Research Journal of Pharmacognosy (RJP) 10(1), 2023: 15–22
Received: 20 May 2022
Final revision: 1 Aug
Accepted: 13 Sep 2022
Published online: 26 Sep 2022
DOI: 10.22127/rjp.2022.328371.1839

Original article

Fennel-Lemon Balm Syrup for Alleviating Hot Flash in Post-Menopausal Women, a Pilot Study

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Abstract

Background and objectives: Hot flash is one of the most common problems in post-menopausal women. The usual treatment is hormone therapy with estrogen and progesterone, which presents side effects such as heart attack, cancer, and depression. In Iranian traditional medicine, some prescriptions have been recommended for treatment of hot flash; in the present study, a syrup was formulated based on traditional medicine and the efficacy in hot flash was evaluated in a pilot study in post-menopausal women. **Methods:** *Foeniculum vulgare* (fennel) and *Melissa officinalis* (lemon balm) were used for preparing the syrup. Physicochemical and microbial quality control tests were performed and the syrup was standardized based on rosmarinic acid and total phenolics content. The effect in post-menopausal women was evaluated in a pilot study with Carpenter Hot Flash Related Daily Interference Scale questionnaire. **Results:** The results of the quality control and accelerated stability tests after six months were in agreement with the acceptance criteria. The pH, density, viscosity, dry residue, total phenolics and rosmarinic acid contents were 5.29, 1.12 g/cm^3, 42.15 cP, 43.43, 4 mg/mL (as pyrogallol) and 1.28 mg/mL, respectively. In the pilot study, the number and intensity of hot flash decreased ($p<0.05$); however, there were no significant differences between the number and intensity of night sweating before and after the intervention ($p>0.05$). **Conclusion:** Considering the promising effect of the formulated syrup on hot flash and the acceptable quality and stability of the product, it can be suggested in larger clinical trials for confirming the efficacy.

Keywords: *Foeniculum vulgare*; hot flash; HPLC; *Melissa officinalis*; menopause

Citation: Tansaz M, Faridi N, Hajimehdipoor H, Ara L, Keramatian B, Hamzeloo-Moghadam M. Fennel-lemon balm syrup for alleviating hot flash in post-menopausal women, a pilot study. Res J Pharmacogn. 2023; 10(1): 15–22.

Introduction

Permanent cessation of menstruation, the end of the reproductive years of a woman, is known as natural menopause which is the result of natural loss of ovarian follicular function. There will be also changes in neuroendocrine and immunology systems [1]. The predominant symptoms are hot flash and night sweats [2]. Hot flash improves over time but 10-15% of post-menopause women experience moderate to severe symptoms for 10 years or more. It is not very clear what causes hot

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flash but the hypothalamus and the related thermoregulatory zone are involved. With loss of estrogen this zone is narrowed and by using estrogen it widens. Also, neurokinin-B receptors are under research for regulating the temperature and inhibiting hot flash [3]. During hot flash, the patient experiences intense warmth, sweating in the face, neck and chest, flushing, and chills. The duration is about one to five minutes. Sometimes, hot flash lasts even for an hour [4]. Due to peripheral vasodilation, the temperature and blood flow of the skin increase in the face, arms, chest, abdomen, back, and legs. Before occurrence of hot flash, the temperature of the core increases likely due to augmented metabolic rate and decreased vasoconstriction. There is also an increase in sweating [5].

Fennel (*Foeniculun vulgare* Mill., Apiaceae family) and lemon balm (*Melissa officinalis* L., Lamiaceae) are well-known plants in human history. They have been used to alleviate symptoms of diseases especially in women. In this regard, fennel is a more familiar herbal remedy. Recently, much research has been focused on human studies about these two plants and their role in overcoming gynecological diseases; however, hot flash has not been covered in this field. A combination of lemon balm and fennel has been recommended in Iranian traditional medicine (ITM) references [6] which is still recommended today by ITM specialists to women with some gynecological disorders including hot flash. The focus of the present study was to provide a standardized modern dosage form of the recommended mixture for convenient use in patients with hot flash. The efficacy of the product was also evaluated in a pilot study.

