

The Effect of *Hypericum Perforatum L.* on Severity of Early Menopause Symptoms

Research Article

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Abstract

Objective: Menopause might lead to physical, mental problems for women and also disruption their life quality. Despite the existence of a single treatment to remove the disorders, herbal medicine is referable to chemical one in that they alleviate the related symptoms. The present research study aims to investigate the effect of *Hypericum Perforatum L.* on severity of early symptoms of menopause. **Materials and Method:** This double blind clinical trial study was conducted on 70 menopause women (two 35-person groups) picked out by a purposive sampling procedure. The first group received 160 mg *Hypericum Perforatum L.* (Perforin pill) while the second one received a placebo (ineffective pill). Menopause symptoms of 2, 4, 6, and 8 weeks after taking the pill or placebo were recorded in the 'Kupperman index' for menopause symptoms. The gathered data were then analyzed via independent t-test, one-way ANOVA, and repeated measure variance. Significance level was $P \leq 0.05$. **Results:** The age average in the medicine group was 50.49 ± 2.74 and in the placebo group was 50.63 ± 2.87 . Body Mass Index (BMI) showed an overweight in both groups (27.29 ± 0.75 , 27.23 ± 0.64). Furthermore, comparing the 'Kupperman index' for symptoms between the two groups in 6, 4, and 8 weeks after intervention revealed that the *Hypericum Perforatum L.* significantly had positive effects on alleviation of early menopause symptoms compared to placebo ($P \leq 0.001$). **Conclusion:** The results indicated that *Hypericum Perforatum L.* might alleviate the severity of early menopause symptoms. Thus, given its being economical and also its slight side effects, it is recommended as a suitable and desirable replacement for counterpart chemical medicine.

Keywords: Menopause, *Hypericum Perforatum L.*, 'Kupperman index'.

Introduction

The transition from fertility to menopause is a phenomenon that all women experience throughout the world (1). This physiological phenomenon is an important stage in the life of women, which is followed by the loss of the activity of the follicles of the ovaries and the reduction of female sex hormones (estrogen), menstrual cycles are completely discontinued (2) and gradually the fertility and eventually the person faces a new biological condition (3).

There is a difference between menopause in different societies. This difference depends on many factors and factors, such as the extent to which countries, races, and their social and economic status develop and develop (4).

The statistics and information available for the growing and increasing number of postmenopausal women in the whole world are projected to reach 1.11

billion by the year 2025 (1).

Although menopause is a natural phase of women's lives, many are a distressing period that experiences many problems before and after, often resulting in reduced health due to symptoms. (5,6). One of the symptoms that women experience during menopause include sleep disorders, mood disorders, genitourinary disorders (such as urgency in urination, dyspnea and vaginal atrophy and painful intercourse), vasomotor disorders (such as hot flashes), Night sweats and palpitations), joint pain and stiffness, forgetfulness and increased risk of osteoporosis and hair loss (7-12).

The severity of the symptoms experienced in postmenopausal women is different, in such a way that a woman may not experience any of the symptoms, or only experience one or more or even all of the symptoms. Some people may experience severe symptoms and vice versa, others may have only mild symptoms. In addition, the severity of symptoms in one person may also vary in different days. According to these cases, it is impossible to predict menopause symptoms and to cure the treatment (13), and ultimately pressure the health care system and impose significant costs on them (14). Therefore, any attempt to maintain and promote the health of postmenopausal women will

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have a beneficial effect on reducing health costs (15).

Currently, menopausal disorders and complications are typically treated and controlled by methods such as hormone therapy, including the use of synthetic estrogen (16) but due to the complications of hormone therapy (increased risk of vascular events and breast cancer) and concerns about these complications; the long-term admission of this therapeutic approach is low (17) and ultimately leads to a reduction in the use of this method and the switch to alternative therapies to relieve menopausal symptoms (18).

Some studies have shown that about 32.9% of women in the world have switched to complementary medicine, of which about half of them use complementary medicine solely to treat menopausal symptoms (19). Medicinal plants are widely used today to prevent and treat various types of disorders and diseases, and every day human knowledge is added to the identification, the mechanisms of exposure and the ingredients involved in the manufacture of herbal medicines. One of the plants that today is considered by many due to its numerous properties and much research on it and is one of the most widely used herbal remedies in the whole world; it is *Hypericum Perforatum* L. or tea grass (20). This herb is a perennial herb and wilderness, with yellow flowers that are similar to the vegetable parts of the plant. This plant is native to the regions of Europe, West Asia and North Africa (21). The plant contains various compounds and chemicals, including anthraquinone derivatives (naphthodentrons), flavonoids, tannins, some phenols, fluoroquinolones, volatile oils, hyperfluorine and hypressinum. The industrial preparations of this plant are based on the two substances of Hypericin and Pseudo-Hypericin (22). The results of study by Caning et al. Indicated that flowering plants were significantly more effective than placebo in improving the behavioral and physical symptoms of premenstrual syndrome (23). Volker and colleagues in their study showed that combination therapy of black cohosh with grass is beneficial for the improvement of mental symptoms and hot flashes in postmenopausal women (24).

