



Effect of *Vitex agnus-castus* on Depression of Postmenopausal Women: A Randomized Clinical Trial

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Abstract

Background: During menopause, women undergo biological, social, and psychological changes and are sensitive to stressors, especially anxiety and depression. Decreased estrogen in postmenopausal women causes mood swings, especially depression and anxiety.

Objectives: We aimed to determine the effect of the *Vitex agnus-castus* extract on depression in postmenopausal women referring to a bone density measurement center in Shiraz.

Methods: In a randomized controlled trial, 60 postmenopausal women were randomly divided into an intervention group and a control group. In the intervention group, the research units were assigned to two groups of *Vitex agnus-castus* tablets and placebo, using random permuted blocks with a block size from one to six for each eligible case. After three months, depression was evaluated by the Edinburg Postnatal Depression Scale (EPDS) in both groups. Then, the results were analyzed using the independent t-test for quantitative variables. The obtained data were analyzed by a statistician using SPSS21.

Results: Based on the results, the two groups were homogeneous in terms of the level of education, occupation, and housing, and a significant decrease was observed in the mean depression score in the Agnugolgroup ($P < 0.001$).

Conclusions: Because depression increases during menopause, it is recommended that it should be used as a supplement during menopause.

Keywords: *Vitex agnus-castus*, Depression, Menopause, Women, Herbal Medicines

1. Background

During menopause, women undergo a wide range of biological, social, and psychological changes. They may be sensitive to stressors, especially anxiety and depression (1, 2). Postmenopausal women are physically susceptible to various illnesses and disabilities, as the results of Manzouri (2010) and Abbasinia (2016) studies in Tehran showed that 70% of older women, including postmenopausal women, belonged to this group and their anxiety and depression disorders were at a moderate level (3, 4).

Depression often begins with a situation where many changes in human life occur. Menopause also increases the risk of depression due to menstruation, the marriage of their children, loneliness of the mother, death of a spouse, retirement, etc. (5). Most menopausal women are in situations where they are both emotionally and professionally responsible for family life, so helping them with their psychological problems is a service to the family and com-

munity. Depression and anxiety can lead to complications that can be attributed to physical problems caused by depression and anxiety, psychological problems in the family, or the transmission of depression to others, and eventually suicide, which is usually followed by untreated depression (6).

Studies have shown that reduced estrogen in postmenopausal women causes mood swings, especially depression and anxiety. More than 70% of women around the time of menopause cry from the simplest issues and become irritable and restless, and more than 60% of them suffer from anxiety, depression, and memory loss (7). Herbal medicines that reinforce the hormonal, immune, and nervous systems can be noticed. The consumption of medicinal herbs can help treat the underlying causes of imbalance (8). Due to the high prevalence of depression, especially among women, and the side effects of the use of chemical drugs in its treatment, such as nausea, weight

gain, and insomnia, particular attention has been paid to omega-3 sources in recent years for the treatment of diseases, especially mental illness and depression (9). Besides, *Vitex agnus-castus* is one of the medicinal plants in traditional Iranian medicine, which is used in cases, e.g., for the reduction of sexual desire and increase in the amount of milk used. It is less commonly used in menopause. Therefore, due to the limited number of studies, this drug was assessed in this study.

2. Objectives

We decided to evaluate the therapeutic effect of *Vitex agnus-castus* on the treatment of depression in women.

3. Methods

This study was a Randomized Clinical Trial (RCT) conducted on 60 postmenopausal women referring to the Bone Density Center of Shiraz Namazi Hospital who had the inclusion criteria to enter the study. Convenience sampling was performed on those selected cases referring to the research environment at the time of the researcher's attendance. The study was conducted as a double-blind study to both the researcher and the patient. The inclusion criteria were postmenopausal women who were willing to participate in the study, no history of taking any hormonal medicine, and no history of allergy to herbal medicines. The exclusion criteria were an allergic reaction to medication and a lack of interest in continuing participation.

The research units were assigned to two groups of *Vitex agnus-castus* tablets and placebo using random permuted blocks with a block size from one to six for each eligible case (Figure 1). In the intervention group, coated tablets were used containing the dried fruit extract of the *Vitex agnus-castus* plant weighing 3.2-4.8 mg. The tablets were prepared by Goldaru Pharmaceutical Company in Iran, and a placebo (starch compounds) was made at the Shiraz School of Pharmacy. Therefore, two questionnaires were used, including demographic information and the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is used to identify women with postpartum depression. Chu et al. conducted a study in Korea in 2009-2010 and showed the sensitivity and reliability of this scale to be 92.4% and 86%, respectively. Validity and reliability of the study tool by Chu et al. were the basis of this study (10). The menopausal women completed the informed consent form. Women in control and experimental groups received three *Vitex agnus-castus* and placebo tablets per day. After three months, women were contacted, the questionnaire was completed by women, and the results were analyzed by the

independent t-test for quantitative variables. The obtained data were analyzed by a statistician using SPSS21.

