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The Effects of a Special Food (Fried Eggs With Grape Molasses) on Threatened Miscarriage in Combination With Conventional Therapies: A Randomized Clinical Trial

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Abstract

Objectives: Threatened miscarriage is a common disorder in early pregnancy and is seen in 20% of pregnant women. Currently, there is no effective therapeutic solution for this condition. This study aimed to determine the effects of a special food (fried egg with grape molasses) on threatened miscarriage in combination with conventional therapies.

Materials and Methods: This randomized controlled clinical trial was conducted on 93 pregnant women with mild or moderate vaginal bleeding up to 16 weeks of gestation in two groups. The control group (n = 47) used progesterone 400 mg suppository daily with abstinence from sexual intercourse and physical activity. The intervention group (n = 46) consumed fried eggs with grape molasses and the routine treatment like the control group. The treatment was considered successful if the pregnancy continued up to 20 weeks. Finally, the risk of abortion (miscarriage rate) and the duration of vaginal bleeding were compared between two groups.

Results: The risk of abortion in the control group was about 26% (12 of 45 pregnancies), while in the intervention group, it was 15% (7 of 45 pregnancies). This result was not statistically significant between the two groups (Risk ratio: 0.69, 95% CI: 0.37-1.30, P= 0.197). Additionally, no significant difference was detected regarding the duration of vaginal bleeding between the intervention and control groups (P= 0.699).

Conclusions: There is no significant statistical relationship between the consumption of "fried eggs with grape molasses" and reduction of abortion risk.

Keywords: Threatened abortion, Eggs, *Vitis*, Functional food, Persian Medicine

Introduction

Threatened miscarriage refers to vaginal bleeding, without cervical dilatation and fetal loss, during the first half of pregnancy. It is seen in 16 to 25% of pregnancies. About half of these pregnancies lead to "miscarriage". One of the predictive factors for abortion is infertility. Infertility and abortion have similar pathways in manifestation and treatment (1-4).

The standard care in threatened abortion is hydration and rest. There is no high-quality evidence to advise other therapies, though they have physiological roles in pregnancy development. For example, progestogen is not recommended for treating threatened abortion (5), but it is a common medication in some countries, including Iran. Therefore, there is a need for other treatment options such as nutritional therapy. The clinical nutritional studies are very limited in this field, while food can affect diseases and gene expression (6). A healthy diet in early pregnancy has decreased the risk of spontaneous abortion (4,7). Consumption of the proper foodstuff before and during pregnancy improves fertility and has crucial effects on the mother and child's health and favorable pregnancy outcomes (8). Among the healthy and useful foods, eggs with grape molasses have beneficial properties for miscarriage prevention, from the viewpoint of Persian medicine (PM).

Eggs' nutrients are limitedly available in many other foods and introduced as a functional food (9). Egg consumption by pregnant mothers significantly improves their nutrient intake profile (10) and can reduce miscarriage (7). Eggs are known as natural resources of antioxidants to reduce oxidative damage, as are known grapes (11). The grape can prevent miscarriage with some mechanisms (12).

On the other hand, according to the records of PM literature, fried eggs are used for the sexual drive booster and fertility. Eggs, especially egg yolk, are extraordinary food because of the abundant nutrients, rapid and easy digestion, and their role in strengthening the body, heart, and brain. Avicenna (980-1037 AD) believed that the egg yolk is suitable for weak or bleeding. Besides, grape

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Key Messages

- This study did not show a strong relationship between consumption of "fried eggs with grape molasses" and risk reduction of miscarriage. Therefore, it can be used in combination with conventional therapies.

molasses and grape have a high nutritional value and are a body booster. Grape molasses are recommended in compounds to treat visceral weakness (13,14). Grape molasses are *Shire-ye Angoor* or *Dooshab* in Iran, *Pekmez* in Turkey, and *Debs-e Enab* in Arabic countries. The combination of well-cooked fried eggs and grape molasses with butter is called "*Khagineh*" in the Persian cuisine culture.

Given the limitations of prescribing medication during pregnancy, finding safe, inexpensive, and easy-cooking-method food could be a treatment option for reducing abortion. Therefore, this study evaluated the effect of consuming *Khagineh* (fried eggs with grape molasses) in continuing the pregnancy successfully beyond 20 weeks of gestation in women with threatened miscarriages.

