



The Effect of *Pimpinella anisum* on Treatment and Recurrence of Menopausal Hot Flashes: A Randomized, Controlled, Multicenter, Double-Blind, Parallel-Group Clinical Trial

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Abstract

Background: Considering the high prevalence of hot flashes and the controversies in its treatments, the present study evaluated the effect of *Pimpinella anisum* extract on the treatment and recurrence of hot flashes in women referred to the health centers of medical sciences universities in Tehran, Iran in 2019.

Methods: The present double-blind controlled parallel-group clinical trial included 72 menopausal women with chief complaint of hot flashes. The participants were randomly assigned into two equal groups ($n = 36$ each) of experimental (receiving three *P. anisum* capsules) and control. The severity and frequency of hot flashes were measured by Visual Analogue Scale (VAS) before the treatment, eight weeks after the treatment, and four weeks after discontinuation of the medication. The data of patients, including their diet, were recorded in the questionnaires and information forms. The data were analyzed using SPSS 19, and the intra-group results were analyzed using the repeated measures analysis of variance (ANOVA). Also, to compare the scores between the groups, *t*-test, and Mann-Whitney-Wilcoxon (MWW) were used.

Results: The frequency of hot flashes in the *P. anisum* group was 7.89 ± 5.67 before the treatment, 1.04 ± 1.24 eight weeks after the treatment, and 4.21 ± 2.03 in the four-week follow-up period. The severity of hot flashes among the *P. anisum* group was 11.50 ± 9.78 , 1.90 ± 2.77 , and 5.78 ± 1.92 before the treatment, eight weeks after the treatment, and four-week follow-up ($P = 0.001$), respectively. However, the severity and frequency of hot flashes did not change significantly in the placebo group ($P = 0.75$). No side effects were seen in any of the groups.

Conclusions: *Pimpinella anisum* was effective in reducing the frequency and severity of hot flashes.

Keywords: Menopause, Menopausal Women, Hot Flash, Vasomotor Hot Flash, *Pimpinella anisum*

1. Background

Menopause is a natural phenomenon that results from loss of ovarian activity and permanent cessation of menstruation. The most common symptoms are hot flashes described as periodic feeling of heat and sweating associated with chills, palpitations, anxiety, pressure in the head and chest, a burning sensation, nausea, choking, and lack of focus (1), which normally last for three minutes (2).

Hot flashes usually occur around 50 - 52 years of age, along with a decline in estrogen production (3). About 80% of women experience hot flashes within the first three months after menopause, and women in industrialized countries spend about one third of their lives in

menopause (4).

The pathophysiology of hot flashes is unknown. However, reduction and cessation of estrogen production plays an important role in changing brain neurotransmitters and instability in the hypothalamic thermoregulatory center. Although hot flashes and sweats do not jeopardize life (5), they result in anxiety, severe discomfort, and social dysfunction, ensure time and women's careers, and eventually reduce their quality of life (6).

The treatment of choice for hot flashes is estrogen replacement therapy which reduces the symptoms up to 80 - 90%, but it also causes side effects like heart attack, cardiovascular diseases, infarction, thromboembolism, and breast cancer (7). Furthermore, 10% of women are banned

from consuming estrogen. Therefore, hormone therapy is applied in less than 20% (8). Studies in Iran have shown that only 9.1% of women prefer to use hormones to treat hot flash (9).

Several other medications like progestin, antihypertensive medications, anti-dopaminergic medications, ergot alkaloids with mild painkillers, tranquilizers, antidepressants, alpha-adrenergic agonists (10), vitamins E have been recommended for treating hot flashes (11). Although these medications are effective and have some benefits, they have many adverse effects like irregular vaginal bleeding, constipation, breast tenderness and pain, mood swings (12), addiction (2), myocardial infarction (13), endometrial cancer, gall stones, hypertension, breast cancer thrombophlebitis, and glucose intolerance (14), which sometimes restrict hormone replacement therapy in older ages.