4. Results

First, the Kolmogorov-Smirnov test was used to investigate the normal distribution of quantitative variables. Based on the results, all quantitative variables had a normal distribution, and parametric tests were used for their analysis. Based on the results of the independent t-test, the two groups were homogeneous in terms of education, occupation, and housing. In the Agnugol group, the mean scores of depression were 7.3 ± 6.7 before the intervention and 2.8 ± 4.7 after the intervention. In the control group, the scores were 8.1 ± 7.9 before the intervention and 7.8 ± 7.8 after the intervention. The paired t-test showed a significant decrease in the mean depression scores in the Agnugol group ($P < 0.001$), but in the placebo group, it was not significant based on paired t-test results ($P = 0.133$) (Table 1).

Table 1. Comparison of the Mean Depression Scores Before and After Intervention in the Intervention and Control Groups

Depression	Intervention group	Control group	P Value
Before intervention	7.3 ± 6.7	8.1 ± 7.9	0.729
After intervention	2.8 ± 4.7	7.8 ± 7.8	< 0.001
Changes	4.5	0.3	< 0.001
P Value	< 0.001	0.133	

The independent t-test results showed homogeneity in terms of age, menopausal age, menopausal duration, body mass index, length of the marriage, number of births, number of pregnancies, number of children, and number of abortions.

5. Discussion

According to the results of this study, *Vitex agnus-castus* reduced depression in postmenopausal women compared to placebo, which is consistent with studies in which *Black cohosh* and *Valerian* were effective in the treatment of postmenopausal depression (11-13). Similar to some studies, Chasteberry flower and John's wort were effective in treating menopausal depression (14). In a study, Asgari et al. showed that licorice affected the physical dimensions of the quality of life. In the study, before the intervention, the quality of life of 60 postmenopausal women in the two groups did not differ significantly, but one month after the intervention in the overall quality of life and dimensions of

