

# Comparison the Effect of *Echium amoenum* Extract with Fluoxetine on Depression in Menopausal Women. A Double-blind Randomized Controlled Trial

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## Abstract

**Introduction:** Depression is one of the most commonly reported complaints among menopausal women. Herbal medicines appear to be one of the safe and inexpensive treatments for women suffering from the symptom. Therefore, the present study aimed to compare the impact of *Echium amoenum* extract with fluoxetine on depression in menopausal women. **Methods:** This double-blind randomized clinical trial was performed on 72 menopausal women referred to Health Center No. 7 in Ahvaz, Iran. Participants were randomly assigned in two intervention ( $n = 36$ ) and control groups ( $n = 36$ ). *E. amoenum* extract capsule and fluoxetine capsule were packed in similar envelopes with a code number, and then, the participants of both groups received 60 capsules for 8 weeks. The Hamilton depression rating scale (HAM-D) was used to diagnose and analyze the severity of depression. The severity of depression was assessed before intervention and in the 4<sup>th</sup>, 6<sup>th</sup>, and 8<sup>th</sup> weeks after the intervention. Data analysis was performed using SPSS version 21 software through independent *t*-test, Chi-square, and repeated measures tests. P-value was set less than the significance level (0.05). **Findings:** At the beginning of the study, the comparison of mean depression scores in both intervention ( $19 \pm 0.477$ ) and control ( $18.90 \pm 0.440$ ) groups did not show a significant difference ( $P = 0.889$ ). However, a statistically significant difference was observed in the mean score of depression in both groups in the 4<sup>th</sup> week of intervention ( $P \leq 0.01$ ). No statistically significant difference was found between the mean score of depression in both groups at the end of the study ( $P = 0.1$ ). Mean scores of depression in participants receiving *E. amoenum* extract before the intervention also significantly decreased after intervention ( $P < 0.001$ ). **Conclusion:** According to the results, hydroalcoholic extract of *E. amoenum* can improve the symptoms of depression in menopausal women, without any side effects.

**Key words:** Depression, *Echium amoenum*, menopause

## INTRODUCTION

Menopause is one of the most critical stages of the women's life, which can be accompanied by a large number of physiological and psychological changes.<sup>[1,2]</sup> The number of post-menopausal women is also expected to increase. It is estimated that there will be 1.1 billion post-menopausal women in the world by 2025.<sup>[3]</sup> An estimated 6000 women reach menopause

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in the United States every day, and it is predicted that, in 2021, of menopausal age will be living in Iran.<sup>[4]</sup> Due to continuous decline in ovarian activity and various physical and mental symptoms, menopause can lead to some changes in the life quality of women.<sup>[5]</sup> Most notable among these are vasomotor disorders, mood disorders, sleep disturbances, or changes in sexual dysfunction, which can be bothersome to women.<sup>[4]</sup> According to the National Institutes of Health, about one in every five women can expect to develop clinical depression during the transition to menopause.<sup>[6]</sup> The prevalence of depression of post-menopausal women was reported 34.7% in some regions in Iran.<sup>[7]</sup> Insomnia and hypersomnia, anorexia nervosa and bulimia nervosa, feelings of worthlessness, fatigue or loss of energy, feelings of sadness and guilt, and frequent thoughts of death, suicide, and suicide attempt are among the most common symptoms of depression.<sup>[8]</sup> The results of several studies indicate that depression in menopausal women is positively related with osteoporosis, metabolic syndrome, cardiovascular disease, and a significant decrease in work performance.<sup>[9]</sup> Today, several medications have been used for the treatment of depression. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, citalopram, and others are frequently used as first-line antidepressants, with many problematic side effects, including gastrointestinal problems (involving stomach and intestines), nervousness, headache, tolerance, and sexual dysfunction.<sup>[10]</sup> In addition, evidence-based data suggest that regular exercise, light therapy, omega-3 fatty acids, yoga, and St. John's wort are among different forms of "alternative" and non-drug treatment of depression.<sup>[11,12]</sup> The use of complementary/alternative medicine therapies has increased dramatically in the past decade because they have the potential to interact with other medications prescribed by physicians.<sup>[13]</sup> With a scientific name "*Echium amoenum*. L.," borage is a plant indigenous to Iran from boraginaceae family, which grows naturally in the northern parts of Iran, especially in Mazandaran and Azerbaijan. This plant has been used in Iranian traditional medicine due to its therapeutic and sedative effects, including saponin, Vitamin C and E, tannin, and mineral salts.<sup>[14,15]</sup> Saponin is exclusively found in a Chinese herbal medicine called ginseng, and several studies have shown its effectiveness to improve the memory and lower anxiety levels.<sup>[16]</sup> According to the results of a study, oral intake of *E. amoenum* extract increased neurotransmitter levels of dopamine and serotonin in depression rats.<sup>[17]</sup> In addition, the results of another study by Komaki *et al.* (2015) confirmed the anxiolytic effect of *E. amoenum* extract.<sup>[18]</sup> Bargard *et al.* also found that the aqueous extract of *E. amoenum* has a positive effect on the treatment of mild-to-moderate major depressive disorder.<sup>[16,19]</sup> Despite the antidepressant impact of *E. amoenum* extract in humans and existence of multiple drug therapy problems, there have been no reports in literature comparing the antidepressant impact of this plant with chemical treatments. Therefore, the present study aimed to compare the effectiveness of fluoxetine, a selective SSRI, with *E. amoenum* on the depressive symptoms of menopausal women to find an