Alternative therapies like diet, sports, aromatherapy, homeopathy, meditation, and herbal medicine have increased in the past decade, all of which have been effective in alleviating menopause symptoms (15). In fact, using herbal medicines and phytoestrogens represent a diverse group of non-steroidal natural products, which seem to have some estrogenic effects and are often marketed as food supplements. The population being exposed to phytoestrogens is potentially increasing, in part because of an unfavorable risk-benefit profile of hormone replacement therapy (16). Furthermore, few studies have investigated the impacts of herbs containing phytoestrogen like soy (17), licorice (18, 19), and *Pimpinella anisum* (20). In this regard, *P. anisum* (aniseed) (21) has been used as antispasmodic, carminative, expectorant, and galactagogue for centuries (22).

Pimpinella anisum L. is an annual herb indigenous to Iran, India, Turkey, and many other warm regions in the world. Chemical studies have demonstrated the presence of eugenol, anethole, methylchavicol, anisaldehyde, and estragole as the major compounds of the fruit essential oil of *P. anisum*. Eugenol and estragole have been reported to show anesthetic, hypothermic, muscle relaxant, and anticonvulsant activities. Furthermore, anethole possesses muscle relaxant effect. *Pimpinella anisum* has estrogenic effects and is nearly free from adverse effects, and its simple use has attracted the attention of researchers and postmenopausal women (23). This medicine is available in different forms such as pills, syrups, drops, and oil (22).

2. Objectives

Considering the high prevalence of hot flashes, its adverse effects and treatment challenges, as well as people's increased tendency to complementary medicine and

herbs, the present study aimed at determining the effect of *P. anisum* extract on treatment and recurrence of hot flashes of postmenopausal women in Tehran, Iran in 2019.

3. Methods

3.1. Study Design

The present double-blind, randomized controlled parallel-group clinical trial was registered at www.irct.ir (code: IRCT201103284317N4). The patients were randomly assigned into two groups of experimental and control. Considering the type I error probability of 5%, power function of 80%, and effect size of 6%, the sample size was determined as 72 individuals using the following formula:

$$N = \frac{2(Z_{\alpha} + Z_{\beta})^2}{(Es)^2} \quad (1)$$

$$Es \text{ (Effect size)} = 0.6$$

$$Z_{\beta} = 0.85$$

$$Z_{\alpha} = 1.96$$

3.2. Sampling

Using a purposeful sampling method, the researcher attended the selected health centers and invited patients by reviewing their files. The aims of the study were explained to all participants, and a written informed consent was obtained from them prior to the study. Then, according to inclusion and exclusion criteria, the participants were randomly assigned into two groups of experimental and control (table of random numbers based on computer random sequence).

The inclusion criteria were being literate or having a literate person at home, aged 45 - 60 years old, body mass index (BMI) < 29, amenorrhea for one to three years, experiencing hot flashes and not taking any medications or hormones to alleviate them, no history of known diseases, not taking antidepressants and tranquilizers, being married or passage of at least one year of their husband's death, not having experienced major stressors (death of first-degree relatives, divorce, etc.) during the last six months, not being vegetarian, not having history of allergy to herbal medications, and no history of estrogen-receptor positive cancers in participants or their first-degree relatives.

The exclusion criteria included consuming phytoestrogen foods for three consecutive days, unwillingness to continue cooperation and any unknown side effects during the study.

3.3. Setting and Data Collection

We included patients referred to the health centers of medical sciences universities in Tehran, Iran, from 2 May 2018 to 1 February 2019. Questionnaires and information forms were used, and the validity of the research tool was confirmed using content validity and test-retest reliability with a correlation coefficient of 94%. The first questionnaire included demographic data, menstrual history, pregnancy history, physical activity, frequency and severity of hot flashes, and methods used to treat hot flashes; this questionnaire was completed before beginning the treatment. The second questionnaire included the patients' activities during the previous week, including sports, unpleasant life events, and the methods used to treat hot flashes; this questionnaire was completed by the researchers at the end of each week. The third questionnaire assessed the severity of hot flashes experienced by participants using the Visual Analog Scale (VAS) at the end of each week. The first information form was filled out by the participants and included such information as daily food consumption from two weeks before starting the treatment until the end of the study. The participants were asked to avoid foods containing phytoestrogens during the study days. The second information form contained frequency and severity of hot flashes on a daily basis, and was filled out by the participants from two weeks before starting the treatment until the end of the study. Forms were collected at the end of each week. A Weighting Scale (Seca, Iran) and metal tape (made in Italy) were used to measure weight and height, respectively. The rigid metal tape was used so that climatic conditions would not affect it. The reliability of the scale was initially measured using a two-kg weight and was calibrated using the same weight after every ten measurements.

