





Effect of Topical Lettuce (*Lactuca sativa* L.) Seed Oil on Childhood Sleep Disorders: a Randomized Double-Blind Controlled Trial

Mahdieh Ranjbar¹ , Suleiman Afsharypour², Fereshteh Shakibaei³, Mohammad Mazaheri^{1*} 

¹Department of Persian Medicine, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

²Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.

³Behavioral Sciences Research Center, Medical School, Isfahan University of Medical Sciences, Isfahan, Iran.

Abstract

Background and objectives: Sleep disorders are among the most common complaints in childhood. Considering the pitfalls regarding safety and efficacy of conventional treatments for sleep disorders in children and based on the Persian medicine literature and results of recent animal and clinical investigations, this study was conducted to evaluate the effect of topical lettuce seed oil in these patients. **Methods:** The study was a double-blind randomized controlled trial in 3-6 years old children with sleep disorders. They were randomly assigned to receive either topical placebo oil and clonidine capsule or lettuce seed oil and placebo capsule for three weeks. Lettuce seed oil was prepared using cold press method. Persian version of "BEARS" pediatric sleep questionnaire was used before and after the intervention. Data analysis was performed using SPSS software (version 20) and $p < 0.05$ was considered as statistically significant. **Results:** At the end of study, 67 patients out of 72 completed the study. Similar to control group, children in intervention group significantly improved regarding bedtime issues ($p < 0.001$), excessive daytime sleepiness ($p = 0.003$), night awakenings ($p = 0.008$), and problems in regularity and duration of sleep ($p < 0.001$); however, no significant change was observed regarding the snoring in both groups. **Conclusions:** Topical use of lettuce seed oil on forehead and temporal areas of children could be considered as a safe and effective treatment for sleep disorders. However, further studies with larger sample size, longer duration of follow-up, and with the use of objective outcome measures are warranted.

Keywords: herbal medicine; integrative medicine; *Lactuca sativa*; Persian medicine; sleep disorders

Citation: Ranjbar M, Afsharypour S, Shakibaei F, Mazaheri M. Effect of topical lettuce (*Lactuca sativa* L.) seed oil on childhood sleep disorders: a randomized double-blind controlled trial. Res J Pharmacogn. 2020; 7(3): 47-54.

Introduction

Sleep is one of the basic needs of human being which is essential for maintaining health and having a good quality of life. The need for sleep varies depending on age, genetic background, and physical and psychological situations. Generally, sleep need is about 11-12 hours a day night in pre-school ages, 10 hours in school ages, and 8-9 hours in adolescents [1]. Sleep is more

important in childhood as it has a direct effect on the mental and physical development.

Sleep disturbances are among the most common behavioral complaints in children; however, due to the variability in presentations, it seems to be underdiagnosed [2]. The prevalence among Western and Asian children has been reported as 24-40% and 70.1-82.8%, respectively [3,4].

* Corresponding author: Mazaherimohammad@med.mui.ac.ir

Prevalence of pediatric sleep disorders in Iran is 41.6 to 50.4% which shows an increasing trend [5-7].

Symptoms of insomnia and sleep disorders in children are different from adults and could present with mood changes, attention and memory deficit, and disturbed learning. Childhood sleep problems can not only affect their health and quality of life, but also be a cause of tension and stress in families and even cognitive disorders in adolescents [8].

Two main treatment strategies for sleep disorders in conventional medicine are cognitive behavioral therapy (CBT) and pharmacotherapy. Benzodiazepines are among the most common drugs used as hypnotic. Zolpidem and Eszopiclone are other pharmacological agents used for pediatric insomnia. However, many of these drugs may cause complications such as daytime sleepiness, headache, dizziness, retrograde amnesia, and drug dependency. Moreover, there is a lack of strong evidence for safe effective hypnotic drugs for children [9]. These limitations in addition to the increasing trend for using traditional and complementary medicines [10], have caused much more attention to these treatment options. However, there is still a lack of strong evidence for their efficacy [11].

