Original Article | Artículo Original

Efficacy of pumpkin oil (a Persian medicine product) in the treatment of chronic insomnia: A randomized double-blind clinical trial

[Eficacia del aceite de calabaza (un medicamento persa) en el tratamiento del insomnio crónico: un ensayo clínico aleatorizado doble ciego]

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Abstract

Context: According to Persian medicine text, there are some topical herbal remedies for insomnia such as pumpkin oil as a nasal drop.

Aims: To evaluate the effect of pumpkin oil (a Persian medicine product) in patients with chronic insomnia.

Methods: This study was conducted as a randomized double-blind clinical trial on pumpkin oil efficacy in 74 patients with chronic insomnia. The participants received two drops of intranasal pumpkin oil or placebo every night for two weeks. The effects of pumpkin oil and placebo on the pattern of sleep and sleep quality were assessed at baseline and at the end of two weeks of treatment by Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI) questionnaires.

Results: The scores of the ISI questioner were statistically different between groups after two weeks of intervention and patients in the pumpkin oil group had fewer scores for ISI questioner (p<0.001). The reduction of the total score of the Pittsburgh questioner was 10.08 ± 3.21 in the pumpkin oil group and 0.28 ± 0.98 (p<0.001) in the control group.

Conclusions: Pumpkin oil could have a significant positive effect on the quantity and the quality of sleep in patients with chronic insomnia.

Resumen

Contexto: De acuerdo con el texto de la medicina persa, existen algunos remedios herbales tópicos para el insomnio, como el aceite de calabaza como aplicado como gota nasal.

Objetivos: Evaluar el efecto del aceite de calabaza (un producto de medicina persa) en pacientes con insomnio crónico.

Métodos: Este estudio se realizó como un ensayo clínico aleatorizado doble ciego sobre la eficacia del aceite de calabaza en 74 pacientes con insomnio crónico. Los participantes recibieron dos gotas de aceite de calabaza intranasal o placebo todas las noches durante dos semanas. Los efectos del aceite de calabaza y el placebo sobre el patrón de sueño y la calidad del sueño fueron evaluados al inicio y al final de dos semanas de tratamiento mediante cuestionarios del Índice de Gravedad del Insomnio (ISI) y el Índice de Calidad del Sueño de Pittsburgh (PSQI).

Resultados: Las puntuaciones del interrogador ISI fueron estadísticamente diferentes entre los grupos después de dos semanas de intervención y los pacientes en el grupo de aceite de calabaza tuvieron menos puntuaciones para el interrogador ISI (p<0,001). La reducción de la puntuación total del interrogador de Pittsburgh fue de 10,08 ± 3,21 en el grupo de aceite de calabaza y 0,28 ± 0,98 (p <0,001) en el grupo de control.

Conclusiones: El aceite de calabaza podría tener un efecto positivo significativo en la cantidad y la calidad del sueño en pacientes con insomnio crónico.

Keywords: clinical trial; insomnia; oil; nasal drop; Persian medicine; pumpkin.

Palabras Clave: aceite; calabaza; ensayo clínico; gota nasal; insomnio; medicina persa.

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INTRODUCTION

Sleep is a complex and physiological condition that plays an important role in our body's function and health. Sleep is a vital process and is needed for various processes, such as learning, cellular repair and brain development. It can be impaired by certain factors including noise, stress and sickness (many factors such as noise, stress and illness can impair it) (Stone et al., 2008, Askari, Rahimi et al., 2016). According to statics, more than 27% of people worldwide have sleep disorders. Chronic sleep disturbances can induce memory loss, slower reaction, emotional disorders and impaired immune response (Orzeł-Gryglewska, 2010). Clinically, inadequate sleep can lead to an increased risk of depression, fatness, dyslipidemia, hypertension and type 2 diabetes (Postuma et al., 2009; Mason et al., 2012).

Different hypnotic drugs have been approved in order to treat insomnia, including benzodiazepine receptor (BZR) and melatonin receptor agonists, as well as histamine antagonists (Limandri, 2018). To some specialists, the benzodiazepine receptor agonists are the best choice and have been used for about 50 years (Roehrs and Roth, 2012). However, it has been reported that they possess several side effects, including psychomotor retardation, memory impairment, paradoxical disinhibiting, depression and emotional blunting, tolerance and dependence and short-term withdrawal symptoms. These effects may be amplified in the elderly (Longo and Johnson, 2000; Helft et al., 2014).

