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Original Articles

Estro G-100 herbal extract and hot flashes in postmenopausal women: A randomized double-blinded controlled trial

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ABSTRACT

Objective: The present study aimed to determine the efficacy of EstroG-100 herbal extract on hot flashes in postmenopausal women.

Material and methods: This randomized, double-blind, placebo-controlled trial was performed on postmenopausal women recruited from two university hospitals complaining of hot flashes. The intervention group received two extract capsules (daily for 12 weeks), and the control group received two placebo capsules (daily for 12 weeks). Finally, the frequency and severity of hot flashes (F&S) were subjectively reported and compared weekly during the treatment for 12 weeks.

Results: Out of 120 randomized participants, 35 entered the final analysis for each group. In the third week, participants of the control group significantly reported more moderate hot flashes than other group (MD=1.00, $P = 0.004$). However, in terms of mild (MD=0.74, $P = 0.057$) and severe (MD=0.60, $P = 0.064$) hot flashes, the groups did not differ. In the sixth week, mild (MD=1.51, $P<0.001$), moderate (MD=1.54, $P<0.001$), and severe (MD=1.22, $P<0.001$) hot flashes were significantly reported more in the control group compared with another group.

Conclusion: The present study revealed that EstroG-100 herbal extract could improve hot flashes in postmenopausal women.

Introduction

Hot flashes are temporally sensations of heat mainly experienced by postmenopausal women.[1] These women complain of sweating, the sensation of heat, palpitations, anxiety, irritability, and even panic. This phenomenon results from dilating skin vessels and a consequent decrease in core body temperature.[2] The severity of hot flashes may be influenced by several factors, for instance, climate, diet, lifestyle, women's social roles, attitudes toward the end of life, fertility, and aging.[3]

The irritating nature of hot flashes prompted medical interventions in recent years. Hormone therapy (HT), especially with estrogens, was more commonly used until it was discovered that many adverse effects could follow HT. HT's most worrisome adverse effect is the increased risk of developing hormone-dependent malignancies, for instance, breast cancer.[4,5]

Thus, clinicians employed complementary therapies to relieve menopause symptoms. Among all herbal supplements, EstroG-100™ has gained much attention in recent years. It is a mixture of root extract of three plants (*Cynanchum wilfordii Hemsley, Phlomis umbrosa Turczaninow*, and *Angelica gigas Nakai*), which is concentrated and spray-dried.[6] It has several benefits, including anti-inflammatory,[7] antioxidative,[8–10] anti-cancer,[7] and anti-atherosclerotic properties.[8–10] Additionally, EstroG-100™ may have the same effects as HT to relieve hot flashes.[7,10,11] Based on previous studies, EstroG-100 improved menopause symptoms without adverse effects.[12,13]

This study aimed to determine the efficacy of EstroG-100 herbal extract on hot flashes in postmenopausal women.

The precis: EstroG-100 herbal extract could reduce the severity and frequency of hot flashes in postmenopausal women with no adverse effect.

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Materials and methods

Study design and setting

This randomized, double-blinded controlled trial was conducted between February and May 2021 at the Taleghani and Imam Hossein hospital's gynecology clinic. Both hospitals are affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. The study protocol was accepted by the Iranian Registry of Clinical Trials (ID: IRCT20220716055479N1)

Sampling and participants

Sampling was based on the consecutive method. The inclusion criteria were: postmenopausal women with hot flashes, body mass index (BMI) <40 kg/m^2, having normal pelvic ultrasound and mammography, and willingness to participate in the study. Also, we excluded the individuals with the following features: consumption of dietary supplements to relieve menopause syndromes; a history of using estrogen or progesterone products in the last three months; any suspicion of breast and endometrial malignancies; irregular vaginal bleeding one year after menopause; a history of uncontrolled hypertension, thyroid diseases, diabetes mellitus, kidney or liver dysfunction, vascular thrombosis, premature ovarian failure, or mental disorders; consumption of psychoactive drugs; alcohol or substance abuse; a history of hysterectomy; a history of breast cancer in first-degree family members; and not consuming the prescribed medicine or not completing the follow-up.

