

Effect of Fennel on the Health Status of Menopausal Women: A Systematic and Meta-analysis

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Objectives: The aim of the present study is the systematic and critical investigation of the effectiveness of fennel on the climacteric symptoms among menopausal females.

Methods: A search of the trials studying the effect of fennel on menopausal females was conducted in 2017 using the MEDLINE and Scopus databases and the Cochrane Library with the following keywords: fennel, *Foeniculum vulgare*, and menopause.

Results: Fennel combined with officinalis is more effective in the attenuating of sleep disorders compared to Citalopram. The comparison of these two groups regarding the mean bone mineral density and bone mineral content ($P = 0.14$, $P = 0.504$); the total hip femoral ($P = 0.42$, $P = 0.66$); the trochanter ($P = 0.075$, $P = 0.07$); the intertrochanter ($P = 0.84$, $P = 0.93$); and the femoral neck ($P = 0.43$, $P = 0.64$) did not show any significant statistical differences; however, a statistically significant difference regarding the vasomotor symptoms ($P < 0.01$) was found. The other significant differences are related to the values of the total cholesterol ($P = 0.103$); low-density lipoprotein cholesterol, or LDL-C ($P = 0.104$); high-density lipoprotein cholesterol, or HDL-C ($P = 0.266$); triglyceride ($P = 0.679$); body weight ($P = 0.212$); body mass index ($P = 0.041$); waist and hip circumferences ($P = 0.365$); and fat distribution ($P = 0.337$) between the two groups. The standardized mean difference (SMD) values of sexual activity (SMD = 0.638; $P < 0.001$), and maturation value (SMD = 0.601; $P = 0.003$) are highly significant among the fennel-treated women compared with the placebo group.

Conclusions: According to the findings of the present study, fennel is important in the relieving of vasomotor symptoms, vaginal itching, dryness, dyspareunia, sexual function, sexual satisfaction, and sleep distribution. (**J Menopausal Med 2018;24:67-74**)

Key Words: Foeniculum · Health status · Menopause · Meta-analysis

Introduction

The menopause as a natural biological phenomenon experienced by all women¹⁻³ refers to the permanent cessation of the menstrual cycle as a result of ovarian dysfunction.⁴ The menopause is characterized by estrogen deficiency that is associated with the vaginal atrophy, bone loss, mood varia-

tions and hot flashes.⁵

One of the major causes of mortality and morbidity in elderly women is osteoporosis that imposes huge financial burden on the society.^{6,7} Among which, there are several complications following the use of chemical medications in treating the osteoporosis; for example, raloxifene that is associated with some adverse effects of vein thrombosis and

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pulmonary embolism.⁸ Reportedly, the menopause females frequently suffer from the psychological symptoms such as anxiety and depression⁹; in this regard, benzodiazepines and antidepressants have a wide therapeutic application for the mood variations among menopausal women, resulting in complications like sleepiness and dependence as well as anticholinergic and cardiotoxic effects.⁹ The hormone therapy has shown to protect the bone mass and to improve vasomotor symptoms and vaginal dryness. The hormone replacement therapy lost its therapeutic value due to unexpected side effects reported by the Women's Health Initiative, such as increased risk of cardiovascular and breast cancer and venous thrombosis.^{10,11}

Following the mentioned healthcare concerns, the use of phytoestrogens has attracted further attentions in treating the menopause-related disorders, including fennel (*Foeniculum vulgare*). It has been extensively employed by Iranian traditional medicine in the management of carminative, diuretic, tonic,¹² nausea, flatulence, colic, spleen and gall bladder digestive complaints,¹³⁻¹⁵ depression and anxiety, vaginal atrophy, bone density, fat distribution, osteoporosis, sexual function, lipid profiles, quality of life (QOL) and sexual satisfaction. This medicinal plant contains phenolic compounds, flavonoids (flavonoid glycosides and flavonoid aglycons), phenolic acids, hydroxycinnamic acids, coumarins and tannins.¹⁵ To the best of our knowledge, this is the first systematic review investigating the fennel effects on the menopause symptoms.

Materials and Methods

The trials studying the effect of fennel on the menopause were searched on databases of MEDLINE, Scopus, Google Scholar, and Cochrane Library (Cochrane Central Register of Controlled Trials) using the keywords of (fennel and *Foeniculum vulgare*) and menopause in any language in 2017. The respective publications were identified by manual manner among the references of studies.

