Complementary Therapies in Clinical Practice 36 (2019) 170–175

Contents lists available at ScienceDirect

Complementary Therapies in Clinical Practice

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

Effect of sweet almond syrup versus methylphenidate in children with ADHD: A randomized triple-blind clinical trial

Monireh Sadat Motaharifard[a], Mohammad Effatpanah[b], Mehrdad karimi[a], Shahin Akhondzadeh[c], Habibollah Rahimi[d], Seyed Ali Yasrebi[e], Fatemeh Nejatbakhsh[a,*]

[a] Department of Iranian Traditional Medicine, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran
[b] Ziaeian Hospital, School of Medicine, International Campus, Tehran University of Medical Sciences, Tehran, Iran
[c] Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran
[d] Clinical Research Development Unit-Matini/Kargarnejad Hospital, Kashan University of Medical Sciences, Kashan, Iran
[e] Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

ARTICLE INFO

Keywords:
sweet almond
DHD
Persian Medicine
Iranian Traditional Medicine
functional food

ABSTRACT

Background and purpose: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common health disorders among children. Some patients do not respond to methylphenidate or cannot tolerate its side effects. Sweet almond syrup as a Persian Medicine preparation has been used for many years. This study aims to evaluate the efficacy and safety of sweet almond for ADHD children.

Materials and methods: Fifty children aged 6-14 years with ADHD were recruited to the study. The participants were randomly assigned to two groups to receive either methylphenidate or sweet almond syrup. The outcomes were assessed using the Parent and Teacher ADHD Rating Scale every two weeks for 8 weeks.

Results: Results showed that the two treatments had similar effects on symptom reduction in ADHD children. No significant differences were observed between the two groups ($F = 2.3$, $df = 1$, $p = 0.13$, $F = 0.57$, $df = 1$, $p = 0.47$).

Conclusion: Sweet almond may be an effective treatment for ADHD children.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental behavioral disorder in children with increasing incidence rate [1]. The global prevalence of ADHD is highly heterogeneous, yet is estimated at 5.29% in some studies. It is usually more common in boys than girls [2]. Although the etiology of ADHD is not completely understood, imbalance in dopaminergic and noradrenergic neurotransmission is one of the main causes [3]. This disorder is characterized by various symptoms of inattention, hyperactivity, and impulsivity according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [4].

Psychostimulant medications such as methylphenidate (MPH) and amphetamines play an important role in the treatment of ADHD [5]. However, up to 30% of all children with ADHD do not respond to medications or suffer from medication-related adverse effects such as reduced appetite, mood changes, and sleep disturbances [6]. Therefore, there is a need to find alternative methods to relieve the symptoms of ADHD while these medication-related side effects are avoided.

Complementary and alternative medicine (CAM) is defined as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine" [7]. Although various studies have documented the use of CAM among children and adolescents, most have lacked the scientific rigor to establish clear benefits. The most common types of CAM are herbal/dietary supplements, acupuncture, massage, chiropractic, and homeopathy. Meanwhile, the most commonly studied diseases and symptoms in children treated with CAM are pain, headache, ADHD, asthma, and colic [8].

CAM is appealing to parents who like more natural interventions for their children, so approximately 50% of parents of children with ADHD use CAM alone or in combination with other drugs or substances [9]. Persian Medicine (PM), as one of the complementary medicine schools, provides different strategies to prevent and treat diseases in various life stages such as childhood.

Nuts and their oil have been widely used in traditional medicine for the treatment of a variety of illnesses. For instance, Iranian people knew sweet almond (fruits of *Prunus amygdalus* var. dulcis) and its nutritional

* Corresponding author. Building of the Ahmadiyeh, No 27, Corner Alley Tabriz, Sarparast Shomali Str, Taleghani Ave, Tehran State, Iran.
E-mail addresses: m-motaharifard@razi.tums.ac.ir (M.S. Motaharifard), m.effatpanah@gmail.com (M. Effatpanah), mehrdadkarimi@yahoo.com (M. karimi), S.akhond@neda.net (S. Akhondzadeh), rahimi_136@yahoo.com (H. Rahimi), Yasrebi.seyedali@gmail.com (S.A. Yasrebi), nejatbakhsh@tums.ac.ir (F. Nejatbakhsh).

https://doi.org/10.1016/j.ctcp.2019.07.008
Received 17 June 2018; Received in revised form 21 June 2019; Accepted 19 July 2019

values from the past and used it in their diet. Masters of PM have believed that sweet almond has some medicinal properties, in addition to nutritional values, which can promote health and/or prevent diseases. Accordingly, they considered it as a functional food [10]. Functional foods are thought to provide positive effects on specific body functions and prevent or mitigate diseases. These foods support child development for the prevention and treatment of diseases and for enhancing neurodevelopmental potentials [11].