Persian Medicine (PM) is one of the oldest medical systems based on the humoral medicine [12]. It considers different treatment strategies including herbal therapy. Herbal medicine itself has a very long history of usage as a popular branch of complementary medicine [13,14]. Many herbal formulations have been recommended in Persian medicine sources by Iranian scholars who were not unfamiliar with sleep disorders. For instance, they have explained different types of insomnia, their signs and symptoms, causes, and treatment options while describing the importance of having normal sleep. In this regard, they have suggested some topical treatment options including taking bath with tepid water, pouring the decoction of some herbs such as lettuce and violet on head, and anointment of navel, palm, and sole with violet-sweet almond oil [15,16]. Some of their suggested herbs have been evaluated in different dosage forms for their efficacy on sleep disorders [17]. For example, aromatherapy with *Rosa damascena* essential oil [18], combination of *Melissa officinalis* and *Nepeta menthoides* [19],

and violet oil [20] have shown their effectiveness through clinical trials.

Lettuce (*Lactuca sativa* L.) which is also known as “Khas” (in Arabic) and “Kahoo” (in Persian) in PM textbooks, has been recommended as one of the most effective sleep-inducing herbs (known as “Monavvem”) in PM [21]. It is a member of the Asteraceae family which is commonly used as salad. From a temperamental point of view, it is moderately cold and wet in nature. It is to be mentioned that the quadruple qualities of hotness, coldness, wetness, and dryness are building blocks of the theory of temperament and humors in PM [22]. In this perspective, moderate moisture in brain is essential for a normal sleep based on the theories of PM, lettuce exerts its sleep-inducing effect through increasing the wetness in the brain. A study investigating the effective materia medica in treating insomnia revealed that *Lactuca sativa* L. is one of the most effective medicinal herbs in this regard [21]. In addition to PM, other traditional and folkloric medicines have mentioned the hypnotic properties of lettuce [23]. Not only animal studies, but also some clinical investigations have shown the positive effect of lettuce on sleep disorders; however, no clinical study has been conducted so far to investigate the effect in children [23-26]. Accordingly, the present investigation was conducted to evaluate the efficacy of topical lettuce seed oil compared to clonidine in childhood sleep disorders.

Materials and Methods

Ethical considerations

Local Ethics Committee of Isfahan University of Medical Science approved the study proposal (ID: 30535). Moreover, we registered the study in the Iranian Registry of Clinical Trials (ID: IRCT20170725035284N2). Following the CONSORT guideline, participants were also asked for signing the informed consent form before the enrollment. Participants were asked to report any side effect at any time of the study. The contact number of principal researcher was available to answer parent's questions.

Preparation of drug and placebo

Lettuce seeds were purchased from Pakan Bazr, Esfahan. For proper authentication, a herbarium sample of the seeds was prepared and checked at the Herbarium of Pharmacognosy Department, Faculty of Pharmacy and Pharmaceutical

Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. It was confirmed as *Lactuca sativa* L. (Voucher no.: 3405).

Lettuce seed oil was prepared using cold press method at the School of Pharmacy Isfahan University of Medical Sciences. Details of the oil analysis using gas chromatography-mass spectrometry (GC-MS) method have been outlined in our previously published papers [27,28].

Grape seed oil was used as the placebo oil. It is a safe inert oil without any known sleep aiding properties which is widely used as a vehicle in cosmetic products. Clonidine capsules (500 mg) contained 0.05 clonidine and sugar powder, while the sugar powder was the only content of placebo capsules. It is to be mentioned that clonidine is a safe and efficient drug proposed as the first line treatment for pediatric insomnia [29].

Study design

The study was a randomized controlled trial with 1:1 allocation ratio. Based on a previous study [7], the sample size was calculated as 36 for each group considering $\alpha=0.05$, $\beta=0.1$, $d=0.025$, $p=0.36$, $q=0.64$ and power= 90% applied in the following formulation:

$$n = \frac{(z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 pq}{d^2} \approx 30$$

In addition to the statistician who analyzed the data, both investigator and participants were unaware of the group allocation as for the blindness of the trial.

Inclusion and exclusion criteria

After signing the informed consent form by one of the parents, children at the age range of 3-6 years who had been diagnosed by a pediatric psychiatrist to have sleep disorders including problem in initiation of sleep, problem in continuity of sleep, daytime sleepiness, irregular sleep, snoring, primary insomnia, and secondary insomnia (due to the diseases such as attention deficit hyperactivity disorder, major depression disorder, and anxiety disorder) were enrolled in the study from June 2018 to February 2019. The following children were not involved (none-enter criteria): those with positive history of allergic reactions, children who had acute diseases which required medical care (such as heart disease, brain disease, acute diarrhea, cold, pain, etc.), and those with secondary insomnia due to other medical/psychiatric diseases including autism,

enuresis, panic attack, apnea, restless leg syndrome, parasomnia, and bruxism. Exclusion criteria were considered as drug reaction, non-compliance (missing two consecutive doses), illness or using any interacting drug with night sleep during the three weeks of intervention, and refusing to participate in the study.