1. Inclusion criteria

The study inclusion criteria were randomized controlled trials (RCTs), postmenopausal women and assessment of the

fennel effects on at least one menopausal symptom.

2. Data extraction

Two separate assessors extracted the data, including sample size, type of intervention and control, duration of treatment, dose and outcomes. Consensus-based discussion eliminated any disagreement (Table 1).

3. Assessment of publication bias

Publication bias was measured using Cochrane Collaboration's 'Risk of bias' tool (Table 2).

4. Statistical analysis

The main effect size was considered to be the standardized main difference (SMD). Pooling studies were performed using a random statistical model. Cochrane Q test ($P < 0.05$) and I^2 index were calculated to obtain the heterogeneity. The analyses were statistically carried out using a Comprehensive meta-analysis version 2 (Biostat, Englewood, NJ, USA).

Results

Process of studies selections was display in Fig. 1. In total, 10 studies (five duplicate publications) were included to systematic review. Some studies were reported as qualitative and some other studies that had sufficient information included in meta-analysis.

1. The fennel combined with officinalis (Melissa) effect on sleep disorder

Only one study by Shirazi et al.¹⁶ assessed the effectiveness of fennel combined with officinalis (Melissa) in treatment of sleep disorder. Sixty menopausal women with sleep disturbances were randomized into one of three groups (Melissa, citalopram, and placebo) for a 2 months follow-up period. Melissa group received 300 mg of fennel combined with 300 mg of officinalis daily (once a day). Citalopram group received 20 mg of citalopram and then the dose increased to 30 mg after one week. The patients were asked to complete Pittsburgh Sleep Quality Index (PSQI) Questionnaire before and again after treatment. PSQI had seven components: subjective sleep quality, sleep latency, sleep

Table 1. Characteristics of 10 studies (5 duplication publications) included in our systematic review

| References | Length of study (weeks) | Measurement outcome | Drop out (%) | Type of treatment/Control group | No. of subjects (active/placebo) |
|---|-------------------------|---|--------------|---|---|
| Ghazanfarpour et al. ³ | 12 | Anxiety, depression | 18.2% | 30% capsules filled with 100 mg fennel, three times a day/Placebo | 25/24 |
| Shirazi et al. ¹⁶ | 8 | Sleep disorder | 0.0% | 300 mg of fennel combined with 300 mg of officinalis daily/Placebo | 30/30 |
| Yaralizadeh et al. ^{18*} Najar et al. ^{19*} | 12 | Vaginal atrophy, sexual satisfaction | 0.0% | Fennel 5% vaginal cream/Placebo | 30/30 |
| Ghazanfarpour et al. ¹⁷ | 12 | Vaginal atrophy | 13.0% | 30% capsules filled with 100 mg fennel, three times a day/Placebo | 25/27 |
| Kian et al. ²⁰ | 8 | Score of sexual and vasomotor of MENQOL | 11.0% | 30% capsules filled with 100 mg fennel | 45/45 |
| Saghafi et al. ^{23*} Afiat et al. ^{24*} Ghazanfarpour et al. ^{22*} | 12 | Body composition, lipid profile, BMD, and BMC of the spine, femoral neck, intertrochanteric, and trochanter | 15.0% | 30% capsules filled with 100 mg of fennel, three times a day/Placebo | 30/30 |
| Abdali et al. ²¹ | 8 | FSFI | 0.0% | Hypericum perforatum (total dose 160 mg of hypiran), fennel tables per day (total dose 90 mg)/Placebo | Hypericum perforatum (n = 33), fennel (n = 33), hypiran, placebo (n = 32) |

*Duplicate publications

MENQOL: menopause-specific quality of life questionnaire, BMD: bone mineral density, BMC: bone mineral content, FSFI: female sexual function index