With life expectancy increase, women spend almost one third of their life in menopause period. Causing problems such as mental and physical disorders, menopause is likely to threaten the health of family and society, which is, in turn, dependent on mothers' health. Thus, it is essential to pay special attention to the health of menopause women. Since there is no complete and single treatment for removing these problems, different researchers have tried to examine the effects of various chemical and herbal medicines. However, given the country's research priorities in terms of herbal medicine and limited studies in this regard and also given contractor results in Farsi and Latin articles, the present study tried to examine the impact of *Hypericum Perforatum* L. on early symptoms of menopause.

Materials and Methods

The present research study is a double blind clinical trial with an ethics permission from Ahwaz medical sciences university numbered U-88221 and clinical trial record number of

IRCT2016040820053N2R1. The study was conducted on 70 menopausal women who referred to treatment-hygienic centers in 2009 in Izeh county. The criteria to enter into the study were: age of 45-60 years old, amenorrhea for at least 12 months, having at least two signs of menopause based on Kooperman's index, and having literacy. Besides, from among criteria to exclude from the study were: women suffering from unnatural menopausal symptoms that is, cessation of menstruation resulted from hysterectomy and radiotherapy, known systematic diseases such as endocrine disorders (thyrotoxicosis), abundant use of phytoestrogens and specific diet in general, having known physical or mental disease, using sexual hormones, allergy to herbal plants, athlete women, using anti-depression medicine, using herbal medicine, BMI higher than 30, and immigration of under study units. The sample size was determined to be 70 by considering the previous related studies and also statistics experts' comments via the following formula:

$$n = \frac{(z_1 - \frac{\alpha}{2} + z_1 - \beta)^2 [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

The sampling procedure was based on purposive sampling and then the research units were assigned randomly in two 35-person groups of control and experimental. First, the purpose of the study was explained to all the units and their informed written consent was received. They were also assured that in case they had any sudden intolerable side effect or became unwilling to continue the study, they could stop taking part in the study. All in all, 80 persons started the study. However, at the beginning of the study 10 of them exited the study due to lack of willingness to participate in the study and the study was conducted on 70 persons.

Intended data were gathered via 'Kupperman index' for menopausal symptoms and also demographical questionnaire. The former is a scale that examines the most important symptoms of menopause. This scale has been used for more than 50 years in different studies related to menopause signs. The modified version of this scale that was used in the present study consisted of 9 important menopausal symptoms including hot flash, night sweat, insomnia, anger, depression, fatigue, headache, polyurea, and bladder pain. These symptoms are scored based on a four-degree likert scale from zero (lack of symptom) to three (severe) (0=no symptom, 1=slight, 2=medium, 3=severe). To weigh the score, the score of hot flash is multiplied by 4, score of night sweat, insomnia, and anger are multiplied by 2, depression, fatigue, headache, polyurea, and bladder pain scores are multiplied by 1. The maximum score of the scale is 45. Finally, its validity has already been confirmed (25).

Blinding was done in this way that the medicine (*Hypericum Perforatum* L. in form of Perforan pill) and placebo were coded by another person and were put in similar packs in a way that neither the researcher nor the subjects had any information on the packs and the

research units selected and used one of the packs while referring to the centers. Both of the groups were given the Kooperman scale and they were asked to record the symptoms 2, 4, 6, and 8 weeks after using the medicine or placebo. The medicine and placebo were prescribed three times a day (one in the morning, and two in the afternoon with a glass of water) for two months (the forms and drugs were given to the units in two stages). The medicine included 160 mg of dried hydro-alcoholic extract of *Hypericum Perforatum L.* (in form of Perforan pill) that included 300 microgram of effective *Hypericum Perforatum L.* produced by Isfahan Gol-Daroo company in 30-number packs (26).

