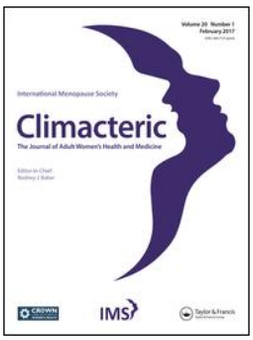

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ORIGINAL ARTICLE

Efficacy and safety evaluation of *Cimicifuga foetida* extract in menopausal women

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ABSTRACT

Objective: The aim of this study was to evaluate the efficacy and safety of long-term treatment with *Cimicifuga foetida* extract in menopausal women.

Methods: A prospective, randomized, controlled clinical trial was conducted. A total of 96 early postmenopausal women were randomly assigned to three groups: group A received 1 mg estradiol valerate daily plus 4 mg medroxyprogesterone acetate on days 19–30; group B received 1 mg estradiol valerate daily plus 100 mg micronized progesterone on days 19–30; group C received 100 mg *C. foetida* extract daily. The efficacy was evaluated. Safety parameters were recorded.

Results: A total of 81 patients completed the treatment and follow-up visit. The modified Kupperman Menopausal Index scores decreased after 3 months in all groups. No significant changes were observed in the liver, renal function and components of metabolic syndrome in group C ($p > 0.05$). There were no significant differences in the incidences of metabolic syndrome among the three groups ($p > 0.05$). After 24 months, the endometrial thickness increased significantly in group B ($p = 0.014$), but not in *the C. foetida* extract group ($p > 0.05$).

Conclusions: *C. foetida* extract is safe and effective for the treatment of menopausal symptoms in postmenopausal women.

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KEYWORDS
Menopausal women; Cimicifuga foetida; metabolic syndrome; endometrial thickness

Introduction

It is estimated that more than 80% of women suffer from menopausal symptoms, such as hot flushes, sweating, and sleep disorders, as well as psychological symptoms that can seriously endanger a woman's physical and mental health[1]. Many researchers have sought to improve the quality of life of older women.

Hormone replacement therapy (HRT) was first introduced in the 1940s. However, for several decades, the role of HRT has been debated[2]. There has been no definitive conclusion on the relationship between HRT and cardiovascular disease. In addition, combined estrogen/progestogen therapy, but not estrogen alone, increases the risk of breast cancer after long duration of use[3]. Women are looking for more natural or safer treatments for hot flushes, night sweats, and other menopausal symptoms.

The genus Cimicifuga, commonly known as Sheng Ma in China, has long been used in China, Europe, and North America because of its high medicinal value and health benefits[4]. Many studies have demonstrated its effectiveness in alleviating menopausal symptoms[5,6]. In Europe and the USA, black cohosh (*Cimicifuga racemosa L.*) has been used as a safe and effective alternative to HRT since the mid-1950s[6]. However, many studies examining its effectiveness have been limited to short durations. The effectiveness and safety of the long-term use of black cohosh have not been identified. In China, Cimicifuga was first recorded to cure diseases in Shen Nong's herbal classic dating back 2000 years ago. The present study aimed to evaluate the long-term effectiveness and safety of the *C. foetida* extract, a species of genus Cimicifuga, in treating menopausal symptoms in China.

Methods

Subjects

This prospective, randomized, controlled trial was conducted at the Department of Gynecology of Peking Union Medical College Hospital, China. The project was approved by the relevant Ethics Committee. Written informed consent was obtained from all participants prior to therapy, and they received detailed information about the study.

A total of 96 women were recruited for the study between July 2009 and July 2010. After providing informed consent, the patients were randomly assigned to three groups. To be included in the study, the women had to be early menopausal (defined as experiencing amenorrhea for longer than 6 months and less than 5 years), 40–60 years old, serum estradiol <30 pg/ml, and follicle stimulating hormone >40 IU/l, with climacteric symptoms. We excluded patients if

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they had taken HRT during the 3 months prior to the first examination or had contraindication for HRT or other medicine influencing the results.

