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Original Article

Efficacy of Femarelle for the treatment of climacteric syndrome in postmenopausal women: An open label trial

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ABSTRACT

Objective: To assess the effects of 2 months of treatment with Femarelle for climacteric syndrome in Taiwanese postmenopausal women.
Materials and methods: A multi-center, open-label trial of 260 postmenopausal women, age ≥ 45 years with vasomotor symptoms. Women were enrolled after obtaining a detailed medical history and a thorough physical examination. They then received Femarelle (640 mg/d) twice daily for 8 weeks. The primary outcome was the changes in the frequency and severity of hot flushes from baseline to 4 weeks (1 month) and 8 weeks (2 months). Changes of general climacteric syndrome were assessed using a modified climacteric scale designed by Greene.
Results: The frequency and severity of hot flushes were significantly improved with Femarelle use ($p < 0.001$). After 8 weeks of treatment, the percentage of women with various climacteric syndromes was reduced (from 100% to 20.9% for hot flushes, from 97.7% to 87.9% for psychological symptoms, from 93.8% to 78.8% for somatic symptoms, and from 87.8% to 74.9% for sexual symptoms). General climacteric syndrome scores also significantly decreased, from 20.8 ± 0.7 at the time of enrollment to 12.9 ± 0.7 after 8 weeks of Femarelle treatment ($p < 0.0001$). Participants experienced improvement of various climacteric symptoms and signs after 8 weeks of treatment (75.1% for hot flushes, 68.7% for psychological symptoms, 70.6% for somatic symptoms, and 69.0% for sexual problems respectively). After 4 weeks and 8 weeks of treatment with Femarelle, patients showed statistically significant improvement in climacteric symptoms ($p < 0.0001$). Three women (1.2%) withdrew from the study after 4 weeks of treatment due to adverse effects.
Conclusion: Femarelle significantly improved climacteric symptoms in Taiwanese postmenopausal women. However, further evaluation is needed regarding the safety of long-term consumption.

Introduction

Hormone therapy (HT) has been recognized as the most effective treatment for climacteric syndrome, especially hot flushes. However, reports from the Women Health Initiative trial [1,2] and the Million Women Study [3] have raised concerns regarding the side effects of HT. Therefore, the need for a complementary and alternative treatment to relieve climacteric symptoms has been extensively studied.

Phytoestrogen is generally defined as any plant substance or metabolite that induces biological responses through mimicking or modulating the actions of endogenous estrogens, usually by

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binding to estrogens receptors. These compounds are weakly estrogenic so it has been proposed that phytoestrogens may play a role in estrogen-related conditions, such as menopausal symptoms and postmenopausal osteoporosis. Phytoestrogens can be generally classified into the following groups: isoflavones, coumestans, and lignans. Isoflavones, which have been the most extensively studied phytoestrogens, are found predominately in soybeans and soy product-containing foods [4].

Although the present available data on using isoflavone as a form of treatment is either still inconclusive or only shows a slight improvement in symptomatic relief, the general trend focuses on using soy isoflavones as a supplement. However, isoflavones cannot represent all phytoestrogens so further evaluation regarding the effects of phytoestrogens with different compositions, methods used to isolate the various components of phytoestrogens, concentrations of bioavailable phytoestrogens, and the effects of the use of a combination of various phytoestrogens in addition to isoflavones may be needed.

Unlike general soy isoflavone products, Femarelle (Se-cure Pharmaceuticals, Yavne, Israel) is the combination of phytoestrogen compounds aside from isoflavone, such as lignans and coumestans. It has been reported that Femarelle is manufactured with a unique isolation enzymatic process to ensure that the entire family of phytoestrogen compounds, as is found in tofu, remains in their naturally intact form and is therefore able to increase its bioavailability to the body [5,6]. As such, Femarelle is capable of providing high efficacy and selectivity and has been described as a "new phyto-selective estrogen receptor modulator" [7,8].