Materials and Methods

Study Design and Participants

In this randomized clinical trial, 330 women aged between 12-55 years old who were referring to the Perinatology Clinic of Vali-asr hospital and Persian Medicine Clinic, Tehran University of Medical Sciences, Tehran, Iran from August 2016 to November 2018 were enrolled. Initially, the women with mild or moderate vaginal bleeding up to 16 weeks of pregnancy were assessed. The control group should have abstained from consuming fried eggs with grape molasses in their daily diet, while the intervention group should have included this type of food in their diet. All participants underwent an ultrasonography examination, and fetus viability with a normal gestational sac at five weeks of gestations, yolk sac at six weeks, or fetal heart activity at seven weeks of pregnancy or later was verified. In this study, if the amount of vaginal bleeding was limited to spotting, it was considered mild, and if it was necessary to use 1 to 2 vaginal pads that changed over time, it was deemed moderate. When more than two pads were soaked, it was considered heavy vaginal bleeding. At the end of the bleeding, the colored discharge was considered spotting.

Our exclusion criteria included severe vaginal bleeding, the suspected passage of any fetal or pregnancy materials, fever, history of diabetes, chronic hypertension, recurrent abortion (more than three times), use of low molecular weight heparin, open cervix in the examination as well as, absence of normal gestational sac at five weeks, lack of yolk sac, embryo, or heart activity at seven weeks of gestational age, incomplete or missed abortion, multiple gestation sacs, molar pregnancy, fetal or uterine anomalies, placenta previa without subchorionic hematoma, cervical disorders such as polyps in ultrasound. The data of all participants, including baseline characteristics, 24-hour dietary recall, pregnancy losses before 20 weeks, and duration of vaginal bleeding were collected through self-administered structured questionnaires.

Interventions

Food Control Testing

Several grape molasses samples were sent to the Food Quality Control Lab to measure the maximum sucrose of samples. According to the Iranian National Standardization Organization, the acceptable maximum sucrose of grape molasses is 1 g/mL. One of the standards and pasteurized samples of the grape molasses (GolBehan Food Production Co, Azarshahr, Tabriz, Iran) was selected and purchased. Finally packed in 400 g packets and delivered to the patients by courier or in-person.

Study Protocol

Participants were randomly divided into two groups. The control group received 400 mg of progesterone suppository (Cyclogest®, Actavis, Singapore) without sexual intercourse and physical exertion. Progesterone was used daily until two days once the bleeding had stopped. Then up to one week, suppositories were prescribed every other day. The intervention group received a combination of Khagineh and Cyclogest daily. It is also recommended to abstain from sexual intercourse and physical activity. Khagineh was also consumed daily, up to two days after discontinuation of the spotting, and then was continued every other day for a week.

Khagineh Recipe

The method of Khagineh preparation was given to the intervention group as follows: "Beat together one egg and 25 g of grape molasses with salt until blended. Heat 5 g of pasteurized cow butter in a pan until it becomes hot. Pour the blended eggs onto the pan and brown on both sides".

Dietary Intake

To estimate the usual dietary intake patterns and adjust the impact of diet calories and eating habits in the two groups, we collected the "24-hour dietary recall" per individual in two days. Then, we analyzed them by the Nutritionist IV software (Hearst Corporation, San Bruno, CA), which was modified for Iranian foods. We gave the dietary guide to pregnant women and the number of recommended daily servings to both groups. For the intervention group, we emphasized that during the consumption of Khagineh every day, they should not eat another egg-containing dish.

Assessments and Follow up

The outcomes were evaluated through the participants' self-recorded diaries. We contacted the women and recorded the possible adverse effects every day during the

first days of intervention. Then, we checked them weekly until the bleeding stopped or the miscarriage occurred. When vaginal bleeding increased, we re-evaluated the participants by ultrasound to detect fetal viability. We continued the treatment whenever the bleeding decreased, or there was no difference. In this study, we considered the colored discharge at the end of the bleeding as spotting. Finally, we terminated treatment according to the protocol when the spotting stopped. In addition to following the participants in their 20th week of pregnancy, we followed up with them at the end of pregnancy.

