The effect of Salvia officinalis extract on symptoms of flushing, night sweat, sleep disorders, and score of forgetfulness in postmenopausal women

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ABSTRACT

Background: Complications of hormone therapy (as replacement) during menopause prompted us to research on alternative therapies including herbal therapy in this regard. **Objectives:** The effect of Salvia officinalis extract on symptoms of flushing, night sweat, sleep disorders, and score of forgetfulness in postmenopausal women on Namazi Hospital Bone Density Center in Shiraz 2015. **Methods:** In a double-blind randomized controlled clinical trial, 66 postmenopausal women complaining of menopausal symptoms were divided into two groups of intervention and control, respectively. The intervention group received S. officinalis tablets (containing 100 mg S. officinalis extract), with a dose of three tablets a day for 3 months, while the control group received placebo tablets with the same prescription order. MRS (Menopause Rating Scale) and PSQI (Pittsburgh Sleep Quality Index) questionnaires were completed at the beginning and end of the study. The checklists of hot flushing and night sweating were completed a week before the intervention and at weeks 2, 4, 6, 8, 10, 12 during the intervention. Finally, the data were analyzed through $SPSS_{18}$ software, using paired t-test, ANOVA. A significant level of 5% was considered. **Results:** According to the paired t-test, the mean score of flushing, palpitation, sleeping disorders, muscle and joint aches, depression, nervousness, anxiety, and sexual desire and satisfaction significantly decreased by 1.6, 0.4, 1.6, 2.1, 1.4, 1.2, 1.6, and 0.8 units, respectively, in the intervention group compared to the control group ($P < 0.001$). Therefore, the mean score of PSQI significantly decreased by 3.8 units in the intervention group after the intervention (9.4 ± 3.7 vs 5.6 ± 1.9 ($P < 0.05$). **Conclusions:** Salvia extract improved menopausal symptoms such as flushing, night sweat, heart palpitations, muscle and joint pain, depression, anxiety, sleep disorders, and sexual desire.

Keywords: Flushing, menopause, Salvia officinalis extract, sleep, sweat

Access this article online

Quick Response Code:

Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_913_19

Introduction

Reduced level of estrogen in the menopause women leads to a wide range of symptoms. Hot flushes are the most common symptom of menopause.[1] Racial and cultural differences play an

important role in the incidence of flushing in eastern and western societies.[2] In the study, the prevalence of flushing was reported 46.4% and 41.2% in Spanish and American women and the prevalence of night sweat was 34.7% and 36.9%, respectively.[3] In a study done in Tehran, the prevalence of flushing and night sweat was reported 59.5% and 38.2%, respectively.[4] A study in gynecologic clinics at the Royal Women's Hospital, Melbourne has been shown in postmenopausal women forgetfulness and less satisfying memory than women before menopause.[5] Other studies have also referred to sleep problems, hot flashes, mood disorders, sexual dysfunction, weight gain, and cognitive decline in postmenopausal women.[6-8] Over the past decade, the use of complementary and alternative medicine (CAM) to treat female problems such as menopause, premenstrual syndrome, sexual disease has increased.[9-14] The standard treatment for menopause symptoms is a hormonal replacement.[15] The standard treatment for menopausal symptoms is hormone replacement therapy (7), which temporarily improves women's quality of life, but can pose serious risks over the years.[16] There are many options for managing menopausal symptoms when they affect the quality of life.[17] The researchers reported that other interventions other than HT should be considered.[18] Phytoestrogen is one of the alternative and supplement options. Phytoestrogens are plant compounds that have estrogenic activity.[19] Phytoestrogens can be found in a wide range of herbal products such as valerian, Black cohosh, chamomile, Hypericum, Licorice, Fennel, Soya, Red clover, and Salvia. Salvia officinalis has numerous common names. Some of the best-known are sage, common sage, garden sage, golden sage, kitchen sage, true sage, culinary sage, Dalmatian sage, and broadleaf sage. The specific epithet officinal refers to plants with a well-established medicinal or culinary value.[20] The phytoestrogen flavonoids present in this plant is used to reduce menopause symptoms.[21] There is a limitation of studies on the effectiveness of salvia in managing menopausal symptoms, as there are various studies on herbal medicine effects other than salvia on menopausal symptoms like black cohosh. Therefore, menopause is a turning point in the life of women, and if it is a physiological process and a general event, reducing estrogen secretion can cause many health problems. This physiological process has a number of effects that are harmful to one's life. As one of the potential effects of menopause and lowering sex hormones, are Complications of Menopausal symptoms and reduced quality of for women.[22,23]