Regular use of sweet almond has such beneficial effects as neuroprotective activities [12], antidiabetic effect [13,14], reduced risk of cardiovascular diseases [15], as well as increased HDL cholesterol and decreased LDL cholesterol levels [16]. Furthermore, its immunostimulant activity [17] along with antioxidant and antiradical effects have also been recognized [18]. Sweet almond is an effective and healthy food for both mind and body [19]. Animal studies have suggested that sweet almond can improve memory and learning [12,20]. It has also stress-relieving and anxiolytic effects like those of diazepam [19].

Based on the principles of PM, it was hypothesized that sweet almond would be useful for the treatment of ADHD in children. The aim of this study was to evaluate the efficacy and safety of sweet almond compared with the standard treatment through a randomized controlled trial.

2. Materials and methods

2.1. Trial setting and design

This randomized, triple-blind, single-center clinical trial was conducted between November 2015 and February 2017 in Ziaeian Hospital, Tehran, Iran. The trial was registered in Iranian Registry of Clinical Trials with the registration number: IRCT2015050922165N1. It was also approved by the Ethics Committee of Research Center at Tehran University of Medical Sciences in accordance with the Declaration of Helsinki (IR.TUMS.REC.1394.195). The study design and aims were explained to both children and their parents or guardians and written informed consent was obtained from the patients' parents or guardians.

2.2. Participants

The participants were 50 outpatient children (33 boys and 17 girls) aged between 6 and 14 years who clearly met the DSM-5 diagnostic criteria for ADHD [4], and who were recruited from outpatient child clinic of Ziaeian Hospital. A child and adolescent psychiatrist confirmed the diagnosis of ADHD before the participants were recruited into the study. All patients had been newly diagnosed with mild to moderate ADHD of combined subtype according to the DSM-5. They should have not taken any non-pharmacological treatment, other psychotropic medications, or CAM during the study.

Children were excluded from the study if they had significant chronic medical conditions such as cardiovascular diseases, gastrointestinal disorders, seizures, and organic brain disorders, and if they were clinically current drug abusers or dependent on drugs within the last 6 months. In addition, patients were excluded if they had any developmental disorders, other psychiatric disorders or intellectual disabilities (intelligence quotient < 70). The children should not have had a history of allergy to sweet almond and its products. If severe side effects and drug intolerance occurred during the study and parents or patients were not satisfied with the treatment, they would be excluded from the sample. The participants underwent a standard clinical assessment comprising a medical history, a psychiatric evaluation, and a structured diagnostic interview.

2.3. Interventions

The patients included in the study were randomized in a 1:1 ratio using a computer-generated code to receive either sweet almond syrup or methylphenidate (Ritalin®, Novartis, Switzerland). Fifty-nine patients were randomly assigned using the sealed envelope method to receive methylphenidate (MPH) at a dose of 1 mg/kg/day and a therapeutically ineffective syrup 5 cc/day (three times a day) as a placebo (Group 1) or sweet almond syrup 5 cc/day (three times a day) and a therapeutically ineffective tablet as a placebo (Group 2) during an 8-week triple-blind, randomized clinical trial. The patients received a 5-mg tablet (half of MPH or placebo tablet) twice daily in the first week, followed by a 10-mg tablet twice daily. The patients weighing beyond 30 kg received a 10-mg tablet thrice daily from the third week of the study.

The person who administered the medications, the assessor, and patients along with their parents were blinded to the allocation of study groups. Both sweet almond and placebo syrup as well as methylphenidate and placebo tablets were identical in appearance, color, smell and label. No recommendations were made to alter diet. The participants were only asked to refrain from consuming sweet almond and almond products during the study.

2.4. Drug preparation

Methylphenidate tablets (10 mg) were procured from the Novartis Pharmaceutical Company, Switzerland. The placebo tablets were also made by the Iranian Institute of Medicinal Plants. The sweet almond syrup was prepared based on the principles of PM by adding almond extract to simple syrup [10]. The placebo syrup was prepared based on the simple syrup formula of the British Pharmacopoeia [21] including approved color additives (magnolia Co. E−150a). Both syrups were made in the Traditional Pharmacy Department of the School of Traditional Medicine and supplied in 125-mL bottles, containing either sweet almond syrup or placebo. Laboratory tests were performed for different microorganisms, which lied within the normal range.

2.5. Standardization of syrup

The sweet almond syrup was standardized based on essential oils content. The oil of the sample was extracted according to the procedure recommended by Folch et al. [22]. The extent of the moisture obtained from the drying method was about 20.7%. In addition, the Soxhlet method evaluated the total fat content as about 6.3% of dry matter. The fatty acid profile determined by gas chromatography analysis was in good agreement with the value previously reported for almond [23]. The major monounsaturated fatty acid content was oleic acid (C18:1), while the amount of palmitoleic acid (C16:1) was negligible. The linoleic acid (C18:2) was the only polyunsaturated fatty acid present in the sample. The main saturated fatty acids were palmitic acid (C16) and stearic acid (C18).