Randomization, blinding and concealment of allocation

Computer-generated block randomization with block size of 4 was used for random allocation of intervention and control groups. The randomization list was prepared using the "Random allocation software" which is a software for generating random allocation sequencing of parallel group trials [30]. Study design was in a way that neither the patients nor the investigator were aware of the group allocations. Moreover, shape, color, and container of drugs and placebos were the same to conceal the allocations.

Intervention

The participants were selected from the children who referred to pediatric psychiatry clinics of Isfahan by convenience sampling. Details of the study were explained to the parents whose children met the inclusion criteria. After signing the informed consent form, participants were randomly allocated to intervention and control groups using block randomization list. After collecting the demographic data and other information, the participants were asked to use either lettuce seed oil + placebo capsule or topical placebo oil (grape seed oil) + clonidine capsule for three weeks. Participants had to use the dissolved contents of the capsules in water one hour before sleeping; then, the parents had to gradually anoint the forehead and temporal areas of the children with 7 drops of the oil using a brush. In addition to verbal explanation, a brochure indicating the instructions was given to the parents.

Outcome measurement

We used Persian version of "BEARS" pediatric sleep questionnaire to evaluate the effect of our intervention (table 1). The reliability and validity have been confirmed in a previous study in 2008 [31]. This questionnaire is a simple 5-item (including: "B=Bedtime Issues, E=Excessive Daytime Sleepiness, A=Night Awakenings, R=Regularity and Duration of Sleep, S=Snoring")

screening tool for evaluation of pediatric sleep disorders which was first invented by Owens and colleagues in 2005 [24]. The pre-school ages (2-6 years) part is filled out by the parents in a base of yes or no answers.

Table 1. “BEARS” pediatric sleep questionnaire for pre-school ages (2-6 years)

BEARS domain	Questions	Answer	
		Yes	No
Bedtime issues	Does your child have any problems going to bed or falling asleep?		
Excessive daytime Sleepiness	Does your child seem over tired or sleepy a lot during the day?		
Night awakenings	Does your child wake up a lot at night?		
Problem in regularity and duration of sleep	Does your child have a regular bedtime and wake time?		
Snoring	Does your child snore a lot or have difficulty breathing at night?		

Statistical analysis

The analysis was done in two descriptive and analytical sections. In the descriptive part, the frequency, percentages, mean and standard deviation were used for the data presentation. Comparisons of age and weight were done using T-test. Chi-squared test was applied for comparing gender, keeping place and the level of education. In the analytical part, Chi-squared and Wilcoxon tests were applied for intra-group and inter-group comparisons, respectively. Data analysis was performed using SPSS software (version 20) considering the significance level of $p < 0.05$.

Results and Discussion

The yield of the cold press method for preparing the lettuce seed oil was 25%.

As shown in figure 1, 72 patients were enrolled from whom 67 completed the study. Comparing the demographic data between the groups showed no significant difference at the baseline (table 2). Results from the “BEARS” pediatric sleep questionnaire were analyzed for intra-group and between group comparisons. Before the intervention, there was no significant difference between the groups regarding the five items of the questionnaire. Data analysis revealed that both groups were improved regarding four items of bedtime issues, excessive daytime sleepiness, night awakenings, and problems in regularity and duration of sleep ($p < 0.05$). Although both groups significantly improved regarding bedtime issues, this improvement was significantly higher in control group (p -value=0.01). This is while no improvement about snoring was occurred in both groups (table 3). In the intervention group, one patient reported eye irritation after anointment for several times which had been easily resolved after simple irrigation. Three others reported: delirium (one episode), late awaking (in first ten days of the study), and morning nap (3 times). On the other hand, two cases of weakness and frailty (most of the days during the study), two cases of thirst and dry mouth (most of the days during the study), and cold sweating after consumption of drug (4 times) was reported in the control group. It should be mentioned that all of these side effects were mild in severity so that did not cause any case of drop out.

The aim of this study was to evaluate the effect of topical lettuce seed oil on childhood sleep disorders. The sleep aiding effect in children was observed in this clinical trial which is in line with the Persian Medicine sources.