The purpose of the present study is to assess the efficacy of Femarelle for the relief of hot flushes, as well as of general menopausal symptoms in postmenopausal women.

Materials and methods

Between December 2012 and January 2014, a multicenter, open-label clinical trial of Femarelle was conducted. Two hundred and sixty postmenopausal women, enrolled at seven medical hospitals in Taiwan, met the inclusion criteria and did not transgress the exclusion criterion. The institutional review board or ethical review board at each of the seven institutions approved the protocol of the present trial and the trial was conducted in accordance with their protocols. All patients provided written informed consent prior to their enrollment.

At enrollment, each patient underwent a detailed medical and gynecological history taking, which was then followed by a physical examination. The inclusion criteria were listed as follows: peri- and postmenopausal women should be aged $\geq$ 45 years and should at least have hot flush symptoms, women who are not currently taking HT or have stopped HT for > 1 month, and have not taken phytoestrogen supplements for > 1 week. Participants who have experienced cessation of menstruation for < 1 year received blood hormone evaluation and met the following criteria for enrollment: follicle-stimulating hormone $\geq$ 35 mIU/mL and estradiol < 30 pg/mL. Exclusion criteria included women with soybean allergy and those with a history of breast cancer and/or endometrial cancer.

The present trial consisted of a 1-week screening period and a 8-week treatment period. Throughout the treatment period, Femarelle (640 mg/d) was orally administered twice daily to each participants for 8 weeks. Participants visited the hospital a total of three times (1st visit at screening, 2nd visit at Week 5 after completion of 4 weeks of medication, and 3rd visit at Week 9 after completion of 8 weeks of medication) for general evaluation and to return completed questionnaires at each of the visits.

Assessment of efficacy

Assessments included questionnaires regarding the frequency and severity of hot flushes and symptomatic changes of general menopausal syndrome, according to women's menopause health manual designed by the Health Promotion Administration from the Ministry of Health and Welfare, Executive Yuan in 2011. This scale was modified from the climacteric scale designed by Greene [9]. The data of hot flushes were collected by patient diaries. This climacteric scale takes into consideration common climacteric symptoms, including vasomotor symptoms (hot flushes), psychological symptoms (irritability, depression, loss of interest, anxiety, sleep disturbances, and fatigue), somatic symptoms (dizziness, headache, back pain, joint pain, myalgia, increased facial hair, and skin dryness), and sexual symptoms (decreased libido, decreased sexual acceptance, vaginal dryness, and dyspareunia). For each of the symptoms mentioned above, a score of 0, 1, 2, or 3 was given for no, mild, moderate, or severe intensity respectively.

The primary endpoint for efficacy was the changes in the frequency and severity of hot flushes from baseline to Week 4 and Week 8. The secondary endpoints for efficacy were the changes in the general climacteric syndrome from baseline to Week 4 and Week 8.

Statistical analysis

Descriptive statistics were summarized for the characteristics of study variables, including frequencies, percentages for categorical data, median, means, and standard deviation for continuous variables. Comparison among groups categorized by nominal variables, such as other therapy, cause of cessation, and last menstrual period time, were performed using analysis of variance. Follow-up pairwise comparisons such as 2-sample *t* test and 2-sample Chi-square or Fisher's exact tests for continuous and categorical variables were made if overall tests were significant. Trend of levels in ordinal outcome, such as intensity level of hot flashes was estimated and tested using the general linear regression method. Generalized Estimating Equations method was used to estimate the time effect. All tests were two-sided and a p value < 0.05 was considered as statistical significance. All statistical intention-to-treat analyses were performed using SAS version 9 (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

Results

From December 2012 until January 2014, there were 260 women who met the initial criteria for inclusion into our analysis. Data on their current age, age at menopause, body weight, smoking, and causes of menstrual cessation are summarized in Table 1. As shown in Figure 1, of these 260 participants, complete data are available for 236 of the women at the conclusion of 4 weeks of treatment and for 221 women at the end of 8 weeks of treatment. Most of the women who withdrew from the study were due to

Table 1
Baseline characteristics of enrolled women.