2.6. Outcome measurement

The main outcome was measured using the Parent and Teacher ADHD Rating Scale, which is a valid measurement of attention and behavioral abnormalities. The ADHD Rating Scale has been used extensively in school-age children in Iran [24–27]. This 18-item scale that rates ADHD symptoms using a 4-point Likert-type scale is based on the DSM-5 criteria for ADHD. A score of at least 20 was required for entry into the study. The treatment outcomes were assessed with the use of the ADHD Rating Scale at baseline and 14, 28, 42, and 56 days after intervention. In order to monitor any possible side effects, the Common Terminology Criteria for Adverse Events (CTCAE, v4.03, 2010) was applied in all follow-up visits.

2.7. Statistical analysis

In order to check similarity of the two groups, the Chi-square and Fisher's exact tests were used for categorical variables, and the independent *t*-test was performed for continuous variables. The efficacy of the administered drugs between and within groups was compared by using a two-way repeated measures analysis of variance (rANOVA) as the main analysis. The homogeneity was checked by means of the Box's M. The Mauchly's sphericity test was also used to test for the condition of sphericity. In addition, the main side effects and the withdrawal rate of the study groups were compared using the Chi-square and Fisher's exact tests. The two groups were considered as a between-subjects factor (group) and the five measurements during the treatment were taken as the within-subjects factor (time). The results are presented as mean ± standard deviation (SD). The significance levels were set at $p < 0.05$.

The sample size was calculated to be 15 patients in each group on the basis of following assumptions: a mean difference (MD) of 5 on the Teacher and Parent ADHD Rating Scale, study power of 0.8, and a two-tailed significance level of 0.05 according to the final differences between the two groups. To account for possible attrition of up to 10%, 50 patients were recruited to the study (25 patients per group).

3. Results

3.1. Participants

Out of the 96 patients who were referred to the hospital, 59 patients entered the trial and were randomized to receive either MPH (n = 29) or sweet almond syrup (n = 30). Excluded from the final analysis, nine patients withdrew from the study before the first follow-up visit due to parents' lack of collaboration. Further details are shown in the CONSORT (Consolidated Standards of Reporting Trials) flow diagram (Fig. 1).

No significant difference was found between the two groups for such certain demographic/clinical characteristics as gender. According to the independent *t*-test, a significant difference was found between age, weight, and height ($p < 0.05$), although these differences were not clinically significant and did not require to be adjusted in the main analysis (Table 1). The mean age of the 50 patients included in this study was 7.1 ± 1.36 years with a male:female ratio of 2:1.

Table 1
Demographic/clinical characteristics of the participants.

	Sweet almond group	MPH group	p-value
Boy, n	16	17	
Girl, n	9	8	
Age (mean ± SD)	6.6 ± 1.0	7.5 ± 1.5	0.02
Weight (mean ± SD)	23.7 ± 6.6	30 ± 11.6	0.02
Height (mean ± SD)	128.1 ± 7.5	133.7 ± 9.9	0.03
Type of ADHD	All combined	All combined	1

ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate hydrochloride; SD, standard deviation.

3.2. Outcomes

3.2.1. The parent ADHD Rating Scale

The mean ± SD of the Parent ADHD Rating Scale scores of the two groups are presented in Fig. 2 (total score) and Table 2 (subscales). There was no significant difference in the baseline Parent ADHD Rating Scale scores between the two groups (38.8 ± 8.8 *vs* 35.6 ± 6.0, $p = 0.25$). Based on the analysis, the results showed a significant treatment effect over time ($F = 83.7$, $df = 4$, $p < 001$). This suggests a decreased Parent ADHD Rating Scale scores over time for the study groups.

There was no significant difference between the two groups with regard to the Parent ADHD Rating Scale scores ($F = 2.3$, $df = 1$, $p = 0.13$). Analytical comparison of the Parent ADHD Rating Scale scores in hyperactivity and inattention categories (Table 2) indicated no statistically significant differences between the two groups in any of the visits ($p > 0.05$). There was no interaction between the type of drugs and time variable ($F = 1.1$, $df = 4$, $p = 0.37$). In other words, both treatment groups exhibited a similar declining trend, which was linear, in ADHD symptoms over the 8-week period (Fig. 2).