It has been demonstrated that some herbal agents are effective in ameliorating insomnia disorder including *Valeriana spp.* (Trauner et al., 2008), *Humulus lupulus* (Butterweck et al., 2007), *Zizyphus jujube* (sour date) (Hajhashemi and Safaei, 2015), *Valeriana officinalis* (Ziegler et al., 2002), *Passiflora incaranta* (passion flower) (Grundmann et al., 2008), *Eschscholzia californica* (California poppy) (Rolland et al., 2001), *Piper methysticum* (Boonen and Häberlein, 1998) and *Lactuca sativa* (Yakoot et al., 2011).

Persian medicine (PM) is a traditional medical system based on humoral medicine with a rich literature about insomnia. In PM, insomnia is called "*Sahar*" that is defined as excessive wake that is out of normal range and is considered as a temperamental disease, mainly caused by brain dystemperament (Sina, 2005). In PM, temperament means the dominant quality of the composite object and it is made of the interaction of four basic elements hot, cold, wet, and dry. They mention that insomnia is caused by dryness in brain (Moradi et al., 2013). An ideal healthy state of an individual is depending on temperament. Dystemperament, which identified as vulnerability of temperament to alteration, leads to different types of diseases such as insomnia (Emtiazy et al., 2012).

The basis of treating insomnia in PM, especially insomnia due to the dryness of brain, is to moisturize the brain, which can be done by nutrition, using spice or massage therapy (Khorasani, 2001; Masoudi, 2008).

According to the theories of humoral medicine, this defect can be resolved by food or drugs with wet temperament. Based on PM manuscripts, one of the most cited and widely recommended medicinal herbs to treat insomnia is *Cucurbita spp.*, which can be used in the form of nasal drop (Aghili Khorasani, 1999; Haghjoo et al., 2019). Nasal route of drug administration is specifically used in treatments of neurologic disease in PM (Hamedi et al., 2013) and was introduced by Galen (Aghili Khorasani, 1999).

Pumpkin (*Cucurbita moschata* Duchesne), commonly known as Gharea, belongs to the family *Cucurbitaceae* is a medium sized plant grown for its fruits and edible seeds (Elemo et al., 2002). It has some properties in PM references such as antidepressant, anti-inflammatory effect and treatment of jaundice and insomnia (Noor Mohammadi and Haji, 2013). Pumpkin contributes to nutrition though an abundant supply of minerals, vitamins and especially carotene (Gwanama et al., 2001). Seeds are good sources of protein, fats, carbohydrate and minerals (Bello et al., 2008). Popularity

of pumpkin in various systems of traditional medicine for several ailments (anti-diabetic, anti-hypertensive, anti-tumor, immunomodulation, antibacterial, anti-hypercholesterolemia, intestinal anti-parasite and anti-inflammation) focused the investigators' attention on this plant (Caili et al., 2006; Xia and Wang, 2006).

According to PM texts, pumpkin oil has been suggested for insomnia as nasal drop. Also, it has showed potentiated pentobarbital hypnosis without toxic influence in mice (Baradaran Rahimi et al., 2018). Since there is no study on hypnotic effect of pumpkin oil in clinical trial, the present study was conducted to evaluate the hypnotic effects and efficacy of pumpkin oil in patients with chronic insomnia.

MATERIAL AND METHODS

Trial design

The present study was designed as a double-blind randomized clinical trial, which was conducted to compare the efficacy and safety of pumpkin oil with placebo in patients with insomnia. The Medical Ethics Committee of Iran University of Medical Sciences approved the protocol of the study (IR.IUMS.REC.1396.9321309013) and a signed informed consent form was obtained from each participant. All participants signed a written informed consent before recruiting in the study. The trial was registered at the Iranian registry of clinical trials (www.irct.ir) under the registration number of IRCT20180424039397N1 and a verbal explanation concerning the study prior to obtaining consent for their participation.

Patients

The participants were recruited from sleep clinic in Baharloo Hospital of Tehran University of Medical Sciences, Tehran, Iran, from April to August 2017.

The sample size was calculated using the formula for comparing two means, considering type 1 error=0.5, power=80%, standard deviation for insomnia severity 4 for each group and attrition rate= 20%. Thirty-seven patients were assigned to each group for observing three score difference between groups.

