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The effect of a kind of whey protein (*Ma'oljobon*) on Insomnia: A randomized clinical trial

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1. Introduction

Sleep is a fundamental need of man and a qualitative mode of it is decisive in the continuance of physical and mental health; as well as recovering from diseases [1]. Insomnia is one of the most common sleep disorders which is defined as a difficulty in the start of sleeping or lack of vigorous and refreshing sleep [2]. The disease, by itself or in combination with other diseases, can cause problems for people. The prevalence of insomnia is variously reported in different countries. In India 33% of the individuals report insomnia in a period of their lives, but 13% continuously and chronically suffer from it [3]. In the studies conducted in Iran, the percent of insomnia is reported as 59%, which is higher than the mean universal percent [4].

Sleep duration declines with advancing age (i.e.an expected total sleep length of 7.5 h and sleep latency in 80% to 6 h and in 77% at the age of 85). Women have a longer total sleep length and latency than men of the same age [5]. Various complications of insomnia such as daily fatigue, drowsiness during daytime, having problem in concentrating and thinking, memory complication, restlessness and agitation, increasing of anxiety and depression, unsuitable social and professional function, increased risk of traffic and industrial accidents; as well as the high cost of curing the disease and its complications require the significance of assessing the problem and employing treatments that have fewer sideeffects [1,2].

Numerous researches have been done in order to find an appropriate drug or treatment for insomnia and various ones are still being conducted. Benzodiazepines are frequently prescribed to treat insomnia but they increase the probability of adverse effects such as amnesia, slowness, sleepiness, confusion, nervousness, forgetfulness, irritability, and dizziness [3,6]. Other therapeutic methods for insomnia include behavior therapy, cognition therapy, biofeedback, stimulus control, cognitive-behavioral therapy, light therapy, and chronotherapy. Complementary treatments such as herbs, auricular acupuncture, relaxation exercises, homeopathy, aromatherapy, particular diets, and nutritious foods are also used in treating insomnia and sleep quality [7–10].

In Persian medicine, insomnia is equal to "*Sahar*", which is defined as long and abnormal sleeplessness changing the brain temperament [11,12]. While normal sleep strengthens the body, long wakefulness causes the body to weaken and the brain to become hot and dry-tempered [13]. From this point of view, the cause of insomnia is the warmness and/dryness of the brain's temperament; and, thus, the cold and/moist foods and drugs can treat the complication. It is also possible to moisten the brain by manual massage [14–16].

Ma'aljobon is a kind of whey protein that is said to have a wet and cold temperament in Persian medicine and is recommended as a moistening food for dry tempered patients. It is a liquid which is derived down during cheese producing process through adding either rennet or acid (e.g. lactic acid, acetic acid, or citric acid) to milk. The whey protein, due to its important biological content has nutritive, preventive, and curative properties. It is used in bakery, preparing snacks, formulated baby foods, properly formulated foods for athletes, pastry making, and processing of meat [17]. The biological elements in the whey protein including lactoferrin, betalactoglobulin, alpha-lactalbumin, glycomacropeptide and immunoglobulins affect the immunity system. Probably, the primary mechanism that triggers these properties is the changing of intracellular cysteine hydrochloride into glutathione which is a powerful antioxidant. The whey protein derived from the cheese made from cow milk has as much glutathione increasing capacity as mother's milk [18].

The antioxidant property of whey protein, particularly regarding its

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glutathione increasing capacity manifests its critical effects; thus, it is called an anti-aging product [19].

Various studies have also exhibited that whey protein consumption increases the ability to deal with stress through increasing serotonin [20,21]. In the American Journal of Clinical Nutrition in 2002 the results of a study regarding the effect of alpha-lactalbumin, one of the outstanding proteins of whey, on the increase of cerebral serotonin and the improvement of memory in those involved in stress were reported [20]. Regarding these known and reported properties of whey protein and high prevalence of insomnia and the disabilities following it, a drug with more similarities to foodstuffs but without similar side-effects *Ma'aljobon* (a kind of whey protein) seems to be a good choice for insomnia patients. Since there was no scientific study to support this property; the current study was designed and aimed at comparing the effect of *Ma'aljobon* in comparison with placebos on hypertensive patients suffering from insomnia.

2. Materials and methods

2.1. Type of study

The present double-blind, two-group randomized controlled trial was part of the study "The effect of *Ma'aljobon* On Stage 1 Hypertension, 2017–2018".

