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The effect of *Hypericum perforatum* on postmenopausal symptoms and depression: A randomized controlled trial

Alieh Eatemadnia, Somayeh Ansari*, Parvin Abedi, Shahnaz Najar

Midwifery Department, Menopause & Andropause Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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ABSTRACT

Objectives: *Hypericum perforatum* (St John's wort) is an herbal plant that has antidepressant activity and contains ingredients such as flavonols derivatives, bioflavonoids, proanthocyanidins, xanthones, phloroglucinol, and naphthodianthrones. This study was aimed to test the effect of *Hypericum perforatum* on hot flashes, menopausal symptoms, and depression in postmenopausal women.

Design & setting: This randomized controlled study was conducted on 80 postmenopausal women aged 45–60 in Izeh, Iran.

Intervention: Two groups received 270–330 μg of *H. perforatum* (n = 40) or placebo (n = 40) tablets three times a day for two months.

Main outcomes: Data were collected using a socio-demographic questionnaire, the modified Kupperman index before the intervention and 2, 4, 6 and 8 weeks after intervention. The Hamilton Depression Rating Scale was used to gather data before the intervention and in the 8th week of intervention. The data were analyzed using an independent t-test, chi-square test, and repeated measure test.

Results: Seventy women completed the study and five women from each group withdrew the study. The frequency and intensity of hot flashes and the score of Kupperman scale significantly decreased in the *H. perforatum* group compared to the control group ($p < 0.001$). In addition, the intensity of depression significantly decreased in the *H. perforatum* group compared to the control group. At the end of the study, 80% of women in the intervention group did not have depression compared to only 5.7% in the control group ($p < 0.001$).

Conclusion: Treatment with *Hypericum perforatum* is an efficient way of reducing hot flashes, menopausal symptoms, and depression in postmenopausal women.

1. Introduction

One of the most critical periods in a woman's life is menopause[1] which is characterized by the end of the reproductive period. Although menopause is a physiological and common event, complications like physical and psychological conditions, as well as emotional and social health experience of postmenopausal women may affect their quality of life.[2] Early postmenopausal symptoms include: hot flashes, insomnia, anxiety, depression, lack of concentration, change of sexual desires, and skin and mucus atrophy. The late menopausal symptoms include cardiovascular disorder and osteoporosis.[3] Menopausal symptoms can be treated using hormone replacement therapy and non-hormonal treatments.[4] Hormone replacement therapy will improve the symptoms of menopause, but it also causes some side effects.[5] For instance, estrogen may cause breast and endometrial cancers, thromboembolism, uterine dysfunctional bleeding and liver diseases; thus, there have been some trends toward using herbs as an alternative and auxiliary treatment.[6]

Hypericum perforatum (St John's wort) is one of the herbal plants that has antidepressant and analgesia like activity and contains components such as flavonol derivatives, biflavones, proanthocyanidines, xanthones, phloroglucinols and naphthodianthrones.[7,8] *H. perforatum* can be used in the treatment of mild to moderate depression. The antidepressant mechanism of this herbaceous plant is due to the suppression of the ingestion of serotonin (5-HT), dopamine (DA) and norepinephrine (NE) from the synaptic cleft of interconnecting neurons.[7–9] This herb could reduce the symptoms of depression and may be used in reducing the symptoms of Alzheimer disease such as pain and depression.[10] Some studies measured the effect of *H. perforatum* on hot flashes among postmenopausal women.[11,12] The effect of this herbal plant on postmenopausal women's quality of life was also examined in another study.[11]

Although there are studies that have assessed the effect of *H.*

* Corresponding author at: Golestan Ave, Ahvaz Jundishapur University of Medical Sciences, Nursing and Midwifery School, Ahvaz, Iran.
E-mail addresses: somayehansari88@yahoo.com (S. Ansari), parvinabedi@ymail.com (P. Abedi).

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perforatum on either postmenopausal hot flashes or depression alone, there is a paucity of studies to consider both these menopausal complications in combination. Thus, this study was designed to examine the effect of *H. perforatum* on menopausal symptoms, hot flashes, and depression among postmenopausal women.