3.4. Intervention

The aniseeds (seeds of *P. anisum*) were purchased from herb shops in Tehran (herbarium code: SBMU-8207) and identified in our laboratory. The seeds were milled by electrical grinder and extracted by 96% ethanol (Maceration method $\times 3$). The solvent was evaporated at 40°C, and the waxy extract was mixed by corn starch. The mixed powder was filled in capsules (size 000). The placebos were prepared by starch in same capsules.

After a two-week control, both groups were matched considering such variables as age, duration of amenorrhea, starting time of hot flashes, as well as frequency and severity of hot flashes. Since the study was double-blind, the medicines were coded by a fellow pharmacist such that neither the researcher nor the participants were aware of the capsule content. The group receiving *P. anisum* took

capsules containing 330 mg *P. anisum* extract, and the placebo group took capsules containing 330 mg starch. All capsules looked similar. The participants took capsules for eight weeks, three times a day. To study the recurrence of hot flashes, the participants were followed up for four weeks after discontinuing the medication.

3.5. Statistical Analysis

The data were analyzed using SPSS version 21. The intra-group average of frequency and severity scores were compared for primary and secondary outcomes using repeated measures analysis of variance (ANOVA), and independent *t*-test was used to compare the scores between the two groups.

4. Results

In this study, 72 postmenopausal women were randomly assigned into two equal groups of experimental and control ($n = 36$ each) (Table 1). To remove the effect of confounding variables, both groups were matched in terms of duration of amenorrhea and frequency and severity of hot flashes. As Table 1 shows, the demographic characteristics were similar in both groups.

The frequencies of hot flashes during the study are presented in Table 2. The *t*-test showed that the mean frequency of hot flashes was similar in both groups before the treatment, but there were significant differences in anisum groups from the first week of treatment (7.89) to the eight week (1.04) and the follow-up period (4.21) ($P = 0.001$). There was no significant reduction in the control group ($P = 0.75$). According to the results of the repeated measure ANOVA, while there was a significant difference between the mean frequency of hot flashes during the treatment and follow-up period in the experimental group ($P < 0.001$), the difference was not significant in the control group.

Table 3 shows the severity of hot flashes in both groups. The results of Mann-Whitney U test showed that these differences were significant in the *P. anisum* group ($P = 0.001$). Also, during the eight weeks of treatment, four patients in the *P. anisum* group experienced spotting. There is no harm or unintended effects in any of the groups. The consort chart and diagram are shown Figure 1.

5. Discussion

According to the results of this study, *P. anisum* reduced the frequency and severity of hot flashes. Also, due to the effects of its phytoestrogens and the herbal medicine, it

Table 1. The Distribution of Research Samples in Terms of Demographic-Obstetric Characteristics in *Pimpinella anisum* and Control Groups ^a