Table 2. Demographic data of the groups at the baseline of the study

	Intervention group	Control group	p-value	
Age (years), Mean (SD)*	4.7 (1.06)	4.57 (1.16)	0.520**	
Gender, N (%)	Female	11 (30.60)	0.990***	
	Male	25 (69.40)		24 (66.70)
Weight (Kg), Mean (SD)	17.26 (3.40)	16.89 (4.55)	0.590**	
Keeping place, N (%)	Kindergarten	11 (30.60)	0.490***	
	Preliminary school	11 (30.60)		8 (22.20)
	Home	14 (38.90)		19 (59.80)
Education of mother, N (%)	Under the diploma	5 (13.90)	0.590****	
	Diploma	16 (44.40)		16 (44.40)
	Bachelor and higher	15 (41.70)		12 (33.30)
Education of father, N (%)	Under the diploma	4 (11.10)	0.170****	
	Diploma	17 (47.20)		16 (44.40)
	Bachelor and higher	15 (41.70)		10 (27.80)

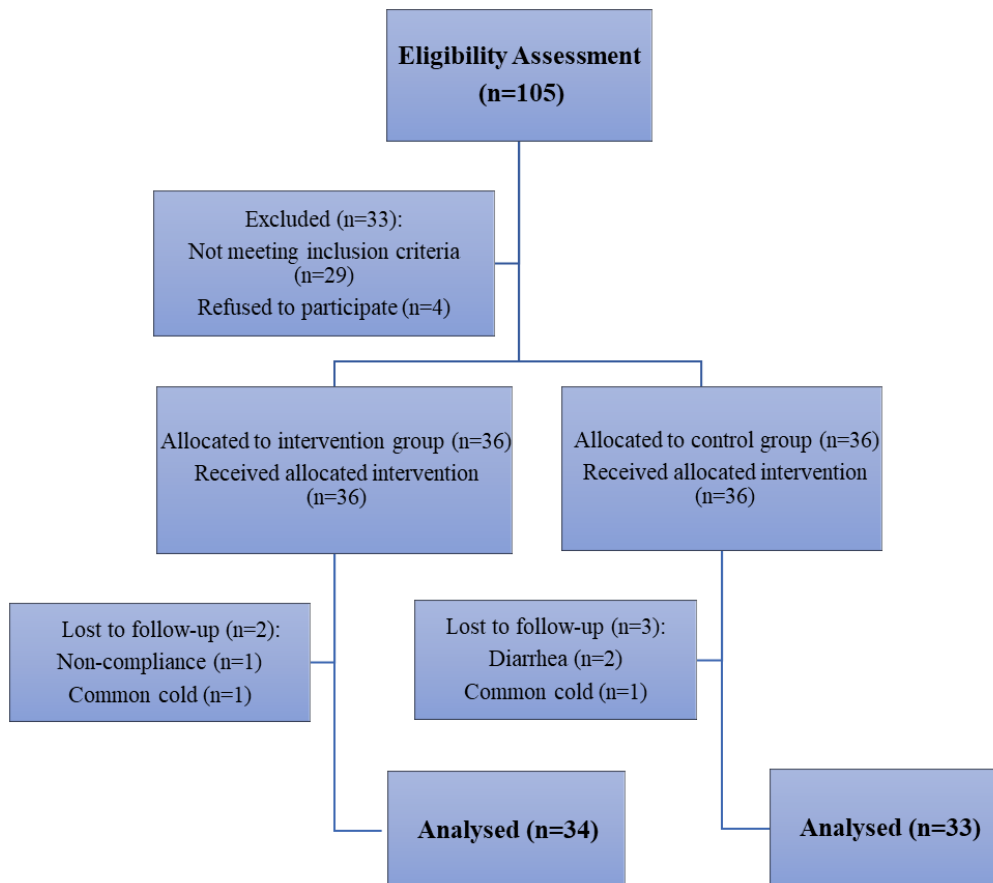
*SD: Standard Deviation; **T test; *** Chi-squared test

Table 3. Results of “BEARS” pediatric sleep questionnaire before and after the study*