2. Materials and methods

This was a double blind randomized controlled trial conducted on 80 postmenopausal women. Illegible for the study were literate women aged45–60 with at least 12 months of amenorrhea, and having at least two menopause symptoms according to the modified Kupperman index. Excluded from the study were; women with unnatural menopause such as oophorectomy, endocrine dysfunction, history of using phytoestrogens, allergy to herbal medicine, severe depression, and body mass index (BMI) more than 30 kg/m^2. The design of this study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Ref No: 4411-20-8-p). This study was also registered in the Iranian registry for clinical trials (Ref No: IRCT2017012510687N4). Each participant signed an informed written consent prior to data collection. Also the participants were allowed to stop using the herbs if they saw any side effects. A total of 80 women participated in this study. The participants were randomly recruited into two groups (40 each).

2.1. Measures

The participants' information was gathered through interview using demographic questionnaire, the modified Kupperman index and Hamilton Scale for Depression. The modified Kupperman index for menopause includes the following symptoms: hot flash and sweating, nervousness, sleep disorders, melancholia, vertigo, weakness, arthralgia and myalgia, headaches, palpitation and formication, depression, exhaustion, worry, frequent urination, and dysuria. In this index the intensity of symptoms ranges from 0-3. Hot flashes and sweating with the highest total intensity are multiplied by 4, nervousness and sleep disorders are multiplied by 2, and the remaining symptoms (melancholia, vertigo, weakness, arthralgia and myalgia, headaches, palpitation and formication) are left without factor. A four- point Likert scale is used for scoring, where 0 is assigned to absence of symptoms, 1 to slight symptoms, 2 to moderate symptoms, and 3 to severe symptoms.[13] The total score of Kupperman index is 45.

The Hamilton scale was applied for assessing depression. Hamilton scale includes 21 questions. Questions 1, 2, 3, 7, 8, 9, 10, 11, 15, and 19 have 5 items and are scored from zero (absence) to 4 (more severe). Questions 4, 5, 6, 12, 13, 14, 17, 18 and 21 are scored from zero (absence) to 2 (severe). Questions 16 and 20 are scored from zero (none) to 3 (severe). Higher scores indicate more severe depression. Scores 0–7, 8–13, 14–18 and greater than 20 indicate normal, mild, moderate and severe depression, respectively.[14]

The frequency and severity of hot flashes during 24 h were asked from the participants. The severity of hot flashes was classified into mild, moderate and severe, where the mild type does not interfere with everyday activities and the severe type interferes with everyday activities.

For measuring weight and height of participants a Seca scale and a stadiometer were used. Weight of the participants was measured while they were standing bare footed with light clothes. The body mass index (BMI) was calculated using the following formula; weight (kg) / $height^2$ (m).

2.2. Setting

Six public health centers in Izeh (Khuzestan Province) were selected for sampling. Eligible women from these centers were randomly assigned into two groups of *H. perforatum* and control using a random table generated by Excel. Both the participants and the researchers were not aware of the intervention.

2.3. Sampling

The following equation was used for sampling:

$$n = \frac{(z_1 - \frac{\alpha}{2} + z_1 - \beta)^2[P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$
$$= \frac{(1.9 + 0.84)^2[0.5 \times 0.5 + 0.196(1 - 0.196)]}{(0.5 - 0.196)^2} \Rightarrow 35$$

In this equation, $\alpha = 0.05$, $1–\beta = 85\%$ and 95% confidence interval the amount of samples were calculated to be 35 in each group. We added 10% for attrition, and the final sample size was considered to be 40 women in each group.

2.4. Intervention

H. perforatum was prepared from an Iranian drug company (Gole Darou Company, Isfahan, Iran). This tablet contains 270–330 μg of *H. perforatum*. The placebo was prepared in the Pharmacy School of Ahvaz Jundishapur University of Medical Sciences. The placebo was similar to *H. perforatum* in terms of shape and color. Women in the intervention group were requested to take three tablets of *H. perforatum* (0.990 mg extract of *H. perforatum*) per day and the control group was asked to take three placebos per day. Each participant received a calendar to record their symptoms once a week. One of the research team members was available to answer the participants' questions on phone. At the end of every two weeks, the participants were requested to attend the clinic, and they received another package of *H. perforatum* or placebo. The modified Kupperman score, as well as the frequency and severity of hot flashes were recorded by the participants every two weeks. The Hamilton Depression Scale was completed at the beginning of the study and at the end of the 8^{th} week.