Randomization and blinding

After eligible participants signed written informed consent, they were randomized (simple randomization using a computer-generated randomization program) at a ratio of 1:1 into the intervention and control groups. In this study, patients and physicians (who prescribed medication and performed the physical examination) were blind to the allocation of the patients in groups (double-blinded).

Interventions

The intervention group received two capsules of EstroG-100 herbal extract (daily for 12 weeks). The patients were informed that the capsules should be used simultaneously or twice daily. The control group received two placebo capsules (daily for 12 weeks). Placebo capsules did not differ from EstroG-100 capsules in terms of appearance, color, and packaging; and contained starch compounds with no adverse effect. The EstroG-100 and placebo capsules were produced by Behestan Behdasht Pharmaceutical Company (Tehran, Iran). EstroG-100 is registered by the Food and Drug Administration of Iran. The drugs were delivered to the participants in three periods: at the beginning of the study, the end of the fourth week, and the end of the eighth week. The participants were told not to use any estrogen or progesterone. They should also maintain their usual lifestyle and avoid taking other supplements to relieve menopause symptoms.

Outcomes

At the first visit, the baseline characteristics of the participants were collected. They were asked to fulfill a form reporting the severity and the frequency of hot flashes within a week. They completed forms weekly, from a week before the beginning of the study until the end of it (The patients were followed for 12 weeks). They are also assured that if they cannot attend, this information will be collected weekly by phone calls. The severity of hot flashes was defined as follows: mild, only sudden hot flashes; moderate, sudden hot flashes with severe sweating; severe, sudden hot flashes with sweating that interferes with daily activities.[14] The primary outcome was the frequency of mild, moderate, and severe hot flashes.

Statistical analysis

Data were processed using SPSS version 23.0. We reported data as percentage, mean, standard deviation, mead difference (MD), and 95% confidence interval (CI). The categorical variables were compared between groups using the Chi-square test. Continuous variables were compared between groups using the independent-samples *t*-test. In this study, a p-value less than 0.05 was considered significant.

Ethical approval

The Research Ethics Committee approved this study of the School of Medicine, Shahid Beheshti University of Medical Sciences (ID: IR.SBMU.MSP.REC.1400.644). All procedures of this study were performed by the declaration of Helsinki and its later amendments.

Results

Out of 120 postmenopausal women complaining of hot flashes, 84 patients were eligible to participate in the current study based on the defined inclusion and exclusion criteria and signed the informed consent. Forty-two patients were assigned either to intervention or placebo groups, 14 were lost to follow-up, and 70 were finally analyzed (Fig. 1). Table 1 presents the baseline characteristics of the participants. The two groups did not differ in baseline characteristics ($P>0.05$).

Figs. 2–4 depict daily reports of hot flashes among participants over time. As shown in Table 2, we also compared hot flashes between groups in three time periods (the third, sixth, and 12th weeks). In third week, participants of the control group significantly reported more moderate hot flashes than another group (MD=1.00, $P = 0.004$). However, in terms of mild (MD=0.74, $P = 0.057$) and severe (MD=0.60, $P = 0.064$) hot flashes, the groups did not differ. In the sixth week, mild (MD=1.51, $P<0.001$), moderate (MD=1.54, $P<0.001$), and severe (MD=1.22, $P<0.001$) hot flashes were significantly reported more in the control group compared with another. Also, the participants reported no drug-related adverse effect.

Discussion

This study aimed to determine the efficacy of EstroG-100 herbal extract on the frequency of hot flashes among postmenopausal Iranian women. Our results revealed that EstroG-100 herbal extract significantly improved the frequency of hot flashes.