Sample Size

The sample size was estimated to be 90 (45 women in each group), by considering the significance level of 95%, the power of 80%, a 10% dropout rate, and 25% difference in the incidence of miscarriage between the two groups based on the Yassaee et al (15) (p1=80%, p2=50%) and used the following formula:

$$n=\left[\frac{(z_{1-\alpha/2}\sqrt{2\bar{p}(1-\bar{p})}+z_{1-\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}}{p_1-p_2}\right]^2$$

Randomization

Blocks of six subjects carried out randomization and treatments' allocation. To concealment of allocation sequence from the researcher, the sequential numbered were sealed in opaque envelopes. A person evaluating the outcomes was blinded to the random allocation process and the type of treatment. Additionally, the statistical expert analyzing the data was blinded to all the processes performed.

Statistical Analysis

All statistical analyses were performed by STATA 16.0 (Stata Corporation, College Station, TX, USA). The baseline characteristics were compared between the two intervention groups using the independent sample *t* test for continuous data and the chi-square test for ordinal data. Modified Poisson regression modeling was used to estimate the risk ratio between the intervention and control groups after adjusting the effects of other variables on the miscarriages. The results are presented as risk ratio (RR) with 95% confidence intervals. The variables considered in the adjustment model were women age, body mass index, gestational age, occupation status, history of miscarriage, treatment type, and nutritional intake (macronutrients, micronutrients, and energy intake). The variable selection was done based on the available evidence about the miscarriage risk factors as much as possible, without overlapping with other measurements to avoid collinearity in the multiple models.

Results

From 330 pregnant women with vaginal bleeding, 93 women were included in the study. Of them, three women were lost to follow-up; two cases were due to induced abortion and one case used traditional astringent medications. Based on intention-to-treat, 90 participants were included in the final analyses (n=45/each group) (Figure 1).

The demographic and baseline characteristics of the participants were summarized in Table 1. No statistically significant differences were observed between two groups in terms of age, gestational age, body mass index, history of

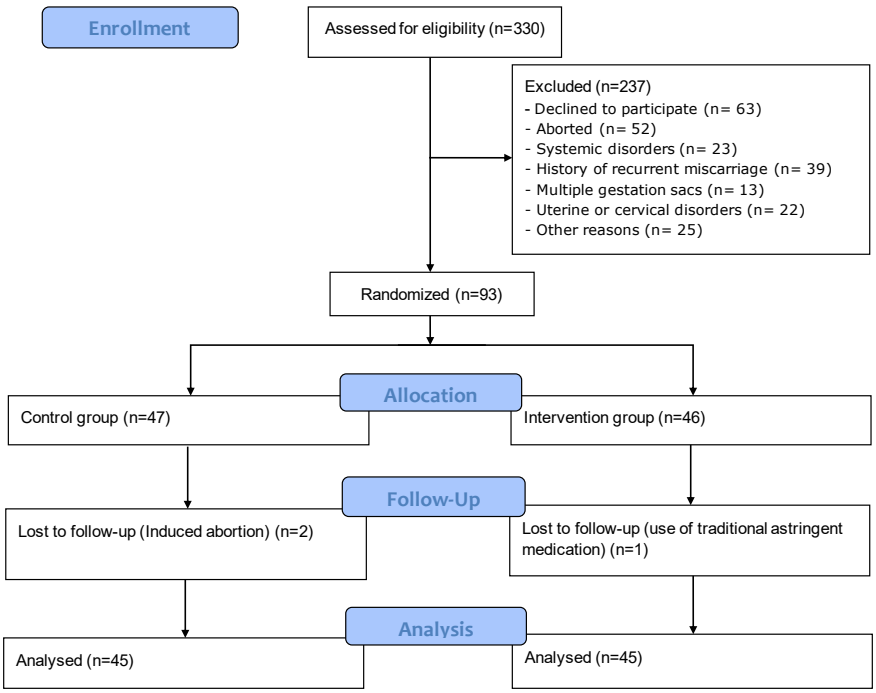

Figure 1. The Study Consort Flowchart.

smoking, alcohol consumption, infertility, use of assisted reproductive technology, and miscarriage.