Variables	<i>Pimpinella anisum</i> (n = 36)	Control (n = 36)	P-Value
Age (y)	52.93 ± 3.38	52.56 ± 3.39	0.29
BMI	23.31 ± 3.66	22.22 ± 2.82	0.44
Spouse's career			0.33
Businessman	20 (55.5)	29 (72.7)	
Employee	7 (19.4)	4 (11.2)	
Worker	9 (25.1)	6 (16.6)	
Level of education			0.09
Illiterate	11 (30.5)	12 (23.3)	
Primary	16 (44.4)	17 (47.2)	
Secondary	5 (14.1)	3 (8.3)	
High school or higher	4 (11.0)	4 (11.2)	
Residence			0.19
Private	18 (50)	18 (50)	
Rental	16 (44.4)	14 (38.8)	
Relatives	2 (5.6)	4 (11.2)	
Parity	3.3 ± 0.4	3.8 ± 0.9	0.09
Age at menarche	12.8 ± 0.3	13.2 ± 0.5	0.33
Time from last menstrual period (y)	1.2 ± 0.3	1.7 ± 0.7	0.24
Living child	3.2 ± 1.2	3.5 ± 0.9	0.61

^a Values are expressed as mean ± SD or No. (%).**Table 2.** Comparing the Frequency of Hot Flashes Before, During, and After the Treatment in the *Pimpinella anisum* and Control Groups ^a

Time of Treatment	Groups		P-Value
	<i>Pimpinella anisum</i> (n = 36)	Control (n = 36)	
Before the therapy	7.89 ± 5.67	6.86 ± 3.15	NS
1st week	4.70 ± 3.61	6.89 ± 3.31	0.002
2nd week	4.17 ± 4.51	6.85 ± 3.28	0.001
3rd week	4.16 ± 2.42	6.82 ± 3.26	0.001
4nd week	2.82 ± 2.30	6.81 ± 3.25	0.001
5nd week	2.33 ± 2.10	6.77 ± 3.28	0.001
6nd week	1.92 ± 1.80	6.79 ± 3.24	0.001
7nd week	1.48 ± 1.60	6.91 ± 3.30	0.002
8nd week	1.04 ± 1.24	6.73 ± 3.22	0.001
1st week of follow-up	1.23 ± 1.31	6.83 ± 2.98	0.001
2nd week of follow-up	1.44 ± 1.18	6.71 ± 3.32	0.001
3nd week of follow-up	3.76 ± 1.75	6.85 ± 3.26	0.001
4nd week of follow-up	4.21 ± 2.03	6.78 ± 3.22	0.001
Test result over time	P = 0.001	P = 0.75	

^a Values are expressed as mean ± SD.

Table 3. Comparing the Severity of Hot Flashes in the Two Groups Before the Treatment, During the Treatment, and After the Follow-Up Period Based on the Pain Ruler Scale ^a

Groups and Hot Flash Severity	Before the Treatment	After the Treatment	After the Follow-Up Period	P-Value
<i>Pimpinella anisum</i>				0.001
Mild	10 (27.8)	32 (88.9)	26 (72.2)	
Moderate	20 (55.5)	4 (11.1)	10 (28.8)	
Severe	6 (16.7)	0 (0)	0 (0)	
Total	36 (100)	36 (100)	36 (100)	
Control				NS
Mild	7 (19.4)	8 (22.2)	10 (27.8)	
Moderate	25 (69.9)	23 (63.9)	21 (58.3)	
Severe	4 (11)	5 (13.9)	5 (13.9)	
Total	36 (100)	36 (100)	36 (100)	

^a Values are expressed as or No. (%).

prevented the recurrence after four weeks of discontinuing the medication. Several studies on the effect of phytoestrogenic plants, like licorice have shown that these herbs had alleviating effects on heart diseases, breast and endometrial cancers, and osteoporosis, and they relieved menopausal symptoms, especially hot flashes (18-21), and improved memory and sleep patterns (24). Nahidi et al. reported the efficacy of *P. anisum* in reducing the frequency and severity of hot flashes among women in Ghazvin, Iran (20, 21). One of the strong points of the present study was the duration of treatment (eight weeks), which was twice the duration of the study by Nahidi et al. We also observed the frequency and severity of hot flashes declined until two weeks after discontinuing the medication, which indicates how long the medication can be effective. Nahidi et al. reported the same results (18, 20).