2.2. Study design

Data gathering was performed from October 2017 to March 2018 in Birjand cardiovascular Clinic (Birjand, Iran). The inclusion criteria were insomnia complaint confirmed by ISI questionnaire (obtaining 4 or > 4 points in the first question), and age between 20 and 80 years for both sexes. The exclusion criteria included stage 2 hypertension or higher, end-organ disorders, having other diseases (e.g. cardiac, hepatic, renal, diabetes, and malignancies), pregnancy, breastfeeding, specific allergy to the interventions of the study, drug abuse (e.g. alcohol …), taking contraceptive tablets, psychiatric drugs, and hypnotic drugs.

ISI questionnaire is a self-reporting one that assesses a patient's cognition of his/her own insomnia severity and consists of the following seven questions: **1a**. The difficulty at the start of sleep, **1b**. The problem in sleep continuity, **1c**. Early waking up, **2**. Satisfaction with the present sleep pattern, **3**. Complication of functioning during the day, **4**. Noticeability of one's sleep problem to others **5**. Upsetting and disturbance due to sleeplessness.

The answers to the queries were based on Likert scale having 5 choices. In question 1, the answers varied from "never" to "very severe" and won from 1 to 5 points, respectively. The answers to questions 2, too, obtained 1–5 points; i.e. from" very satisfied"-"very unsatisfied". In questions 3, 4, and 5, the answers got from 1 to 5 points; that is, varying from "none"-"a lot".

The Iranian version of the questionnaire has been provided by Yazdi et al. and its reliability and validity have been approved [22]. This questionnaire was filled out by each patient and under the supervision of the researcher.

Determining the sample population and randomization were done for the main study and the assessment of sleep problems of the participants were done at the same time. Regarding $\alpha = 0.05$, $\beta = 80\%$, and effect size = 0.6 with respect to systolic and diastolic blood pressure; and 20% attrition of the participants, 114 patients were calculated and assessed for insomnia.

In order to assess hypertension, the patients were divided into two groups A and B using a block randomized method. For random concealment, the number of each case together with the letters A or B was written down on a paper and was put into an entirely closed envelope. In the beginning of the study, 43 cases in the drug group and 37 patients in the placebo group had sleep and hypertension problems.

The patients in the intervention group consumed 25 g of *Ma'aljobon*, dissolved in 200 cc of warm water, both at fasting time (between 6 a.m. and 7 a.m.) and at 6 p.m. They were advised to walk a little after consumption and avoid sleeping or washing and without a substantial change to their habitual food intakes. The cases in the control group consumed the same dose of maltodextrin powder in the same way. Since the study was a double-blind one, the same boxes for the two kinds of powder were used and the therapist was unaware of the type of A or B. The length of the study was 6 weeks after the end of which ISI questionnaire was again filled up by each participant.

The hematologic factors including FBS, lipid profile, liver function test, hematocrits, and platelets were assessed both in the beginning and the end of the study.

2.3. Drug and placebo provision

The recommended liquid form of *Ma'aljobon* in Persian medicine textbooks, because of having more than 93% moisture, is liable to contaminate and its transportation is hard and expensive. Regarding the largeness of the study population (i.e. about 120) and a six-week consumption of whey protein and the fact that it was not available in pharmacies it was found that whey protein production method employed in Iran Niak Pharmacology Company was similar to that of Mirabzadeh's study to produce a qualitative sample of that recommended form of whey protein in Persian medicine [23]. Thus, the dry powder of Niak's whey protein, available in Iranian pharmacies, was used.

The complete final process of producing this kind of whey protein powder in Niak Pharmacology Company is explained below:

First of all, 1800 kg cow milk is boiled for 20 min. Then, when its temperature lowers to 75 C° 250 kg of oxymel and 5 kg of vinegar are mixed with the milk so that it is separated. The obtained solution is sprayed at 250 liters per hour at the input temperature of 120 C° and output of 50C° through a spray dryer. With regard to the tenderness of proteins to heat, a drying freezer machine is used in the company to dry the obtained whey protein [24]. Finally, each 300 g of it is packed in polyethylene packages.

In our study, the placebo used was maltodextrin powder which is produced through enzymatic hydrolysis of cornstarch using α –amylose resulting in a lighter molecule that is called maltodextrin. The drug and the placebo had the same dose and packages; neither the researcher nor the patients were aware of the quality of interventions.

