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Effect of the mixed herbal medicines extracts on menopausal symptoms: A randomized clinical trial study

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ABSTRACT

Background: Menopause cause many symptoms, which may impair quality of life the women. The study aims to determine the effectiveness of mixed herbal medicinal extracts on menopausal symptoms.

Method: A randomized, triple-blind, placebo-controlled clinical trial was conducted on 120 peri-menopausal women for 12 weeks. All participants took herbal extracts drops orally daily. They were randomly allocated into four groups: placebo (C), A (250 mg chamomile, 30 mg fennel, 15 mg saffron), B (1000 mg chamomile, 120 mg fennel, 60 mg saffron), and D (500 mg chamomile, 60 mg fennel, 30 mg saffron).They completed a demographic and MRS questionnaire at week 0, 6.12.

Result: 108 participants successfully completed the assessment. No significant differences in demographic variables were seen between the four groups. The median MRS score was significantly reduced in group B from 27.5±3 to 7.5±5. In group D, it was significantly reduced from 29±12 to 22±9.25The effect size in this study was 0.92.

Conclusion: Study showed significant improvement in menopausal symptoms especially in group B.

Keywords: menopause, herbal medicine, alternative medicine

INTRODUCTION

Menopause disturbs all aspects of a woman's life and annually affecting 25 million women worldwide. WHO (World Health Organization) estimates that 1.2 billion women will be postmenopausal by 2030 (1). Menopause is described as the transition from the reproductive phase of a woman to the non-reproductive, it occurs in many industrial countries on average at age 51. However, in Iran, according to Rajaeefard 's study the mean age of menopause was 48.18 years (2). Hence, menopause starts between the age of 40 and 50 and is marked by the reduction of estrogen levels (3). Most of these problems can be effectively treated with HRT (hormone replacement therapy). However, HRT may cause serious risk hazards to one's health, and is therefore only recommended for temporary, limited therapy (3). The possible adverse effects of long-term HRT have lead women to seek out alternative therapies (4). Nowadays, complementary and alternative therapies to treat menopausal symptoms in place of HRTare pharmaceutical and botanical (5). Because menopause includes a variety of symptoms (such as hot flashes, night sweats, genital problems such as vaginal dryness, dysuria and urinary disorders, sexual dysfunction and lack of sexual satisfaction, dyspareunia, pain, skeletal, heart problems and cardiovascular disorders, memory problems, and mood disorders and depression) a combination of several plants with the least side effects to reduce most symptoms is often required. Yakoot and change on the effects of the herbal combination reported helpful consequences on menopausal symptoms (6, 7). According to the literature, many medicinal plants can be effective in improving menopausal symptoms. For example, chamomile and fennel as phytoestrogens, alleviate hot flashes, strengthen the reproductive and urinary system, and increase sexual desires. Fennel has a positive effect on osteoporosis (8-10). Chamomile is also effective in digestive system dysfunction and it can be used as a sedative (11, 12). Saffron is effective in relieving depression because it is a mood modifier, as well as improving heart and vascular problems and sexual dysfunction in menopausal women (13-15). The effect of these herbal extracts on menopausal symptoms was the aim of our study.