Inclusion criteria

- Willingness to participation.
- Being 20 to 65 years old.
- Meeting the defined criteria for primary insomnia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)(Association, 2013) for at least three nights a week in at least six-month period.
- The criteria for primary insomnia according to DSM-IV-TR were as follows:

Primary insomnia diagnostic criteria according to DSM-IV-TR were:

1. The predominant complaint is difficulty in initiating or maintaining sleep or having no restorative sleep. Constant complaints of difficulty sleeping or staying asleep or having no restorative sleep.

2. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. Sleep disorders can cause major clinical discomfort or social, occupational, or other major functional disturbances.

3. The sleep disturbance does not occur exclusively during the course of other sleep disorder. Sleep disorders does not occur exclusively during sleep attacks, respiratory sleep disorders, circadian rhythm disturbances, or sleepiness.

4. The disturbance does not occur exclusively during the course of another mental disorder. Sleep disorder does not occur exclusively during another mental disorder (e.g., major depressive disorder, anxiety disorder, delirium).

5. The disturbance is not due to the direct physiological effects of a substance or a general medical condition. The disorder is not caused by the direct physiological ef-

fects of substances (such as drugs being abused or prescribed) or general medical illness).

Patients who had primary insomnia diagnosis and they did not receive any medications and also their first and second question score of Insomnia Severity Index (ISI questionnaire) (Morin et al., 2011) was three or higher than it or the patients that total points of two first questions of the questionnaire was 4 or higher, were entered to the study.

Exclusion criteria

- Chronic heart failure.

- Asthma or severe drug allergy, and history of sever unusual drug reactions to herbs, and allergic rhinitis.

- Cancers.

- Infectious diseases.

- Psychiatric diseases such as major depression, generalized anxiety disorders, psychosis, drugs abuse.

- Neurologic diseases such as Parkinson and Alzheimer diseases.

- Other sleep disorders such as sleep apnea, parallel usage of pharmacologic or no pharmacologic treatment for insomnia, pregnant and lactating women.

Attrition criteria

- Low compliance.

- Severe adverse effect.

- Pregnancy during study.

- Consumption of other sedative drugs during study.

- A total of 100 consecutive patients presenting with insomnia were recruited for the study after taking a careful medical history and performing physical examination.

- Medical history was taken, and physical examination was performed for all patients

and a list of concomitant medications to rule out medical-related or substance-related causes of insomnia was made.

Randomization and blinding

The patients were assigned into two groups through block randomization using quadruple blocks were arranged randomly (n=37 patients per group). Blocks of 4 (AABB, ABAB, BABA, BBAA, ABBA, BAAB)(Roberts and Torgerson, 1998) were randomly selected to make the randomization list. Sequentially numbered opaque sealed envelopes were used for randomization concealment. The drug and the placebo were administered to the patients in similar packages and the same dose (containers were equal in weight and similar in appearance). The patients and the researcher did not know the nature of the interventions.

Interventions

Pumpkin oil was prepared by Tooba Sabz Company and liquid paraffin was purchased from Kimiagartoos Company. Pumpkin oil was prepared on the basis of PM literatures, which prepared from whole pumpkin (without peel) in the base of sesame oil (Aghili Shirazi, 2006).

At first, the study population was randomized into two groups and sleep hygiene was described for both groups. Then, Individuals in control group (n=35) received two drops intra nasal pumpkin oil every night one hour before sleeping for two weeks. The other group (n=39) received placebo drop containing liquid paraffin for two weeks. The patients were blinded to the type of drug allocated to them.

Physical exam and medical history evaluation were performed by a physician. In addition, a urine pregnancy test was performed for women. Finally, the study investigators, a physician evaluated all data obtained from the screening visits for study eligibility. The related adverse effects were assessed based on the self-report symptoms, answering a questioning at the end of two weeks of study, and weekly phone contacts during the 30-day study period.

Drug compliance was assessed through a daily reminder checklist and patients who did not take their prescribed medication correctly (fall off more than twenty percent from the prescription), excluded.

Outcomes

The primary outcome was the effect of pumpkin oil and placebo on the patterns of sleep, which were assessed at baseline and at the end of two weeks of treatment (ISI questionnaire) (Yazdi et al., 2012).

The secondary outcome was the effect of pumpkin oil and placebo on sleep quality (Pittsburgh Sleep Quality Index questionnaire).

The baseline characteristics of the participants of age, sex and marriage was obtained using a data gathering questionnaire.