Medication

Group A (E2 + MPA) received 1 mg/day continuous, estradiol valerate tablets (E2, produced by Delpharm Lille SAS and packaged by Bayer Healthcare Co., Ltd.) plus 4 mg/day medroxyprogesterone acetate (MPA, Shanghai Xinyi Pharmaceutical Co., Ltd.) orally for the last 12 days of each 30-day cycle.

Group B (E2 + MP) received 1 mg/day continuous, estradiol valerate tablets (E2, produced by Delpharm Lille SAS and packaged by Bayer Healthcare Co., Ltd.), plus 100 mg/day micronized progesterone (MP, ZheJiang Aisheng Pharmaceutical Co., Ltd.), orally for the last 12 days of each 30-day cycle.

Group C (*C. foetida* extract) received 100 mg daily continuous *C. foetida* extract (Ximingting tablets, ShanDong LvYe Pharmaceutical Co., Ltd.).

Definition of metabolic syndrome

Metabolic syndrome was defined (for women) as central obesity (a waist circumference >80 cm) plus any two of the following four additional factors: increased triglyceride levels ≥1.7 mmol/l, high density lipoprotein (HDL) cholesterol levels <1.29 mmol/l (or specific treatment for lipid abnormalities), systolic blood pressure values ≥130 mmHg or diastolic blood pressure values ≥85 mmHg (or treatment of previously diagnosed hypertension), and fasting glucose levels (FBG) ≥ 5.6 mmol/l (or previously diagnosed type 2 diabetes)[7].

Outcome measurements

The symptoms of menopause were assessed through a modified Kupperman Menopausal Index (mKMI). It included 13 symptoms (hot flushes/sweating, paresthesia, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgia and myalgia, headaches, palpitations, formication, urinary infection and sexual complaints). A scale ranging from 0 to 3 points is used to describe the severity of the complaints. The highest score is 63. The Menopause-Specific Quality of Life (MENQOL) questionnaire was used to evaluate patients' quality of life[8]. The Chinese version consisted of 27 items which were divided into four categories of vasomotor (three items), psychosocial (seven items), physical (14 items) and sexual (three items) sections[9]. The severity of each symptom was assessed on a seven-point scale. In this questionnaire, higher scores are associated with lower quality of life[10]. The Hospital Anxiety and Depression Scale was used to evaluate anxiety and depression in the participants. The higher scores indicate the more obvious state of anxiety or depression.

Safety measurements

Weight, height, waist and hip circumference, and blood pressure were measured, and physical and gynecological examinations were performed at each follow-up. Menopause age (years) and menopausal duration (months) were recorded. Lipid parameters, FBG, liver and renal function were processed using an automated analyzer, AU5800® (Beckman Coulter, USA). Endometrial thickness was measured using a LOGIQ 5 PRO digital ultrasonic diagnostic instrument (GE company) at 5–9 MHz.

Statistical analysis

SPSS Version 20.0 was used for data management and statistical analysis (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to check the normality of distribution of analyzed variables. The results were presented as the mean ± standard deviation. In between-group comparisons, one-way analysis of variance (ANOVA) was used if the data showed normal distribution and equal variance; when $p < 0.05$, Least significant difference (LSD) was chosen for *post hoc* multiple comparisons. If the data did not show normal distribution or equal variance, then the Mann–Whitney *U*-test or Kruskal–Wallis test was used for the comparison. Enumeration data were presented as frequencies and rates, and the χ^2 test (the Fisher exact test) was used for rate comparison. Statistical significance was set at 0.05.

Results

General information

At the end of the 24-month study period, a total of 81 women (84.38%) completed the study, and their data were included for the statistical analysis. However, one woman in group A refused the ultrasound test at the 24-month visit, and her data were excluded from statistical analysis when assessing endometrial thickness. Characteristics of the 81 patients in the three groups were comparable, in terms age, menopause age, duration of menopause, systolic and diastolic blood pressures and height (Table 1).