The placebo pills were similar to the main medicine in terms of size, color, shape, weight, and packing. During the study time, the researcher was in phone contact with all of the research units to ensure about the exact use of drugs and if they had any question, she answered them. The gathered data were then analyzed by SPSS 13 in general and descriptive tests such as frequency table, mean, SD, and analytic tests including independent t-test, one way ANOVA, and repeated measure variance in particular. Finally, the significance level was considered to be $P \leq 0.05$.

Results

The results of the study that was carried out on 70 menopausal women revealed that 54.3 percent of women in the medicine group and 60 percent of the women in the placebo group were within the age range of 45-50 years old. 37.1 percent of the medicine group and 22.9 percent of the placebo group were unmarried and 100 percent of the two groups had lower than diploma degree. 57.2 percent of menopausal women in the medicine group and 42.9 percent of the placebo had severe hot flash and no significant difference was observed between the two groups in terms of the above-mentioned features ($P \geq 0.05$). Finally, the two groups were homogeneous in terms of age, BMI, menstruation cease time period, times of hot flash within 24 hours, and Kooperman's symptoms index ($P \geq 0.05$) (Table 1).

Table 1. Demographic characteristics of Menopausal Women in two groups

Group variable	Placebo Mean & SD	Medicine Mean & SD	p-value
Age (years)	50.63 ± 2.87	50.49 ± 2.74	0.832
BMI	27.29 ± 0.75	27.23 ± 0.64	0.734
Menstruation cease time (month)	30.89 ± 12.5	28.66 ± 13.6	0.48
Hot flash times in 24 hours	4.09 ± 0.98	4.26 ± 0.98	0.467
Kooperman Index	26.37 ± 6.89	26.09 ± 6.82	0.862

Comparison of scores gained from the 'Kupperman index' via independent t-test in the two groups uncovered that there was a significant difference between the two groups in scores of 4, 6, and 8 weeks after the intervention ($P \leq 0.001$). Furthermore, the

repeated measure variance results showed that time pass had significant impact on alleviation of the symptoms in the medicine group ($P \leq 0.001$) (Table 2).

Table 2. Comparison of Kooperman index in menopausal women before and after intervention

Group Time	Medicine Mean & SD	Placebo Mean & SD	p-value
Before the study	26.09 ± 6.82	26.37 ± 6.89	0.862
Week 2	25.49 ± 6.65	26.33 ± 6.97	0.565
Week 4	18.31 ± 6.78	26.26 ± 7.44	0.001
Week 6	9.06 ± 6.21	26.11 ± 7.02	0.001
Week 8	6.49 ± 4.61	26.06 ± 7.02	0.001
p-value	<0.001	0.12	

Discussion

The results of this study, which was carried out to investigate the effect of *Hypericum Perforatum L.* on severity of early symptoms of menopause, revealed that *Hypericum Perforatum L.* had a positive impact on early menopause symptoms. Using three 160 mg pills *Hypericum Perforatum L.* (Perforan) daily for a two month time period bear significant effect on alleviating the symptoms compared to the placebo. The study by Walker et al. also uncovered that there was a significant difference between the experimental and control groups after using Rhymifin pill (a combination of *Hypericum Perforatum L.* and black Kohosh) compared to the time when only black Kohosh without *Hypericum Perforatum L.* was used (24). Similarly, Chung et al. also used a combination of *Hypericum Perforatum L.* and black Kohosh in the intervention and observed a significant alleviation in the menopausal symptoms (27). The similarity of these two studies findings might be due to their use of 'Kupperman index' and time period of 4 and 8 weeks.

In the study by Motaghi Dastenaiee et al., physical symptoms of menopause such as night hot flash, sleep problems, heart disorders, and muscle-joint disorders reduced significantly after four weeks while after two weeks there was observed no significant reduction in some signs (28). In a similar vein, the study by Salehi, the extract of Isoflavone of trifolium Pratenes had effects on menopause symptoms and although a considerable reduction in the symptoms was observed in the sixth week, it was not statistically significant (29). The findings of these studies are in line with those of the present study and these similarities with further severity might recommend that herbal medicine could positively help to alleviate the severity of menopausal symptoms (30). As the studies findings indicate, as time passed by, the scores of the 'Kupperman index' decreased meaning that menopausal symptoms reduce with use of *Hypericum Perforatum L.*

The study by Abbasian et al., in which the effect of Perforan (*Hypericum Perforatum L.*) on temperature signs of pre-menstrual syndrome was examined, showed that using *Hypericum Perforatum L.* significantly reduce anger, depression, unreasonable crying, and feeling of loneliness. The present study also

showed that as he above-mentioned symptoms reduced, the 'Kupperman index'scores also decreased. PMS that starts a few days before the next one, is typically followed by reduction of Strogen secretion that is the main factor for this syndrome. This is also one reason for comparing the effect of *Hypericum Perforatum L.* on PMS and menopause (31).