The Insomnia Severity Index (ISI) questionnaire is a short subjective instrument for measuring insomnia symptoms and consequences (Morin et al., 2011). The ISI is composed of seven items assessing sleep onset, sleep maintenance, early awakening, interference with daily functioning, perceived prominence of impairment attributed to the sleep problem, concerns about sleep problems, and satisfaction with sleep patterns. Perceived severity of each item is rated on a zero through four scales. A total score ranging from zero to 28 is obtained from summing the seven ratings.

The Pittsburgh Sleep Quality Index questionnaire consists of nine items but because question five investment grade 10 options, so the whole questionnaire is rated 19 items that in a Likert range of 4 degrees of 0 to 3 to be. This questionnaire has seven items as follows: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction (Buysse et al., 1989).

These questionnaires were translated into Farsi language by Yazdi et al. (2012) and were validated

previously in patients with insomnia in Iran.

In order to assess the adherence during study, patients were advised to fill a check list after using the medications every night.

Statistical analysis

The data were analyzed by the per protocol method using SPSS software (version 17). Mean and standard deviation was used to describe the quantitative variables, and number and frequency percentage were employed for the qualitative variables.

Comparison of qualitative variables between groups was performed using the Chi-square test. Quantitative variables were compared between groups using Mann-Whitney U test. P value less than 0.05 was considered as statistically significant.

RESULTS

Of the 100 patients who were assessed for eligibility, all underwent randomization. Five patients from the control group and one patient from the placebo group were lost to follow up (because of no immediate impact of the drug in the control group and because of taking narcotic drug in the placebo group) and 10 patients from the intervention group and 10 from the placebo group discontinued intervention (because of unsatisfied with the odor of the drug, no immediate impact of the drug and pregnancy in the control group , and taking narcotic drug in placebo group). A total of 35 patients in pumpkin oil group and 39 patients in placebo group completed the study and were analyzed. Fig. 1 shows the CONSORT flow-diagram.

Demographic and clinical factors

The patients aged 22-64 years with the mean and standard deviation of age 41.6 ± 11.8. Mean age in the two groups did not show a significant difference. Demographic characteristics of patients are presented in Table 1.

Figure 1. CONSORT flow diagram of the study.
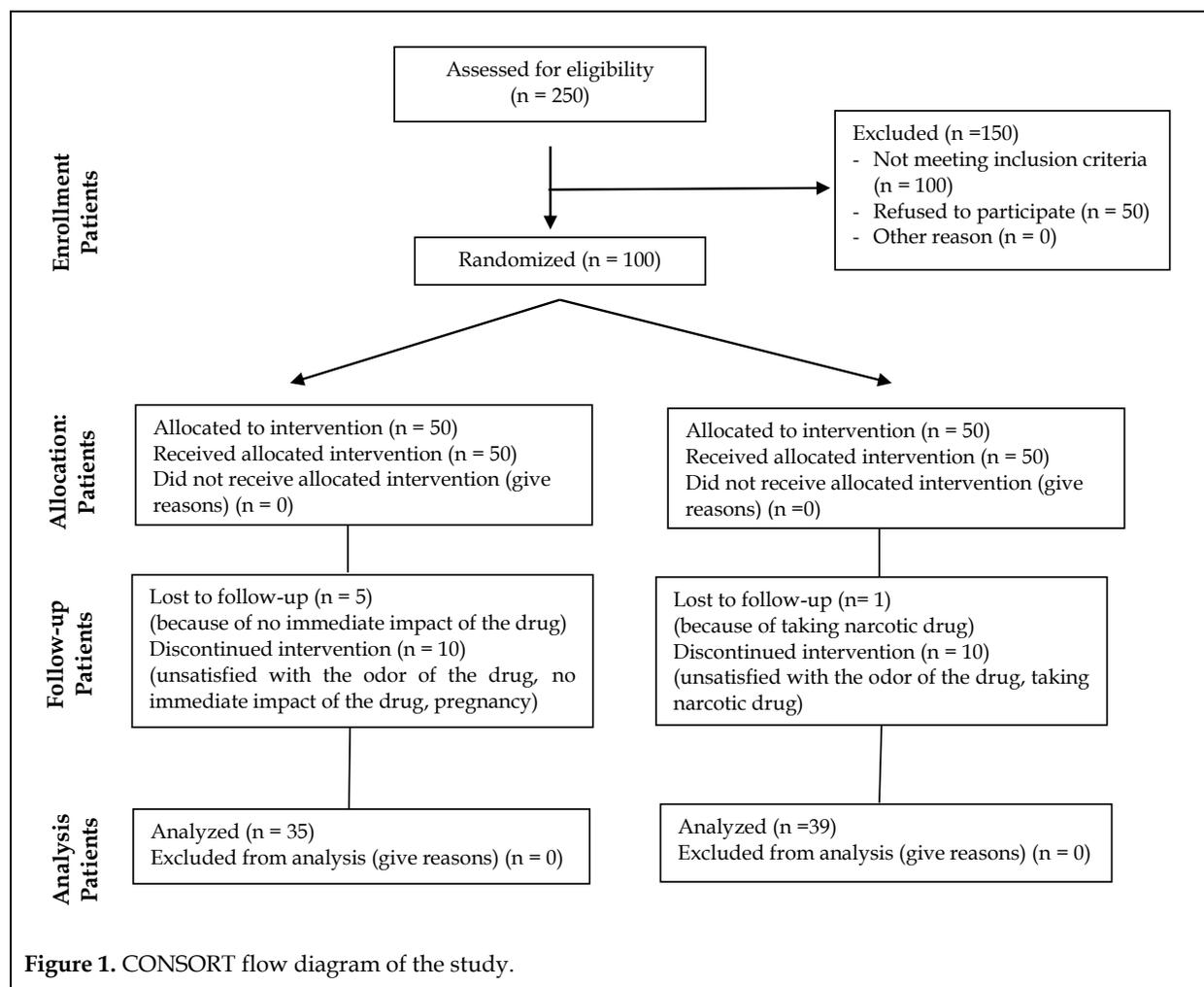
Table 1. Demographic characteristics of patients with chronic insomnia (n = 74).