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METHODS

1. **Study Participants and Design**: We conducted a randomized clinical trial and placebo controlled study at the Medical University of Mashhad, Iran. This research was approved by Ethics Committee approval of the Mashhad University. The study was triple blind and was conducting on women with menopausal symptoms. All the eligible participants were peri - menopausal women. Inclusion criteria included: cease of menstruation within 12 months of our study or presently experiencing menopausal symptoms and age range 45-65.
2. **Randomization and Blinding:** An independent data manager carried out randomization by using random allocation sequence. Allocation concealment was achieved through sequentially numbered, sealed envelopes. After the baseline questionnaire was completed, eligible participants were assigned to one of the four study groups by consecutively opening the envelopes as they entered the study. The probability of being allocated to the placebo group (C) and medicinal groups (A, B, D) was equal (1:1:1:1). Participants, the research staff and analysts were unaware of their assignment to the treatment or placebo.
3. **Sample Size:** Data from previous studies were used to calculate sample size. (16). Equal sample size for each group was anticipated at about 27 women; therefore, a total sample size of 108 participants was required, but we enrolled 120 participants considering the 10% attrition rate. For more confidence, at the beginning of the research, a pilot study was carried out and the effect size obtained was 0.92.
4. **Data collection scales:** For data collection, a demographic and MRS[1] questionnaire were used. Demographic data included: age, BMI, and education level of the study subject and her spouse and their occupations. The standardized MRS questionnaire is a health-related scale that collects comprehensive data. It measures three dimensions: somatic symptoms of menopause (vasomotor), psychological, and urogenital. This questionnaire has been used in many clinical studies and epidemiology research to determine the frequency and Severity of menopausal symptoms in middle-aged women and according to many studies; it has a high reliability and validity (17-19). This questionnaire has internal and external validity and reliability as established by previous studies (20, 21). Simbar determined the reliability by Cronbach's alpha (r_a= 0.933) (22). In this study, the reliability of the questionnaire was examined by the Cronbach's alpha (r_a=0.9).
5. **Intervention:** The plant extracts and placebo agents were supplied by Exir Golesorkh Pharmaceutical Co., Ltd. The main plant extract components were fennel, chamomile, and saffron. In other similar studies, the fennel dose was 120 mg a day, for saffron it was 60 mg daily, and for chamomile it was 1000 mg a day (23-25). In our study, we examined the effect of these three herbs in 3 concentrations. The high dose (group B) contained a combination of 120 mg of fennel extract, 60 mg of saffron extract, and 1000 mg of chamomile extract. In medium dose (group D) was 60 mg fennel extract, 30 mg saffron extract, and 500 mg chamomile extract. In low dose (group A) was 30 mg fennel extract, 15 mg saffron extract and 250 mg chamomile extract and placebo (group C) (sterile dH2O). Selected women received a complete written and oral description of the study before signing an informed consent form. Next, the women were randomized in to one of four study groups. All study participants completed demographic and MRS questionnaires under the same circumstances at baseline, 6th week, and then at 12th week. Then for 12 weeks one group received placebo, 3 other groups received medium, low and high dose of extract 25 drops daily. Since this was a triple-blinded trial and only the pharmacist was aware of the contents of the bottle, each participant was given a bottle that was labeled with A, B, C, or D. At that time, the women were also requested to report if they experienced any adverse effects.

Outcome measures: Menopause symptoms

6. **Statistical Analysis:** Data analysis was conducted using SPSS (version 23) statistical software. The level of significance was set at P< 0.05. Differences in group characteristics and baseline values were analyzed using the following: Kruskal-Wallis test for continuous variables with abnormal distributions, Anova for normally distributed Quantitative variables, and the Kolmogorov-Smirnov test to detect the normality of variables. To compare treatment effects on the outcome measures within and between group changes, the Wilcoxon and Friedman test were used. Also prism 6 software was used to create the graphs.

RESULTS

108 women fulfilled the eligibility criteria and successfully completed the baseline assessment with complete data for the entire 12-weeks clinical trial. Study retention was excellent (90%). One participant in group B and one participant in

[1] Menopause Rating Scale

Table 1: *Background data*

Characteristic	groups	A	B	C	D	P
	Age Median	51.53	51.63	51.50	51.20	**0.985**
	BMI Median	22.53	22.66	22.73	22.64	**0.983**
Woman Job Number	housewife	17	16	16	19	**0.827**
	Employee	13	13	12	10	
	Worker	0	1	2	1	
spouse Job Number	Unemployed	0	0	0	0	**0.455**
	employee	26	20	24	23	
	Free job	4	9	4	6	
	Worker	0	1	2	1	
Woman Education Number	illiterate	1	4	4	3	**0.846**
	Diploma	16	13	12	14	
	Collage education	13	13	14	13	
Spouse Education Number	illiterate	1	3	2	2	**0.849**
	Diploma	12	9	10	13	
	Collage education	17	18	18	15	