In 1992, the American Medical Association recommended that postmenopausal women consider using HT to relieve menopause symptoms –since postmenopausal women have low estrogen levels, especially estradiol (E2). As a result, HT was considered the best alternative for improving the health of postmenopausal women, and the vast majority of clinicians prescribed it. Nevertheless, in a study by the Women's Health Initiative on postmenopausal women between 50 and 79 years, compared with placebo, HT with a combination of estrogen and progesterone increased the incidence of breast cancer and cardiovascular disorders by 26% and 29%, respectively.[5] Thus, as an alternative to HT, there was a growing interest in producing efficient herbal medicines with negligible adverse effects, such as Chinese herbal medicines, isoflavones, black cohosh, and pomegranate.

Cynanchum wilfordii Hemsley, Phlomis umbrosa Turczaninow, and Angelica gigas Nakai have been used as traditional herbal remedies in Korea and China.[11] *Cynanchum wilfordii* contains ingredients inhibiting the damage of DNA, protein, and cell membrane lipids. It also have ingredients with the phenolic ring which can bind to estrogen receptor and act as agonist or antagonist. Triterpene glycosides (derived from *Phlomis umbrosa*) and wilforside and cyanuricuoside (derived from *Cynanchum wilfordii*) are different types of saponin improving hot flashes by the