Thus, obtaining accurate and reliable information from the practice of primary care physicians is one of the primary and essential needs of women in the premenopausal phase. Women need to know what awaits them and whether their experiences are normal or not. Proper lifestyle is the cornerstone of middle-aged women's health management programs. It can provide a basis for improving the quality of physical and mental performance during the following years of life.[24,25] Sanchez *et al.* found that as many as 80% of women aged 18–55 have lifestyle-related risk behaviors that are preventable.[26] It is also predicted that in 2020 noncommunicable lifestyle-related diseases will cause 7 out of 10 deaths in developing countries.[27] The present study aimed

to know the effect of Salvia officinalis extract on symptoms of flushing, night sweat, sleep disorders, and score of forgetfulness in postmenopausal women at Namazi Hospital Bone Density Center in Shiraz 2015.

Materials and Methods

The study is a double-blind randomized controlled clinical trial was carried out from July to November 2015, that approved by the ethics committee of shiraz university of medical sciences and proposal No is: 94-10255, ethic code: IR.SUMS.REC.1394.185). The population of this study consisted of all menopause women who referred to Namazi Hospital Bone Density Center affiliated to Shiraz University of Medical Sciences. Based on the Sadeghi *et al.* study in 2013 and the formula below, the sample size for each group is calculated 38. But, due to a financial constraint on the purchase of a new kit for 5 people, the sample size for each group was reduced to 33 people.[28] However, during the study, 2 participants in the interventional group and 5 patients in the placebo group were excluded from the study due to incomplete use of the pills, and finally, 59 patients completed the study [Figure 1]. Totally, 66 individuals were selected through purposive sampling technique and were divided into two groups using block permutation method. For example; group A, B as AABB, and another group of BABA, were named. Sampling continued until samples were completed.

The inclusion criteria were postmenopausal women who were willing to participate in the study, no history of taking any hormonal medicine, and no history of allergy to herbal medicines. The exclusion criteria were an allergic reaction to medication and a lack of interest in continuing participation.

$$n_1 = n_2 = 2 \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2 (\sigma_1^2 + \sigma_2^2)}{d^2}$$