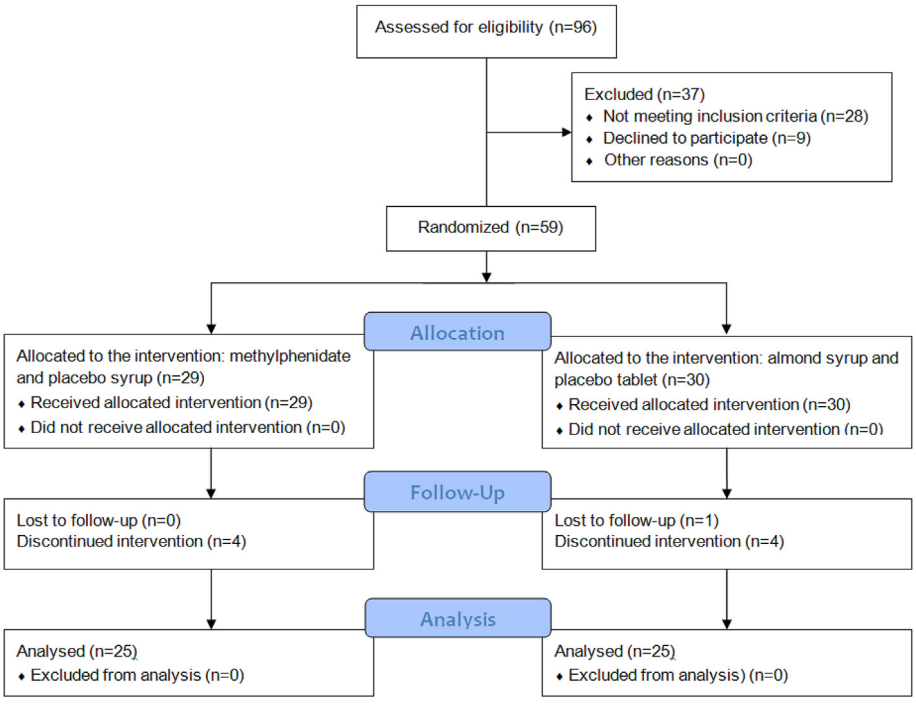

Fig. 1. CONSORT flow diagram of the study participants.

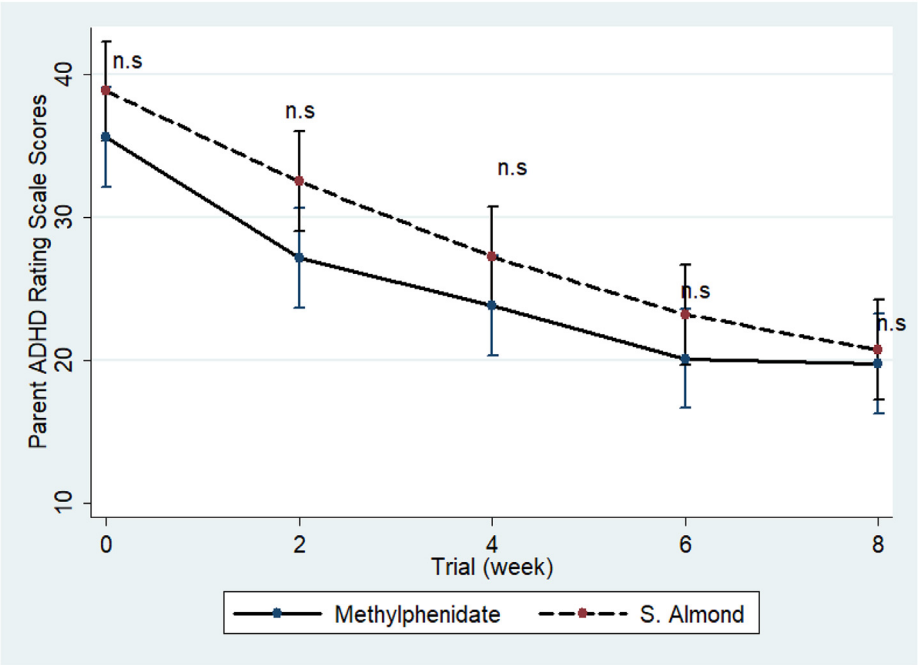

Fig. 2. Repeated measures for comparison of the effects of two treatments on the Parent ADHD Rating Scale score during the study period. Values are presented as mean ± standard deviation. *ADHD, attention-deficit/hyperactivity disorder; n. s, non-significant.*

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

Time of measurements	Sweet almond group	MPH group	p-value
Parent ADHD Rating Scale (Hyperactivity), mean ± SD			
Baseline	20.8 ± 4.2	19.0 ± 4.8	0.15
Week 2	17.4 ± 5.4	14.2 ± 4.7	0.02
Week 4	15.1 ± 6.0	12.8 ± 5.9	0.16
Week 6	12.7 ± 5.9	10.9 ± 6.3	0.29
Week 8	11.3 ± 5.9	10.8 ± 6.3	0.78
Parent ADHD Rating Scale (Inattention), mean ± SD			
Baseline	17.9 ± 4.5	16. ± 3.3	0.23
Week 2	15.0 ± 4.8	12. ± 4.2	0.10
Week 4	12.0 ± 4.7	11.0 ± 4.5	0.43
Week 6	10.5 ± 4.3	9.1 ± 4.4	0.28
Week 8	9.4 ± 4.7	8.9 ± 4.3	0.71
Teacher ADHD Rating Scale (Hyperactivity), mean ± SD			
Baseline	18.4 ± 4.6	18.9 ± 6.2	0.75
Week 2	16.4 ± 5.6	14.5 ± 7.3	0.30
Week 4	13.5 ± 4.8	12.3 ± 7.2	0.49
Week 6	11.9 ± 5.0	11.3 ± 6.7	0.70
Week 8	10.6 ± 5.1	10.8 ± 6.8	0.90
Teacher ADHD Rating Scale (Inattention), mean ± SD			
Baseline	17.0 ± 4.2	17.8 ± 4.9	0.54
Week 2	15.6 ± 4.5	13.8 ± 5.3	0.19
Week 4	13.2 ± 4.9	11.5 ± 4.9	0.23
Week 6	12.4 ± 5.6	9.6 ± 5.1	0.07
Week 8	10.3 ± 5.5	9.6 ± 4.9	0.61

ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate hydrochloride; SD, standard deviation.