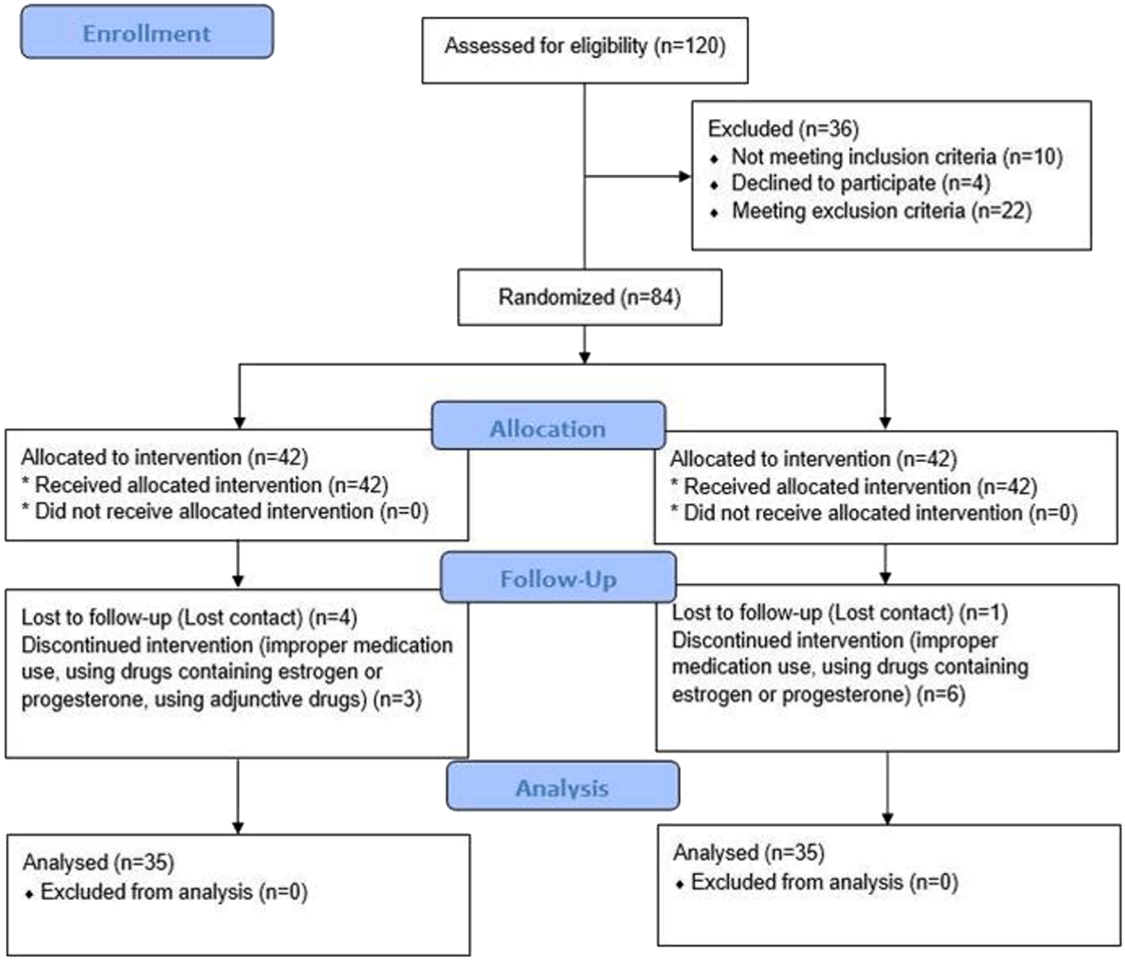

Fig. 1. The CONSORT flow diagram of the study.

Table 1
Baseline characteristics of the participants.

Variables	Total (n = 70)	Intervention group (n = 35)	Control group (n = 35)	P-value
Age (years)	50.75 ±2.41	51.14±2.54	50.37±2.23	0.183
Body Mass Index (kg/m2)	29.09 ±4.66	28.01±3.99	30.17±5.07	0.052
Marital status				0.840
Married	61(87.1)	30(85.7)	31(88.6)	
Unmarried	3(4.3)	2(5.7)	1(2.9)	
Divorced	6(8.6)	3(8.6)	3(8.6)	
Education				0.120
Elementary	41(58.6)	17(48.6)	24(68.6)	
High school	22(31.4)	15(42.9)	7(20.0)	
University	7(10.0)	3(8.6)	4(11.4)	
Employment				0.159
Unemployed	49(70.0)	21(60.0)	28(80.0)	
Employed	10(14.3)	6(17.1)	4(11.4)	
Retired	11(15.7)	8(22.9)	3(8.6)	
Menopause duration (months)	7.32 ±0.09	8.88±0.10	5.76±0.08	0.370
Daily reports of hot flashes				
Mild	4.34 ±2.05	4.77±2.49	3.91±1.40	0.081
Moderate	3.27 ±1.60	3.57±1.68	2.97±1.48	0.119
Severe	3.00 ±1.40	3.20±1.76	2.80±0.90	0.237

Data were reported as frequency (%) or mean±standard deviation.

activation of estrogen receptor. Moreover, *Angelica gigas* contains decursin which is helpful in the expression of progesterone.[12]

EstroG-100 herbal extract has several properties (e.g., anti-inflammatory, antioxidant, anti-cancer, and anti-atherosclerotic effects) that can be used for medicinal purposes. These properties were stated by Joon Heo in 1613 in Dong-Eui-Bo-Gam (the most famous book on traditional Korean medicine).[11] Our results demonstrated that EstroG-100 herbal extracts reduced the frequency of hot flashes among postmenopausal women 30, 60, and 90 days after medication onset. The efficacy of the medication increased up to 60 days with no reduction after that, which is in agreement with the previous studies. In 2012, Chang et al. examined the effect of a 12-week EstroG-100 herbal extract on pre-, peri-, and post-menopausal women. His results showed that, unlike the control group, by using the medication Kupperman's menopausal index decreased.[13] Also, in 2005, Lee et al. examined the effects of using Estromon (a combination of several plant extracts) in treating hot flashes in premenopausal women. According to the results, oral administration of two Estromon capsules twice a day for three months significantly improved the symptoms of hot flashes about five times more than the placebo group. He concluded that premenopausal women might benefit from Estromon as a phytoestrogen supplement, significantly improving menopausal symptoms, osteoporosis, serum triglycerides, and human growth hormone without weight gain or serious side effects.[12]