Variables (n = 260)	Mean ± SD/n (%)
Mean age (y)	53.0 ± 5.9 (45–77)
Mean body weight (kg)	57.4 ± 8.0 (37–83)
Smoking	12 (12.7)
Mean age of menopause (y)	48.6 ± 5.0 (26–59)
Natural cessation of menstruation (n = 250)[a]	197 (87.8)
Surgical cessation of menstruation (n = 250)[a]	53 (21.2)

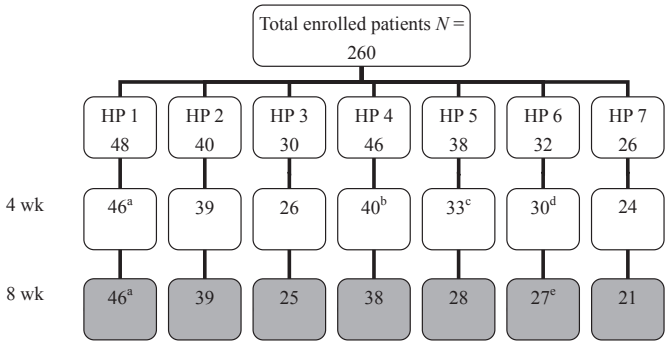
SD = standard deviation.
[a] Ten patients did not answer the question.

personal reasons or adverse side effects. Reported adverse side effects during the trial included breast tenderness ($n = 5$), nausea ($n = 3$), abdominal distention ($n = 2$, withdrawal after 4 weeks of treatment), and headache ($n = 2$, 1 withdrawal after 4 weeks of treatment). The withdrawal rate due to adverse effects was about 1.2%.

In addition to hot flushes, other symptoms and signs experienced by the patients before and after treatment, according to the climacteric scale, are summarized in Table 2. After treatment, the various climacteric scores were decreased (1.82 ± 0.05, 1.40 ± 0.05, and 1.06 ± 0.05 for hot flushes; 7.31 ± 0.30, 4.83 ± 0.27, and 4.16 ± 0.26 for psychological symptoms; 6.63 ± 0.29, 4.76 ± 0.27, and 4.25 ± 0.24 for somatic symptoms; and 5.03 ± 0.25, 3.97 ± 0.27, and 3.38 ± 0.24 for sexual symptoms). The percentage of women with various climacteric syndromes was also reduced (100%, 40.2%, and 20.9% for hot flushes; 97.7%, 93.9%, and 87.9% for psychological symptoms; 93.8%, 84.5%, and 78.8% for somatic symptoms; and 87.8%, 83.1%, and 74.9% for sexual symptoms).

During the course of the 8-week treatment, the frequency and intensity of hot flushes improved day by day after Femarelle use (Figure 2). There is a strong correlation between the duration of Femarelle use and both improvement of frequency (R^2: 0.952, $p < 0.001$) and intensity of hot flushes (R^2: 0.933, $p < 0.001$).

Using a Generalized Estimating Equations model, the scores of general climacteric syndrome were significantly decreased from 20.8 ± 0.7 at enrollment to 15.5 ± 0.6 after 4 weeks of treatment with Femarelle and 12.9 ± 0.7 after 8 weeks of Femarelle use ($p < 0.0001$). In addition, the percentages of the participants experiencing improvement of various climacteric symptoms after 4 weeks and 8 weeks of treatment were 59.8% and 75.1% for hot flushes, 50.8% and 68.7% for psychological symptoms, 61.0% and 70.6% for somatic symptoms, and 56.7% and 69.0% for sexual problems respectively (Figure 3). The differences in the percentage of symptomatic improvement as compared with baseline, as well the correlation between increased symptomatic improvement and duration of use (4 weeks vs. 8 weeks), depicted the significant effects of Femarelle use ($p < 0.0001$).



[a] One patient had a nausea sensation occasionally during the 8-week treatment.