In another study, Nahidi et al. also reported the phytoestrogenic effect of licorice in reducing frequency and severity of hot flashes (18, 19). Mirabi and Mojab studied the effect of valerian on hot flashes, and the results showed a significant difference in the pre-and post-valerian treatment phases (24). In a study by Ye et al., a daily supplement of 84 or 126 mg soybean isoflavones improved menopausal symptoms (25). Heyerick et al. cited in Aghamiri et al. studied the effect of phytoestrogenic plant hop on hot flashes; their results were in line with ours (26). A relevant systematic review and meta-analysis on isoflavones clarified the effect of soybean isoflavones on the frequency and severity of hot flashes (27).

The results of the present study on reducing the frequency and severity of hot flashes were similar to the results of Farzaneh et al., who investigated the efficacy of evening primrose with placebo in improvement of menopausal hot flashes in 56 menopausal women. On the

other hand, percentage of improvement in social activities, relations with others, and sexuality was significantly superior to placebo group (28). Also, Ahsan and Mallick showed the efficacy of soy isoflavones on reducing the frequency and severity of hot flashes, which was in line with the results of the present study (29). However, Van Patten et al. did not find phytoestrogen soy to be effective on reducing the daily frequency of hot flashes in Canadian menopausal women with breast cancer (30). The results can be explained by the fact that cancer is stressful and aggravates hot flashes, and breast cancer can affect mental health and cause anxiety.

Most participants of the present study were suffering from moderate hot flashes while after the treatment and during the follow-up period, most of them had light hot flashes, and no severe hot flashes were reported. The same results were reported by Nahidi et al. investigating the effectiveness of licorice and *P. anisum* (18-21). Meanwhile, in the study by Taku et al., most postmenopausal women suffered from severe hot flashes before the treatment, while most of them had mild hot flashes, and some experienced severe hot flashes after the treatment (27).

A strength of our study is that we investigated the possibility of side effects and the lasting effects of *P. anisum* after discontinuing the medication in the four-week follow-up period. The results showed that the reduction in frequency and severity of hot flashes was significantly different between four-week follow-up period and before starting the treatment, and that the medication remained stable over these four weeks.

It should be mentioned that four samples reported spotting, all in *P. anisum* group, which might be associated with phytoestrogenic effect of *P. anisum* on endometrial wall. So, the causes of spotting were evaluated, and since