Table 2. Assessment of risk of bias using Cochrane Collaboration's 'risk of bias' tool of 10 randomized placebo-controlled trials included in our systematic review

| References | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition) | Selective reporting | Other biases |
|--|---|---|--|---|-------------------------------------|---------------------|--------------|
| Ghazanfarpour et al. ³ | (+)* | (+) | (+) | (+) | (-) | (+) | (+) |
| Shirazi et al. ¹⁶ | (?) [‡] | (-) [†] | (+) | (+) | (+) | (+) | (+) |
| Yaralizadeh et al. ¹⁸ Najar et al. ¹⁹ | (+) | (+) | (+) | (+) | (+) | (+) | (+) |
| Ghazanfarpour et al. ¹⁷ | (+) | (+) | (+) | (+) | (-) | (+) | (+) |
| Kian et al. ²⁰ | (+) | (?) | (?) | (?) | (+) | (+) | (+) |
| Saghafi et al. ²³ Afiat et al. ²⁴ Ghazanfarpour et al. ²² | (+) | (+) | (+) | (+) | (-) | (+) | (+) |
| Abdali et al. ²¹ | (?) | (?) | (?) | (?) | (+) | (+) | (+) |

*(+): low risk of bias

†(-): high risk of bias

‡(?): unclear risk of bias

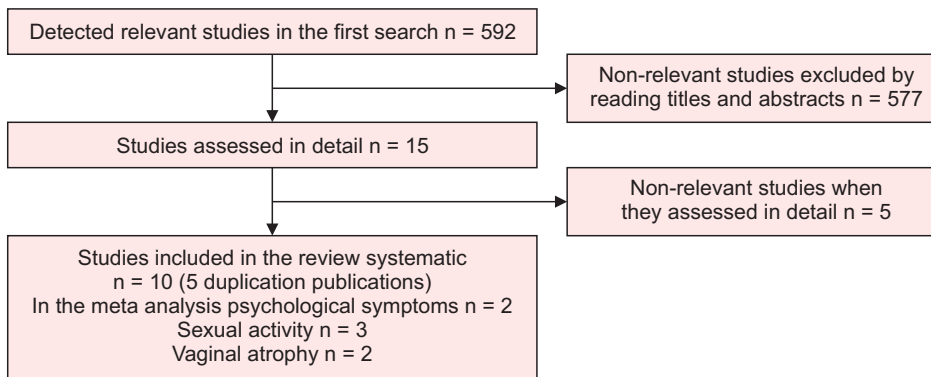


Fig. 1. Study search strategy.

duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daytime dysfunction. Compared to baseline, all seven component of PSQI showed a statistical significant improvement in all of three groups. There was a statistical significant difference between Melissa group compared with both Citalopram and placebo.¹⁶

2. Oral and topical fennel effect atrophy vaginal and sexual function

Two studies investigated fennel effect on atrophy vaginal.^{17,18} One study evaluated oral fennel effect on atrophy vaginal. Sixty menopausal women divided into fennel (n = 30) and vaginal placebo group (n = 30). No significant differences were observed in fennel group in respected to Vaginal Maturation Index ($P = 0.64$), the percentages of the parabasal ($P = 0.191$), intermediate ($P = 0.219$) and superficial ($P = 0.82$). However, paired *t*-test for comparison between before and after showed a significant increase in intermediate and superficial cells and a decrease in the parabasal cells.¹⁷

Yaralizadeh et al.¹⁸ compared the effect of 5% fennel vaginal cream (n = 30) with vaginal cream (n = 30) on vaginal atrophy. A significant increase in the superficial cells ($P < 0.001$) and significant decline in parabasal ($P < 0.001$) and intermediate ($P < 0.001$) was observed in fennel group compared to placebo. Also more improvement was seen in the vaginal cream fennel group compared to the placebo group regarding symptoms itching ($P = 0.017$), dryness ($P < 0.001$), pallor ($P < 0.001$) and dyspareunia ($P < 0.001$) except for burning ($P = 0.14$). Combining the finding of these two studies through random effect model reveal that pooled SMD of maturation value 0.601 ($P = 0.003$) was significant (95%