The primary outcome was the severity of insomnia or changing of the score of the first question of ISI questionnaire. Finally, the data were analyzed by SPSS software (V: 17). The comparison of scores of the ISI questionnaire between two groups was conducted by Mann-Whitney *U* test and $P < 0.05$ was considered as the significant level.

2.4. Ethical considerations

This study has the ethical approval of the Ethical and Research Committee of Iran University of Medical Sciences on 21 Nov 2017; (registration code of IR.IUMS.REC1396.9321309003). It was also registered in Iranian Registry for Clinical Trials under the code of IRCT20140519017756N34.

3. Results

Out of 114 hypertensive patients, 80 had insomnia. Finally, 77 patients (42 from the drug group and 35 from the placebo group) completed the study and three cases that used hypnotic drugs were excluded. (Fig. 1).

The patients aged 34–80 years with the mean and standard deviation of age 53.1 ± 10.3. Mean age in the two groups did not show a significant difference. Mean of the number of drugs taken as hypertension lowering ones in the two groups were not statistically different either. Demographic characteristics of patients are presented in

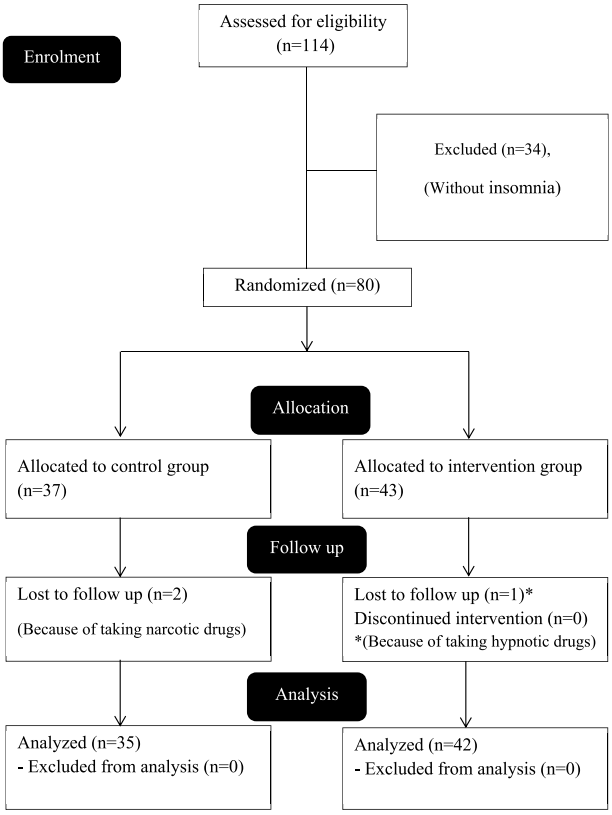

Fig. 1. The trial flowchart.

Table 1
Demographic characteristics of patients with insomnia.

N	Value
Gender No. (%)	
Male	31 (40.3)
Female	46 (59.7)
Marital Status N (%)	
Single	8 (22)
Married	69 (78)
Age, mean ± SD	53.1 ± 10.3
Weight, kg	74.1 ± 10.3
BMI, kg/m^2	23.76 ± 7.23
Occupational Status N (%)	
Employed	42 (40)
Unemployed	35 (60)

BMI: body mass index; SD: standard deviation.

Table 1. They were 31 male and 46 female.

The scores of questions of ISI questions in the two groups before and after intervention are demonstrated in Table 2. Moreover, comparison of the decrease in insomnia scores is shown in Fig. 2.

Although the points allotted to the answers given to the queries of the questionnaire were statistically identical at the beginning of the study, at the end a significant difference between the two groups was observed regarding the points given to question 1 answers; which reveals a sleeping pattern improvement in *Ma'aljobon* group (P = 0.001). Moreover, it was found that sleep satisfaction level in *Ma'aljobon* group was significantly higher than that in the control group (see question 2) at the end of the study (P = 0.03).

According to Table 2, the change of the points allotted to all the answers to ISI queries was significantly higher in the drug group compared with the placebo group all throughout the study; e.g. the points given to question 1 answers in the drug group and control group was 36.2% and 7.3%, respectively (P < 0.001).

Table 2
The score of ISI questionnaire in the two groups before and after the intervention.