The present study showed that this herbal extract mostly improved hot flashes within 60 days of consumption. Various studies have reported different times of maximum effect, which may be due to the mechanism of action of the drugs. Studies on the effects of selective

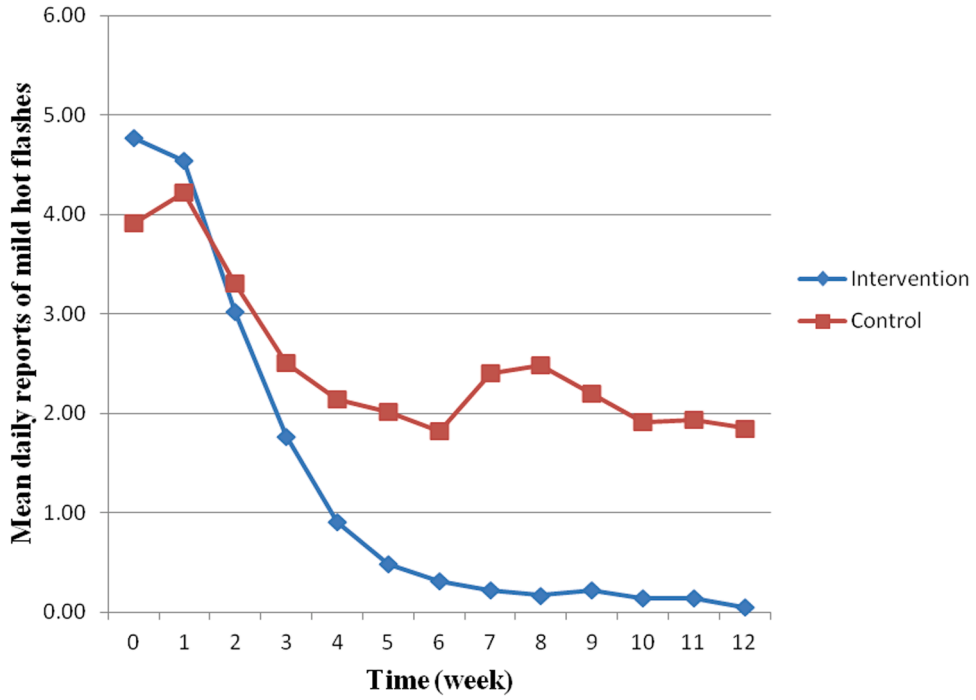

Fig. 2. Daily reports of mild hot flashes among participants over time.