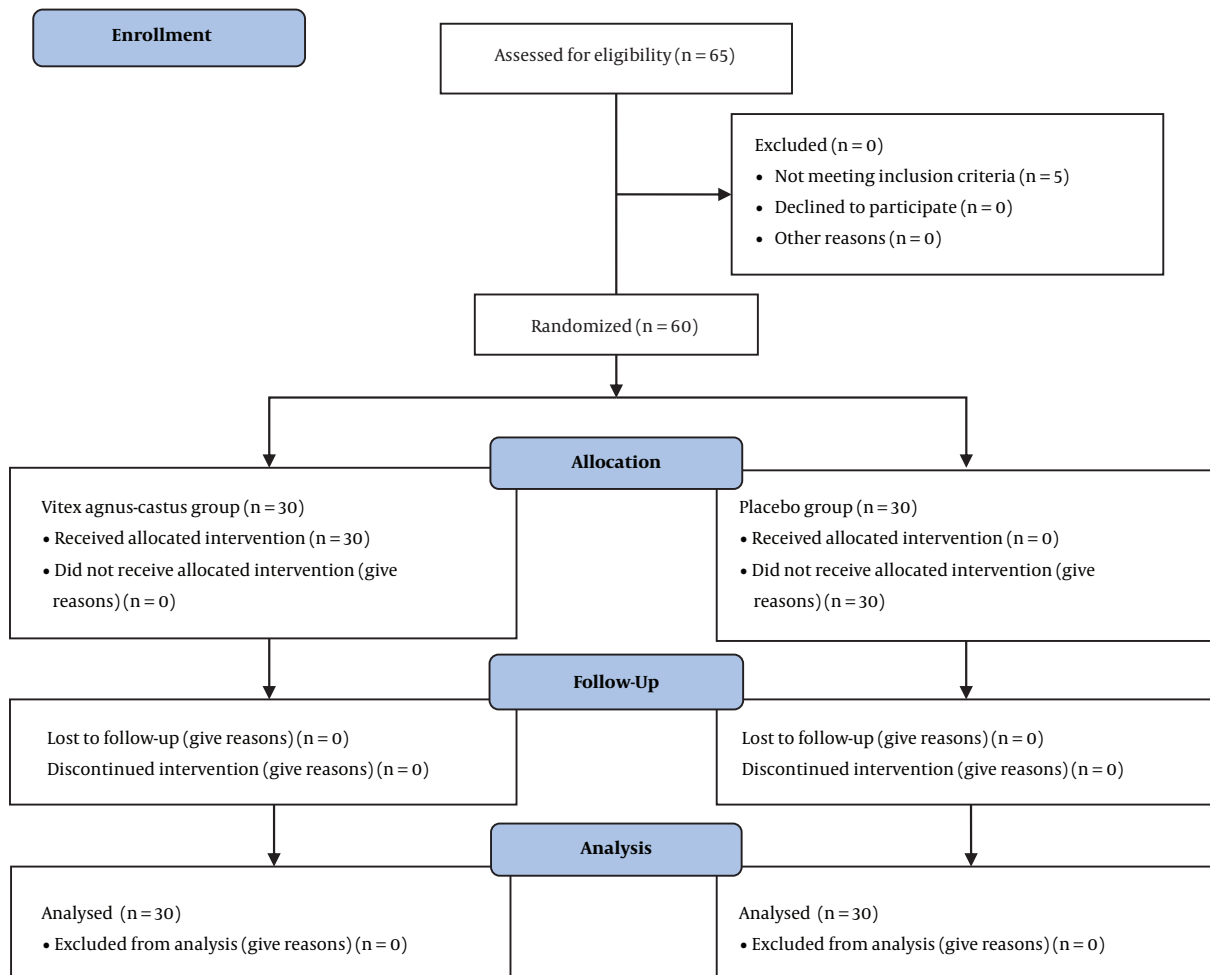


Figure 1. Flow diagram of the study

vasomotor, psychosocial, and physical differences were observed, showing that the consumption of licorice in postmenopausal women improved the quality of life (15). The results of the present study, in which the extract of the *Vitex agnus-castus* plant could improve depression in postmenopausal women and indirectly enhanced the quality of life of women, are consistent with the findings of other studies (16-18).

Plants containing phytoestrogens (estrogen-like compounds) have a special place among the herbs that are recommended for the treatment of menopausal symptoms (19). A positive association between menopausal symptoms and anxiety and depression and mental health scores has also been reported in other studies (20-22). Cognitive and psychological functions may change in menopause. *Vitex agnus-castus* contains substances called phytoestro-

gens. The structural similarity of these substances with estrogens has caused dopaminergic properties by binding to dopamine D2 receptors (23). Phytoestrogens have a high tendency to bind to beta estrogen receptors than to alpha estrogen receptors. This form of receptors is most commonly expressed in the ovaries, uterus, brain, and bladder, so it can create a hormonal balance in the woman's body (24). However, in the studies by Zang (2016) and Bahri et al. (2013), there was no statistically significant relationship between the depression score and the severity of menopausal symptoms (25, 26). The differences in the results of these studies may be due to the differences in the tools used in this study, as well as the cultural and ethnic differences of the study populations. Since the quality of life of postmenopausal women is an important health issue in different societies and is one of the main goals of health care in

this period, depression and anxiety can be easily prevented by treating their symptoms, and it is possible to improve the quality of life of postmenopausal women provided that menopausal symptoms are the causes of psychological disorders such as anxiety and depression (26). Although no significant side effects were observed in this study with the use of *Vitex agnus-castus*, more detailed studies with larger sample sizes are recommended to evaluate the efficacy and safety of this drug. Rarely, itching and minor gastrointestinal upset have been reported.

One of the strengths of this study was that it was a double-blind clinical trial. Individual, genetic, and mental status differences of the research units influenced the way they responded to the questionnaire, which was beyond the control of the researcher. However, these differences were eliminated as much as possible by randomization. This was among the limitations of the present study.

5.1. Conclusion

The extract of *Vitex agnus-castus* has antidepressant properties. As the rate of depression increases during menopause, it is, therefore, suggested that it be used as a supplement during menopause.

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Footnotes

Authors' Contribution: MA and NT prepared the first draft of the manuscript, and MA made critical revisions to the paper and responded to the reviewers' supervision and guidance on doses and the construction of herbal medicine and placebo capsules.