3.2.2. The teacher ADHD Rating Scale

The mean ± SD of the Teacher ADHD Rating Scale scores of the two groups are presented in Fig. 3 (total score) and Table 2 (subscales). There was no significant difference in the baseline Teacher ADHD Rating Scale scores between the two groups (35.5 ± 7.9 vs 36.8 ± 8.7, $p = 0.49$). The results, however, showed a significant treatment effect over time ($F = 74.1$, $df = 4$, $p < 0.001$). The differences between the two groups on the Teacher Rating Scale scores were not significant ($F = 0.57$, $df = 1$, $p = 0.47$); therefore, the effect of sweet almond syrup and MPH was similar.

Analytical comparison of the Teacher ADHD Rating Scale scores in hyperactivity and inattention category (Table 2) showed no statistically significant differences between the two groups in any of the visits ($p > 0.05$). The trend of two treatment groups was similar over time and the difference was not significant ($F = 2.24$, $df = 2$, $p = 0.06$).

3.3. Safety and tolerability

No serious adverse events were observed during the study. All noticed adverse effects were mild to moderate and transient. According to Table 3, the adverse events were more commonly reported in patients receiving MPH. Loss of appetite and trouble in sleeping were the most common side effects in the MPH group. In patients receiving sweet almond syrup, the most frequently reported adverse event was increased appetite. The frequency of appetite changes, sadness, and sleeping late were significantly different between the sweet almond and MPH groups ($p < 0.05$).

4. Discussion

In the last decade, ADHD has been on the rise in children. Although methylphenidate has been considered as an effective treatment for ADHD in several studies [28–30], the need for long-term therapy and side effects are the main problems for these patients. The aim of this study was to evaluate the efficacy of sweet almond syrup on children with ADHD. The results suggested that sweet almond and methylphenidate are effective in the treatment of ADHD. No significant difference was observed between the two drugs at the end of the trial.

There is a lack of studies investigating alternative methods such as herbal products for the treatment of ADHD. The results of a study by Ko et al. suggest that Korean red ginseng (KRG) extract compared with placebo may be an effective and safe alternative treatment for children with inattention and hyperactivity symptoms. It may have neuroprotective and antioxidant effects and elevate dopamine and norepinephrine levels [31]. In another study, Li et al. found that Ningdong granule, a traditional Chinese medicine preparation, was effective for children with ADHD compared with methylphenidate. Ningdong granule can improve the metabolism of dopamine and cause fewer side

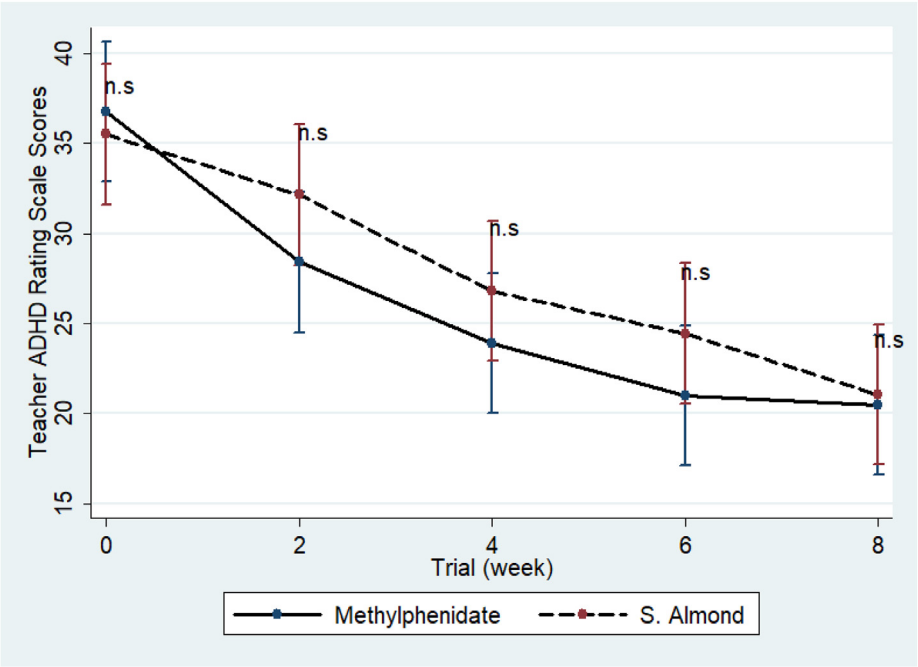

Fig. 3. Repeated measures for comparison of the effects of two treatments on the Teacher ADHD Rating Scale score during the study period. Values are presented as mean ± standard deviation. *ADHD, attention-deficit/hyperactivity disorder;n.s, non-significant.*

Table 3
Frequency of the side effects in the two study groups.