Material and Methods

Ethical considerations

The research followed the guidelines of the Declaration of Helsinki for humans and was approved by the ethics committee of Shahid Beheshti University of medical Sciences (code: IR.SBMU.RETECH.REC.1398.697). This study was registered at Iranian Registry of clinical trials (IRCT20200112046087N4). Informed consent was obtained from the participants of the study.

Chemicals

HPLC grade ethanol (Duksun, South Korea), 2-propanol (analytical grade), O-phosphoric acid (analytical grade) were purchased from Merck (Germany). Potassium sorbate and the standard of rosmarinic acid were prepared from Sigma-Aldrich (USA).

Plant material

Fennel fruits (*Foeniculun vulgare* Mill.) and lemon balm leaves (*Melissa officinalis* L.) were provided from Tehran local market and the identity was confirmed by botanists at the Herbarium of Traditional Medicine and Matreia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences. Voucher samples were deposited at TMRC Herbarium for future reference (HMS-547 and HMS-546 for *Foeniculum vulgare* and *Melissa officinalis*, respectively).

Quality control assessment of ingredients

Quality control assessment of the syrup ingredients were evaluated according to the monographs of Iranian herbal pharmacopeia (IHP) [7].

Preparation of the syrup

Fennel fruits were ground by mill and lemon balm leaves were crushed by hand. They were mixed in equal amounts according to the traditional reference [6], then water was added to the plants; the mixture was heated to boiling and filtered afterwards. The final condensed syrup contained 40% sucrose and 0.2% potassium sorbate as the preservative. The final concentration was adjusted according to the traditional reference equal to 0.2 g/mL of dried powder of fennel and lemon balm each.

Quality control assessment of the syrup

Appearance, pH, density, viscosity, dry residue, cap locking, crystallization and the temperature stability were evaluated. Also, the content of rosmarinic acid as a marker and the total phenolic contents were measured [8]. Microbial content was evaluated according to British Pharmacopea protocols to monitor the microbial content [9].

Accelerated stability tests

Accelerated stability tests were conducted according to ICH guidelines [10] for the syrup at the time of production and on the third and sixth month from production at 40 °C and 75% humidity.

Total phenolics content

Two mL of the herbal syrup was adjusted to 50 mL by distilled water. To measure the total phenolics content, 400 µL of this solution was transferred into a 5 mL flask; 200 µL of Folin-Ciocalteu reagent and 2 mL of water were added afterwards. Finally, the volume was set to 5 mL with aqueous sodium carbonate 29%. The mixture was left in the dark for 30 minutes. The absorbance was recorded at 760 nm by ELISA reader with distilled water as the blank [11].

Total phenolics content of the syrup was calculated using the calibration curve of pyrogallol. To draw the pyrogallol calibration curve, solutions of pyrogallol in distilled water (0.25, 0.125, 0.025, 0.0312 mg/mL) were used and the curve was plotted.

Rosmarinic acid content

Sample preparation: Ten mL of the syrup was adjusted to 100 mL with ethanol: water (60:40) as the solvent; then, 2.5 mL of this solution was set to the volume of 50 mL. The standard solution of rosmarinic acid (0.1 mg/mL) was also prepared with the same solvent.

An Agilent Technologies equipped with a vacuum degasser, auto-sampler and a UV detector high performance liquid chromatography (HPLC) system was used. An ACE C_{18} column (250 × 4.6 mm, 5 µm) was maintained at 40 °C. UV spectra were collected at 330 nm for chromatograms [12]. The mobile phase consisted of acetonitrile and phosphoric acid (0.085%) in a gradient mode (Table 1). The flow rate was 1.0 mL/min and the injection volume was 20 µL. The retention time and UV spectra of rosmarinic acid reference standard were used to confirm the chromatographic peak of rosmarinic acid in the sample. The calibration curve of rosmarinic acid was used for quantization.