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References

- Dalal PK, Agarwal M. Postmenopausal syndrome. *Indian J Psychiatry*. 2015;57(Suppl 2):S222-32. doi: [10.4103/0019-5545.161483](https://doi.org/10.4103/0019-5545.161483). [PubMed: [26330639](https://pubmed.ncbi.nlm.nih.gov/26330639/)]. [PubMed Central: [PMC4539866](https://pubmed.ncbi.nlm.nih.gov/PMC4539866/)].
- Yazdanpanahi Z, Nikkholgh M, Akbarzadeh M, Pourahmad S. Stress, anxiety, depression, and sexual dysfunction among postmenopausal women in Shiraz, Iran, 2015. *J Family Community Med*. 2018;25(2):82-7. doi: [10.4103/jfcm.JFCM_117_17](https://doi.org/10.4103/jfcm.JFCM_117_17). [PubMed: [29922107](https://pubmed.ncbi.nlm.nih.gov/29922107/)]. [PubMed Central: [PMC5958528](https://pubmed.ncbi.nlm.nih.gov/PMC5958528/)].
- Manzouri L, Babak A, Merasi M. The depression status of the elderly and its related factors in Isfahan in 2007. *Iran J Age*. 2010;4(4):0.
- Abbasinia H, Alizadeh Z, Vakilian K, Ranjbaran M. Effect of Chamomile extract on sleep disorder in menopausal women. *Iran J Obstet, Gynecol Infertil*. 2016;19(20):1-7.
- Jahanbakhshi Z. Malformation and mental health in postmenopausal women, infertile and addicted women. *Women J*. 2016;7:1-14.
- Maddineshat M, Keyvanloo S, Lashkardoost H, Arki M, Tabatabaiechehr M. Effectiveness of Group Cognitive-Behavioral Therapy on Symptoms of Premenstrual Syndrome (PMS). *Iran J Psychiatry*. 2016;11(1):30-6. [PubMed: [27252766](https://pubmed.ncbi.nlm.nih.gov/27252766/)]. [PubMed Central: [PMC488138](https://pubmed.ncbi.nlm.nih.gov/PMC488138/)].
- Asgari K, Hashemi B. Comparing the Performance of Five Brain Systems and mood changes (Anxiety and Depression) with the Level of Estrogen in Postmenopausal and Premenopausal. *Armaghane danesh*. 2016;21(6):617-29.
- Kamalipour M, Akhoundzadeh SH, REZAZADEH SA. Herbal medicines in the treatment of depression and anxiety. *J Med Plants*. 2008;7(Supplement 4):1-7.
- Momeni H, Salehi A, Seraji A. Study of Vitex Agnus Castus and Evening Primrose oil on Body Mass Index (BMI). *Complement Med J Fact Nurs Midwifery*. 2012;2(2):71-80.
- Choi SK, Kim JJ, Park YG, Ko HS, Park IY, Shin JC. The simplified Edinburgh Postnatal Depression Scale (EPDS) for antenatal depression: is it a valid measure for pre-screening? *Int J Med Sci*. 2012;9(1):40-6. doi: [10.7150/ijms.9.40](https://doi.org/10.7150/ijms.9.40). [PubMed: [2221088](https://pubmed.ncbi.nlm.nih.gov/2221088/)]. [PubMed Central: [PMC3222089](https://pubmed.ncbi.nlm.nih.gov/PMC3222089/)].
- Grases G, Colom MA, Fernandez RA, Costa-Bauza A, Grases F. Evidence of higher oxidative status in depression and anxiety. *Oxid Med Cell Longev*. 2014;2014:430216. doi: [10.1155/2014/430216](https://doi.org/10.1155/2014/430216). [PubMed: [24876911](https://pubmed.ncbi.nlm.nih.gov/24876911/)]. [PubMed Central: [PMC4020168](https://pubmed.ncbi.nlm.nih.gov/PMC4020168/)].
- Oktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscü E, Zeyneloglu HB. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. *Adv Ther*. 2007;24(2):448-61. doi: [10.1007/BF02849914](https://doi.org/10.1007/BF02849914). [PubMed: [17565936](https://pubmed.ncbi.nlm.nih.gov/17565936/)].
- Kazemian A, Parvin N, Raeisi Dehkordi Z, Rafeian-Kopaei M. The effect of valerian on the anxiety and depression symptoms of the menopause in women referred to shahrekord medical centers. *J Med Plants*. 2017;16:96-101.
- Ghazanfarpour M, Sadeghi R, Abdollahian S, Roudsari RL. The efficacy of Iranian herbal medicines in alleviating hot flashes: A systematic review. *Int J Reprod Biomed*. 2016;14(3):155-66. doi: [10.29252/ijrm.14.3.155](https://doi.org/10.29252/ijrm.14.3.155).
- Asgari P. [The effect of Glycyrriza glabra on quality of life in postmenopausal women]. *Complement Med J*. 2015;2(5). Persian.
- Sadeghi A H, Bakhshi M, Behboodi Z, Goodarzi S, Haghani H. Effect of sage extract on hot flashes in postmenopausal women. *Complement Med J*. 2013;2(4):324-35.
- Jun JH, Lee HW, Choi J, Choi TY, Lee JA, Go HY, et al. Perceptions of using herbal medicines for managing menopausal symptoms: a web-based survey of Korean medicine doctors. *Integr Med Res*. 2019;8(4):229-33. doi: [10.1016/j.imr.2019.08.004](https://doi.org/10.1016/j.imr.2019.08.004). [PubMed: [31646139](https://pubmed.ncbi.nlm.nih.gov/31646139/)]. [PubMed Central: [PMC6804440](https://pubmed.ncbi.nlm.nih.gov/PMC6804440/)].
- Chen HY, Lin YH, Wu JC, Chen YC, Yang SH, Chen JL, et al. Prescription patterns of Chinese herbal products for menopausal syndrome: analysis of a nationwide prescription database. *J Ethnopharmacol*. 2011;137(3):1261-6. doi: [10.1016/j.jep.2011.07.053](https://doi.org/10.1016/j.jep.2011.07.053). [PubMed: [21824510](https://pubmed.ncbi.nlm.nih.gov/21824510/)].