2.5. Statistics

All data were entered SPSS version 13. The independent *t*-test was used to compare the continuous data of the two groups, while chi-square test was used for categorical data. For comparing the modified Kupperman score of the two groups in different weeks, the Repeated Measure test was applied. $P < 0.05$ was considered significant.

3. Results

At the end of the study, 10 women dropped-out and 70 women completed the study. The reasons for withdrawal are listed in Fig. 1. Table 1 shows the socio-demographic characteristics of the participants in two groups of *H. perforatum* and control. As evident from this table, the mean age of women was 50.49 ± 2.74 and 50.63 ± 2.87 in the *H. perforatum* and control groups, respectively ($p = 0.83$). The two groups did not show any significant difference regarding body mass index, time span from stopping menopause (month), education, economic class, and marital status.

Table 2 shows the frequency of hot flashes and the modified Kupperman's index score of the two groups of *H. perforatum* and control before intervention and 2, 4, 6 and 8 weeks after intervention. As evident from this table, before intervention and two weeks after it, the two groups did not have any significant difference regarding the frequency of hot flashes. However, in week 4 the frequency of hot flashes significantly decreased in the *H. perforatum* group compared to the control group (2.51 ± 0.85 vs. 4 ± 0.86, $p < 0.001$). Also, women in *H. perforatum* significantly had less hot flashes in week 6 and 8 ($p < 0.001$). The repeated measure test showed that two groups had a significant difference in the mean of frequency of hot flashes in week 6

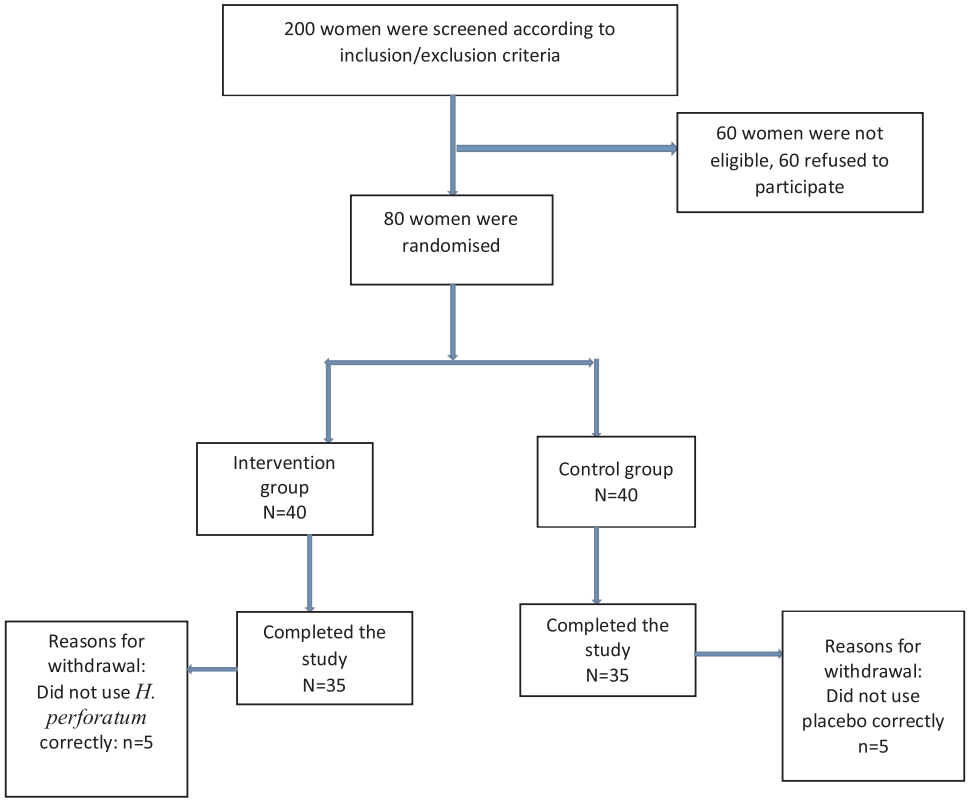

Fig. 1. Flow chart of recruitment and retention of participants in the study.