Table 1. Mobile phase program for analysis of rosmarinic acid in the herbal syrup

Time (min)	Phosphoric acid (%)	Acetonitrile (%)
0	84	16
10	82	18
25	78	22
26	10	90
29	10	90
30	84	16
34	84	16

Pilot study

Study design

The design, process, and possible outcomes were explained to ten women in the age of forty-five to sixty who complained of hot flash and met the inclusion criteria; they completed the informed consent. A physician did the examinations and history taking. Each person was supervised for four weeks without receiving medication. Then, the symptoms were evaluated qualitatively and quantitatively by Carpenter Hot Flash Related Daily Interference Scale questionnaire [13]. Afterwards, the patients were given the herbal syrup one tablespoon twice daily for four weeks. The individual symptoms were re-evaluated by the same questionnaire 15 days post study. During the study, the patients were followed by telephone every week and were examined for the severity and duration of symptoms, as well as possible side effects and how the medication was consumed. If complaints were annoying to the patient, she would be excluded from the study. At the end, the results of the before and after questionnaires were statistically compared and analyzed.

Inclusion criteria

- Absence of menstruation during the last 12 months
- Complaining of hot flash
- Not taking anticoagulants
- No history of cardiovascular disease, diabetes, hypertension, neurological diseases and cancer
- No history of ovarian resection (unilateral or bilateral), removal of the uterus
- Not applying cupping, acupuncture and medication, especially hormonal drugs during the study

Exclusion criteria

- Dissatisfaction
- Start of disease or infection (cancer of the breast, ovary, uterus, or hormone-sensitive diseases such as endometriosis or uterine fibroids)
- Self-medication for hot flash such as clonidine, methyl dopa, bellergal
- Taking herbal medicine or special diet to treat hot flash
- Violation of the inclusion criteria

Statistical analysis

The results extracted from the questionnaires before and after the intervention were compared by non-parametric Wilcoxon signed-rank test; p value level of 0.05 was considered as the significance level.

Results and Discussion

The results of quality control assessment of the ingredients are presented in Table 2. The results assured the quality of the herbal material for preparing the final syrup according to IHP.

The microbial quality control of the formulated syrup was within accepted limits of pharmacopeia. The syrup was brown in color with sweet taste and fennel-lemon balm smell.

Table 2. Quality control results of fennel and lemon balm

Sample	Test	Outcome (%)	Limit (%)
Fennel	Sulphated ash	9.4	NMT 10
	Foreign matter	2	NMT 2
	Acid insoluble ash	0.16	NMT 1.5
	Essential oil	1.6	-[a]
Lemon balm	Total ash	12	NMT 12
	Foreign matter	3	NMT 3
	Moisture content	8.4	NMT 12

a; not mentioned; NMT: not more than

The results of different timings for accelerated stability test are presented in Table 3. The total phenolics content was measured based on pyrogallol calibration curve at the beginning, the third and the sixth months ($y=4.2268+0.1082$, $R^2=0.9972$; $Y= 3.5768x+0.1023$, $R^2=0.9999$; $Y= 4.0618X+0.9938$, $R^2 = 0.9999$, respectively). Rosmarinic acid was detected as the marker in the accelerated stability analysis by HPLC. A sample chromatogram of standard rosmarinic acid and the herbal syrup at the sixth month has been presented in Figure 1.

Due to gastrointestinal problems one patient did not continue the study, so the results of 9 patients were analyzed. The time of last menstruation in patients are shown in Table 4. The most frequency was in patients who experienced their last menstruation between 1 to 5 years ago (40% of patients). None of the patients had a history of spotting and 90% had no chronic disease or thyroid problems and did not smoke. No breast mass was diagnosed in any of the patients.

Table 4. Time of last menstruation in patients

Number of patients	Time of last menstruation
Two (20%)	More than 5 years
Four (40%)	1 to 5 Years
Two (20%)	1 Year
Two (20%)	Less than 1 Year

Before taking the herbal syrup, 5 out of 9 patients (56.6%) had more than 5 hot flashes, 33% of patients had 3 to 5 hot flashes and only 11% of patients had 1 to 3 hot flashes. After the intervention, 44% reported hot flash more than 5 times and about 22% reported hot flash between 3 and 5 and 22% between 1 to 3 times. The condition of no patient worsened after the intervention, so the patient either reported a reduction in hot flash after the intervention, or at least their condition did not change (Table 5).