appropriate alternative relieving the side effects of drug therapy.

## METHODS

This double-blind randomized clinical trial was performed on 72 menopausal women referred to Health Center No. 7 in Ahvaz, Iran. Sampling was conducted after receiving approval from Research Council and obtaining ethical clearance from the Medical Ethics Committee of Ahwaz University of Medical Sciences (IR.AJUMS.REC.1396.325) as well as Iranian Registry of Clinical Trials (IRCT) (IRCT2017051133925N1). Participants were selected using simple random sampling. Inclusion criteria were as follows: An absence of menstruation for at least 12 months, age range between 45 and 60 years of age, and total score from 14 to 22 (moderate-to-severe depression) based on the Hamilton Depression Rating Scale (HDRS). The exclusion criteria included: Taking antidepressants and anti-anxiety medications during the past 3 months, patients with psychiatric and neurological disorders, getting any systemic diseases (hypertension, diabetes, renal, and cardiovascular diseases), taking psychotropic medications, having suicidal thoughts, alcohol consumption, taking herbal medications for treating menopausal symptoms during the past month, use of drugs that interfere with fluoxetine (warfarin, heparin, aspirin, and antidepressant), and surgery such as radical hysterectomy, vaginoplasty, and abnormal.

The sample size was calculated 33 for both groups based on the independent samples *t*-test with a 95% confidence interval and 90% power. The dropout rate was also considered 10% for each group.<sup>[20]</sup> First, demographic and HDRS questionnaires ( $n = 320$ ) were completed by the individual participants. Then, eligible participants ( $n = 72$ ) were included in the study after providing some explanations regarding the objectives and administration procedure as well as obtaining a written consent form. Next, the samples were randomly divided into intervention ( $n = 36$ ) and control groups ( $n = 36$ ) using a two-letter codes (A and B) allocated for participants. Data were collected by means of a self-report questionnaire. The HDRS questionnaire was used to assess the severity of depression. It consists of 17 items with Likert scale of either 0–4. The scores are interpreted as follows: 0–7 = normal, 8–13 = mild depression, 14–18 = moderate depression, 19–22 = severe depression, and 23–>23 = very severe depression. The steps for preparing the medication were as follows. *E. amoenum* flowers were initially collected, and then, their genus and species were identified and confirmed by botanical experts working in Adonis Herb Institute. Next, the samples were rinsed in cold water and then allowed to dry in the shade away from direct sunlight and humidity. After drying, the samples were powdered using an electric grinder. About 50 g of flowers powder was wrapped with a filter paper and then inserted into a Soxhlet tool. The extraction process was carried out for 10 h using a 200 mL ethanol solvent with a