Outcome measurements

There was no significant difference in the mKMI score among the three groups before the treatment ($p > 0.05$). The mKMI scores decreased in the three groups after 3 months, compared with baseline. The women in group A after 9 months and the women in group B after 3 months had lower anxiety scores compared with the baseline measurements. The women in group C demonstrated no changes in the depression scale score (Table 2).

No significant difference was observed in the scores of each domain of the MENQOL questionnaire among the three groups before treatment (all $p > 0.05$). The scores of the vasomotor, psychosocial and physical domains decreased after the treatment in the three groups, but the scores of the sexual domain did not change significantly in group C and group B. *C. foetida* extract had a fast effect on the vasomotor symptoms at 3 months. However, the onset time of the psychosocial and physical symptoms in group C lagged behind those in group A and group B (at 9 months, 6 months,

Table 1. Baseline characteristics of the participants. Data are given as mean ± standard deviation.

	Group A	Group B	Group C	p-Value
Age (years)	52.14 ± 3.18	52.52 ± 3.60	53.58 ± 2.93	0.254[a]
Menopause age (years)	49.68 ± 3.04	50.33 ± 3.29	51.35 ± 2.62	0.129[a]
Duration of menopause (months)	29.54 ± 15.01	27.52 ± 15.48	26.77 ± 14.67	0.782[a]
Systolic blood pressure (mmHg)	111.71 ± 14.07	112.41 ± 13.26	116.31 ± 10.18	0.366[b]
Diastolic blood pressure (mmHg)	71.25 ± 10.15	70.74 ± 8.17	73.50 ± 6.76	0.402[b]
Weight (kg)	60.09 ± 9.08	59.30 ± 7.39	65.50 ± 9.16	0.020[a]
Height (cm)	159.46 ± 4.68	161.44 ± 3.87	158.69 ± 4.27	0.060[a]

[a]One-way analysis of variances (ANOVA); [b]Kruskal–Wallis test.
Weight: the LSD method was used for *post hoc* multiple comparisons; there was no difference between group A and group B ($p = 0.733$), while for group A vs. group C, $p = 0.023$; group B vs. group C, $p = 0.010$.

Table 2. Comparisons of scores of three scales before and after the treatment. Data are given as mean ± standard deviation.

	Baseline	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
mKMI score									
Group A	29.93 ± 8.35	16.68 ± 9.21[a]	16.21 ± 7.66[a]	15.11 ± 7.23[a]	13.89 ± 6.85[a]	12.56 ± 7.18[a]	12.04 ± 6.26[a]	11.59 ± 5.06[a]	12.19 ± 6.96[a]
Group B	29.63 ± 7.33	15.44 ± 8.98[a]	14.85 ± 7.03[a]	11.96 ± 5.82[a]	13.78 ± 6.96[a]	12.00 ± 6.23[a]	12.89 ± 6.55[a]	12.19 ± 6.55[a]	12.44 ± 6.57[a]
Group C	28.69 ± 8.74	20.77 ± 5.88[a]	16.42 ± 6.57[a]	14.50 ± 5.95[a]	17.40 ± 7.31[a]	15.52 ± 6.29[a]	13.46 ± 6.17[a]	12.52 ± 6.50[a]	15.68 ± 6.94[a]
p-Value[b]	0.574	0.030	0.832	0.283	0.105	0.118	0.543	0.919	0.075
Anxiety score									
Group A	5.71 ± 3.84	4.79 ± 3.11	4.07 ± 3.31	3.61 ± 3.13[a]	3.04 ± 2.94[a]	3.41 ± 3.12[a]	3.29 ± 3.02[a]	3.19 ± 3.03[a]	3.04 ± 2.67[a]
Group B	6.30 ± 2.64	4.59 ± 2.82[a]	4.37 ± 2.92[a]	3.44 ± 2.95[a]	4.11 ± 3.15[a]	3.82 ± 3.23[a]	3.11 ± 2.65[a]	2.78 ± 2.33[a]	3.19 ± 2.77[a]
Group C	5.23 ± 3.37	4.50 ± 3.18	3.62 ± 3.15	3.25 ± 2.90[a]	4.12 ± 3.54	3.92 ± 3.33	4.04 ± 3.71	3.52 ± 2.49	3.76 ± 3.15
p-Value[b]	0.546	0.799	0.476	0.978	0.391	0.867	0.754	0.578	0.784
Depression score									
Group A	5.93 ± 4.02	5.75 ± 3.80	5.04 ± 3.54	3.75 ± 2.69[a]	4.41 ± 3.19	4.07 ± 3.23	3.50 ± 3.18[a]	3.67 ± 3.09[a]	3.74 ± 2.88
Group B	5.67 ± 3.88	4.78 ± 3.19	4.41 ± 3.52	4.22 ± 3.07	4.44 ± 3.08	3.59 ± 2.39[a]	3.37 ± 2.72[a]	3.67 ± 3.10[a]	3.96 ± 2.49
Group C	5.42 ± 3.06	5.19 ± 3.37	4.54 ± 3.22	4.50 ± 3.62	5.68 ± 3.89	5.64 ± 4.05	4.19 ± 3.06	3.96 ± 2.37	5.16 ± 3.26
p-Value[b]	0.528	0.638	0.784	0.873	0.359	0.177	0.514	0.425	0.306