[b] One patient complained of headaches occasionally.

[c] Two patients complained of breast tenderness.

[d] Three patients had breast tenderness and two patients complained of nausea.

[e] Three patients withdrew from the study after 4 weeks of treatment, two due to abdominal distention, and one due to headache.

HP = participating medical hospital.

Figure 1. Flow chart for patients enrolled in this study.

Discussion

With an increase in life expectancy, it is inevitable that most women will suffer from climacteric symptoms. With regard to the conclusion of Women Health Initiative trial [1,2] and the Million Women Study [3], complementary and alternative medicines are also becoming increasingly popular. The present study demonstrates that Femarelle, a combination of different phytoestrogen compounds, not only significantly improves the frequency and intensity of hot flushes, but also helps with other climacteric syndrome symptoms, including psychological, somatic, and sexual problems. Although such efficacy is encouraging, several additional factors regarding these results still need to be considered.

Hot flushes are the most common symptoms in peri- and postmenopausal women and can interfere with quality of life and disrupt sleep. Thus, most menopausal women seek medical support due to hot flushes. It has been reported that 10–25% of Chinese women and 10–20% of Indonesian women have hot flashes compared with 58–93% of Western women [10]. It has been proposed that this lower prevalence of hot flashes in Asian women when compared with their Western counterparts is, at least in part, related to the consumption of a diet rich in soy phytoestrogen [11,12]. Soy is a main source of phytoestrogens, especially isoflavone. A meta-analysis of all randomized, controlled trials of isoflavone supplementation showed that isoflavone supplementation may produce a slight to modest reduction in the number of daily flushes in menopausal women and that this benefit may be more apparent in women who experience a higher number of flushes per day. By contrast, another recent meta-analysis reviewing 11 trials on soy isoflavones extracts did not show efficacy in the treatment of hot flushes [13]. Several factors related to these conflicting results have been considered, including isoflavones' relatively short half-life of 6–12 hours [14]. Thus, the efficacy of isoflavone combined with other phytoestrogens has also been studied. A trial conducted by Sammartino et al [15] demonstrated that the combination of 60 mg isoflavones and lignans had a significant reduction in hot flushes compared with placebo. The authors considered that the reduction of vasomotor syndrome may be related to the observation that isoflavones are absorbed earlier than lignans are. Femarelle is the combination of isoflavone, lignans, and coumestans. The present study also confirms the efficacy of combined phytoestrogens therapy, not only through the significant relief of hot flushes in 75.1% of women after 8 weeks of treatment, but also through the significant reduction of the frequency and intensity of postmenopausal hot flushes. Other studies also demonstrated similar results, in which women who received Femarelle for 12 months noted a 76% reduction in vasomotor symptoms [16], as well as a significant improvement in the severity of hot flushes/night sweats (Femarelle baseline 2.17 ± 0.94, final 0.75 ± 0.69, $p < 0.001$) [17].

Except for its effects on hot flushes, a review of the data from the more rigorous trials show that isoflavones do not improve other menopausal symptoms [18], such as psychological, somatic, and sexual symptoms. It has been demonstrated that various phytoestrogens have different effects on the binding affinity and transactivational properties of estrogen receptors in different tissues and cell types [19]. Thus, as selective estrogen receptor modulators, different phytoestrogens may possess compound-specific estrogenic/antiestrogenic effects on various tissues. Most of the studies also revealed that isoflavones do not relieve vaginal atrophy

Table 2
The present menopausal symptoms of enrolled women.