Variable	Group	Mean	P value
Age (mean ± SD) year	Drug	41.6 ± 11.8	0.36
	Placebo	44.1 ± 11.4	
Gender N (%)	Drug	7 (20) male, 28 (80) female	0.76
	Placebo	6 (15.4) male, 33 (84.6) female	
Marriage N (%)	Drug	25 (71.4) married	0.85
	Placebo	30 (76.9) married	
Education N (%)	Drug	Illiterate 0	0.07
		Under diploma 17 (48.5)	
		Academic 18 (51.4)	
	Placebo	Illiterate 2 (5.1)	
		Under diploma 20 (51.2)	
		Academic 17 (43.6)	

Table 2. The score of ISI questionnaire before and after intervention in pumpkin oil group and placebo group.

Question	Group	Baseline (mean ± SD)	p-value*	After two weeks (mean ± SD)	p-value*
ISI1a	Drug	2.7 ± 1.0	0.29	0.8 ± 0.7	<0.001
	Placebo	2.9 ± 1.1		2.7 ± 1.1	
ISI1b	Drug	2.4 ± 1.1	0.51	0.6 ±0.7	<0.001
	Placebo	2.5 ± 1.4		2.3 ± 1.4	
ISI1c	Drug	2.2 ± 0.9	0.36	0.7 ± 0.7	<0.001
	Placebo	1.9 ± 1.2		1.7 ± 1.2	
ISI2	Drug	2.9 ± 0.8	0.55	1.0 ± 0.7	<0.001
	Placebo	3.0 ± 0.5		3.0 ± 0.7	
ISI3	Drug	2.8 ± 0.9	0.93	0.7 ± 0.7	<0.001
	Placebo	2.8 ± 0.8		2.7 ± 0.8	
ISI4	Drug	2.5 ± 0.9	0.21	0.7 ± 0.7	<0.001
	Placebo	2.8 ± 0.6		2.7 ± 0.8	
ISI5	Drug	2.9 ± 0.8	0.90	0.6 ± 0.9	<0.001
	Placebo	2.9 ± 0.4		2.8 ± 0.6	

*Mann-Whitney U test, SD= standard deviation. ISI1a= Difficulty falling asleep; ISI1b=Difficulty staying asleep; ISI1c= Problems waking up too early; ISI2= How satisfied/dissatisfied are you with your current sleep pattern?; ISI3= How noticeable to others do you think your sleep problem is in terms of impairing the quality of your life?; ISI4= How worried/distressed are you about your current sleep problem?; ISI5= To what extent do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) currently?