$\sigma_1 = 4.7$

$\sigma_2 = 3.84$

$d = \mu_1 - \mu_2 = 2.78$

$a = 0.05$

$\beta = 0.2$

Before the intervention, obtaining the informed consent was done. The intervention group received S. officinal as tablets (containing 100 mg S. officinalis extract produced by Gol Daroo company in Isfahan), which was prescribed three tablets a day for 3 months, while the control group received placebo tablets (containing 100 mg starch produced by Shiraz Pharmacy University of Medical Science) with the same prescription order and size in a packed in black cover with a
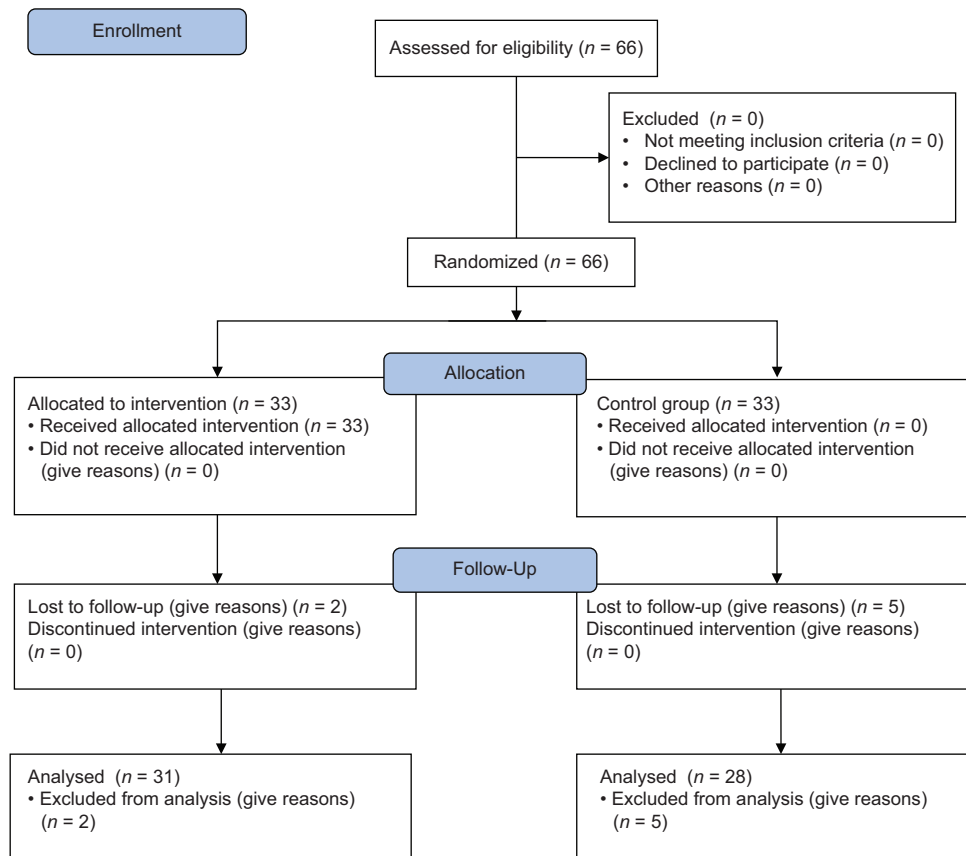
Figure 1: Consort Flow Diagram for sampling

code. The study was conducted as a double-blind study both researcher and patient. The following sections describe the questionnaires were completed by the women, and if needed, the research was made clear. Then, women completed an informed consent, demographic, MRS questionnaire, and Pittsburgh Sleep Quality Index (PSQI) questionnaire initially. Then, they were asked to complete the checklists regarding the symptoms of flushing and sweating (frequency, severity, duration) daily for about a week before the intervention and at weeks 2, 4, 6, 8, 10, 12 during the intervention. MRS and PSQI were refilled 3 months after the intervention. Menopause rating scale (MRS) consists of 11 menopause symptoms in three domains: Physical (4 items), psychological (4 questions), and genitourinary (3 questions). Questions are measured with a 5-point Likert scale from rating 1 (I do not have symptom) to 5 points (severe symptoms).

The total score is 11–55, and the higher the score, the more severe the symptoms. This tool was designed by Garage, and According to Heinemann, the MRS has internal consistency and a reliability coefficient 0.92 and Cronbach's alpha 0.81.[29] In Iranian studies, instrument validity was determined by the content validity method and Cronbach's alpha coefficient for measuring psychological symptoms (0.81) and physical signs (79.8%). Urinary symptoms were reported to be 78%, which is the basis of our study.[30] Pittsburgh Sleep Disorders Questionnaire (PQRS) was created in 1989 by Buysse *et al*. at the Pittsburgh Psychiatric

Institute.[31] The questionnaire has nine questions in its original form, but since the 5th question contains 10 subquestions, the entire questionnaire has 19 items which are graded on a 4-point Likert scale from 0 to 3. It can effectively evaluate sleeping by measuring seven domains: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. Scoring of the answers is based on a 0 to 3 scale, where 3 reflects the negative extreme on the Likert Scale. A global sum of "5" or greater indicates a "poor" sleeper. The sensitivity of the PSQI questionnaire was 89.6%, the specificity 86.5%, the validity of 88%, and the scientific reliability with Cronbach's score was 83%.[32] The validity of the Iranian version of the questionnaire was determined in the study of Hossein Ebadi, according to Montazeri and collegeouse in 2007 with a sensitivity of 90%, the specificity 87%, and Cronbach's score of 88%, which is the basis of this study.[33]

Statistical analysis

The data were analyzed through SPSS software. Before the intervention, ANOVA was applied to compare the mean score of MRS and PQRS between both groups and a paired *t*-test was used to compare the mean score before and after the intervention. Repeated measures ANOVA test was used to compare the frequency and severity of flushing and night sweating in both groups. Besides, $P < 0.05$ was considered statistically significant.