Climacteric symptoms	No treatment score (women %)	4 wk score (women %)	8 wk score (women %)
Vasomotor symptoms:	1.82 ± 0.05 (100)	1.4 ± 0.05 (40.2)	1.06 ± 0.05 (24.9)
Hot flushes	1.82 ± 0.05 (100)	1.4 ± 0.05 (40.2)	1.06 ± 0.05 (24.9)
Psychological symptoms:	7.31 ± 0.30 (97.7)	4.83 ± 0.27 (93.9)	4.16 ± 0.26 (87.9)
Irritability	1.04 ± 0.06 (71.0)	0.68 ± 0.05 (52.7)	0.57 ± 0.05 (46.0)
Depression	1.13 ± 0.06 (74.4)	0.73 ± 0.05 (58.9)	0.66 ± 0.05 (54.5)
Feeling of loss	1.05 ± 0.06 (70.8)	0.67 ± 0.05 (52.0)	0.55 ± 0.05 (45.2)
Nervous	1.24 ± 0.07 (73.6)	0.85 ± 0.05 (65.7)	0.75 ± 0.05 (59.5)
Sleep disturbances	1.54 ± 0.07 (79.6)	1.10 ± 0.06 (71.6)	0.97 ± 0.07 (64.9)
Sense of weakness or fatigue	1.44 ± 0.06 (84.0)	0.98 ± 0.05 (72.4)	0.75 ± 0.05 (61.6)
Somatic symptoms:	6.63 ± 0.29 (93.8)	4.76 ± 0.27 (84.5)	4.25 ± 0.24 (78.8)
Dizziness	0.96 ± 0.06 (69.8)	0.65 ± 0.05 (51.3)	0.61 ± 0.05 (51.1)
Headache	1.03 ± 0.06 (70.3)	0.76 ± 0.05 (60.7)	0.63 ± 0.06 (48.7)
Back pain	1.15 ± 0.06 (75.9)	0.86 ± 0.06 (63.9)	0.75 ± 0.05 (58.9)
Joint pain	1.32 ± 0.06 (79.2)	0.90 ± 0.06 (64.2)	0.80 ± 0.06 (61.5)
Myalgia	1.10 ± 0.06 (70.6)	0.81 ± 0.06 (60.8)	0.67 ± 0.05 (53.1)
Increased facial hair	0.22 ± 0.04 (14.8)	0.14 ± 0.03 (12.5)	0.15 ± 0.03 (13.9)
Skin dryness	1.12 ± 0.06 (71.2)	0.90 ± 0.06 (64.7)	0.75 ± 0.06 (58.2)
Sexual symptoms:	5.03 ± 0.25 (87.8)	3.97 ± 0.27 (83.1)	3.38 ± 0.24 (74.9)
Decreased libido	1.43 ± 0.07 (80.5)	1.10 ± 0.07 (69.0)	0.92 ± 0.07 (61.6)
Decreased sexual acceptance	1.35 ± 0.07 (76.7)	1.13 ± 0.07 (69.3)	0.92 ± 0.07 (60.0)
Vaginal dryness	1.46 ± 0.07 (79.3)	1.12 ± 0.07 (72.1)	0.93 ± 0.06 (64.9)
Dyspareunia	1.13 ± 0.07 (64.1)	0.91 ± 0.07 (55.3)	0.78 ± 0.07 (51.9)

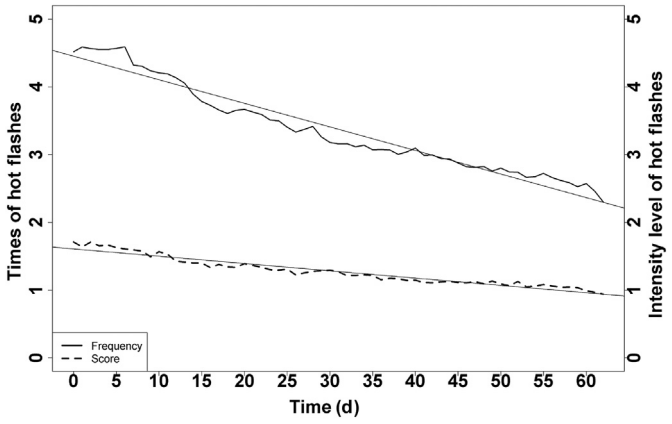


Figure 2. The trend of the frequency and intensity in hot flushes during 8 weeks of treatment with Femarelle were determined and tested using linear regression analysis and generalized estimating equation analysis.