[a]Mann–Whitney test, $p < 0.05$ when compared with baseline; [b]Kruskal–Wallis test, $p < 0.05$ when compared among the three groups.
mKMI score, modified Kupperman Menopausal Index.

Table 3. Comparisons of four domains of the MENQOL score before and after the treatment. Data are given as mean ± standard deviation.

	Baseline	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
Vasomotor									
Group A	5.12 ± 1.21	2.82 ± 1.03[a]	2.46 ± 1.07[a]	2.58 ± 1.11[a]	2.32 ± 1.08[a]	2.17 ± 1.19[a]	2.14 ± 1.31[a]	2.00 ± 1.18[a]	1.54 ± 0.87[a]
Group B	4.73 ± 1.15	2.57 ± 0.80[a]	2.41 ± 1.16[a]	2.01 ± 0.86[a]	2.05 ± 1.00[a]	2.21 ± 1.05[a]	2.10 ± 1.52[a]	2.09 ± 1.10[a]	2.12 ± 1.28[a]
Group C	4.62 ± 1.43	3.63 ± 1.44[a]	3.10 ± 1.20[a]	2.85 ± 1.21[a]	3.35 ± 1.87[a]	2.64 ± 1.37[a]	2.68 ± 1.38[a]	2.43 ± 0.84[a]	2.99 ± 1.66[a]
p-Value[b]	0.199	0.004	0.038	0.018	0.030	0.175	0.079	0.070	0.000
Psychosocial									
Group A	4.65 ± 1.37	3.59 ± 1.48[a]	3.26 ± 1.50[a]	2.89 ± 1.42[a]	3.14 ± 1.30[a]	3.04 ± 1.43[a]	2.70 ± 0.81[a]	2.79 ± 0.90[a]	2.63 ± 1.05[a]
Group B	4.25 ± 1.08	3.41 ± 1.12[a]	3.33 ± 1.15[a]	3.05 ± 1.13[a]	3.11 ± 1.11[a]	3.13 ± 1.16[a]	2.80 ± 1.08[a]	2.69 ± 1.08[a]	2.69 ± 1.06[a]
Group C	4.09 ± 1.05	3.82 ± 1.17	3.59 ± 1.20	3.24 ± 0.99[a]	3.36 ± 1.53[a]	3.22 ± 1.39[a]	3.04 ± 1.28[a]	3.12 ± 1.13[a]	2.78 ± 0.97[a]
p-Value[b]	0.278	0.349	0.587	0.242	0.895	0.847	0.616	0.554	0.807
Physical									
Group A	4.33 ± 1.07	3.60 ± 1.19[a]	3.39 ± 1.20[a]	3.14 ± 1.30[a]	3.24 ± 1.07[a]	3.12 ± 1.14[a]	2.93 ± 0.81[a]	2.79 ± 0.76[a]	2.73 ± 0.95[a]
Group B	4.37 ± 0.92	3.20 ± 0.89[a]	2.96 ± 0.90[a]	2.91 ± 0.95[a]	2.97 ± 0.82[a]	2.85 ± 0.76[a]	2.93 ± 0.90[a]	2.76 ± 0.89[a]	2.84 ± 0.96[a]
Group C	4.06 ± 0.85	3.67 ± 0.88	3.34 ± 0.77[a]	3.12 ± 0.83[a]	3.23 ± 0.87[a]	3.06 ± 0.90[a]	2.95 ± 0.88[a]	3.03 ± 0.77[a]	2.98 ± 0.81[a]
p-Value[b]	0.446	0.186	0.180	0.831	0.740	0.549	0.977	0.601	0.815
Sexual									
Group A	5.25 ± 1.91	3.90 ± 2.03[a]	3.63 ± 2.03[a]	3.21 ± 1.94[a]	3.29 ± 1.91[a]	3.04 ± 1.77[a]	3.10 ± 1.69[a]	3.05 ± 1.78[a]	2.88 ± 2.05[a]
Group B	4.69 ± 1.87	3.98 ± 1.73	4.00 ± 2.10	3.95 ± 1.61	3.71 ± 1.56	3.80 ± 1.64	3.68 ± 2.15	3.94 ± 2.15	3.87 ± 1.95
Group C	4.46 ± 1.47	4.50 ± 1.45	4.19 ± 1.51	3.49 ± 1.66[a]	3.63 ± 1.49[a]	3.63 ± 2.05	4.22 ± 1.73	4.40 ± 1.48	4.06 ± 1.86
p-Value[b]	0.435	0.257	0.322	0.143	0.331	0.167	0.048	0.056	0.010