Complication	Sweet almond group	MPH group	p-value
Decreased appetite	1 (4%)	15 (60%)	< 0.001
Increased appetite	15 (60%)	1 (4%)	< 0.001
Insomnia	2 (8%)	6 (24%)	0.24
Increased sleep	4 (16%)	1 (4%)	0.34
Difficulty falling asleep	3 (12%)	9 (36%)	0.04
Abdominal pain	2 (8%)	6 (24%)	0.24
Headache	None	2 (8%)	0.49
Impulsiveness	1 (4%)	3 (12%)	0.61
Irritability	1 (4%)	6 (24%)	0.09
Nausea	1 (4%)	1 (4%)	1
Vomiting	None	None	None
Constipation	None	1 (4%)	1
Diarrhea	None	None	None
Dry mouth	None	1 (4%)	1
Sadness	None	6 (24%)	0.02
Tic	None	1 (4%)	1
Itching	None	1 (4%)	1

MPH, methylphenidate hydrochloride.

effects [32]. An open-label study showed that the standardized extract of *Bacopa monnieri*, an Ayurvedic medicine, produced significant improvement in ADHD symptoms through its neuroprotective and antioxidant effects as well as dopamine regulation [33]. Shakibaei et al. suggested *Ginkgo biloba* as a complementary treatment to methylphenidate in the treatment of ADHD, especially in children who are primarily inattentive. This herb has proven antioxidative activity and enhances cerebral circulation contributing to its neuroprotective effects [34]. According to Akhondzadeh et al. *Passiflora incarnata* is as effective as methylphenidate in the treatment of ADHD [25], which might be due to its neuroprotective effects and the alteration of serotonergic neurotransmission in the brain [35].

To the best of our knowledge, our study is the first trial evaluating the efficacy and safety of sweet almond in patients with ADHD, although sweet almond has been used in a variety of dosage forms and for several diseases [12–16,18,19]. The definite mechanism for the effect of sweet almond on ADHD is not specified, though it has shown antioxidant and neuroprotective activities and improved memory retention in rats, possibly by elevating acetylcholine levels in the brain [12].

Serotonin is considered as one of the neurotransmitters involved in the regulation of cognitive functions. Its low levels in certain areas of the brain have been assumed as one of the biochemical etiologies of ADHD [9]. Some studies have suggested that long-term intake of sweet almond significantly elevates whole brain serotonin levels [20], so it can be effective in ADHD.

Sweet almond is a rich source of essential amino acids, essential unsaturated fatty acids, vitamins, minerals, and numerous bioactive substances [36]. One of the trace elements found in sweet almond is boron, which has anti-inflammatory effects. Different studies have indicated that boron plays a role in improving human brain functions, short-term memory, and cognitive performance [37,38]. Further, different studies have suggested that ADHD and other neurodevelopmental disorders are associated with deficiencies in essential unsaturated fatty acids that are necessary for brain development [39]. Moreover, animal studies have shown that a chronic deficiency in omega-3 fatty acids affects dopamine levels and its receptors in the prefrontal cortex of the brain and reduces the brain functions [40]. Therefore, correcting fatty acids levels with sweet almond as a rich source of unsaturated fatty acids can improve ADHD symptoms.

Neurobiological studies in patients with ADHD have demonstrated a lack of connectivity in key brain regions, inhibitory control deficits, and delayed maturation in multiple brain regions [30]. According to PM references, sweet almond as a functional food yields beneficial effects on specific functions of the brain and is very useful in preserving the vitality of the brain and reinforcing its functions. Furthermore, it has neurodevelopmental potential and can help to regulate the brain functions. Masters of PM have emphasized that sweet almond protects the brain tissue and improves memory, concentration, and mental alertness [10].

The safety and lower side effects of sweet almond syrup in comparison with MPH can be an important advantage in this study and be a reason for its prescription for ADHD, alone or as an alternative to the stimulant medications. Less abuse potential of sweet almond syrup compared with MPH is another important advantage for this drug. In

addition, one important difference in the two methods of treatment in this study was that our drug was administered in syrup form whose use is more convenient for children. These findings suggest that we can prescribe sweet almond for a long time for children with ADHD.

The most important limitations of our study were the small number of participants, lack of a placebo group, use of only a fixed dose of sweet almond syrup, the short duration of follow-up, and not considering the recurrence rate after discontinuing the treatment.

5. Conclusion

The results of this study suggest that sweet almond syrup can be an effective and safe complementary and alternative medication in the treatment of childhood ADHD. Sweet almond can be used as an effective treatment for children with ADHD, alone or in combination with stimulant drugs especially in order to reduce the side effects of such medications. Nevertheless, our study is relatively small and further trials with larger sample size, various drug dosages, and longer treatment and follow-up duration are warranted. The mechanisms of action of sweet almond on symptoms of ADHD are also needed to be investigated.