Table 1
Socio-demographic characteristics of participants in two groups of *H. perforatum* and control.

Variables	*H. perforatum* N = 35 Mean ± SD or N (%)	Control N = 35	P value
Age (y)	50.49 ± 2.74	50.63 ± 2.87	0.83
Body mass index (kg/m^2)	27.23 ± 0.64	27.29 ± 0.75	0.73
Time span from stopping menopause (month)	28.66 ± 13.6	30.89 ± 12.5	0.48
Education			
Primary	17(48.6)	19(54.3)	0.63
High school	18(51.4)	16(45.7)	
Economic situation			
Good	1(2.9)	3(8.5)	0.58
Fair	16(45.7)	15(42.9)	
Inappropriate	18(51.4)	17(48.6)	
Marital status			
Married	22(62.9)	27(77.1)	0.19
Single	13(37.1)	8(22.9)	

Table 2
Comparison of frequency of hot flashes and Kupperman index before and after intervention in two groups of *H. perforatum* and control.

Variables	*H. perforatum* N = 35 Mean ± SD	Control N = 35	P value	P value using repeated measure
Frequency of hot flashes				
Before intervention	4.26 ± 0.98	4.09 ± 0.98	0.46	
Week 2	4.26 ± 0.98	4.09 ± 0.98	0.46	< 0.001
Week 4	2.51 ± 0.85	4 ± 0.86	< 0.001	
Week 6	1 ± 0.97	3.99 ± 0.88	< 0.001	
Week 8	0.6 ± 0.84	3.97 ± 0.96	< 0.001	
Kupperman index score				
Before intervention	26.09 ± 6.82	26.37 ± 6.82	0.862	
Week 2	25.49 ± 6.65	26.33 ± 6.97	0.565	< 0.001
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	

and 8 ($p < 0.001$).

Also Table 2 indicates that the mean of the modified Kupperman's score was significantly lower among women in the *H. perforatum* group compared to those in the control group in weeks 4, 6 and 8 ($p < 0.001$).

Table 3 shows the intensity of hot flashes in two groups of *H. perforatum* and control before intervention and 2, 4, 6 and 8 weeks after intervention. As can be observed in this table, before intervention and 2 weeks after it, the two groups did not have any significant difference regarding intensity of hot flashes ($p > 0.05$). However, in week 4, women in the *H. perforatum* had significantly fewer hot flashes compared to the control group (8.6% of women were without hot flashes compared to only 2.8% in the control group ($p < 0.001$). Also, at the end of the 8th week, 62.9% of women in the *H. perforatum* were free of hot flashes compared to only 2.9% in the control group ($p < 0.001$).

Table 4 shows the intensity of depression before and after intervention in two groups of *H. perforatum* and control. According to this table, there was not any significant difference between the intensity of depression before intervention. However, after intervention, 80% of women in the *H. perforatum* did not have depression and 20% experienced mild depression compared to 5.7% and 80% (with no depression and light depression) in the control group ($p < 0.001$).

Table 3
Comparing the intensity of hot flashes before and after intervention between two groups of *H. perforatum* and control.

Variables	*H. perforatum* N = 35				Control N = 35			
	No hot flash	Light	Moderate	Severe	No hot flash	Light	Moderate	Severe
	N (%)							
Intensity of hot flashes								
Before intervention	0	4(11.4)	11(31.4)	20(57.2)	0	4(11.4)	16(45.7)	15(42.9)
Week 2	0	4(11.4)	14(40)	17(48.6)	0	4(11.4)	16(45.7)	15(42.9)
Week 4*	3(8.6)	13(37.1)	19(54.3)	0	1(2.8)	3(8.6)	16(45.7)	15(42.9)
Week 6*	15(42.9)	17(48.6)	3(8.6)	0	1(2.9)	4(11.4)	19(54.3)	11(31.4)
Week 8*	22(62.9)	13(37.1)	0	0	1(2.9)	4(11.4)	19(54.3)	11(31.4)

Using repeated measure test two groups showed a significant difference before and after intervention ($p < 0.001$).
* Two groups had significant difference in week 4, 6 and 8 ($p < 0.001$).