In the intervention group, the miscarriage rate was 15.55% (95% CI: 6.49 to 29.45), while the abortion was 26.66% (95% CI: 14.26 to 41.13) in control group (RR: 0.69, 95% CI: 0.37 to 1.30, $P=0.197$). The miscarriages were not significantly different between the two groups based on multiple analysis (RR: 0.97, 95% CI: 0.70 to 1.35, $P=0.876$). Besides, no significant difference was detected either in the duration of vaginal bleeding in the intervention (9.29 ± 9.02) or control (10.56 ± 12.29) groups (MD: -0.84, 95% CI: -5.16 to 3.47, $P=0.699$) (Table 2).

Tables 3 presents the baseline nutrient intakes in the intervention and control groups. As seen, fat, carbohydrate, and protein intake in the intervention group were significantly higher than in the control group. As a result, the total energy intake by the intervention group was higher than by the controls.

These results were obtained from the study samples 24-hour dietary recalls of two days of diet in. The nutrients shared from prenatal supplements have not been included. According to the results, the nutrient intakes of the control group are lower than those of the intervention group (Table 3).

Discussion

This study assessed the efficacy of fried egg with grape molasses in combination of conventional therapies (progesterone suppository, rest, and avoidance of sexual intercourse) in pregnancies with threatened abortion (miscarriage). Although the number of abortions in the control group was nearly twice that of the intervention group, the analysis of the results did not show a significant statistical relationship between the consumption of "fried eggs with grape molasses" and reduction of abortion risk.

Most nutritional studies about threatened miscarriage have been observational studies. These case-control studies with the Food Frequency Questionnaire, have assessed dietary indicators during pregnancy and the risk of miscarriage (4,7,16). For example, eating more eggs reduced the risk of spontaneous abortion (7). In contrast, in the other study, egg consumption (twice a week or more) did not affect abortion (4).

Varieties of factors are involved in threatened abortion

Table 1. Outcomes of Study in Intervention and Control Groups

Variables	Intervention Group (n=45)	Control Group (n=45)	*P* Value
Abortion rate	7 (15.55%)	12 (26.66%)	0.876[a]
Duration of vaginal bleeding (days)	9.29 ± 9.02	10.56 ± 12.29	0.699[b]

[a] Based on chi-square; [b] Based on independent *t* test.

Table 2. Energy and Nutrients' Intakes in Two Study Groups

Variables	Intervention Group (n = 45)	Control Group (n = 45)	*P* Value[a]
Age (y), Mean ± SD	31.26 ± 4.60	30.82 ± 4.06	0.629
Gravidity, Mean ± SD	1.91 ± 1.04	2.11 ± 1.02	0.361
Gestational age (wk), Mean ± SD	8.82 ± 3.06	8.57 ± 2.62	0.667
BMI (kg/m^2), Mean ± SD	25.81 ± 4.15	25.29 ± 4.07	0.552
Education, No. (%)			
Non-academic	12 (26.7)	9 (19.6)	0.455
Academic	33 (73.3)	37 (80.44)	
Occupation, No. (%)			
Yes	31 (68.9)	26 (57.8)	0.274
No	14 (31.1)	19 (42.2)	
Smoking, No. (%)			
Yes	42 (93.3)	41 (91.1)	0.841
No	3 (6.7)	4 (8.9)	
Alcohol, No. (%)			
Yes	44 (97.8)	43 (95.6)	0.557
No	1 (2.2)	2 (4.4)	
Infertility history, No. (%)			
Yes	37 (84.4)	41 (91.1)	0.334
No	8 (15.6)	4 (8.9)	
Use of ART, No. (%)			
Yes	38 (84.4)	41 (91.1)	0.334
No	7 (15.6)	4 (8.9)	
Abortion history, No. (%)			
Yes	12 (26.7)	25 (55.6)	0.078
No	33 (73.3)	20 (44.4)	

BMI: Body mass index; ART: Assisted reproductive technology.

[a]Independent *t* test.