[a]Mann–Whitney test, $p < 0.05$ when compared with baseline; [b]Kruskal–Wallis test, $p < 0.05$ when compared among three groups.
MENQOL score, the Menopause-Specific Quality of Life questionnaire.

respectively), but the effects were long-lasting. No significant difference was observed in the scores in the psychosocial and physical domains among the groups (all $p > 0.05$). The data are shown in Table 3 and Figure 1.

Safety measurements

The incidence of metabolic syndrome (MetS), the levels of triglycerides, HDL cholesterol, and FBG, and blood pressures and waist circumference were measured in our study. No significant between-group differences were found in triglycerides, blood pressure and waist circumference at baseline ($p > 0.05$). The patients in group C had a lower HDL cholesterol level and a higher FBG level at baseline. There was no significant difference in the changes in triglycerides, FBG, blood pressure and waist circumference in the three groups ($p > 0.05$). HDL cholesterol was obviously decreased in the group A patients ($p = 0.019$), but not in groups B and C

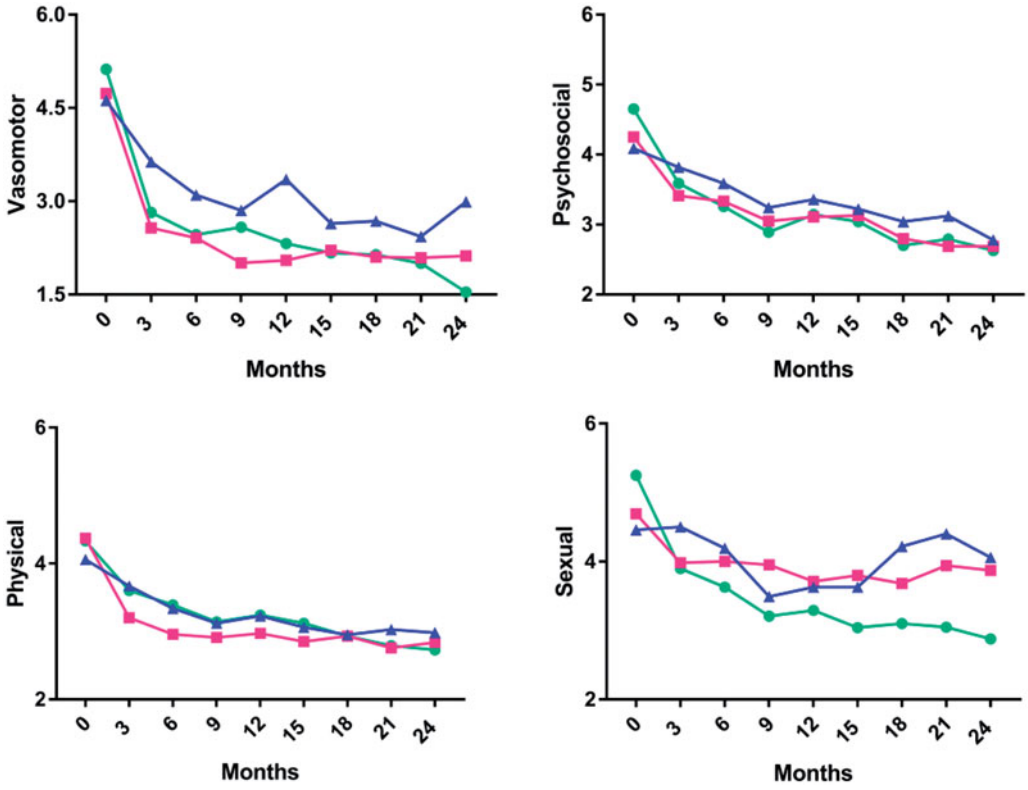

Figure 1. Comparisons of vasomotor, psychosocial, physical and sexual domains of MENQOL questionnaire before and after the treatment. Circle symbols, group A; square symbols, group B; triangle symbols, group C.

($p > 0.05$). The data are shown in Table 4. There were no differences in the occurrence rates of MetS among the three groups (Table 5).

We found no significant between-group differences at baseline in the factors related to liver and renal function, including alanine transaminase (ALT) and creatinine ($p > 0.05$). There was no significant difference in ALT before and after the therapy in each group ($p > 0.05$). However, the creatinine level showed a remarked post-treatment decline in the three groups (all $p < 0.001$). All data are shown in Table 4.