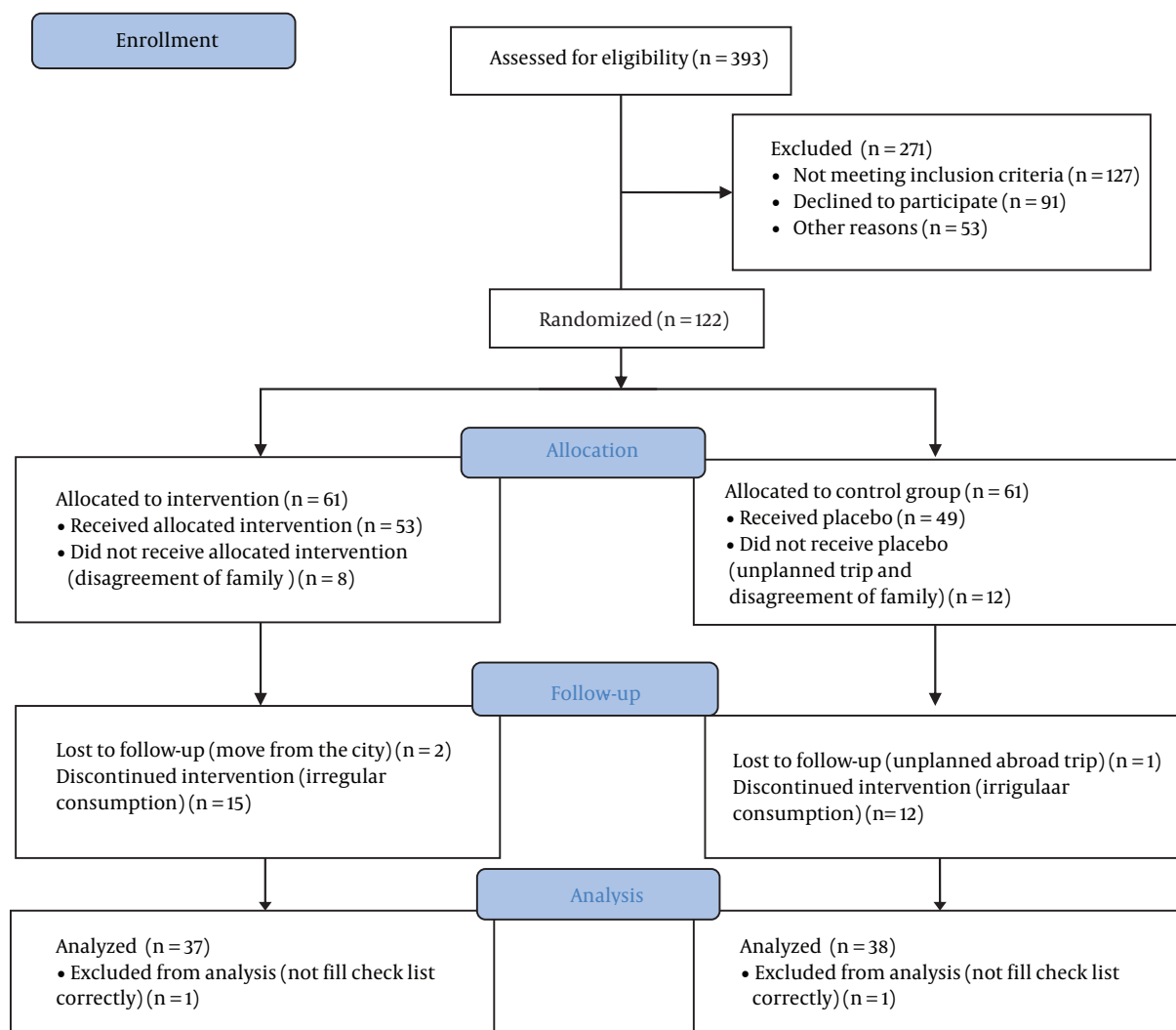


Figure 1. CONSORT 2010 flow diagram

there was no structural disorder, the dosage of *P. anisum* was reduced.

In our study, no side effects were reported, and most of the participants expressed their satisfaction with reduction of pain and burning during intercourse, which might be due to *P. anisum* phytoestrogens. We precisely evaluated and closely controlled foods containing phytoestrogens that could affect *P. anisum* effectiveness during the treatment and in the follow-up weeks. We also excluded the patients who had consumed phytoestrogen-rich foods for three consecutive days. The main limitation of this study was that we did not assess sterogen serum level of participants at the beginning and end of the survey.

5.1. Conclusions

Pimpinella anisum is an effective herbal medicine on reducing the severity and frequency of hot flashes, and it is a simple, non-invasive, safe, and effective treatment for post-menopausal women. Hence, it is recommended to prescribe this medicine in different forms and inform post-menopausal women about different treatments and their advantages and side effects so that they can freely choose the type of therapy.

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Footnotes

Authors' Contribution: The idea and design of this research was belong to Fatemeh Nahidi, sampleing and data collection were done by Elham Zare, pharmacological act and responsibility was on Faraz Mojab and ststistical analysis was held by Hamid Alavi Majd. Preparing and editing the manuscript were done by Elham Zare.

Clinical Trial Registration Code: IRCT code of this study is IRCT201103284317N4 (Link: <https://en.irct.ir/trial/4583>).

Conflict of Interests: Fatemeh Nahidi, Elham Zarem Faraz Mojab and Hamid Alavi Majd declare that they have no conflict of interest.

Data Reproducibility: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: It was accepted in 18th research council of Pharmacological Sciences Research Center by MP/835/2011) from the Ethics Committee of Shahid Beheshti University of Medical Sciences, and it complies with the statements of the Declaration of Helsinki (Code: 5695-114-01-87).

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Informed Consent: Informed consent was obtained from all subjects and a parent and/or legal guardian for vulnerable population.

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