Results

Based on ANOVA test, mean age, menopause age, duration of menopause, body mass index (BMI), duration of marriage, number of parity, pregnancy, and children, abortion were $P = 0.747$, $P = 0.409$, $P = 419$, $P = 0.151$, $P = 0.069$, $P = 0.054$, $P = 0.079$, $P = 0.054$, and $P = 0.719$ in the intervention and control groups; therefore, they were homogeneous with no significant statistical difference ($P > 0.05$). Demographic characteristics are shown in [Table 1]. Before the intervention, mean score of PSQI ($P = 0.384$) and MRS ($P = 0.842$) showed no significant difference between both groups. The mean score of severity of flushing and night sweats a week before intervention ($P = 0.33$) and from 2 weeks (33.0) to 8 weeks after intervention ($P = 0.225$) showed no significant difference; it was significant at 10 ($P = 0.003$) and 12 ($P \leq 0.001$) weeks after the intervention compared to the control group. According to the paired *t*-test, the mean score of flushing, palpitation, sleeping disorders, muscle and joint aches, depression, nervousness, anxiety, and sexual desire and satisfaction significantly decreased by 1.6, 0.4, 1.6, 2.1, 1.4, 1.2, 1.6, and 0.8 units, respectively, in the intervention group compared to the control group. The most and least decrease in menopausal symptoms has belonged to joint and muscular discomfort, which decreased by about 1.2 units (2.8 ± 1.3 before and 0.7 ± 0.6 after intervention). Besides, using a paired *t*-test, the mean of forgetfulness score after intervention was reduced in comparison with before intervention in the salivary group, which was statistically significant ($P < 0.001$), but in the control group, there was no significant difference ($P = 0.326$). [Tables 2 and 3]. Repeated measures ANOVA revealed no significant difference in flushing frequency and severity between both groups before and at 2, 4, 6, 8 weeks after the intervention. However, the difference was significant at 10 and 12 weeks after the intervention. No significant difference was reported in night sweating between both groups before and at 2, 4, 6, 8 weeks after the intervention. However, the difference was significant at 10 and 12 weeks after the intervention ($P < 0.001$) [Table 4]. Regarding the paired *t*-test, the mean score of PSQI significantly decreased by 3.8 units in the intervention group after the intervention ($P < 0.05$) [Table 5].

Table 1: Demographic characteristics of the sociaty reserch

Variable	n (%)		PV
	Salvia officinalis extract	Control	
Education			0.783
Illiterate	6 (19.4)	4 (14.8)	
Elementary	12 (38.7)	13 (48.1)	
Secondary school	4 (12.9)	4 (14.8)	
Diploma	8 (25.8)	5 (18.5)	
Academic	1 (3.2)	1 (3.7)	
Total	31 (100)	27 (100)	
Occupation			
Employed	2 (6.5)	2 (7.4)	0.604
Housewife	29 (93.5)	25 (92.6)	