BEARS item	Group	Before intervention N (%)	After intervention N (%)	P-value*
Bedtime issues	Intervention	31 (91.20)	11 (32.40)	<0.001
	Control	28 (84.80)	2 (6.10)	<0.001
** p-value		0.42	0.01	
Excessive Daytime Sleepiness	Intervention	15 (44.10)	6 (17.60)	0.003
	Control	15 (45.50)	3 (9.10)	0.005
** p-value		0.91	0.30	
Night Awakenings	Intervention	15 (44.10)	5 (14.70)	0.008
	Control	17 (51.50)	3 (9.10)	0.001
** p-value		0.54	0.48	
Problem in Regularity and Duration of Sleep	Intervention	31 (91.20)	17 (50)	<0.001
	Control	31 (93.90)	10 (30.30)	<0.001
** p-value		0.66	0.10	
Snoring	Intervention	9 (26.50)	8 (23.50)	0.310
	Control	5 (15.20)	4 (12.10)	0.310
** p-value		0.20	0.18	

* Intra-group comparison using Chi-squared test.

** Inter-group comparison using Wilcoxon test.

**Figure 1.** The CONSORT diagram of the study

Our findings revealed that application of topical lettuce seed oil on forehead and temporal areas of the children before sleep, significantly improved some of the most common sleep problems except snoring. This effect was similar to that of

clonidine as the standard treatment. Because of the traditional recommendations about its hypnotic property, *Lactuca sativa* L. seed oil has been recently investigated from the pharmacological and toxicological aspects. It

possesses antimicrobial, anti-inflammatory, antioxidant, analgesic, neuroprotective, and hypnotic properties (sedative dose: 500 mg- 1.25 g, orally) [23,25]. The LD₅₀-value of the hydro-alcoholic extract of *Lactuca sativa* L. has been found to be 4.8 g/Kg [26].

Different classes of secondary metabolites including phenols, flavonoids, and terpenoids are accounted for biological activities of *Lactuca sativa* L. Its sesquiterpene lactones are responsible for the sedative effect [32,33]. Our previous investigations revealed that *Lactuca sativa* L. seed oil contains a mixture of saturated and unsaturated fatty acids including linoleic, palmitic, oleic, arachidic, myristic, and stearic acids [27,28].

Although no FDA-approved medication has been introduced for childhood sleep disorders, clonidine is commonly prescribed by pediatricians as an off-label sleep aid in children [34]. It has shown to be safe and well tolerated; though the complications in children have been reported to be mild or transient, there is still need for good evidence regarding its safety and efficacy [35].

A pilot study in geriatric patients with sleep disorders has shown that oral consumption of lettuce seed oil can improve their sleep [36]. In another clinical trial, daily consumption of lettuce seed (1000 mg) for two weeks significantly reduced insomnia in pregnant women [23]. In addition to human trials, animal studies have also shown its sleep aiding effects [37,38]. The present study showed that in addition to efficacy, using topical dosage form of lettuce seed oil was feasible and safe in children without any serious side effect. The results of this study once again confirmed the sleep enhancing effect of lettuce seed oil in a human trial; however, further clinical investigations with larger sample sizes and longer durations of follow-up are needed. Moreover, objective outcome measurements should be considered in future studies in order to obtain more rigorous results which sheds light on the mechanisms of action.

Acknowledgments

This paper was derived from the thesis by Mahdieh Ranjbar as a part of fulfillment of Ph.D. degree in Persian medicine from Isfahan University of Medical Sciences (grant number: 396539). The authors would like to thank all of the participants for their cooperation. Moreover,

Dr. Arash Najimi and Dr. Mohammad Masoud Azhar are appreciated for their cooperation in data analysis and case selection, respectively.

Author contributions

Mahdieh Ranjbar contributed in data gathering and final preparation of the manuscript; Suleiman Afsharypuor contributed in study design, drug preparation, and revising the final manuscript; Fereshteh Shakibaei contributed in study design, patient selection, and proof reading of the final paper; Mohammad Mazaheri was the main designer of the study who observed the conduction and proof reading of the final manuscript