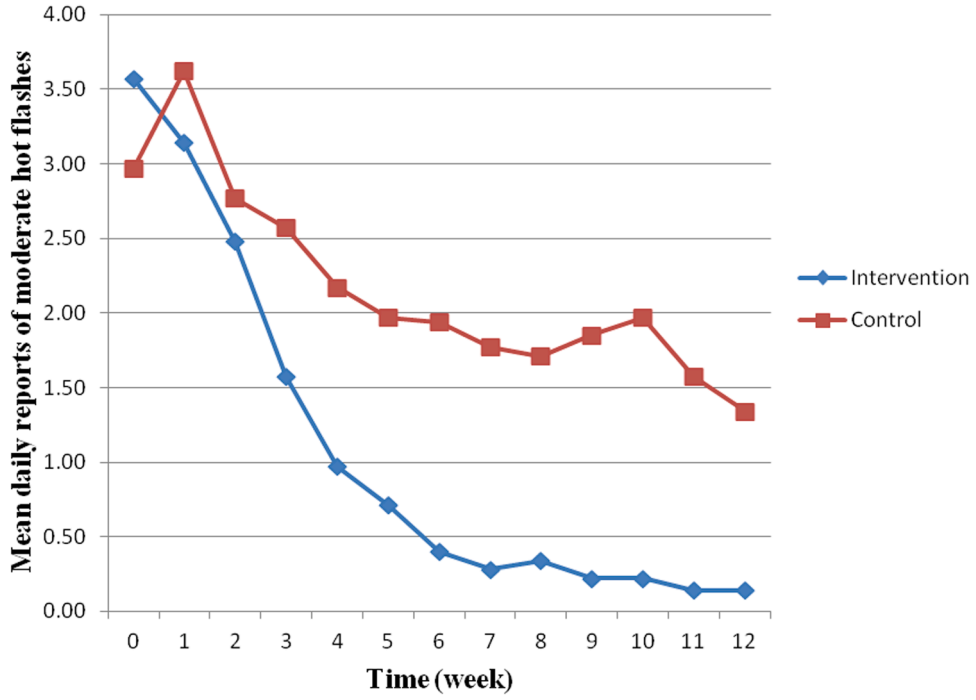

Fig. 3. Daily reports of moderate hot flashes among participants over time.

serotonin reuptake inhibitors (SSRIs) on hot flashes reported intervals between the start of using the drug and its therapeutic effects. The minimum reported interval of efficacy reported in these drugs seems to be five weeks.[15,16] A study comparing the effects of progesterone with venlafaxine on hot flashes revealed that after six weeks of medication, progesterone and venlafaxine reduced hot flashes in patients by 79% and 55%, respectively.[17] Another study that evaluated the effects of acupuncture in the treatment of hot flashes reported the onset of treatment and time of the maximum effect of about three weeks and eight weeks, respectively,[18] which is similar to our findings. It seems that among non-hormonal therapies used to manage menopause symptoms, the effect of this herbal extract would manifest faster. However, it is unknown how long this medication lasts in controlling hot flashes, which further studies will clarify.

Despite some studies on EstroG-100 herbal extract, its mechanism of action is still not well known. The study by Kim et al. showed that EstroG-100 herbal extract did not induce any estrogenic activity or stimulate the production of estrogen-responsive precursors in MCF-7

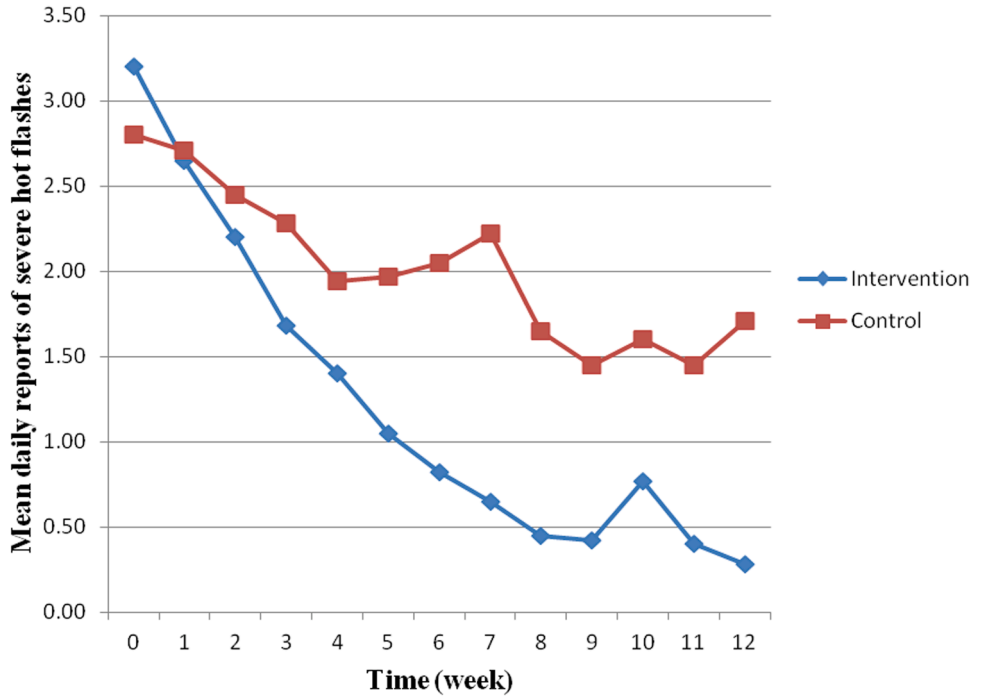

Fig. 4. Daily reports of severe hot flashes among participants over time.