Endometrial thickness measured with transvaginal ultrasonography before the treatment was similar in all groups ($p > 0.05$). The mean endometrial thickness did not change considerably after the treatment in group A and group C ($p = 0.077$, 0.903, respectively). However, post-therapy, the thickness increased significantly in group B ($p = 0.014$); the mean value increased by 28.45%. The results are shown in Table 4.

The incidence of patients with endometrial thickness $\geq$5 mm is shown in Table 5. Before the treatment, there were no significant between-group differences in the incidence of endometrial thickness $\geq$5 mm in the groups ($p = 0.217$). At 12 months, 12 more patients had endometrial thickness $\geq$5 mm in group B. After the treatment at 24 months, the number of patients with endometrial thickness $\geq$5 mm increased by two, eight, and three in groups A, B, and C, respectively.

Causes of discontinuing therapy

Fifteen women discontinued the study, four in group A, five in group B and six in group C. In group C, two patients discontinued therapy due to unbearable headache, and four reported personal reasons. No severe adverse reactions were observed in the groups (data not shown).

Discussion

Plants of the genus Cimicifuga are the largest genera in the Cimicifugae family, which is composed of about 28 species that are widely distributed in temperate regions of the northern hemisphere[4]. For obstetricians and gynecologists, the most familiar genus of the Cimicifuga drug is black cohosh, a type of C. racemosa L that has been widely used in Europe and the USA to treat menopausal symptoms. However, the effects of long-term use of black cohosh are unclear.

There are about nine species of the genus Cimicifuga in China[4], one of which, *C. foetida*, grows in the forest at an altitude of 1700–2300 m above sea level. It is widely used as an herbal remedy for sore throat, macula, cold, and headache. In the present study, we assessed the effectiveness of Ximingting tablets, which are extracted from *C. foetida* to treat menopausal syndrome.

We conducted a prospective, randomized, controlled trial to compare the efficacy and safety of *C. foetida* extract with other two HRT groups. After 3 months of treatment, the mKMI scores were obviously decreased in all groups.