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

- [1] Sheldon SH, Ferber R, Kryger MH. Principles and practice of pediatric sleep medicine. USA: Elsevier Health Sciences, 2005.
- [2] Carter KA, Hathaway NE, Lettieri CF. Common sleep disorders in children. *Am Fam Physician*. 2014; 89(5): 368-377.
- [3] Acebo C, Sadeh A, Seifer R, Tzischinsky O, Hafer A, Carskadon MA. Sleep/wake patterns derived from activity monitoring and maternal report for healthy 1-to 5-year-old children. *Sleep*. 2005; 28(12): 1568-1577.
- [4] Meltzer LJ, Moore M. Sleep disruptions in parents of children and adolescents with chronic illnesses: prevalence, causes, and consequences. *J Pediatr Psychol*. 2008; 33(3): 279-291.
- [5] Panaghi L, Kafashi A, Seraji M. Epidemiology of sleep disorders in primary school students in Tehran. *Iran J Psychiatry Clin Psychol*. 2004; 10(1): 50-58.
- [6] Nafeiy Z, Shakiba M, Kashavarzian F. The prevalence of sleep disorders in 1 to 2 year infants referring to health centers in Yazd, 2008-2009. *Toloo Behdasht*. 2009; 8(26): 39-45.
- [7] Ozgoli G, Sheikhan Z, Soleimani F, Nasiri M, Amiri S. Prevalence of sleep disorders among children 4-6 years old in Tehran province, Iran. *Iran Red Crescent Med J*. 2016; Article ID e22052.

- [8] Khazaie T, Portaghali P, Jamali O, Khazaei S, Miri N, Sarhadi S, Moosavi S. Sleep pattern and common sleep problems of school children in Birjand. *Modern Care*. 2012; 9(3): 257-263.
- [9] Wiener JM, Dulcan MK. Textbook of child and adolescent psychiatry. Arlington: American Psychiatric Publishing, 2004.
- [10] Hashempur MH, Ghasemi MS, Daneshfard B, Ghoreishi PS, Lari ZN, Homayouni K, Zargaran A. Efficacy of topical chamomile oil for mild and moderate carpal tunnel syndrome: A randomized double-blind placebo-controlled clinical trial. *Complement Ther Clin Pract*. 2017; 26: 61-67.
- [11] Sarris J, Byrne GJ. A systematic review of insomnia and complementary medicine. *Sleep Med Rev*. 2011; 15(2): 99-106.
- [12] Atarzadeh F, Daneshfard B, Dastgheib L, Jaladat A, Amin G. Early description of diet induced blistering skin diseases in medieval Persia: Avicenna's point of view. *Skinmed*. 2016; 14(5): 367-370.
- [13] Golshani SA, Daneshfard B, Mosleh G, Salehi A. Drugs and pharmacology in the Islamic Middle Era. *Pharm Hist (Lond)*. 2015; 45(3): 64-69.
- [14] Daneshfard B, Yekta NH, Khoshdel A, Heiran A, Cheraghi R, Yarmohammadi H. The effect of *Delphinium denudatum* (Jadwar) on fatigue: a randomized double blind placebo-controlled clinical trial. *Complement Ther Med*. 2019; 46: 29-35.
- [15] Nimrouzi M, Daneshfard B, Tafazoli V, Akrami R. Insomnia in traditional Persian medicine. *Acta Med Hist Adriat*. 2019; 17(1): 45-54.
- [16] Petramfar P, Zarshenas MM, Moein M, Mohagheghzadeh A. Management of insomnia in traditional Persian medicine. *Forsch Komplementmed*. 2014; 21(2): 119-125.
- [17] Feizi F, Namazi N, Rahimi R, Ayati MH. Medicinal plants for management of insomnia: a systematic review of animal and human studies. *Galen*. 2019; Article ID 1085.
- [18] Keyhanmehr AS, Movahhed M, Sahranavard S, Gachkar L, Hamdieh M, Nikfarjad H. The effect of aromatherapy with *Rosa damascena* essential oil on sleep quality in children. *Res J Pharmacogn*. 2018; 5(1): 41-46.
- [19] Ranjbar M, Salehi A, Rezaeizadeh H, Zarshenas MM, Sadeghniaat-Haghighi K, Mirabzadeh M, Firoozabadi A. Efficacy of a combination of *Melissa officinalis* L. and *Nepeta menthoides* Boiss. & Buhse on insomnia: a triple-blind, randomized placebo-controlled clinical trial. *J Altern Complement Med*. 2018; 24(12): 1197-1203.
- [20] Feyzabadi Z, Rezaeitlab F, Badiie S, Taghipour A, Moharari F, Soltanifar A, Ahmadpour MR. Efficacy of violet oil, a traditional Iranian formula, in patients with chronic insomnia: a randomized, double-blind, placebo-controlled study. *J Ethnopharmacol*. 2018; 214: 22-28.
- [21] Feyzabadi Z, Aliasl F, Qaraaty M, Aliasl J. Effective materia medica in treatment of insomnia in Iranian traditional medicine. *Med Hist J*. 2016; 7(23): 51-68.
- [22] Kalantari T, Bahmani M, Heydari ST, Daneshfard B, Nematollahi Z, Nimrouzi M. Effect of temperament on happiness and job satisfaction in university employees. *Pak J Med Health Sci*. 2018; 12(2): 915-917.
- [23] Pour ZS, Hosseinkhani A, Asadi N, Shahraki HR, Vafaei H, Kasraeian M, Bazrafshan K, Faraji A. Double-blind randomized placebo-controlled trial on efficacy and safety of *Lactuca sativa* L. seeds on pregnancy-related insomnia. *J Ethnopharmacol*. 2018; 227: 176-180.
- [24] Owens JA, Dalzell V. Use of the 'BEARS' sleep screening tool in a pediatric residents' continuity clinic: a pilot study. *Sleep Med*. 2005; 6(1): 63-69.
- [25] Said S, Kashef HE, Mazar ME, Salama O. Phytochemical and pharmacological studies on *Lactuca sativa* seed oil. *Fitoterapia*. 1996; 67(3): 215-219.
- [26] Ghorbani A, Rakhshandeh H, Sadeghnia HR. Potentiating effects of *Lactuca sativa* on pentobarbital-induced sleep. *Iran J Pharm Res*. 2013; 12(2): 401-406.
- [27] Afsharypuor S, Ranjbar M, Mazaheri M, Shakibaei F, Aslani A. Analysis of fatty acid composition of crude seed oil of *Lactuca sativa* L. by GC-MS and GC methods. *Trends Pharm Sci*. 2018; 4(2): 95-98.
- [28] Afsharypuor S, Ranjbar M, Mazaheri M, Shakibaei F, Aslani A. Essential oil constituents of seeds and fresh leaves of garden lettuce (*Lactuca sativa* L.) grown in Isfahan, Iran. *Res J Pharmacogn*. 2018; 5(3): 1-5.
- [29] Dulcan MK, Ed. Dulcan's textbook of child