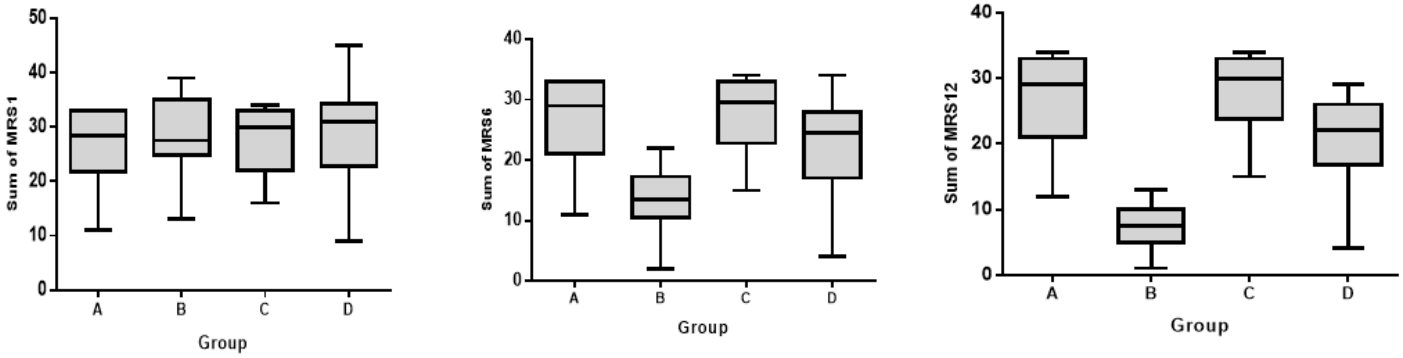

Figure 1: *Comparison of the MRS scores at first, 6th and 12th week of treatment in 4 groups*

group D withdrew because of flushing and one participant in group D, four participants in group A, and five participants in group C withdrew because they did not experience any change in their menopausal symptoms.

Confidence interval was 95%. Test results for data normalization that were obtained by the Kolmogorov- Smirnoff indicated that age and BMI in all the subjects were not normal (P = 0.01, 0.04). Mean scores of MRS questionnaire were not normal (P <0.001). There were no differences between groups regarding demographic data (**Table 1**).

Statistically significant difference was not observed in the MRS score in the first week. However, significant differences were in the sixth (p<0.001) and twelfth weeks (P<0.001) (**Figure 1**).

We compared the MRS score in the first week with the sixth and twelfth week and sixth week with the twelfth. No statistically significant differences were seen between group A and C, but statistically significant differences were seen between group B (p<0.001) and D (p<0.001) in all weeks (**Figure 2**).