Questions	Group	Baseline Mean (SD)	After 6 weeks Mean (SD)	Percent of score changes Mean (SD)
Q 1: 1 a.,1 b,1 c.	Drug	4.9 (2.1)	2.9 (1.4)	36.2 (27.5)
	Placebo	4.1 (1.5)	3.8 (1.5)	7.3 (16.1)
	p value[a]	0.15	0.01	< 0.001
Q 2	Drug	1.7 (1)	1.1 (0.7)	32.9 (34.9)
	Placebo	1.6 (0.8)	1.5 (0.7)	4.2 (14.2)
	p value[a]	0.68	0.03	< 0.001
Q 3	Drug	1.8 (1.2)	0.1 (0.8)	35.5 (35.3)
	Placebo	1.5 (0.9)	1.3 (0.8)	5.2 (16.6)
	p value[a]	0.25	0.28	< 0.001
Q 4	Drug	1.6 (1)	1 (0.7)	32 (36)
	Placebo	1.4 (1)	1.2 (0.8)	8.8 (24.6)
	p value[a]	0.23	0.58	0.004
Q 5	Drug	1.6 (1.2)	1 (0.8)	31.8 (32.9)
	Placebo	1.3 (1)	1.2 (0.9)	7.7 (23.7)
	p value[a]	0.38	0.48	0.002

SD: Standard Deviation, Q 1a. The difficulty at the start of sleep, Q 1b. The problem in sleep continuity, Q 1c. Early waking up, Q 2. Satisfaction with the present sleep pattern, Q 3. Complication of functioning during the day, Q 4. Noticeability of one's sleep problem to others Q 5. Upsetting and disturbance due to sleeplessness.

[a] Mann Whitney *U* test for comparison between groups.

The changes of blood factors in the two groups including lipid profile, liver enzymes, hematocrits, and platelet count did not reveal a significant difference. Reduction in FBS, hematocrit, and platelet level was more in the *Ma'aljobon* group than that in the maltodextrin group; yet, the difference was not statistically significant.

4. Discussion

It was found that a six-week consumption of *Ma´aljobon* improved sleep quality in patients who suffered from insomnia and stage 1 hypertension, and the difference between the two groups was significant. In addition, patients' satisfaction with their sleep pattern was statistically higher in the Ma'aljobon consumers than group B.

After surveying the previous literature, we were certain that no studies had been carried out aimed at assessing the curative effect of Ma'aljobon on insomnia; thus, the present study is the first one in this respect.

The quality of the whey protein produced through different methods is evaluated by assessing the content of its main proteins; i.e. alpha-lactalbumin and beta-lactoglobulin. The study by Mirabzadeh et al. revealed that the most percentage of proteins and amino acids, they got was under the condition in which the whey protein was taken from 100 g of milk by adding 13.7 cc of oxymel and 0.3 cc of vinegar at 75 C°; and the amount of alpha-lactalbumin and beta-lactoglobulin were 8093 ± 289 ppm and 11635 ± 308 ppm, respectively [23]. This amount of protein was the most percentage in different methods of producing whey protein; and the main way of providing it according to Iranian traditional sources, as adopted in the present study.

Mehrbani et al. carried out a study in 2015 in which the effect of whey protein and dodder seed on 42 patients with atopic dermatitis was assessed. Among the outcomes of the study were elasticity increasing, the skin softness and moisture, and treatment of insomnia as a result of daily consumption of 30 g of whey protein powder (produced by vinegar) dissolved in 400 cc of water [25]. This study result about insomnia was in concordance with our findings.

Both melatonin and serotonin are made from tryptophan amino-acids, which are increased by the whey protein [20]. The human body cannot produce tryptophan and the food substances containing it are limited [26,27]. Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced in the brain, which triggers sleep [28,29]. The

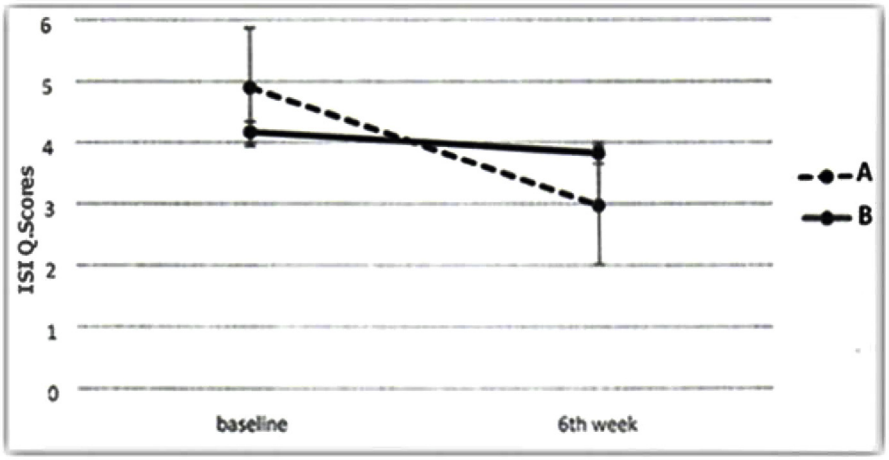

Fig. 2. Changes in insomnia severity during 6 weeks (Drug = A, Placebo = B, ISI Q. = Insomnia Severity Index questionnaire).