Four patients out of nine improved and five patients reported no change in the number of hot flashes. Wilcoxon test showed that the number of hot flash significantly reduced after the intervention. ($p = 0.045$).

Before taking the herbal syrup, 3 out of 9 patients had a severe condition, but none of them remained in a severe condition after the intervention. Moderate condition was reported by 33% of patients at the beginning of the study; however, at the end and after the intervention, the highest rate of 5 patients, equal to 55.6%, was reported for mild hot flash. The patients' condition either got better or at least did not change. The difference between the severity of hot flash before and after the intervention was statistically significant $p = 0.028$ and five patients reported improvement.

Table 3. Results of accelerated stability test of the herbal syrup

Tests	Results[a]		
	Start	3rd Month	6th Month
Appearance	Color: brown; taste: sweet; smell: mixed of fennel and lemon balm	Color: brown; taste: sweet; smell: mixed of fennel and lemon balm	Color: brown; taste: sweet; smell: mixed of fennel and lemon balm
pH	5.21	5.32	5.29
Density (g/cm^3)	1.10	1.12	1.12
Viscosity (cP)	50.40 cp	43.24 cp	42.15
Dry residue ± SD (%)	41.50±0.30	43.32±.20	43.43±0.10
Cap locking	None	None	None
Crystallization	None	None	None
Total phenolics content±SD **(mg/mL)**	3.9±0.1	4.0±0.2	4.0±0.1
Rosmarinic acid content±SD **(mg/mL)**	1.31±0.10	1.34±0.03	1.28±0.05

[a] Data are expressed as means ± SD; the stability results showed no significant differences after 6 months