Discussion

The effect of Salvia was studied on physical, psychological, and urogenital symptoms for 12 weeks. Finally, it was shown that Salvia significantly improved this symptoms (except dementia, urinary incontinence, and vaginal dryness) compared to the control group. Plants containing phytoestrogens (estrogen-like compounds) have a special place among plants, which are advised to treat menopausal symptoms. Phytoestrogens (plant-based compounds) are non-steroidal plants[34,35] containing polyphenolic compounds with 1-3 hydroxyl group (OH) similar to the hydroxyl group in phenolic estrogen circle.[36] Thus, a low level of estrogen after menopause is relatively compensated by phytoestrogens to improve the symptoms of menopause. Accurate pathophysiology of hot flushes is complicated and unknown. However, there is the premise that the region of temperature regulation is narrowed in women suffering from hot flushes which causes the increase of sensitivity for temperature change and hot flashes.[37] Noradrenaline plays a leading role through adrenergic $\alpha 2$ receptors in regulating the temperature which causes vascular vasodilation and loss of heat and decline of central temperature. Gonadal steroids regulate the central noradrenaline[38]; there is the hypothesis that the decline of sexual hormones causes an increase in hypothalamus noradrenaline and stimulation of LHRH secretion for gonadotropins secretion. At the same time, increase in hypothalamus noradrenaline (not its peripheral metabolites) at the vicinity of the center of temperature regulation in LHRH neurons gives rise to hot flushes.[39] In the study is effective and another study is not effective in declining the menopause symptoms.[40] In the study in Iran, Perforate St John's-wort and chasteberry flower, which contain phytoestrogen, decrease the menopausal symptoms and hot flushes.[2] In this study, the post-treatment score of forgetting after the invention as compared with pre-treatment has decreased 1 unit in common sage groups and this reduction of forgetting score was statistically significant. However, it was not significant when compared with the control group. This has been known well that stopping of ovary estrogen can affect the cognitive performance in women; in contrast, treatment with hormone and phytoestrogen can minimize the cognitive changes in menopausal women. The role of estrogen in cognitive performance is associated with the expansion of estrogen receptors in some regions of the brain related to learning and memory such as the hippocampus and basal forebrain.

In the study, common sage increased the memory and temper and this effect was applied through inhibition of acetylcholinesterase.[41] Similarly, Salvia has a protecting effect against toxic effects of $A\beta$ in the brain neurons. Rosmarinic acid in the Salvia has antioxidant and anti-apoptosis effects and protects the neurons against the toxicity of $A\beta$.[42] Also, in the study, Salvia enhanced the memory.[43] Study findings showed that the average of post-intervention sleep score in common sage groups has been decreased 3.8 unit when compared with preintervention and this decline of sleep score was statistically significant. However, in the control group, after treatment,

Table 2: Comparison of the average menopausal rating scale (MRS) before and after between the intervention and control groups				
Variable		Mean±SD		*P***
		Intervention Group	Group control	
Hot flashes - night sweats	Before	1.46±1.84	1.62±1.64	0.588
	After	0.37±0.16	1.58±1 1.7	<0.001
P*		<0.001	0.326	
Heart discomfort	Before	1.13±4 0.7	1.36±2 1.3	0.197
	After	0.58±0.26	1.38±1.29	<0.001
P*		0.001	0.326	
Sleep problems	Before	1.49±0 1.9	1.10±2.39	0.344
	After	0.53±0.29	1.06±6 2.3	<0.001
P*		<0.001	0.326	
Joint and muscular discomfort	Before	1.31±2.77	1.04±2.96	0.763
	After	0.63±0.74	1.07±2.96	<0.001
P*		<0.001	0.998	
Depressive mood	Before	1.37±2.00	1.29±2.04	0.953
	After	0.71±5 0.6	1.23±2.04	<0.001
P*		<0.001	1	
Irritability	Before	1.32±1.84	1.18±1.86	0.382
	After	0.67±0.58	1.19±1.82	<0.001
P*		<0.001	0.573	
Anxiety	Before	1.36±2.13	1.31±2.00	0.925
	After	0.72±0.52	1.35±1.96	<0.001
P*		<0.001	0.573	
Physical and mental exhaustion	Before	1.41±2.23	1.43±1.46	0.088
	After	1.16±0.89	1.43±1.39	0.634
P*		<0.001	0.326	
Sexual problems	Before	1.19±1.81	1.58±2.14	0.619
	After	0.97±0.87	2.11±1.57	0.002
P*		<0.001	0.326	
Urinary incontinence	Before	1.31±1.13	1.49±1.07	0.501
	After	0.81±1.11	1.07±1.49	0.369
P*		0.016	1	
Dryness of vagina	Before	1.25±1.19	1.47±1.36	0.83
	After	1.06±1.21	1.36±1.47	0.7
P*		0.103	1	