production and release of the hormone in the brain are concordant with the time of the day. It decreases in the morning, but increases in the afternoon. The light at night can prevent its production and insomnia lowers its level [30]. There are modern drugs containing melatonin compounds for treating insomnia [31]. In Scheer FA et al.'s study, it was discovered that melatonin decreases blood pressure, too [32]. Their study supports our study in that increase of melatonin level both decreases blood pressure and cures insomnia, as well.

Whey protein contains alpha-lactalbumin that is among the main proteins in the body having 6% of tryptophan; so, it is among the richest food substances that increase the body's tryptophan. The study by P. Antila et al., which was a double-blind one having a casein placebo control group, was done on 23 cases with high stress and 29 with low stress showing that the whey protein, due to its richness in alpha-lactalbumin, manufactured a higher amount of tryptophan compared to other amino acids in the plasma of both groups. As regards the possibility of the increase in cerebral serotonin by tryptophan, which is more outstanding than other aminoacids, in the high-stress group the memory capacity had significantly increased [20]. Considering the positive and critical role of serotonin, as a neurotransmitter in man's neural-behavioral processes, it is certain that cerebral serotonin production is very important as it strengthens man to cope with the psychologic disorders like insomnia [20].

As mentioned above, alpha-lactalbumin is a precursor from which tryptophan is manufactured; and a large percentage of it is used to produce serotonin and melatonin. Thus, daily consumption of 50 g of *Ma'aljobon* powder by patients having insomnia improves the sleeping process and lowers hypertension through increasing alpha-lactalbumin, tryptophan, and-as a result-increasing of melatonin. It is predictable that both serotonin levels of the patients would increase and their temper would improve, too. This can be dealt with in the following studies. It can be said that the mechanism of improving the sleep quality through whey protein consumption is associated with both melatonin and serotonin level increasing. According to Persian medicine , this occurrence perhaps improves insomnia because of the moistening property of whey protein and increasing the moisture of the nervous system [11]. Since according to Persian medicine, any drug or food is more easily absorbed during fasting time or when the stomach is empty, *Ma'aljobon* was administered in the morning fasting time and in the evening.

In two review studies in 2014 and 2015 single herbs which were effective on insomnia were identified; among which the most advantageous ones were Lactuca sativa L., Viola odorata, and Cucurbita moschata whose sedative and hypnotic effects have been shown in animal or human studies [33,34]. Feizabadi et al.'s study in 2018 demonstrated the positive effect of intranasal violet oil (as a moistening agent of the brain) to those suffering from insomnia [16]. According to Persian medicine, all the above herbs have a cold and wet/moist nature/temperament that increases the moisture of the brain and body tissues [14,35]. Persian medicine scholars believe that the moistening property of a food/herb can have a positive impact on the quality and quantity of sleep [35]. The above studies support the view of Persian medicine regarding the role of moistening substances in the treatment of insomnia.

4.1. Study limitations

The present study was a part of a double-blind, placebo-controlled, randomized clinical trial titled “The effect of a product of Persian Medicine (*Ma´aljobon*) on hypertensive patients referring to Birjand CVD clinic ”. Thus, sampling and randomization were first on the basis of systolic and diastolic blood pressure. Of course, the distribution of various factors such as age, sex, and job/profession were made homogeneous in the two groups in order to study insomnia.

It is suggested that other studies with more study samples should be done, which would only aim at exploring the effect of *Ma´aljobon* on sleeping disorders. Besides, the product must be compared with other common hypnotic drugs regarding their effects and the extent of patients' satisfaction.

5. Conclusion

It was found that *Ma'aljobon* was able to reduce the severity of insomnia and improve sleep quality, significantly. With respect to the availability, low cost, and no side-effects of *Ma'aljobon* as a food, it can be an effective modality that can be recommended to the hypertensive patients with insomnia along with other common medications.

Conflicts of interest

All the authors declare that they have no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.01.001.

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