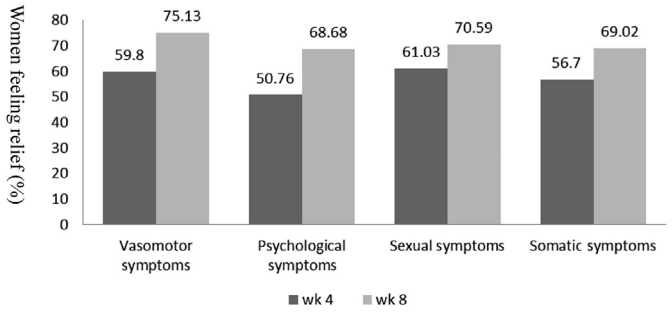


Figure 3. Percent of patients who reported improvement of major climacteric symptoms at 4 weeks and 8 weeks of treatment with Femarelle. Statistical significance was noted by analysis using generalized estimating equations ($p < 0.0001$).

[20–22]. By contrast, Nachtigall et al [23] investigated the efficacy of using a combined isoflavone and lignan supplement on vaginal epithelium. That study observed a significant reduction in vaginal pH from 7.7 ± 2.2 at baseline to 4.9 ± 1.4 at Week 12 ($p < 0.0001$) and a significant improvement in the maturation index in 10 out of 12 women. Although this study was limited by a small patient population and a relatively short duration, differences compared with previous reports on isoflavone use for vaginal atrophy may be related to the different affinities and transactivational potencies of phytoestrogens in different tissues and thereby resulting in tissue-specific variability. However, the present study also revealed a significant reduction in vaginal dryness score (baseline 1.49 ± 0.07, at 4 weeks 1.14 ± 0.07, at 8 weeks 0.94 ± 0.07, $p < 0.0001$) and dyspareunia (baseline 1.15 ± 0.08, at 4 weeks 0.93 ± 0.08, at 8 weeks 0.81 ± 0.07, $p < 0.0001$; data not shown).

Researches regarding the use of a combination of phytoestrogens, such as Femarelle, compared with HT for its effectiveness on climacteric syndrome have been conducted. In an animal study using ovariectomized rats, Femarelle increased allopregnanolone and β-endorphin levels in the brain, which were comparable to those of ovariectomized rats treated with estradiol [24]. These findings may, in part, explain the clinical effect of Femarelle on menopausal symptoms. In the present study, aside from hot flushes, a significant reduction of psychological, somatic, and sexual problems related to brain-derived symptoms, such as sleep disturbance, mood changes, and sexual dysfunction, was also noted. In addition, it was also reported that when menopausal symptoms were assessed using the Kupperman index, a significant decrease in score was noted in both DT56a (Femarelle) and HT treatment for 12 months (mean difference in Kupperman score, DT56a group: −3.98, HT group: −5.601, no treatment group: +1.76, $p < 0.001$) [17]. This study also demonstrated a significant decrease in modified Greene climacteric scale score.

In all of the literature reviewed, few side effects have been reported after phytoestrogen use, with the most serious related to gastrointestinal discomfort [25]. The present study also revealed rare adverse effects, including nausea, abdominal distention, headache, and mastalgia. Even after reviewing previous reports, there is little evidence that phytoestrogens cause endometrial hyperplasia or other adverse health effects when used at routine doses for a short period of time in postmenopausal women [26]. However, there is no information available regarding the effects of long-term consumption.

In conclusion, Femarelle was found to significantly relieve hot flushes and other menopausal symptoms within the 1st 4 weeks of

treatment and this trend continued following 8 weeks of treatment. However, limitations of this study included the absence of a control group and a short period of treatment. Although Femarelle can be considered as an alternative treatment to HT for postmenopausal women with climacteric syndrome, safety of long-term consumption warrants further evaluation.

Conflicts of interest

The authors have stated no conflicts of interest relevant to this article.

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