Table 2. Energy and Nutrients' Intakes in Two Study Groups

Variables	Intervention Group (n = 45)	Control Group (n = 45)	*P* Value[a]
Energy (kcal)	2136.91 ± 200.95	1523.82 ± 179.24	< 0.001
Macronutrients			
Carbohydrate (g)	289.39 ± 55.11	200.95 ± 45.20	< 0.001
Protein (g)	67.88 ± 20.45	50.77 ± 14.51	< 0.001
Fat (g)	82.87 ± 20.94	60.50 ± 17.64	< 0.001
Dietary fiber (g)	18.82 ± 7.11	13.46 ± 5.06	< 0.001
Micronutrients			
Vitamins			
Vitamin A (mg)	963.07 ±1360.49	796.38 ± 1066.77	0.519
Vitamin E (mg)	23.54 ± 11.6	15.54 ± 6.36	< 0.001
Vitamin K (mg)	127.69 ± 97.57	76.21 ± 50.14	0.002
Vitamin C (mg)	127.13 ± 113.52	98.19 ± 84.94	0.174
Vitamin B2 (Riboflavin) (mcg)	1.39 ± 0.57	1.05 ± 0.39	0.002
Vitamin B6 (Pyridoxine) (mg)	1.93 ± 0.79	1.44 ± 0.67	0.002
Vitamin B12 (Cobalamin) (mg)	2.74 ± 1.49	2.15 ± 1.02	0.03
Folate (mg)	359.52 ± 121.11	236.57 ± 80.14	< 0.001
Minerals			< 0.001
Iron (mg)	14.62 ± 3.78	9.12 ± 2.39	< 0.001
Magnesium (mg)	296.92 ± 107.66	203.7 ± 57.07	< 0.001
Zinc (mg)	9.27 ± 2.9	6.60 ± 1.7	< 0.001
Manganese (mg)	4.57 ± 1.17	3.20 ± 1.02	< 0.001
Calcium (mg)	710.28 ± 329.95	550.92 ± 252.03	0.012
Phosphorus (mg)	1153.64 ±358.17	819.55 ± 218.84	< 0.001
Copper (mg)	1.34 ± 0.46	0.89 ± 0.26	< 0.001
Selenium (mg)	0.05 ± 0.02	0.03 ± 0.01	< 0.001
Others			
Methionine (mg)	1019.95 ± 561.03	806.9 ± 403.95	0.042
Cholesterol (mg)	244.04 ± 165.99	157.41 ± 97.51	0.003

Data presented as mean ± SD; [a] Independent *t* test.

mechanisms such as excessive inflammation, immune suppression, toxic agent or oxidative stress, insufficient secretion of some hormones, etc. Different parts of grapes elevate the anti-inflammatory cytokines (such as IL-4 or IL-10), reduce the pro-inflammatory mediators (e.g., IL-1β, IL-6, IL-8, IL-17, TNF-α, and IFN-γ), and probably control excessive inflammation in miscarriage (12). In this regard, pregnant women who consumed more pro-inflammatory diet have an abortion twice as women who consumed more anti-inflammatory diet (16).

Systemic and placental oxidative stress have a crucial role in miscarriage and recurrent abortion (17). Reduced antioxidants in the pregnant women can cause threatened miscarriage (18). Increased intake of antioxidant-rich food can improve gestational outcomes in women with a history of recurrent miscarriage (19). Therefore, oral intake of antioxidants can be useful in preventing miscarriage by detoxifying and repairing oxidation damage (17). Egg yolk is a recommended foodstuff for protection against oxidative stress (20). The antioxidant power of the grape is greater than that of vitamin C and E (11). The important point is that the antioxidant activity of grape molasses is greater than that of grape; for example, total phenol content of grape molasses was higher than that of grape and even higher than that of raisins and red grape (21). Grape (*Vitis vinifera* L.) can reduce abortion at least with six mechanisms: immunomodulatory and anti-inflammatory, antioxidant, anti-microbial, anti-stress, anti-contraction, and hormonal activities (12).

In our study, the energy and nutrients intakes were higher in the intervention group than in the control group. In this regard, Bermudez-Millan et al identified the cultural beliefs of low-income pregnant Latinas about egg consumption during pregnancy and methods of egg preparation with the food frequency questionnaire and a single 24-hour dietary recall. They showed that the women, who consumed eggs in their diets, had higher intakes of protein, fat, beta-carotene, selenium, lutein and zeaxanthin, vitamin E, vitamin K, etc. Finally, they concluded that egg consumption in these women significantly contributes to their diet's overall nutrient intakes and nutrient density (10). One of the required nutrients in healthy pregnancy and fetus brain and memory development is "choline". The egg yolk is an excellent source of choline. Pregnant women need choline twice as much compared to non-pregnant women (22). People with high dietary choline intake have lower blood homocysteine levels (23). Hyperhomocysteinemia is a risk factor for recurrent abortion and fetal neural tube defects, whereas plasma homocysteine levels drop in normal pregnancy (17).