19. Zeidabadi A, Yazdanpanahi Z, Dabbaghmanesh MH, Sasani MR, Emamghoreishi M, Akbarzadeh M. The effect of *Salvia officinalis* extract on symptoms of flushing, night sweat, sleep disorders, and score of forgetfulness in postmenopausal women. *J Family Med Prim Care*. 2020;**9**(2):1086–92. doi: [10.4103/jfmpc.jfmpc_913_19](https://doi.org/10.4103/jfmpc.jfmpc_913_19). [PubMed: [32318472](https://pubmed.ncbi.nlm.nih.gov/32318472/)]. [PubMed Central: [PMC7114003](https://pubmed.ncbi.nlm.nih.gov/PMC7114003/)].
20. Worsley R, Bell R, Kulkarni J, Davis SR. The association between vasomotor symptoms and depression during perimenopause: a systematic review. *Maturitas*. 2014;**77**(2):111–7. doi: [10.1016/j.maturitas.2013.11.007](https://doi.org/10.1016/j.maturitas.2013.11.007). [PubMed: [24365649](https://pubmed.ncbi.nlm.nih.gov/24365649/)].
21. Seritan AL, Iosif AM, Park JH, DeatherageHand D, Sweet RL, Gold EB. Self-reported anxiety, depressive, and vasomotor symptoms: a study of perimenopausal women presenting to a specialized midlife assessment center. *Menopause*. 2010;**17**(2):410–5. doi: [10.1097/gme.0b013e3181bf5a62](https://doi.org/10.1097/gme.0b013e3181bf5a62). [PubMed: [20216277](https://pubmed.ncbi.nlm.nih.gov/20216277/)].
22. Shariat Moghani S, Simbar M, Rashidi Fakari F, Ghasemi V, Dolatian M, Golmakani N, et al. The Relationship Between Stress, Anxiety and Depression With Menopausal Women Experiences. *Avicenna J Nurs Midwifery Care*. 2018;**26**(5):333–40. doi: [10.30699/sjnhmf.26.a5.333](https://doi.org/10.30699/sjnhmf.26.a5.333).
23. van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus extracts for female reproductive disorders: a systematic review of clinical trials. *Planta Med*. 2013;**79**(7):562–75. doi: [10.1055/s-0032-1327831](https://doi.org/10.1055/s-0032-1327831). [PubMed: [23136064](https://pubmed.ncbi.nlm.nih.gov/23136064/)].
24. Jelodar G, Askari K. Effect of Vitex agnus-castus fruits hydroalcoholic extract on sex hormones in rat with induced polycystic ovary syndrome (PCOS). *Physiol Pharmacol*. 2012;**16**(1):62–9.
25. Zang H, He L, Chen Y, Ge J, Yao Y. The association of depression status with menopause symptoms among rural midlife women in China. *Afr Health Sci*. 2016;**16**(1):97–104. doi: [10.4314/ahs.v16i1.13](https://doi.org/10.4314/ahs.v16i1.13). [PubMed: [27358619](https://pubmed.ncbi.nlm.nih.gov/27358619/)]. [PubMed Central: [PMC4915426](https://pubmed.ncbi.nlm.nih.gov/PMC4915426/)].
26. Bahri N, Afiat M, Aghamohamadian HR, Delshad Noughabi A, Bahri N. Investigating the relationship between severity of menopausal symptoms and depression, anxiety and other menopausal symptoms. *Iran J Obstet, Gynecol Infertil*. 2013;**16**(43):14–20.