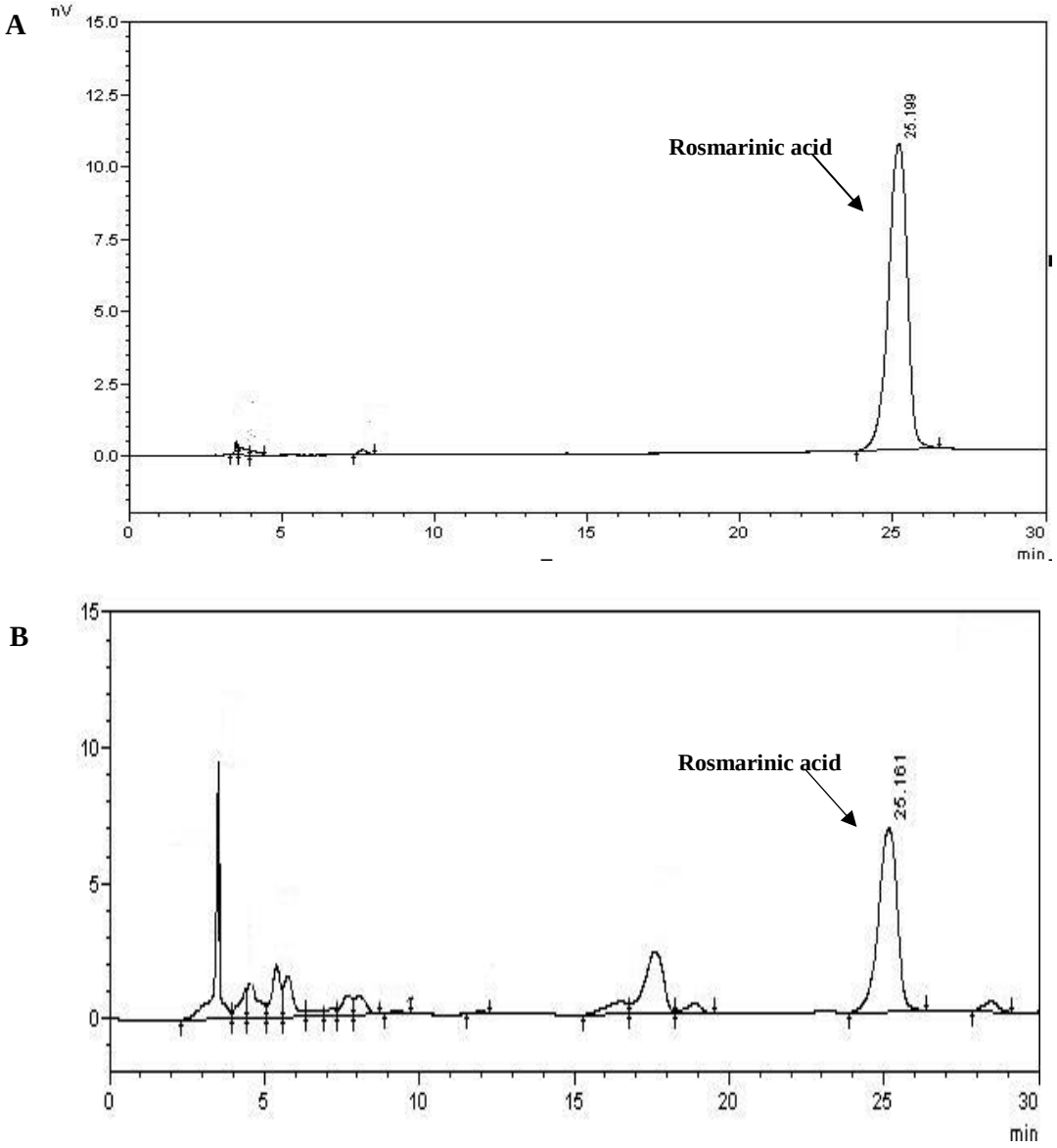

Figure 1. HPLC chromatogram of rosmarinic acid standard material (A) and the herbal syrup (B)

Table 5. Number and intensity of hot flash in patients

Number of hot flash	Before intervention	After intervention	Intensity of hot flash	Before intervention	After intervention
More than 5	56.6	44	**Severe**	33	0
3 to 5	33	22	**Moderate**	33	22
1 to 3	11	22	**Mild**	22	55.6
None	0	11	**No complaint**	11	22

The difference before and after the intervention was not significant (p = 0.08).

After taking the intervention, four out of nine patients reported improvement, four people did not change and condition in one person got worse, the change was not significant (p = 0.17).

Estrogenic medications are common treatments for hot flash of menopausal women [14]. In his article about fennel and anis in 1980, Puleo has mentioned fennel as an estrogenic plant. There are some studies relating to other clinical symptoms in post-menopausal women after using fennel. For example: evaluating the effect of fennel capsules vs placebo in a double-blind, randomized, placebo-controlled trial in 60 post-menopausal women resulted in borderline or significant improvement in patients with depression or anxiety [15]. Oral fennel did not

show promising results in a clinical study that was focused on improving the Maturation Vaginal Index and maturation values [16], but in another study with a vaginal cream of fennel 5%, the symptoms of vaginal atrophy in post-menopausal women improved [17], which may suggest the greater influence of topical use in case of vaginal atrophy. Fennel was the component of a triple herbal mixture which was given in different doses in menopausal women to evaluate the effects in 12 weeks. At the end of the study, the groups that had received a daily amount of 1000, 120, 60 mg of chamomile, fennel, and saffron, respectively showed significant improvement in physical, psychological and urogenital domains [18].

Daily consumption of 2 g of oral fennel powder in 80 post-menopausal women for 8 weeks resulted in significant improvement in menopausal symptoms regarding the Kupperman index and Hurlbert index of sexual desire. However, the levels of estradiol or the sexual desire did not change significantly [19]. In a somewhat similar study, the effects of fennel oil in soft capsules (100 mg fennel essential oil in each capsule) twice daily, was compared to placebo in 90 post-menopausal women. The group that received fennel capsules showed a significant decrease in the mean of Menopause Rating Scale (MRS) score [20]. A secondary analysis of 47 patients out of 60, who had finished a previous clinical trial with fennel and placebo, showed that after the study and a three-month follow up, there was a slight increase in body weight and fat distribution in patients in the fennel group but the difference in body weight, BMI, waist, and hip circumferences was not significant [21]. The effect of fennel on lipid profile of post-menopausal women was evaluated in a double blind, randomized and placebo-controlled study. Sixty women were enrolled and given either fennel capsules of 30 mg fennel oil, or placebo three times a day. At baseline and after three months of follow up, total blood cholesterol, cholesterol fractions, and triglycerides were evaluated. There was a little change in LDL-C, triglyceride and HDL-C in fennel group but with no significant difference [22].

