groups over the study period.

Table 3

Comparison of the ADHD teacher rating scores between the two study groups.

Variable	Group	Baseline	Week 2	Week 6	Time	Treatment	Time × treatment
Inattention	Ginkgo	21.03 ± 4.49	15.87 ± 4.12	13.74 ± 4.04	F = 880.88	F = 0.26	F = 8.79
	Placebo	19.72 ± 4.58	15.51 ± 4.15	13.75 ± 3.85	P ^b < 0.001	P ^b = 0.610	P ^b = 0.004
	P ^a	0.269	0.742	0.987			
Hyperactivity-impulsivity	Ginkgo	16.12 ± 5.90	12.70 ± 4.54	10.93 ± 4.06	F = 191.89	F = 0.04	F = 1.65
	Placebo	15.51 ± 5.63	12.27 ± 4.55	11.20 ± 4.43	P ^b < 0.001	P ^b = 0.834	P ^b = 0.203
	P ^a	0.683	0.713	0.806			
Total score	Ginkgo	37.48 ± 8.48	28.58 ± 6.50	24.67 ± 5.71	F = 458.66	F = 0.70	F = 2.22
	Placebo	35.24 ± 6.23	27.51 ± 5.30	24.10 ± 4.62	P ^b < 0.001	P ^b = 0.406	P ^b = 0.141
	P ^a	0.251	0.492	0.672			

^a Independent Sample t-Test for comparing means between the two groups.^b ANOVA repeated measures test for assessing time effect, treatment effect, and interaction between time and treatment.

score in the *G. biloba* (mean difference [CI95%] = −1.32 [−0.43 to −2.21], $P = 0.004$). Difference between the two groups regarding changes in teacher rating score of hyperactivity-impulsivity ($P = 0.203$) or total score ($P = 0.141$) were not significant, Table 4.

The clinical treatment response rate was significantly higher with *G. biloba* compared with placebo based on the ADHD-RS-IV parent rating (93.5% vs. 58.6%, $P = 0.002$). Compared with placebo, the relative risk [CI95%] of no response was 0.15 [0.03 to 0.63] with *G. biloba* and the absolute risk reduction [CI95%] was 0.34 [0.13 to 0.53]. But, treatment response rate was not different between the two groups by the ADHD-RS-IV teacher rating (83.9% vs. 79.3%, $P = 0.451$, relative risk of no response [CI95%] = 0.77 [0.26 to 2.28]), Table 4.

3.5. Effects of Ginkgo versus placebo on general functioning (CGAS)

General functioning was significantly increased in both groups after treatment (both P values <0.001). There was no difference between the *G. biloba* and placebo groups regarding change in the CGAS after treatment ($P = 0.901$), Table 4.

3.6. Side effects

Side effects in the *G. biloba* group were included nausea (12.9%), headache, diarrhea, and loss of appetite (6.4%), and constipation

and abdominal pain (3.2%). In the placebo group, side effects were included loss of appetite (24.1%), nausea and diarrhea (6.4%), and headache, palpitation, constipation, and abdominal pain (3.4). In general, limited and mild side effects were occurred. Difference

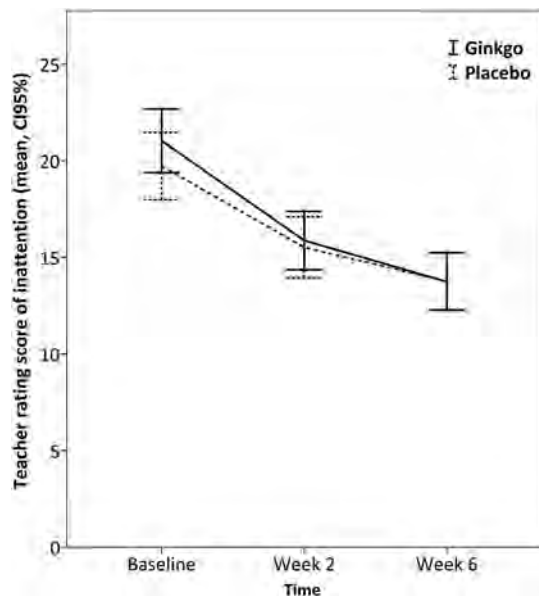


Fig. 4. Trend of changes in the teacher rating score of inattention symptoms in the study groups over the study period.

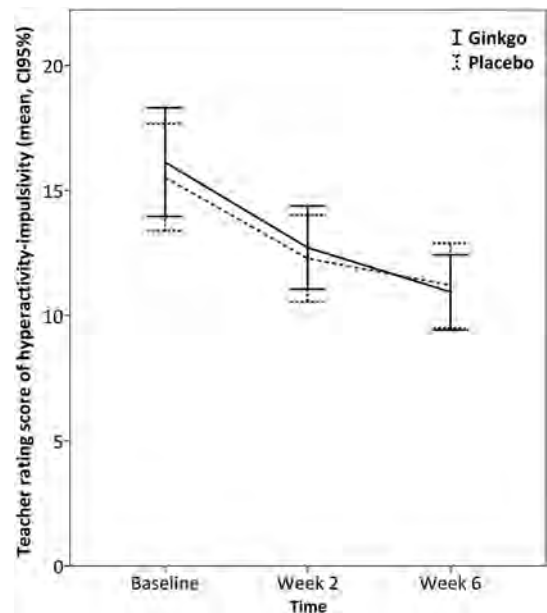


Fig. 5. Trend of changes in the teacher rating score of hyperactivity-impulsivity symptoms in the study groups over the study period.

Table 4

Comparison of changes in the ADHD parent and teacher rating scores between the two study groups.