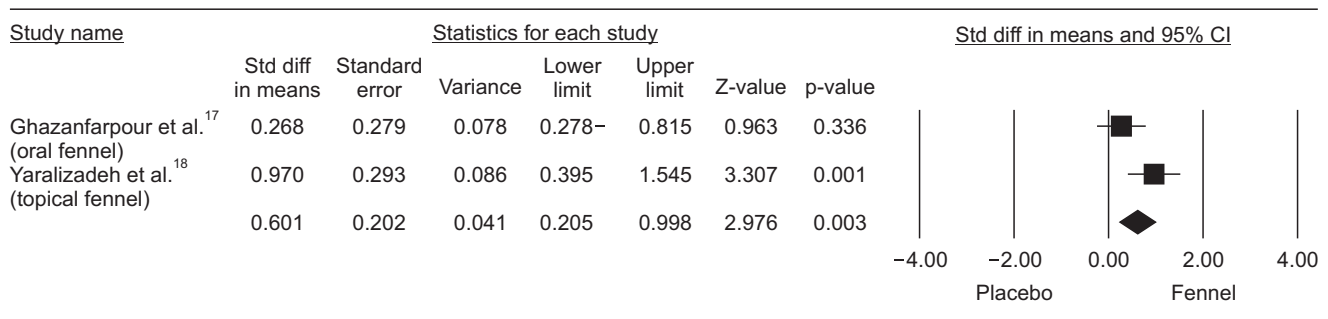
confidence interval [CI], -0.205 to 0.998) and any heterogeneity ($I^2 = 66.74$, $P = 0.083$) was not observed between two studies (Fig. 2).

3. Fennel effect on sexual function and sexual satisfaction

Three studies investigated the effect of fennel on sexual function and sexual satisfaction. Najjar et al.,¹⁹ in duplicate study, performed the first study. They assessed the fennel effect on sexual satisfaction. Treatment with fennel improved significantly sexual satisfaction compared to control group. Also patients in fennel group reported lower dyspareunia score than those in control group.

Seconded trial conducted by Kian et al.²⁰ They assessed the effect of fennel on score sexual of menopause-specific QOL (MENQOL), 90 patients randomized into fennel (n = 45) and placebo (n = 45) group. In both group fennel (24%) and placebo group (13%), mean score of sexual domain decreased significantly. The result of covariance analysis indicated a significant difference between two group ($P = 0.013$).²⁰

The third trial by Abdali et al.²¹ compared three arms: fennel, Hypericum perforatum and placebo. They conducted a blind placebo-controlled clinical trial on 120 menopausal women. Patients were randomized into one of three groups. The 33 patients received three tablets Hypericum perforatum (total dose 160 mg of hypiran), 33 patients received three fennel tables per day (total dose 90 mg) and the last 32 patients received three tablet placebo per day. Sexual function was measured using the female sexual function index. Inter-group comparison showed a significant difference in Hypericum perforatum ($P < 0.001$), fennel ($P < 0.001$) and placebo ($P < 0.001$) across three-time interval (baseline, 4



Meta analysis

Fig. 2. Effects of fennel on vaginal atrophy. ■: point estimate, ◆: combined overall effect of the intervention. CI: confidence interval.

and 8 weeks). Comparison among groups showed a significant difference at 8 weeks ($P = 0.007$) but these difference was not significant at baseline ($P = 0.172$) and week 4 ($P = 0.477$). Both fennel ($P = 0.012$) and Hypericum perforatum ($P = 0.029$) were difference from placebo at week 8.²¹ Combining the finding of these three studies through random effect model reveal that pooled SMD of sexual activity was highly significant than in women treated with fennel compared to placebo (SMD = 0.611; $P < 0.001$; 95% CI, 0.330–0.839; heterogeneity; $I^2 = 57.58$, $P = 0.095$) (Fig. 3).

4. The effect of fennel on vasomotor symptom

Only one trial by Kian et al.²⁰ assessed the effect of fennel on vasomotor domain of the MENQOL questionnaire. Vasomotor include three symptoms: hot flash, night sweet and sweating. Vasomotor domain decreased significantly from 15.17 to 8 in fennel group ($P < 0.001$) and from 13.22 to 15 ($P = 0.02$) in placebo group. Inter group comparison between two group was significant ($P < 0.01$).