Conflicts of interests

We declare no conflicts of interest.

Acknowledgments

This study was part of Ph. D thesis of Dr. Monireh Sadat Motaharifard under the supervision of Dr. Fatemeh Nejatbakhsh. The study was supported by a grant from the Tehran University of Medical Sciences and Health Services (Grant No. 95-01-86-31723). We sincerely thank all patients and families who participated in this study, as well as the personnel of the child and adolescent psychiatry clinic of Ziaeian Hospital who helped us in conducting the study. We are also thankful to Dr. Ali Ghobadi for preparing the sweet almond syrup for the patients.

References

[1] G.V. Polanczyk, E.G. Willcutt, G.A. Salum, C. Kieling, L.A. Rohde, ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis, Int. J. Epidemiol. 43 (2) (2014) 434–442.
[2] G. Polanczyk, M.S. de Lima, B.L. Horta, J. Biederman, L.A. Rohde, The worldwide prevalence of ADHD: a systematic review and metaregression analysis, Am. J. Psychiatry 164 (6) (2007) 942–948.
[3] R.W. Root II, R.J. Resnick, An update on the diagnosis and treatment of attention-deficit/hyperactivity disorder in children, Prof. Psychol. Res. Pract. 34 (1) (2003) 34.
[4] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, fifth ed., APA, United States of America, 2013 (DSM-5), Washington, DC.
[5] D.D. Tarver J, K. Sayal, Attention-deficit hyperactivity disorder (ADHD): anupdated review of the essential facts, Child Care Health Dev. 40 (6) (2014) 762–774.
[6] E.J. C.D. Sonuga-Barke, T. Wigal, M. DeBacker, J. Swanson, Adverse reactions to methylphenidate treatment for attention-deficit/hyperactivity disorder: structure and associations with clinical characteristics and symptom control, J. Child Adolesc. Psychopharmacol. 19 (6) (2009) 683–690.
[7] S.A. Tabish, Complementary and alternative healthcare: is it evidence-based? Int. J. Health Sci. 2 (1) (2008) V).
[8] J. Snyder, P. Brown, Complementary and alternative medicine in children: an analysis of the recent literature, Curr. Opin. Pediatr. 24 (4) (2012) 539–546.
[9] J. Pellow, E.M. Solomon, C.N. Barnard, Complementary and alternative medical therapies for children with attention-deficit/hyperactivity disorder (ADHD), Altern. Med. Rev. 16 (4) (2011) 323.
[10] M.H. Aghili Khorasani, Makhzan-ol Advieh, Tehran University of Medical Sciences, Tehran, 1992, pp. 708–709 (persian).
[11] J. Barker, C.D. Meletis, Functional foods for childhood development, Altern. Compl. Ther. 10 (3) (2004) 131–134.
[12] Z. Batool, S. Sadir, L. Liaquat, S. Tabassum, S. Madiha, S. Rafiq, S. Tariq, T.S. Batool, S. Saleem, F. Naqvi, Repeated administration of almonds increases brain acetylcholine levels and enhances memory function in healthy rats while attenuates memory deficits in animal model of amnesia, Brain Res. Bull. 120 (2016) 63–74.
[13] M.N. Qureshi, S. Numonov, A. Abudurexiti, H.A. Aisa, Phytochemical investigations and evaluation of antidiabetic potential of Prunus dulcis nuts, LWT-Food Science and Technology 66 (2016) 311–317.
[14] A.E. Cohen, C.S. Johnston, Almond ingestion at mealtime reduces postprandial glycemia and chronic ingestion reduces hemoglobin A 1c in individuals with well-controlled type 2 diabetes mellitus, Metabolism 60 (9) (2011) 1312–1317.
[15] S. de Pascual-Teresa, D.A. Moreno, C. García-Viguera, Flavanols and anthocyanins in cardiovascular health: a review of current evidence, Int. J. Mol. Sci. 11 (4) (2010) 1679–1703.
[16] A.J. Esfahlan, R. Jamei, R.J. Esfahlan, The importance of almond (Prunus amygdalus L.) and its by-products, Food Chem. 120 (2) (2010) 349–360.
[17] A. Puri, R. Sahai, K.L. Singh, R. Saxena, J. Tandon, K. Saxena, Immunostimulant activity of dry fruits and plant materials used in Indian traditional medical system for mothers after child birth and invalids, J. Ethnopharmacol. 71 (1) (2000) 89–92.
[18] A.J. Sfahlan, A. Mahmoodzadeh, A. Hasanzadeh, R. Heidari, R. Jamei, Antioxidants and antiradicals in almond hull and shell (Amygdalus communis L.) as a function of genotype, Food Chem. 115 (2) (2009) 529–533.
[19] Z.H. Sahib, Assessment of anxiolytic activity of nuts of Prunus amygdalus Dulcis (almond) in mice, Med J Babylon 11 (4) (2014) 817–824.