Table 4
Comparison of depression intensity before and after intervention in two groups of *H. perforatum* and control.

Variable	*H. perforatum* N = 35			Control N = 35			P value
	N (%)						
	No depression	Light	Moderate	No depression	Light	Moderate	
Before intervention	0	23(65.7)	12(34.3)	0	27(77.1)	8(22.9)	0.06
After intervention	28(80)	7(20)	0	2(5.7)	28(80)	5(14.3)	< 0.001

4. Discussion

This work was designed to assess the effect of *H. perforatum* on hot flashes and depression among postmenopausal women. The results of this study showed that *H. perforatum* could significantly reduce the mean and frequency of hot flashes as well as the modified Kupperman's score compared to the control group.

Al-Akoum et al, conducted a study on 47 women who were randomly assigned into two groups of *H. perforatum* and control and followed them for 12 weeks. According to their results, after 12 weeks, a non-significant reduction in the daily hot flashes, hot flash score ($p > 005$) and menopause-specific quality of life ($p = 0.01$) was observed.[11]

Abdali et al, also conducted a study on 100 women who were randomly assigned into two groups of St John's Wort extract or placebo and followed them for 8 weeks. Their results showed that in the 4th and 8th week of the study, the severity of hot flashes significantly reduced in the St John's Wort group compared to the control group ($p < 0.001$),[15] which is in line with our findings. Similar to our study, Uebelhack et al also recorded a substantial decrease in the intensity of hot flashes ($p < 0.001$).[16]

In the present study, the modified Kupperman's index on the intensity of hot flashes indicated a significant reduction of scores in the *H. perforatum* group compared to the control group, which is in agreement with the results obtained by Chung et al, where the Kupperman's index showed a significant decrease after using *H. perforatum*.[17]

Our results indicated that *H. perforatum* could significantly reduce the severity of depression of postmenopausal women after 8 weeks. *H. perforatum* has been proposed to act as an inhibitor of MAO-A and NAO-B, inhibit the synaptosomal uptake of serotonin, dopamine and norepinephrine, and down regulate the beta-receptors and up-regulate 5-HT2 receptors in the frontal cortex.[18]Also *H. perforatum* may have an effect on acetylcholinesterase, the reduction of degradation rate of acetylcholine,[19] and a decrease in serotonergic activity.[20] Grube et al conducted a study on 111 middle aged women in order to assess the effect of St. John's wort extract on psychological symptoms of middle aged women. Results showed that after 12 weeks of treatment, women in the St. John's Wort extract showed significant improvement in psychological and psychosomatic symptoms,[21] which is in line with our findings. Schrader et al, also conducted a study on 159 patients to evaluate the effect of St John's Wort (ZE117) on mild and moderate depression by administering 250 mg of St John's wort twice daily and following the participants for 6 weeks. Results showed that St John's Wort could reduce the depression by 50%, while only 15% of the placebo group responded to treatment.[22] Although the study of Schrader et al, was conducted on both men and women, their results are in line with ours.

Gastpar (2005) examined the comparability of the effects of *H. perforatum* and sertraline in comparison with placebos in order to decrease depression. The obtained results indicated that *H. perforatum* could significantly reduce the depression score.[23] These findings are also in line with our results.

4.1. Strengths and limitations of the study

This study assessed the effect of *H. perforatum* on postmenopausal complications as well as depression. While most studies assessed the effect of *H. perforatum* on frequency and severity of hot flashes or depression solely, we recruited women who had both menopausal symptoms and mild or moderate depression, and we intensively followed all women for 8 weeks. The limitation of study is; while some studies followed their participants until 12 weeks, we only followed women for eight weeks, but it is worth-mentioning that we did not recruit severe depression.

5. Conclusion

Treatment with *H. perforatum* is an efficient way for reducing the frequency and severity of hot flashes, menopausal symptoms, as well as depression in postmenopausal women. Using this herb in postmenopausal women is recommended.

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Declaration of interest

None

Authors' contribution

AE, SN, SA and PA were involving in design and conception of the study. AE was responsible for data gathering. SN, AE, SA and PA were responsible for data analyzing and interpretation. SA and PA were involving in writing of paper. All authors are in agreement with the content of the manuscript.

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