5. The effect of fennel on bone density postmenopausal women

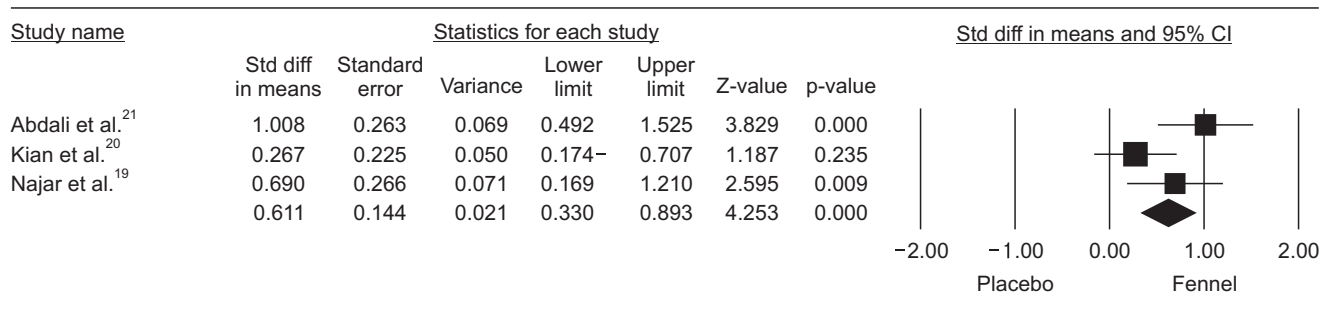
Only one trial evaluated the short-term effectiveness of treatment with fennel on bone density in postmenopausal women. Women randomized into two groups fennel ($n = 30$) and placebo ($n = 30$). Subjects took three capsules daily for 12 weeks. Each fennel soft capsule contained 30% fennel oil. Bone mineral density (BMD) and bone mineral content (BMC) of the spine, femoral neck, intertrochanteric, and trochanter were measured at baseline and after 12 weeks. Inter comparison of two groups regarding mean BMD and BMC at

lumbar spine ($P = 0.14$, $P = 0.504$), total hip femoral ($P = 0.42$, $P = 0.66$), trochanter ($P = 0.075$, $P = 0.07$), intertrochanter ($P = 0.84$, $P = 0.93$) and femoral neck ($P = 0.43$, $P = 0.64$) was not statistically significant.²²

6. The effect of fennel on depression in postmenopausal women

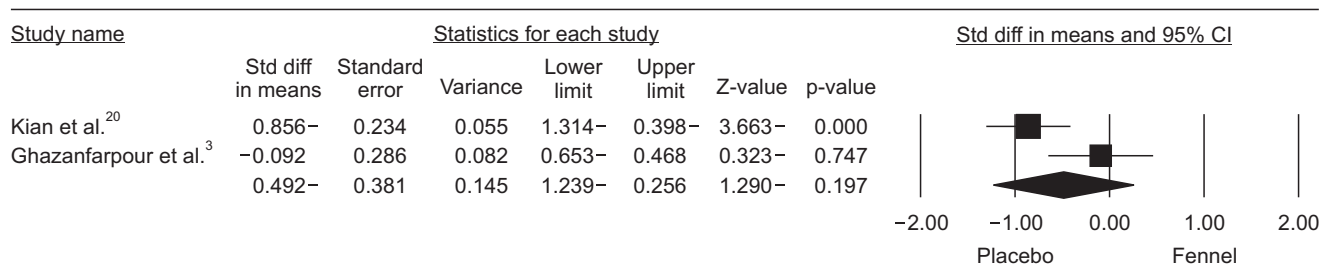
Two studies investigated fennel effect on psychological symptoms.^{3,20} Ghazanfarpour et al.¹⁷ conducted a randomized clinical trials on forty nine Iranian postmenopausal women who randomized to fennel ($n = 25$) and placebo ($n = 24$). Fennel group received capsule containing fennel and placebo group received placebo capsule. Zung's Self-Rating Depression Scale (SDS) and Hospital Anxiety and Depression Scale (HADS) were measured baseline and again after 12 weeks. Inter group comparison (fennel and placebo) did using t -test showed no significant difference regarding HADS subscale depression ($P = 0.83$) and anxiety ($P = 0.83$) and SDS ($P = 0.91$). In 44% patient in fennel group and 37.5% in placebo group were depression. After administration of fennel, depression level decreased borderline significant ($P = 0.058$). In 40% patient in fennel group and 45.8 patients in placebo group, the diagnosis of anxiety were confirmed. A significant improvement ($P < 0.01$) was seen after treatment with fennel.³

Only one trial by Kian et al.²⁰ assessed fennel effect on psychological domain of the MENQOL questionnaire. Score of socio-psychological of MENQOL decreased significantly from 30.77 ± 11.40 to 19.48 ± 7.68 in fennel group ($P < 0.001$) and decreased significantly from 28.12 ± 10.18 to 25.20 ± 8.58 ($P < 0.001$) in placebo group. Inter group



Meta analysis

Fig. 3. Effects of fennel on sexual activity. ■: point estimate, ◆: combined overall effect of the intervention. CI: confidence interval.