Alternative medicine is one of medical issues that is developing among experts and consumers. They are especially gaining wide information in terms of herbal medicine as it pays special attention to selection of treatment method. Fortunately, our country is rich in terms of existence of herbal plants. *Hypericum Perforatum L.* is extant in mountains as a self growing plant and that is why, it has a less price in the country compared to other countries (32).

From among the strengths of the present study are evaluation of menopause symptoms before the intervention stage and determining the effect of *Hypericum Perforatum L.* in four consecutive periods that, in turn, helped to reach better results. Furthermore, from among its weak points is determination of effectiveness till eight weeks after using the medicine that given the gradual impact of *Hypericum Perforatum L.* and other herbal plants on menopause symptoms, it was better to examine its effect to some weeks after that as well. One restriction of the study was also lack of equality in absorbtion of materials of the drugs in different persons and also their perspective toward the purpose of the study that affected their responding to the questionnaire.

Conclusion

Given the findings of the current research study, *Hypericum Perforatum L.* is effective on alleviation of early symptoms of menopause. Menopause is a natural phenomenon in the life of women and its symptoms are usually painful for them. On the other hand, given the economical aspect of *Hypericum Perforatum L.*, its easy and wide availability due to its abundance in the country, and more importantly, its effectiveness on alleviation of menopausal pains and having slight side effects in comparison to chemical drugs, it is recommended to use *Hypericum Perforatum L.* as a suitable and effective replacement for counterpart chemical drugs.

Conflict of Interests:

The authors reject any kind of conflict of interests with organizations and persons.

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References

1. Theroux R. Women's decision making during the menopausal transition. *J Am Acad Nurse Pract* 2010; 22(11):612-21.
2. Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas* 2010; 67(3):233-8.
3. Pérez JAM, Garcia FC, Palacios S. Epidemiology of risk factors and symptoms associated with menopause in Spanish women. *Maturitas*. 2009;62(1):30-6.
4. Mohammad K, Sadat Hashemi SM, KhalajAbadiFarahani. Age at menopause in Iran. *Maturitas* 2004; 49: 321-326.
5. Russo R, Corosu R. The clinical use of a preparation based on phytoestrogens in the treatment of menopausal disorders. *Acta Biomed Ateneo Parmense*. 2003;74(3):137- 143.
6. Reed SD, Ludman EJ, Newton KM, Grothaus LC, Lacroix AZ, Nekhlyudov L, et al. Depressive Symptoms And Menopausal Burden In The Midlife. *Maturitas* 2009;62(3):306-10.
7. Taavoni S, Haghani H. Valerian/lemon balm use for sleep disorders during menopause. *Complementary therapies in clinical practice*. 2013;19(4):193196.
8. Li C, Samsioe G, Borgfeldt C, Lidfeldt J, AgardhC.D, Nerbrand C. Menopause related symptoms: what are the background factors? Aprospectivepopulation-based cohort study of Swedish women(The women's Health in Lunda Area study). *Am J Obstet Gynecol*. 2003; 189: 1646 -53.
9. Ağıl A, Abıke F, Daşkapan A, Alaca R, Tüzün H. Short-term exercise approaches on menopausal symptoms, psychological health, and quality of life in postmenopausal women. *Obstet Gynecol Int*. 2010; 2010:274261.
10. Lima JE, Palacios S, Wender MC. Quality of life in menopausal women: a Brazilian Portuguese version of the Cervantes Scale. *Sci World J*. 2012; 2012:620519.
11. Hess R, Thurston RC, Hays RD, Chang CC, Dillon SN, Ness RB, et al. The impact of menopause on healthrelated quality of life: results from the STRIDE longitudinal study. *Qual Life Res* 2012; 21(3):535-44.
12. Rohr UD, Volko CD, Schindler AE. Comparison Of Steady State Development And Reduction Of Menopausal Symptoms After Oral Or Transdermal Delivery Of 17-B-Estradiol In Young Healthy Symptomatic Menopausal Women. *Horm Mol Biol Clin Investig*. 2014 ;18(3):123-36.
13. Carpenter JS, Byrne MM, Studts JL. Factors related to menopausal symptom management decisions. *Maturitas*. 2011;70(1):10-5.
14. Mewes JC, Steuten LM, Duijts SF, Oldenburg HS, van Beurden M, Stuiver MM, et al. Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients. *J Cancer Surviv*. 2015; 9: 126-35.
15. Duche L, Ringa V, Melchior M, Varnoux N. Hot Flushes , Common Symptoms, And Social Relations Among Middle-Aged No Menopausal French Women In The Gazel Cohort. *Menopause*. 2006; 13(4): 592-99.
16. Beck V, Rohr U, Jungbauer A. Phytoestrogens derived from red clover : an alternative to estrogen replacement therapy? *J Steroid Biochem Mol Biol*. 2005 Apr;94(5):499-518.

17. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310(13):1353-68.
18. Geller SE, Shulman LP, van Breemen RB, Banuvar S, Zhou Y, Epstein G, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. *Menopause*. 2009 Nov-Dec;16(6):1156-66.
19. Posadzki P, Lee MS, Moon TW, Choi TY, Park TY, Ernst E. Prevalence of complementary and alternative medicine (CAM) use by menopausal women: a systematic review of surveys. *Maturitas* 2013; 75(1):34-43.
20. Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. *Archives of internal medicine*. 2006;166(14):1453-65.
21. Peron, A.P., Mariucci, R.G., de Almeida, I.V., Düsman, E., Mantovani, M.S., and Pimenta V.E. (2013) Vicentini Evaluation of the cytotoxicity, mutagenicity and antimutagenicity of a natural antidepressant, *Hypericum Perforatum L.* (St. John's wort), on vegetal and animal test systems. *BMC complementary and alternative medicine*. 13(1): p. 97.
22. Barnes J, Anderson LA, Phillipson JD. St John's wort (*Hypericum Perforatum L.*): a review of its chemistry, pharmacology and clinical properties. *J Pharm Pharmacol* 2001 May;53(5):583-600. Review.
23. Canning S, Waterman M, Orsi N, Ayres J, Simpson N, Dye L. The Efficacy of *Hypericum Perforatum* (St John's Wort) for the Treatment of Premenstrual Syndrome. *CNS drugs*. 2010;24(3):207-25.
24. Volkre B, Stammwitz U, Friede M, Henneicke-von Zepelin HH. "Black cohosh with or without St. John's wort for symptom-specific climacteric treatment— results of a large-scale, controlled, observational study". 2007; 57 (4) : 405 – 14.
25. Bahri N, Afiat M, Aghamohamadian H.R, Noughabi A.D, Bahri N. Investigating the relationship between severity of menopausal symptoms and depression, anxiety and other menopausal symptoms. *I ranian Journal of Obstetrics, Gynecology and Infertility* 2013, 16(43): 14-20.
26. Soltanzadeh, A. Dissertation for obtaining a doctoral degree in medicine. Qazvin University of Medical Sciences & Health Services. Title: Anticancer properties of medicinal herb extracts. 2014. Pages 69.
27. Chung D-J, Kim H-Y, Park K-H, Jeong K-A, Lee S-K, Lee Y-I, et al. Black Cohosh and St. John's wort (GYNO-Plus®) for climacteric symptoms. *Yonsei medical journal*. 2007;48(2):289-94.
28. Motaghi Dastenaei B, Safdari F, Raisi dehkordi Z, Karimian Z. The Effect of Evening Primrose Plant on Physical Symptoms of Menopause. *J Babol Univ Med Sci*. 2017;19(2):34-40.
29. Salehi, Kobra, Ehsanpour, Zolfaghari, Salehi, Student. Effect of red clover isoflavone extract on menopausal symptoms. *Journal of Gorgan University of Medical Sciences*. 2013 Jun 1; 15 (2): 21-8.
30. Diana M, Burger HG, Bone KM, Cohen MM, Teede HJ. "hypericum Perforatum with vitex agnus – castus in menopausal symptoms : a randomized, controlled trial. 2009; 16 (1) :156 – 63.
31. Abbasinia K, Hosini F. A comparative study of the effects of omega-3 and perforan on severity mood symptoms in premenstrual syndrome. *Complementary Medicine Journal of faculty of Nursing & Midwifery*. 2013 Dec 15;3(3):529-40.
32. Pakgozar M, Ahmadi M, Salehi surmaghi M, Mehran A, Akhondzadeh S. Effect of *Hypericum Perforatum L.* for treatment of premenstrual syndrome. *JMP*. 2005; 3 (15) :33-42.