Table 4. Effects of three groups on components of metabolic syndrome. Mean change = (value at 24 months after treatment − value at baseline)/(value at baseline)*100%. Data are given as mean ± standard deviation.

Parameters	*Baseline*	*24 months after treatment*	*Mean change (%)*	*p-Value*
Triglycerides (mmol/l)				
Group A	1.45 ± 0.76	1.36 ± 0.77	2.58	0.739[a]
Group B	1.45 ± 0.77	1.61 ± 1.06	25.74	0.923[b]
Group C	1.76 ± 0.89	1.77 ± 0.82	13.44	0.517[b]
HDL cholesterol (mmol/l)[c]				
Group A	1.53 ± 0.31	1.45 ± 0.29	−4.81	0.019[a]
Group B	1.52 ± 0.33	1.53 ± 0.31	1.69	0.471[a]
Group C	1.34 ± 0.23	1.28 ± 0.25	−4.47	0.052[a]
Fasting blood glucose (mmol/l)[d]				
Group A	5.12 ± 0.40	4.99 ± 0.43	−2.28	0.068[a]
Group B	5.14 ± 0.39	5.13 ± 0.40	−0.08	0.946[a]
Group C	5.48 ± 0.47	5.48 ± 0.60	0.02	0.989[a]
Systolic blood pressure (mmHg)				
Group A	111.71 ± 14.07	110.00 ± 13.01	−0.95	0.560[b]
Group B	112.41 ± 13.26	109.82 ± 12.13	−1.22	0.500[b]
Group C	116.31 ± 10.18	118.85 ± 9.93	2.63	0.114[a]
Diastolic blood pressure (mmHg)				
Group A	71.25 ± 10.15	69.82 ± 8.82	−1.10	0.390[b]
Group B	70.74 ± 8.17	68.89 ± 8.59	−1.52	0.623[a]
Group C	73.50 ± 6.76	74.08 ± 6.49	1.52	0.271[a]
Waist circumference (cm)				
Group A	78.21 ± 7.59	76.56 ± 7.72	−1.74	0.526[a]
Group B	75.37 ± 7.58	76.30 ± 7.73	1.40	0.161[a]
Group C	80.69 ± 7.67	80.89 ± 6.93	0.57	0.376[b]
Endometrial thickness (mm)				
Group A[e]	3.41 ± 0.81	3.79 ± 1.50	11.15	0.077[a]
Group B	3.22 ± 0.76	3.93 ± 1.44	28.45	0.014[b]
Group C	3.46 ± 0.59	3.73 ± 1.68	6.70	0.903[b]
Alanine transaminase (IU/l)				
Group A	23.62 ± 11.71	23.93 ± 13.36	7.10	0.820[b]
Group B	25.67 ± 17.13	18.59 ± 6.51	−11.85	0.082[a]
Group C	19.72 ± 8.30	22.19 ± 10.28	22.95	0.503[b]
Creatinine (μmol/l)				
Group A	72.73 ± 8.52	56.41 ± 7.67	−22.06	0.000[a]
Group B	73.79 ± 6.45	55.48 ± 6.58	−24.74	0.000[a]
Group C	74.35 ± 9.77	57.50 ± 10.48	−22.36	0.000[b]

[a]Student's test; [b]Wilcoxon Mann–Whitney test; [c]for HDL cholesterol, there was no difference between group A and group B ($p = 0.901$), while for group A vs. group C, $p = 0.013$, and for group B vs. group C, $p = 0.024$; [d]for fasting blood glucose, there was no difference between group A and group B ($p = 0.795$), while for group A vs. group C, $p = 0.004$, and for group B vs. group C, $p = 0.007$; [e]one woman refused transvaginal ultrasound after 2 years.