Grape molasses contains 100 mg of iron and 4000

mg of calcium per kilogram. It is a good foodstuff for prophylaxis of iron deficiency anemia (24). One study that was done on 56 children, aged 6-36 months, found that in healthy infants, iron absorption from grape molasses was comparable to that from ferrous sulfate (25). In folk medicine, people believe that a mixture of grape molasses and butter decreases postpartum hemorrhage (26) and increases the mother's energy and milk (27).

Therefore, it seems that eggs with grape molasses can play a positive role in reducing the risk of miscarriage. Similarly, this food reduced the risk of miscarriage by 42% relative to the control group in the present study, but not statistically significant. Probably consumption of this food only in pregnant women with symptoms of "weakness" would reduce the miscarriage significantly. According to PM, pregnancy loss has at least 30 etiologies. Khagineh can manage some causes of abortion, such as fetal and maternal weakness, especially genital system "weakness". In the other hand, both egg yolk and grape molasses act through the body tonification, and reduce the adverse pregnancy outcomes. Therefore, they can protect the fetus. "Fetal protector" is a term in PM, that protects the fetus by reducing the complications in the early and late pregnancy and confers health to newborns for future years of life (21,22).

About 47%-80% of patients use complementary alternative medicine before pregnancy or during pregnancy. Concerning the interest of pregnant women in using medicinal herbs to prevent threatened abortion (28, 29); there are some clinical studies on evaluating these medicines. Most of these studies are about the effects of Chinese herbal medicines to treat threatened miscarriage (30-32). For example, in one study, the abortion rate in the control group (progesterone and vitamin E) was 30%. In contrast, in the combined group (Chinese herbal medicines + Western medicines), it was 8.62% (32), compared with our study results, 26% and 15%.

Consequently, we suggest the design of studies with specific fetal-protector foods. In the next step, clinical trials can be designed with fetal-protector medications in threatened abortion. Confirming or rejecting this hypothesis requires further studies with larger sample sizes. Today, we can use food and nutrition science to prevent or treat the prevalent pregnancy complications and find new and proper foodstuffs, either alone or combined with medicinal therapy.

Limitations

One of the strengths of this study was the existence of homogeneous samples due to strict eligibility criteria. Of the 330 women assessed for eligibility, only 93 participants were included in the present study. Nevertheless, slightly expanding the exclusion criteria could accurately reflect daily practice and include more participants in our study.

In this study, the colored discharge was considered spotting at the end of the bleeding, as vaginal bleeding during pregnancy culturally important for Iranian women. Additionally, if the amount of bleeding was measured in our study, the bleeding volume of the intervention group was probably less than that of the control group. Bleeding is directly proportional to adverse obstetric outcomes due to threatened miscarriage (2,3). On the other hand, if the pregnancy outcomes were followed up in our study, the adverse outcomes in the intervention group would probably be fewer than those in the control group, as poor maternal dietary intake is associated with adverse pregnancy outcomes (33).

Due to gastrointestinal problems in early pregnancy, some patients found this food was difficult to tolerate for. These patients were encouraged to continue eating Khagineh through follow-up and phone calls.

Conclusions

A proper diet before and during gestation can lead to a healthy pregnancy and delivery while also reducing pregnancy complications such as threatened miscarriage. Although the consumption of "fried eggs with grape molasses" could not reduce the incidence of miscarriage significantly, it can be a functional food in miscarriage prevention. Therefore, this food can positively affect threatened abortion in combination with conventional therapies.

Authors' Contribution

FM, MT and KM designed the study and conducted the research. FM, MT, SoH, SB and SeH monitored, evaluated, and analyzed the result of the study. Further, FM, MT and MS reviewed the article. All authors approved the final manuscript and take responsibility for the integrity of the data.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran approved the study protocol (Code: IR.TUMS.VCR.REC.1395.121) after approving in the Traditional Medicine Department (Research code: 9221309003). Then, the study protocol was registered in the Iranian Registry of Clinical Trials (identifier: IRCT2016040627248N1). Written informed consent was obtained from all participants.

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