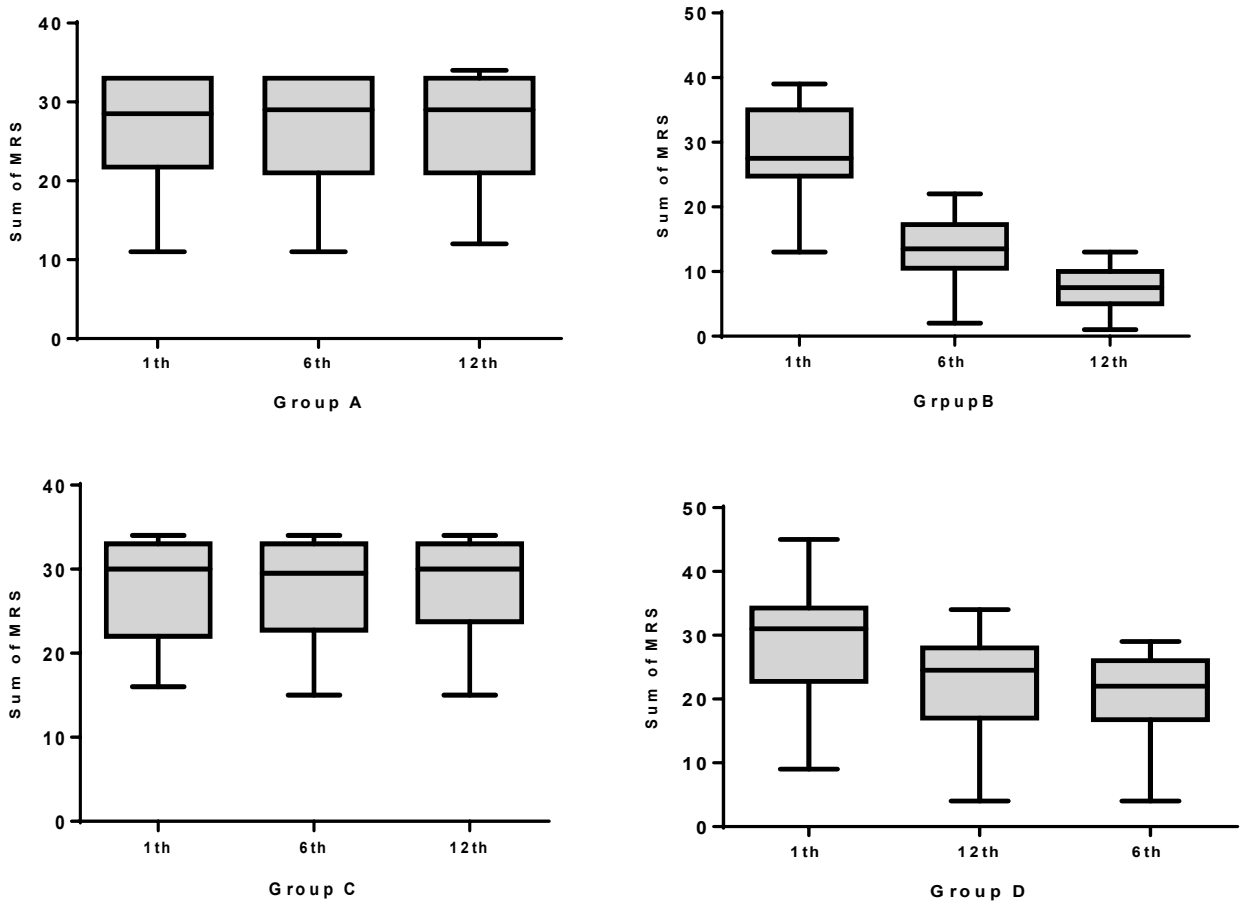

Figure 2: *Comparison of the MRS scores in every group at the 1th, 6th and 12th weeks*

Table 2: *Comparison the median and inter quarter range in MRS score at Different weeks*

Week	MRS 1th week		MRS 6th week		MRS 12th week	
Group	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
A	28.5	11	29	12	29	12
B	27.5	10	13.5	6.75	7.5	5
C	30	18	5.29	10.25	30	9.25
D	29	12	24	11	22	9.25
KOROSCAL -WALLIS	**Chi-square:0.683 P=0.87**		**Chi-square:51.46 P< 0.001**		**Chi-square:68.731 P< 0.001**	

No significant statistical differences in the first week were observed between the groups. However, in the sixth week, there were significant differences between group B ($p<0.001$) and all other groups. A significant statistical difference between groups D and C ($p<0.01$). In week 12 significant statistical difference was also observed between group B and all other groups ($P<0.001$). Significant statistical differences between group D existed, when compared with all other groups at week 12 ($P=0.01$) (**Table 2**).

DISCUSSION AND CONCLUSION

In this study, we evaluated the effects of a compound herbal medicine on menopause symptoms. This randomized, triple-blind, placebo-controlled showed that our herbal extract effectively improved various climacteric symptoms. In MRS score, groups B and D showed significant improvement within groups when compared the sixth and twelfth week with baseline. With comparing groups A and C in the sixth week to the twelfth and first week, their symptoms aggravated. Comparing the groups in the sixth week, group B had the most improvement. In the twelfth week, there was improvement in groups B and D. However, group B showed significant improvement when compared with group D. In consistence of our study, significant decreases in all MRS scores were reported in postmenopausal women after 12 weeks of Traditional Chinese Medicine (26). Akbari reported that fenugreek and flaxseed did not influence the severity and frequency of hot

flushes before eight weeks, but after eight weeks a decrease in severity and frequency was observed in subjects who used fenugreek (27). Our trial also was 12 weeks, but from 6th week, significant improvement were seen. In the effectiveness of an herbal extract, statistically significant improvement was observed in the MRS-II score in both groups after two and four weeks of treatment; the improvement was significantly better in the Lady 4 group (6). Kupfersz reported a decrease only in number and intensity of hot flushes from baseline. There was also a marked alleviation of sleep disturbances and fatigue (16). Also Chang reported, KMI (the mean Kupperman Menopause Index) score was significantly reduced in the EstroG-100 treatment group when compared to that of the placebo group (7). Green reported treatment by qualified herbal practitioners was able to reduce the total scores of the GCS (Greene Climacteric Scale) (28). But, Plotnikoff reported treatment failure in Japanese herbal medicine. TU-025 did not demonstrate efficacy beyond the placebo for reducing the severity and frequency of hot flash symptoms, climacteric symptoms, or disrupted sleep symptoms in post-menopausal American women (29). Although the mechanism underlying menopause symptoms has not been fully clarified, the results of various basic and clinical studies have indicated that dramatic changes in the hormonal environment, especially the sharp decline of estrogen, during menopause play key role. We though most of these herbal medicines, alleviate the menopausal symptoms because of phytoestrogenic effects. In our study we examined two phytoestrogen herbal medicine plus Saffron that had synergism effect on menopausal symptoms. The strengths of the study are that it was a randomized controlled trial of a complex medical intervention of quality complementary and alternative medicine. The length of the trial was adequate to measure changing. No adverse events were observed or reported by participants who received the herbal extracts.The study limitation was the somewhat small size. A larger population is needed to confirm the results and to increase the statistical power of the study.

The 12-week treatment with the herbal compound showed a statistically significant improvement in the various menopausal symptoms in group B.

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