Table 5. The incidence of metabolic syndrome and endometrial thickness ≥5 mm among the three groups. Data are presented as frequencies and rates, and χ^2 test (Fisher's exact test) was used for rate comparison.

	n	*Baseline*	*12 months after treatment*	*24 months after treatment*
Metabolic syndrome				
Group A	28	3 (10.7%)	3 (10.7%)	3 (10.7%)
Group B	27	2 (7.4%)	2 (7.4%)	3 (11.1%)
Group C	26	4 (15.4%)	6 (23.1%)	7 (26.9%)
p-Value		0.621	0.254	0.212
Endometrial thickness ≥5 mm				
Group A	27	3 (11.1%)	8 (29.6%)	5 (18.5%)
Group B	27	0 (0.0%)	12 (44.4%)	8 (29.6%)
Group C	26	1 (3.8%)	2 (7.7%)	4 (15.4%)
p-Value		0.217	0.010	0.484

In the MENQOL questionnaire, climacteric symptoms were classified into four domains. *C. foetida* extract made in China could ease vasomotor, psychosocial and physical symptoms, but did not have a good effect on sexual symptoms, whereas group B had a similar trend. All results showed that *C. foetida* extract had a fast and similar efficacy in easing these symptoms. However, except for the 9-month follow-up, there was no significant difference in the anxiety score. A randomized, double-blind, placebo-controlled, parallel-group trial of the efficacy and tolerability of black cohosh has also reported no statistically significant anxiolytic effect of black cohosh[11]. In addition, no significant difference was found in the depression score at each visit.

Our team concluded that 24 months of using of *C. foetida* extract did not increase the incidence of malignant breast tumors[12]. To compare the safety of *C. foetida* extract, as well as the toxic and adverse effects, the present study investigated variations in the following factors before and after treatment: liver and renal function, endometrial thickness and components of MetS. There is some evidence that Cimicifuga (black cohosh) might result in liver toxicity[13–15]. However, other studies have reported different results. A meta-analysis of randomized, double-blinded and controlled clinical trials showed no evidence that isopropanolic black cohosh extract had any adverse effects on liver function[16]. In our study, there was no adverse effect on liver and renal function after treatment among three groups, even after long-term use.

Our study determined the endometrial thickness through transvaginal ultrasound, and 5 mm was used as the cut-off value to ensure safety[17]. There was no significant difference in the post-treatment endometrial thickness in groups A and C. Patients in group B demonstrated a remarkable increase in endometrial thickness compared with baseline, with a mean of 3.93 mm, and the group had eight additional patients with an endometrial thickness ≥5 mm after the treatment, which may indicate that natural progesterone cannot fully transform the endometrium; thus, it is necessary to evaluate the change in the endometrium during the process of HRT.

In terms of the components of MetS, we found that, among the three groups, there were no differences in the changes in triglycerides, FBG, blood pressure and waist circumference. All three methods may help to attenuate abdominal adipose accumulation, which is often associated with menopause. The HDL cholesterol level in group A showed a clear decline while, in group C, the HDL cholesterol level showed no difference before and after treatment. Synthetic progestin, such as MPA, may have an adverse effect on HDL cholesterol, which is consistent with a prior study[18]. In group C, three more patients had MetS after the treatment. We hypothesized that the greater weight, FBG and lower HDL cholesterol at baseline may play important roles.

Our study has some strengths. First, this follow-up study is by far the longest study of genus Cimicifuga, not just *C. foetida* extract, which is valuable in assessing the availability and security of the long-term use of this drug. Second, we administered follow-up surveys every 3 months for 2 years. We noticed the effective time of the *C. foetida* extract on menopausal symptoms. Third, our paper also compared the effects of natural progesterone and synthetic progestin.

The primary limitation was the sample size in our study. A larger, prospective longitudinal study would provide a better design to evaluate the efficacy and safety of *C. foetida* extract in menopausal women. For this reason, we encourage further research.

Conclusions

The current study identified the efficacy and safety of long-term treatment with *C. foetida* extract made in China in menopausal women. *C. foetida* extract could effectively alleviate vasomotor symptoms after 3 months, and the results endured over time. In addition, *C. foetida* extract appears to be safe and did not harm the liver, renal function, MetS components and endometrial thickness. This study promotes the study of *C. foetida* extract and the medication of women during the menopausal period.

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Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

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