[20] S. Haider, Z. Batool, D. Haleem, Nootropic and hypophagic effects following long term intake of almonds (Prunus amygdalus) in rats, Nutr. Hosp. 27 (6) (2012).
[21] Britsh Pharmacopoeia, The Stationery Offices, London, 2016.
[22] J. Folch, M. Lees, G.H.S. Stanley, A simple method for the isolation and purification of total lipids from animals tissues, J. Biol. Chem. , J. Biol. Chem. 226 (1957) 497–509.
[23] L.S. Maguire, S.M. O'Sullivan, K. Galvin, T.P. O'Connor, N.M. O'Brien, Fatty acid profile, tocopherol, squalene and phytosterol content of walnuts, almonds, peanuts, hazelnuts and the macadamia nut, Int. J. Food Sci. Nutr. 3 (2004) 171–178.
[24] D. Pappas, ADHD Rating Scale-IV: checklists, norms, and clinical interpretation, J. Psychoeduc. Assess. 24 (2) (2006) 172–178.
[25] S. Akhondzadeh, M.-R. Mohammadi, M. Khademi, 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 4 (1) (2004) 9.
[26] S. Akhondzadeh, M. Mohammadi, F. Momeni, Passiflora incarnata in the treatment of attention-deficit hyperactivity disorder in children and adolescents, Clin. Pract. 2 (4) (2005) 609.
[27] B. Salehi, R. Imani, M.R. Mohammadi, J. Fallah, M. Mohammadi, A. Ghanizadeh, A.A. Tasviechi, A. Vossoughi, S.-A. Rezazadeh, S. Akhondzadeh, Ginkgo biloba for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial, Prog. Neuro Psychopharmacol. Biol. Psychiatry 34 (1) (2010) 76–80.
[28] M. Mohammadi, S. Akhondzadeh, Advances and considerations in attention-deficit/hyperactivity disorder pharmacotherapy, Acta Med. Iran. 49 (8) (2011) 487–498.
[29] J.M. Swanson, K. McBurnett, T. Wigal, L.J. Pfiffner, M.A. Lerner, L. Williams, D.L. Christian, L. Tamm, E. Willcutt, K. Crowley, Effect of stimulant medication on children with attention deficit disorder: a “review of reviews”, Except. Child. 60 (2) (1993) 154–162.
[30] J.A. Dopheide, S.R. Pliszka, Attention-deficit-hyperactivity disorder: an update, Pharmacotherapy, The Journal of Human Pharmacology and Drug Therapy 29 (6) (2009) 656–679.
[31] H.-J. Ko, I. Kim, J.-B. Kim, Y. Moon, M.-C. Whang, K.-M. Lee, S.-P. Jung, Effects of Korean red ginseng extract on behavior in children with symptoms of inattention and hyperactivity/impulsivity: a double-blind randomized placebo-controlled trial, J. Child Adolesc. Psychopharmacol. 24 (9) (2014) 501–508.
[32] J.-J. Li, Z.-W. Li, S.-Z. Wang, F.-H. Qi, L. Zhao, H. Lv, A.-Y. Li, Ningdong granule: a complementary and alternative therapy in the treatment of attention deficit/hyperactivity disorder, Psychopharmacology 216 (4) (2011) 501–509.
[33] U. Dave, S. Dingankar, V. Saxena, J. Joseph, B. Bethapudi, A. Agarwal, V. Kudiganti, An open-label study to elucidate the effects of standardized Bacopa monnieri extract in the management of symptoms of attention-deficit hyperactivity disorder in children, Adv. Mind Body Med. 28 (2) (2014) 10–15.
[34] F. Shakibaei, M. Radmanesh, E. Salari, B. Mahaki, Ginkgo biloba in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. A randomized, placebo-controlled, trial, Complement. Ther. Clin. Pract. 21 (2) (2015) 61–67.
[35] K. Jawna-Zboińska, K. Blecharz-Klin, I. Joniec-Maciejak, A. Wawer, J. Pyrzanowska, A. Piechal, D. Mirowska-Guzel, E. Widy-Tyszkiewicz, Passiflora incarnata L. improves spatial memory, reduces stress, and affects neurotransmission in rats, Phytother Res. 30 (5) (2016) 781–789.
[36] S. Yada, K. Lapsley, G. Huang, A review of composition studies of cultivated almonds: macronutrients and micronutrients, J. Food Compos. Anal. 24 (4) (2011) 469–480.
[37] J.G. Penland, Dietary boron, brain function, and cognitive performance, Environ. Health Perspect. 102 (Suppl 7) (1994) 65.
[38] L. Pizzorno, Nothing boring about boron, Integr. Med.: A Clinician's Journal 14 (4) (2015) 35.
[39] A.J. Richardson, Omega-3 fatty acids in ADHD and related neurodevelopmental disorders, Int. Rev. Psychiatry 18 (2) (2006) 155–172.
[40] T. Takeuchi, Y. Fukumoto, E. Harada, Influence of a dietary n-3 fatty acid deficiency on the cerebral catecholamine contents, EEG and learning ability in rat, Behav. Brain Res. 131 (1) (2002) 193–203.