	Ginkgo n = 31	Placebo n = 29	P-value
Changes in ADHD parent rating scores			
Inattention	−7.74 ± 1.94	−5.34 ± 1.85	<0.001 ^a
Hyperactivity-impulsivity	−5.38 ± 2.38	−4.86 ± 2.58	0.417 ^a
Total score	−13.1 ± 3.36	−10.2 ± 3.01	0.001 ^a
Clinical response	29 (93.5)	17 (58.6)	0.002 ^b
Changes in ADHD teacher rating scores			
Inattention	−7.29 ± 1.90	−5.96 ± 1.52	0.004 ^a
Hyperactivity-impulsivity	−5.19 ± 2.83	−4.31 ± 2.45	0.203 ^a
Total score	−12.80 ± 5.02	−11.13 ± 3.43	0.141 ^a
Clinical response	26 (83.9)	23 (79.3)	0.451 ^b
Changes in CGAS			
	8.92 ± 7.37	8.51 ± 5.33	0.901 ^c

Data are presented as mean ± standard deviation or number (%).

ADHD: attention deficit hyperactivity disorder.

^a Independent Sample t-Test.^b Fisher's Exact Test.^c Mann–Whitney U Test.

between the two groups regarding loss of appetite was not statistically significant ($P = 0.075$). There was no difference between the two groups in other side effects (all P values >0.05).

4. Discussion

We evaluated the efficacy of *G. biloba* as a complementary therapy to methylphenidate in treatment of ADHD in children and adolescents. A significantly more improvement was found in inattention symptoms when *G. biloba* was added to methylphenidate. Also, it resulted in a significant increase in overall clinical treatment response with limited side effects. In overall, these results show that *G. biloba* is an effective and safe complementary therapy in the treatment of childhood ADHD.

Previous open-label trials have reported beneficial effects of *G. biloba* for the treatment of ADHD [19–21]. Niederhofer [20] evaluated the effects of *G. biloba* on 6 patients (17–19 years) with attention-deficit disorder. Subjects were treated with the *G. biloba* extract, Egb 761 (200 mg/day), for 4 weeks while received no other medication. This study found a significant improvement of inattention and hyperactivity symptoms after treatment with *G. biloba* [20]. In another study, investigators evaluated the effects of Egb 761 (up to 240 mg/day for 3–5 weeks) in 20 children with ADHD. Evaluating both clinical as well as objective measures, this study found improvements in quality of life, ADHD symptoms, as well as the continuous performance test [21]. Lyon et al. [19] evaluated effects of an herbal extract combination on ADHD symptoms in 36 children. Subjects were treated with 200 mg of *Panax quinquefolium* and 50 mg of *G. biloba* extracts for 4 weeks. Authors used the Conners' Parent Rating Scale for the assessment of ADHD symptoms and found improvement of the core symptoms in more than half of the subjects after treatment [19]. Although these studies showed that *G. biloba* extract may be an effective monotherapy (i.e. alternative therapy) for treatment of ADHD, they were all open-label trials and the observed improvement in symptoms cannot be completely attributed to the herb. The only controlled trial in this regard has been done by Salehi et al. [22] on 50 children with ADHD. This study compared *G. biloba* (80–120 mg/day) and methylphenidate (20–30 mg/day) in treatment duration of 6 weeks. Authors found a mean of 6.52 point decrease in ADHD-RS-IV parent rating score with *G. biloba* compared with 15.92 point decrease with methylphenidate. This study shows that, as a monotherapy and compared with current standard of care, *G. biloba* is not efficacious for treatment of ADHD [22]. Compared with these studies, we studied *G. biloba* extract as a complementary therapy to current standards and found additional benefit of this herb when was added to the methylphenidate.

The mechanisms by which *G. biloba* may improve symptoms of ADHD are not clear. The herb has potent anti-oxidative capacity and enhances cerebral circulation contributing to the neuroprotective effects [29]. A number of studies have shown effects of the *G. biloba* extracts on adrenergic, dopaminergic, cholinergic, serotonergic, and glutamatergic and GABAergic systems [30]. Therefore, a potential mechanism of the herb would be modulation of neurotransmitter synthesis and/or functions. This mechanism seems more plausible since imbalance in the central neurotransmitter systems is implicated in the pathophysiology of ADHD symptoms [18,31]. Also, the anxiolytic and antidepressant effects of the herb may contribute to the improvement in symptoms of ADHD [32]. Further studies are required on the possible mechanisms of action of *G. biloba* on ADHD symptoms.

Our study had a number of limitations. Because current standard of care, i.e. methylphenidate, is available for the treatment of ADHD, it was not possible (due to ethical issues) to add a pure placebo control arm into the study. We used a widely applied

clinical measure of ADHD, the ADHD-RS-IV. However, using objective measures can provide more reliable data on the effects as well as mechanisms of action of *G. biloba* on ADHD symptoms. Short treatment duration and having no drug free follow-up period were other limitations of this study.

In conclusion, this study found that *G. biloba* is an effective and safe complementary therapy in the treatment of childhood ADHD. Although the additional effect of the herb on ADHD symptoms was actually minimal and limited to the inattention symptoms, it resulted in a significant increase in overall clinical treatment response. Further trials with larger sample size, various drug dosages, and longer treatment and follow-up duration are warranted. Also, the mechanisms of action of *G. biloba* on symptoms of ADHD are needed to be investigated.

Authors' contribution

FSh and MR participated in study design, grant writing, patients recruitment, data gathering, and data analysis and interpretation. ES generated the study idea and participated in study design, grant writing, and analysis interpretation. BM participated in study design and data analysis and interpretation. MR prepared the first draft of the manuscript. All authors studied the manuscript, critically revised it, and approved the final submitted version including authorship statement.

Conflict of interest statement

None.

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