temperature of 70°C. The extract was concentrated using a solvent removal device and was placed in a glass container at 40°C for 24 h to dry. Finally, 500 mg of the resultant powder was fitted into a size 00 capsule and kept in a dry and cool place for subsequent use. The capsules were sequentially packaged in similar envelopes, and each participant received 60 capsules (500 mg) for 8 weeks. Another person prepared the envelopes and provided to participants. Questionnaires were filled before the intervention and 4, 6, and 8 weeks after the intervention. Data analysis was performed using SPSS version 21 software through independent *t*-test, Chi-square test, and repeated measures analysis test. *P*-value was set less than the significance level (0.05).

## Findings

Seventy-two menopausal women were examined in the study. During the intervention, three participants were excluded from the experimental group (one for gastrointestinal problems and two for sleepiness) and three from the control group (two for lack of referral and one for headache). As a result, of 66 participants, 33 were assigned to an experimental group, and 33 were assigned to a control group [Figure 1]. The mean age in the intervention group was  $52.27 \pm 3.59$  years and in the control group was  $52.54 \pm 3.75$  years ( $P = 0.776$ ). In addition, the average age of menopause in the intervention group was  $48.24 \pm 3.7$  years and the control group was  $48.81 \pm 2.70$  years ( $P = 0.422$ ). The average body mass index in the intervention group was  $30.02 \pm 5.21$  years and in the control group was  $30.63 \pm 5.88$  years ( $P = 0.669$ ), showing no significant difference. Other sample features have been shown in Table 1. The data analysis showed that the mean depression score in the participants receiving *E. amoenum* extract capsule was  $19 \pm 0.477$  before the intervention and found to increase to  $758 \pm 0.654$  at week 8, indicating a significant reduction before the intervention ( $P < 0.001$ ). This finding confirms the impact of *E. amoenum* extract on improving depression in

menopausal women. Further, according to independent *t*-test, there was no significant difference between the depression mean scores before and after intervention ( $P = 0.889$ ). However, a significant difference was found in the depression mean scores in two intervention and control groups at 4 weeks ( $P \leq 0.01$ ). The comparison of mean depression scores showed no significant difference between the two groups on the 6<sup>th</sup> ( $P = 0.905$ ) and 8<sup>th</sup> weeks ( $P = 0.1$ ) [Table 2]. Furthermore, a significant difference was shown in the depression mean scores at different times based on the results of the repeated measures test ( $P < 0.001$ ) [Table 3].

## DISCUSSION

The present study aimed to compare the effectiveness of fluoxetine, a selective SSRI, with *E. amoenum* on the depressive symptoms of menopausal women. The findings from this study showed no significant difference in the mean score on the HDRS between the two intervention and control groups. In addition, the comparison of depression means scores in both intervention and control groups did not show a significant difference at 5 weeks, suggesting the impact of *E. amoenum* on the treatment of short-term depression in comparison with fluoxetine. However, it was not significant in the long term. Further, there have been no reports in literature comparing the antidepressant impact of this plant with chemical treatments. Data analysis showed a significant decrease in the depression mean scores of participants taking *E. amoenum* extract capsule after the intervention ( $P < 0.001$ ). Our finding supports the impact of *E. amoenum* extract on improving depression in menopausal women and is consistent with the results of the previous studies evaluating the effectiveness of *E. amoenum* extract in the treatment of mild-to-moderate depression disorder and obsessive-compulsive disorder.<sup>[16,19]</sup> These results agree with the findings of the study by Bargard *et al.* (2004) on

**Table 1: Demographic characteristics of participants by group**

Demographic characteristics	n (%)		Significance level
	Intervention group	Control group	
Educational level			
Illiterate	(45.5) 15	(69.7) 23	0.157
Elementary school	(39.4) 13	(27.3) 9	
Secondary school	(12.1) 13	(3) 1	
Associate degree and above	(3) 1	0	
Occupation			
Housekeeper	(97) 32	(93.9) 31	1
Employed	(3) 1	(6.1) 2	
Economic status			
Low	(24.2) 8	(15.2) 5	0.612
Middle	(42.4) 14	(51.5) 17	
High	(33.3) 11	(33.3) 11	