Regarding the studies around lemon balm, in a randomized, double-blind, clinical trial, lemon balm with extract of fennel seeds was used to evaluate their effect on sleep problems of 60 post-menopausal women. The effects were compared to citalopram and to the placebo. The menopause-specific quality of life (MENQOL) questionnaire was used for evaluating the results. The improvement in sleep disturbance was significantly recorded for the treatment group which emphasized the positive effects of lemon balm and fennel in quality of life of post-menopausal women [23]. In another study, a mixture of lemon balm and valerian was given to the treatment group for sleep disturbances during menopause. Hundred women were enrolled in the study and received either the herbal treatment or placebo in two groups. The Pittsburgh Sleep Quality Index (PSQI) was used for assessment. Sleep problems significantly reduced in the treatment group after the intervention [24].

As discussed above, lemon balm and fennel have been used in different studies for alleviating some symptoms of menopause; however, hot flash has not been covered in this field. In our pilot study, the formulated syrup combination of fennel and lemon balm, showed to be efficient in reducing hot flash in post-menopausal women. The intensity and number of hot flash reduced significantly which is promising in alleviating this disturbing symptom in post-menopausal women. During the study, one of the patients reported gastrointestinal issues and did not continue the study, so analysis of the results are based on nine patients that started the study.

Fennel is known to be rich in phytoestrogens and lemon balm is famous for its calming effects. This combination might lead to the effects that were observed in the present study. The formulated syrup was assessed for its quality and stability. The quantified markers in the syrup along with appearance and quality measurements were promising and confirmed that the formulated syrup was of acceptable quality and was stable. Rosamarinic acid and the content of total phenolics did not change much during the accelerated tests. The appearance, pH, density, viscosity, dry residue, and other factors relating the quality of the syrup were acceptable after six months in the stability tests. Also, the microbial quality controls of the syrup were in line with pharmacopeia limits.

The combination of lemon balm and fennel formulation was based on a prescription from Iranian traditional medicine [6]. Nowadays, this combination is recommended by Iranian traditional medicine specialists to women with

some gynecological disorders mainly hot flash. The mixture is prepared as an infusion by the patient herself for each time of use (twice daily). However, with the ready to use modern pharmaceuticals, preparing and using traditional remedies seem uncomfortable to some patients. Formulating effective traditional formulations to modern pharmaceutical products can provide ease of access and tendency for use when prescribed. If herbal medications prove to be worthy and effective, formulating acceptable, convenient dosage forms will help patients to overcome symptoms that are not easily treated with modern medicines, in this case hot flash.

Conclusion

The combination of lemon balm and fennel as a standardized formulated syrup, presented suitable effects on hot flash in post-menopausal women; however, the syrup was not effective in decreasing the intensity and number of night sweating in post-menopausal women. Regarding the stability of the syrup, it is a proper formulation to be evaluated in larger clinical trials for confirming the efficacy.

Acknowledgments

The authors wish to thank the Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences for the financial support (Grant No. 20957).

Author contributions

Mojgan Tansaz was involved in conceptualization and supervision of the clinical parts; Najmeh Faridi, Leila Ara and Behnaz Keramatian contributed to the experimental parts; Homa Hajimehdipoor was involved in analyzing the data; Maryam Hamzeloo-Moghadam contributed to designing and supervision of the study, data analysis, and writing and revising the manuscript.

Declaration of interest

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

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Abbreviations

ITM: Iranian traditional medicine; PM: Persian medicine; IHP: Iranian herbal pharmacopeia; ICH: International Council for Harmonisation