*Paired sample *t*-test, **Independent *t* test

Table 3: Comparison of the impact of sleep before and after the intervention in the intervention and control groups based on PSQI questionnaires			
Group	Mean±SD		*P**
	Intervention Group	Group control	
Before intervention	3.71±9.35	4.19±10.64	0.384
After intervention	1.94±5.61	4.16±10.57	<0.001
P**	<0.001	0.573	

*Independent *t* test, **Paired sample *t*-test

the sleep score average remained the same. The studies show that isoflavonoids decrease insomnia among menopausal women.[44] In a clinical trial in the Switzerland research on menopausal symptoms was showed the intensity and frequency of hot flushes for two months was evaluated. Other variables including symptom in menopause scale (MRS) were evaluated at the beginning and after 2 months. The results showed that the average total number of flushing and symptoms of MRS scale was decreased weekly from 1 to 8 weeks significantly. A study

concluded that Salvia has clinical value in the treatment of hot flushes and associated menopausal symptoms. The results of this study are similar to ours, but there is a difference in the duration and dosage of treatment.[28] In another study, the common sage had no effect on the inhibition of the reuptake of serotonin and acetylcholinesterase[37]; therefore, understanding the impact of mechanisms of Salvia calls for further studies.

The limitation of this study was the preparation of Salvia tablets (Salvia extract) and placebo in exactly the same color as possible. Since Salvia was used in herbal supplement, a comparative study of herbal supplement and synthetic drugs is suggested to improve the symptoms of menopause.

Conclusion

The study showed the influence of Salvia extract on menopausal symptoms such as flushing, night sweats, palpitations, muscle and joint pain, depression, anxiety, sleep disorders, and sexual

Table 4: Mean number and severity of hot flushes before and after the intervention between two groups

The number and severity of hot flashes Time	Intervention Group Mean±SD		Group control Mean±SD		P* Mean±SD	
	Freguency	Severity	Freguency	Severity	Freguency	Severity
A week before the intervention	2.04±2.79	1.21±2.17	1.81±2.00	1.37±2.46	0.243	0.669
Week 2 intervention	2.02±2.71	1.19±2.20	1.81±2.00	1.37±2.46	0.292	0.716
Week 4 intervention	1.75±2.43	1.09±2.33	1.81±2.00	1.35±2.50	0.597	0.839
Week 6 intervention	1.47±2.04	1.04±2.53	1.72±1.86	1.26±2.61	0.873	0.899
Week 8 intervention	0.95±1.21	0.89±2.97	1.73±1.89	1.26±2.61	0.195	0.401
Week 10 intervention	0.58±0.50	0.81±3.40	1.68±1.82	1.25±2.68	<0.001	0.007
Week 12 intervention	0.55±0.32	0.81±3.60	1.68±1.82	1.25±2.64	<0.001	<0.001
P**	<0.001	0.001	0.075	0.115		

*Independent *t* test, **Paired sample *t*-test

Table 5: Comparison of the severity of night sweats before and after the intervention between two groups

Group	Mean±SD		P*
	Intervention Group	Group control	
A week before the intervention	1.17±1.57	1.17±1.11	0.313
Week 2	1.17±1.57	1.17±1.11	0.313
Week 4	1.07±0 1.4	1.12±1.07	0.55
Week 6	0.93±1.03	1.17±1.04	0.991
Week 8	0.77±0.57	1.12±1.00	0.225
Week 10	0.55±0.20	1.11±0.96	0.003
Week 12	0.37±0.07	1.17±1.04	<0.001
P**	<0.001	0.427	

*Independent *t* test, **Paired sample *t*-test

desire. Expansive use of this plant can be suggested in case it is confirmed in further investigations. Regarding the effect of Salvia extract on some menopausal symptoms, it is suggested that multiple chemical compounds of this plant can be isolated and its active compounds are investigated in studies similar to the present study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

There are no conflicts of interest.

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