**Table 2:** Comparison of mean and standard deviation of depression score in menopausal women before and after intervention

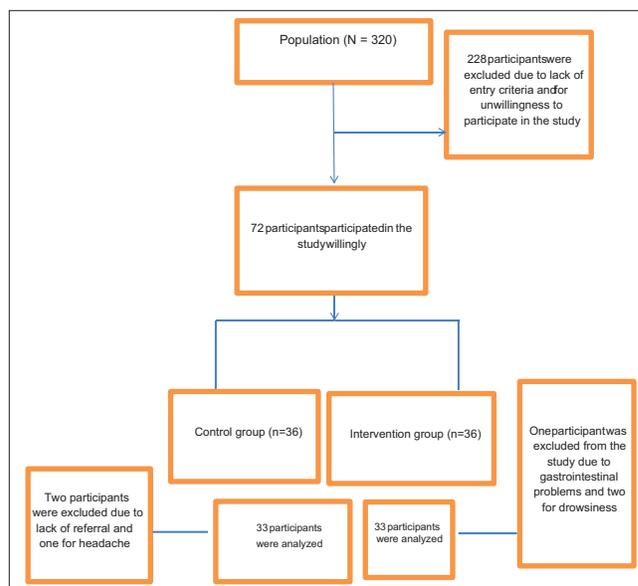
Group	Before intervention	Week 4	Week 6	Week 8	Significance level
Depression score	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Intervention	19±0.477	11/273±0.586	8/97±0.593	7/758±0.654	0.001 ≤
Control	18/909±0.440	13/242±0.459	8/879±0.470	6/485±0.387	0.001 ≤
Significance level	0.899	0.01	0.905	0.1	

SD: Standard deviation

**Table 3:** Comparison of mean depression score in menopausal women at different times

Group	Time	Time	Mean	Significant level
Intervention	1	2	7.727	≥0.001
		3	10.03	≥0.001
		4	11.242	≥0.001
	2	3	2.303	≥0.001
		4	3.515	≥0.001
		4	1.212	≥0.03
Control	1	2	5.667	≥0.001
		3	10.03	≥0.001
		4	11.424	≥0.001
	2	3	4.364	≥0.001
		4	6.758	≥0.001
		4	2.394	≥0.001

35 patients indicating greater improvement of depressed participants from the placebo group.<sup>[19]</sup> Further, in another study (2005) on 33 patients with obsessive-compulsive disorder and depression and anxiety, they found significant differences in the depression mean score between the two groups at 4 weeks ( $P = 0.04$ ) and 6 weeks ( $P = 0.02$ ) after the intervention.<sup>[16]</sup> Faryadian *et al.* (2014) also reported that *E. amoenum* extract increases serotonin and dopamine neurotransmitters in depressed rats (reserpine-induced depression).<sup>[17]</sup> The recent evidences suggest that serotonin is a significant mood modulator, and neurotransmitters (dopamine, serotonin, and melatonin) are necessary for a normal balanced mood, emotions, and sleeping.<sup>[21,22]</sup> It seems that these findings explain the positive impact of *E. amoenum* extract on the improvement of depressive symptoms among the menopausal women. Despite the limited number of our participants, the findings of this study have a number of important implications for future practice. Given a greater interest among the women for the use of herbal remedies for the management of menopause symptoms instead of chemical drugs and their fewer side effects, a further study with more focus on the impact of *E. amoenum* extract on vasomotor symptoms, hot flashes, and sleep disorder during menopause is, therefore, recommended. This study was the first study to undertake a comparative analysis between herbal remedies and chemical medications for the treatment of depression.

**Figure 1:** The procedure for selecting samples

It is beyond the scope of this study to examine the women experiencing severe symptoms in their perimenopause.

## CONCLUSION

According to the results, hydroalcoholic extract of *E. amoenum* can improve the symptoms of depression in menopausal women, without any side effects.

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