Table 2
Comparison of daily reports of hot flashes between groups over time.

	3rd week	P-value	6th week	P-value	12th week	P-value
Mild	0.74 (−0.02–1.50)	0.057	1.51 (1.01–2.01)	<0.001	1.80 (1.27–2.22)	<0.001
Moderate	1.00 (0.32–1.67)	0.004	1.54 (1.08–1.99)	<0.001	1.20 (0.86–1.53)	<0.001
Severe	0.60 (−0.03–1.23)	0.064	1.22 (0.62–1.83)	<0.001	1.42 (1.09–1.75)	<0.001

Data were reported as a Mean difference and 95% confidence interval.
All comparisons were performed using an independent-samples *t*-test.

cells. Moreover, these components had no selective activity against human estrogen receptor (hER)-α and hERβ, non-selective activity against ER, or effects on ER target gene expression. Also, the combination of extracts in EstroG-100 did not induce MCF-7 cell proliferation and uterine weight gain in ovarian mice.[11] Its mechanism of action may be related to the effects of estrogen agonists and/or antagonists, which contribute to bone metabolism and menopause symptoms, while not affecting E2 and follicle-stimulating hormone (FSH) levels.[10,12,19] Cynanchum wilfordii contains components that act as a stilbene derivative, which inhibits deoxyribonucleotide (DNA), protein, low-density lipoprotein (LDL), and cell membrane lipids. Its phenolic ring creates a similar binding to the estrogen receptor, allowing it to act as an estrogen agonist and/or antagonist.[20]

On the other hand, previous studies depicted that the compounds in EstroG-100 have phytoestrogenic effects.[10] So, its mechanism of action appears to be about receptors such as selective estrogen receptor modulators (SERM) rather than direct effects, as well as isoflavones. Phlomis umbrosa and Cynanchum wilfordii contain saponin-riched components,[21,22] which activate estrogen receptors to improve various menopause symptoms.[23,24] In addition, stromone contains Angelica gigas, and its decorsin acts as a coumarin derivative of phytoestrogens to stimulate the growth of sexual organs and to help express progesterone and the Luteinizing Hormone (LH) receptor.[25]

The safety and efficacy of EstroG-100 have been demonstrated in previous studies in mice and humans.[10,12,19,26] In the tissue response study to measure estrogen-specific alkaline phosphatase (ALP) levels in women, *Cynanchum wilfordii, Phlomis umbrosa, and Angelica gigas* increased ALP levels more than any of the individual plant extracts alone, indicating a similar effect.[12] In previous human clinical trials, consumption of EstroG-100 improved menopause symptoms without adverse effects.[12,19] While LDL and high-density lipoprotein (HDL) levels in HT-treated patients altered after E2 administration,[27] EstroG-100 did not affect the weight, biochemical and metabolic markers such as liver enzymes, renal function test, and lipids profile. As first limitation, the current study did not address liver enzymes level; thus, it would be valuable if liver function tests were assessed in future studies, as the liver probably metabolizes the evaluated drug. As another limitation, this pilot study were conducted with a small sample size, which could affect its external validity. Furthermore, it would have been better if the patients were followed for a longer duration to evaluate the possible long-term side effects of the EstroG-100 herbal extract.

Conclusion

The present study revealed that EstroG-100 herbal extract could improve the frequency of hot flashes in postmenopausal women with no adverse effects within the first 60 days of consumption. However, further studies should be performed in the future to investigate the durability of its effect.

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