Meta analysis

Fig. 4. Effects of fennel on psychological symptoms. ■: point estimate, ◆: combined overall effect of the intervention. CI: confidence interval.

comparison between two group was significant ($P < 0.01$).²⁰ Combining the finding of two studies through random effect model reveal that pooled SMD of psychological symptoms was not significant (pooled SMD = -0.492, $P = 0.197$, 95% CI, -1.23 to 0.256). However heterogeneity was significant ($I^2 = 76$, $P = 0.03$) between two studies (Fig. 4).

7. The effect of fennel on composition in postmenopausal women

Only one study by Saghafi et al.²³ investigated the effect of fennel on body composition in overweight and obese postmenopausal women for 3 month. Twenty-two in the fennel group and 25 in placebo group completed the trial. Measure outcomes were body weight, body mass index (BMI) and fat distribution. Comparison of two groups (fennel and placebo) did not show any significant difference regarding body weight, BMI, waist and hip circumferences and fat distribution. Also, difference before and after treatment was not significant treatment regarding these parameters in both groups.²³

8. The effect of fennel on lipid profiles postmenopausal women

One study assessed the effect of fennel on lipid profiles. Sixty postmenopausal women were randomized into fennel group and placebo groups. Measure outcomes were low-density lipoprotein cholesterol (LDL-C), plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides. Comparison of two groups did not show any significant difference in total cholesterol ($P = 0.103$), LDL-C ($P = 0.104$) and HDL-C levels ($P = 0.266$), triglyceride ($P = 0.679$) between the two groups.²⁴

Discussion

As far as know, this is the first study to assess the fennel effect on the menopausal women's health. According to two trials, both routes (oral and topical) had positive effect on vaginal epithelium. However, the fennel had more effect when it applied topically. Based on the two trials,^{3,20} the

fennel had beneficial effects on some psychological disorders such as anxiety and depression. The fennel seems to have more effect in the patients with depression or anxiety disorders. The women treated with the fennel showed reportedly higher sexual function and sexual satisfaction in compared to the placebo group. The menopausal women in the fennel group experienced a slight increase in body weight and fat distribution. The fennel combined with the officinalis was more effective in attenuating the sleep disorders compared with Citalopram. There were not any significant differences in term of total cholesterol, LDL-C, HDL-C levels and tri-glyceride levels between the studied groups.

A trial assessing the effect of the fennel on the bone density found no proactive effect on the bone loss, inconsistent with other in vitro and animal studies. An in vitro study reported the protective effect of the fennel on the bone loss.²⁵ Both low and high doses of the fennel significantly improved the mean BMD and BMC at lumbar spine.²⁶ A possible explanation for this difference might be attributed to only 12-week follow up in current study. It should be noted that the potential beneficial effects of this herb could be proved through further studies with prolonged follow up and larger sample sizes.

Several issues make it difficult to express the beneficial effects of the fennel on the sleep disorders, including high placebo effect, limited studies, and small sample size. The fennel may have indirect effect in treatment sleep disorder through improving depression and anxiety. Accordingly, the direct and indirect effects of fennel on depression and anxiety should be investigated excessively through path analyses.

The conclusions of this review might not be globally generalized because all most of studies performed in Iran. Also, out of 45 studies in systematic review, three studies were published in duplicate sample. High placebo response was found among the studies that met our inclusion criteria. It is recommended that the researches should enter placebo run in phase and then exclude the patients with high placebo effect. Physical activity and nutritional status of the subjects have not been measured during treatments in some studies.

Conclusion

According to the findings, the fennel had been reported important in relieving the vasomotor symptom, vaginal itching and dryness, dyspareunia, sexual function, sexual satisfaction and sleep distribution. Fennel may have the limited positive effect in patients with depression or anxiety disorder but not healthy women. There were no effect on body weight and fat distribution, bone density and lipid profiles. However, these conclusions should be claimed cautiously because of small sample size, limited studies, high placebo effect and lack of physical and nutritional assessments duration treatment.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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