- and adolescent psychiatry. Arlington: American Psychiatric Publishing, 2015.
- [30] Saghaei M. Random allocation software for parallel group randomized trials. *BMC Med Res Method.* 2004; Article ID 26.
- [31] Mohammadi M, Ebrahim Amintehran MF, Ghaleh-bandi MRA, Shoaee S, Ghalehbaghi B. Reliability and validity of Persian version of "BEARS" pediatric sleep questionnaire. *Indian J Sleep Med.* 2008; 3(1): 14-19.
- [32] Noumedem J, Djeussi D, Hritcu L, Mihasan M, Kuete V. *Lactuca sativa*. In: Medicinal spices and vegetables from Africa. Kuete V, Ed. London: Academic Press, 2017.
- [33] Khare CP. Indian herbal remedies: rational Western therapy, ayurvedic and other traditional usage, botany. Berlin: Springer, 2004.
- [34] Nguyen M, Tharani S, Rahmani M, Shapiro M. A review of the use of clonidine as a sleep aid in the child and adolescent population. *Clin Pediatr.* 2014; 53(3): 211-216.
- [35] MacLeod RL, Keen DV. Innovations in practice: 'off-label' clonidine: UK pediatric and child and adolescent psychiatry prescribing practice for sleep problems. *Child Adolesc Ment Health.* 2014; 19(2): 147-150.
- [36] Yakoot M, Helmy S, Fawal K. Pilot study of the efficacy and safety of lettuce seed oil in patients with sleep disorders. *Int J Gen Med.* 2011; 4: 451-456.
- [37] Rakhshandeh H, Dolati K, Hamid RS, Ghorbani A. Effects of lettuce extracts on sleep in mice. *Clin Biochem.* 2011; 44(13): 116-117.
- [38] Kim HD, Hong KB, Noh DO, Suh HJ. Sleep-inducing effect of lettuce (*Lactuca sativa*) varieties on pentobarbital-induced sleep. *Food Sci Biotechnol.* 2017; 26(3): 807-814.

Abbreviations

CBT: cognitive behavioral therapy; GC-MS: gas chromatography–mass spectrometry; PM: Persian medicine