ISI was measured by ISI questionnaire at baseline and at the end of study. The score of ISI questionnaire before and after intervention showed significant difference between control (pumpkin oil) and placebo group after two weeks (Table 2).

Based on the results of the Table 2, the scores of all ISI questions were statistically identical between groups before intervention, but at the end of intervention, statistically differences were observed for all questions.

Another questionnaire is Pittsburgh rating questionnaire that was measured at baseline and at the end of study (Table 3). Based on the results of the Table 3, at the end of interventions, statistically significant differences were observed for the scores of all Pittsburgh questions except of using sleeping medications. According to significant differences between groups at baseline, changes of scores were measured and compared between groups. The changes of scores for all questions were statistically significant between groups and changes in the drug group were higher than control group.

Adverse outcomes

No patient reported any side effects that could be attributable to the use of pumpkin oil at the given dose.

In placebo group, adverse effects were reported by two patients. The most common unpleasant report was postnasal discharge (n=2). It was mild and transient.

DISCUSSION

According to PM, there are some topical herbal remedies, which have been used in different topical dosage form such as oil, ointment, and lotion for insomnia. The most common herbs used topically to treat insomnia in Persian traditional litera-

Table 3. Pittsburgh rating questionnaire questions before and after intervention in pumpkin oil group and placebo group.

Question	Group	Baseline (mean ± SD)	p-value*	After two weeks (mean ± SD)	p-value*	Changes (mean ± SD)	p-value*
Subjective sleep quality	Drug	2.3 ± 0.4	0.361	0.6 ± 0.6	<0.001	1.72 ± 0.77	<0.001
	Placebo	2.2 ± 0.4		2.1 ± 0.5		0.13 ±0.34	
Sleep latency	Drug	2.4 ± 0.7	0.678	0.6 ± 0.6	<0.001	1.72 ± 0.61	<0.001
	Placebo	2.4 ± 0.7		2.3 ± 0.8		0.02 ± 0.16	
Sleep duration	Drug	2.1 ± 0.3	0.049	0.4 ± 0.5	<0.001	2.02 ± 0.84	<0.001
	Placebo	2.0 ± 0.2		1.9 ± 0.2		0.02 ± 0.43	
Habitual sleep efficiency	Drug	2.4 ± 0.6	0.128	2.4 ± 0.6	<0.001	0.66 ± 0.53	<0.001
	Placebo	2.2 ± 0.7		2.2 ± 0.7		0.02 ± 0.16	
Sleep disturbance	Drug	1.5 ± 0.5	0.355	0.8 ± 0.3	<0.001	0.50 ± 0.77	<0.001
	Placebo	1.4 ± 0.5		1.4 ± 0.5		0.02 ± 0.16	
Use of sleeping medication	Drug	0.5 ± 0.8	0.027	0.08 ± 0.2	<0.678	0.33 ± 0.75	<0.001
	Placebo	0.2 ± 0.7		0.2 ± 0.6		0.00 ± 0.23	
Daytime dysfunction	Drug	2.1 ± 0.8	0.364	0.7 ± 0.6	<0.001	1.33 ± 0.75	<0.001
	Placebo	1.9 ± 0.7		1.9 ± 0.7		0.00 ± 0.23	
Total score	Drug	14 ± 2.5	0.011	3.9 ± 2.4	<0.001	10.08 ± 3.21	<0.001
	Placebo	12.6 ± 1.9		12.3 ± 1.9		0.28 ± 0.98	

*Mann-Whitney U test

tures are pumpkin, violet, lettuce, water lily and almond (Fayazi et al. 2011, Haghjoo et al., 2019).

Early Persian practitioners believed that alteration the body nature to wet nature can be useful in the management of some types of insomnia (Khorasani, 2001). In the present study, the hypnotic effects and efficacy of pumpkin oil in patients with insomnia was evaluated. The findings showed that the scores of the ISI and Pittsburgh questionnaire were significantly different between drug and placebo groups after two weeks intervention. The results showed that the quality of sleep was improved in pumpkin oil group.

There are some clinical trials, which were conducted on hypnotic effects of medicinal plants in treatment of insomnia. Feyzabadi et al. (2014) conducted a study to determine the efficacy of *Viola odorata* oil in the treatment of chronic insomnia for one month.

The findings showed that improvements in sleep and ISI scores were significantly greater in patients receiving *Viola odorata* oil as drops before

and after treatment. In another study by Dehghanmehr et al. (2017) the effect of oral saffron capsules on sleep quality in patients with diabetes was evaluated. The results demonstrated that saffron can Improve sleep quality. Also, *Crocus sativus* extracts increased total sleep in mice (Hosseinzadeh and Noraei, 2009).

Yakoot et al. (2011) studied the effects of the *Lactuca sativa* extract on insomnia. The finding showed that the extract improved sleep rating scale scores. Indeed *Lactuca sativa* extract prolonged the pentobarbital-induced sleep duration in mice (Ghorbani et al., 2013).

Efficacy of some species of *Cucurbitacea* family were evaluated in different studies. Acres et al. (2012) demonstrated that pumpkin fruits are nutritionally rich and have anti-fatigue activity in mice. Also pump- kin has other effects such as reducing blood glucose, increasing plasma insulin (Ju and Chang, 2001; Chen et al., 2005; Jin et al., 2013) and reducing serum total cholesterol and triglyceride in diabetic animals (Zhang, 1998). In addition, it

has been widely applied in the treatment of benign prostatic hyperplasia in men, obesity, skin problems and irritable bladder (enuresis) in children (Obi et al., 2009). Hypnotic effect of *Cucurbita pepo* was detected in some investigations.

In an experimental and clinical studies, efficacy of seeds and fruits of *Cucurbita pepo* on nocturia and sleep were evaluated. In a clinical trial, nocturia-improving effects of water extracts *of Cucurbita pepo* seeds were evaluated. It was considered that pepokabo-cha (tea prepared from seeds) improves nocturia and may improve quality of sleep (Saito et al., 2011). Also, in an *in vivo* study, the sleep-prolonging effect of *Lagenaria vulgaris* and *Cucurbita pepo* extracts on pentobarbital-induced sleep were reported by Baradaran Rahimi et al. (2018). The findings showed that extracts would increase sleep duration. The results of the present clinical trial confirmed the previous studies on hypnotic effects of *Cucurbitaceae* family.

According to Iranian traditional texts and also the reports of better drug delivery into central nervous system through intranasal route in humans or animal models of Alzheimer's disease and sleep disorders (Pires et al., 2009), we chose this method of drug administration for insomnia. Advantages of intranasal drug delivery in allopathic medicine include rapid drug absorption, fast onset of action, less side effects, self-administration, non-invasiveness, The common method of treatment for long-term, improved bioavailability, avoidance of gastrointestinal tract and the first-pass metabolism and thus, dose reduction in comparison to oral delivery, and potential for direct delivery of drug to the central nervous system via the olfactory region (Pires et al., 2009).

According to previous phytochemical analysis on pumpkin, different amino acids including alanine, arginine, aspartic acid, glutamic acid, histidine, leucine, isoleucine, glycine, lysine, methionine, phenylalanine, serine, threonine, valine and tyrosine have been detected in pumpkin peel. Also, pumpkin fruit contain different flavonoids such as hesperidin and carotenoids. In chick model, amino acids showed sedative and hypnotic effects (Furuse, 2015). In the other hand hesperidin

and neo-hesperidin showed sedative effect and decreases brain pERK1/2 levels in mice (Fernández et al., 2006; Martínez et al., 2009). Therefore, the hypnotic effect of pumpkin oil may due to present of amino acids or flavonoid components. Future studies are necessitous to determine the active components responsible for hypnotic effect of pumpkin oil. Since there are different herbal remedies in topical dosage forms in PM texts, it is recommended to design further clinical trials to evaluate these topical herbal remedies to treat different type of insomnia. The findings of these studies may lead to introduce new topical herbal drug for insomnia with fewer side effects.

CONCLUSIONS

The result of this study showed that pumpkin oil could have a positive effect on inducing sleep in patients with chronic insomnia. Further studies are suggested for evaluation the mechanism of pumpkin oil involved in insomnia and designing new topical herbal drugs for treatment of insomnia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION:

Contribution	Haghjoo E	Haghighi KS	Dabaghian FH	Shojaii A	Mohammadi Kenari H
Concepts or ideas	x	x		x	
Design	x	x		x	
Definition of intellectual content	x	x	x	x	x
Literature search	x			x	
Clinical studies	x	x			
Data acquisition			x		
Data analysis			x		
Statistical analysis	x		x		
Manuscript preparation	x	x	x	x	
Manuscript editing	x	x	x	x	x
Manuscript review	x	x	x	x	x