Original Article

Evaluation of the Effect of Perforan (*Hypericum perforatum*) on Premenstrual Syndrome Severity of Physical and Behavioural Symptoms in Patients with Premenstrual Syndrome: A Clinical Randomised Trial

Nasim Khademi, Haniyeh Abbassinya[1], Farahnaz Heshmat[2], Mahdis Naafe[3], Abolfazl Mohammadbeigi[4]

Department of Midwifery, Nursing and Midwifery Sciences Development Research Center, Islamic Azad University, Najafabad Branch, Najafabad, [1]Department of midwifery, School of Nursing and Midwifery, Tehran University of Medical Science, [3]Department of midwifery, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, [2]Department of midwifery, Heshmatie Hospital, Isfahan University of Medical Science, Isfahan, [4]Department of Epidemiology and Biostatistics, Neuroscience Research Center, Qom University of Medical Sciences, Qom, Iran

Abstract

Background: Premenstrual syndrome (PMS) is an extensive group of emotional, behavioural and physical symptoms that occur before menstruation. It has a negative impact on activities of daily living, social activities, sexual functioning and quality of life. This study aimed to evaluate the effect of perforan (*Hypericum perforatum*) on the severity of physical and behavioural symptoms associated with PMS. **Materials and Methods:** In a triple-blind clinical trial, 93 students with PMS were randomly divided into two groups, including perforan and control (placebo) groups, and followed for three subsequent cycles. They took capsules daily in the first cycle for 1 month, and in the second and third cycles, they took capsules from 8 days pre-menstruation to 2 days post-menstruation and recorded the severity of physical and behavioural symptoms using a PMS questionnaire. Statistical analyses were performed using SPSS version 20. Repeated measures ANOVA, Chi-squared tests and independent *t*-tests were used to compare the mean scores of the two groups. **Results:** The data showed that there were no significant differences between the two groups before the intervention ($P > 0.05$). Nevertheless, the severity of physical and behavioural symptoms of PMS was significantly lower in the perforan group than the control group. This was the case 1, 2 and 3 months after consumption of perforan ($P < 0.001$). Moreover, a significant difference between the two groups in the decrease of PMS scores was observed by repeated measurement tests ($P < 0.001$). **Conclusion:** Perforan significantly reduces the severity of physical and behavioural symptoms of PMS. Therefore, perforan could be effective in the treatment of physical and behavioural symptoms of patients with PMS. Nevertheless, future studies are necessary to confirm these results.

Keywords: *Hypericum perforatum*, perforan, premenstrual syndrome, symptoms

Introduction

Premenstrual syndrome (PMS) is characterised by the repeated occurrence of disruptive physical and emotional symptoms before menses.[1] It has a negative impact on activities of daily living, interpersonal relationships, social activities, leisure activities, sexual functioning, occupation and quality of life.[2,3] Although the mean prevalence of PMS is 47.8%, 99.5% of Iranian students have reported at least one premenstrual symptom.[4,5] Surveys have suggested that more than 80% of women report PMS when strict diagnostic criteria are applied; the prevalence of severe PMS is estimated at around 2%–6% in women of reproductive age.[4,6] According to research in Iran on the prevalence of PMS among university students, the most

Access this article online

Quick Response Code:

Website: www.aihbonline.com

DOI: 10.4103/AIHB.AIHB_16_20

Address for correspondence: Miss. Haniyeh Abbassinya, School of Nursing and Midwifery, Tehran University of Medical Science, Tehran, Iran.
E-mail: hani.abbassinya@gmail.com

Submitted: 13-06-2020 **Revised:** 12-07-2020
Accepted: 18-08-2020 **Published:** 22-09-2020

How to cite this article: Khademi N, Abbassinya H, Heshmat F, Naafe M, Mohammadbeigi A. Evaluation of the effect of perforan (*Hypericum perforatum*) on premenstrual syndrome severity of physical and behavioural symptoms in patients with premenstrual syndrome: A clinical randomised trial. Adv Hum Biol 2020;10:110-4.

commonly reported symptoms were mood symptoms (72.6%) and somatic symptoms (62.7%).[7] It was reported that the prevalence of PMS is 80.4% among high school students, 68.9% among university students and 54.9% in the general population.[4]

PMS causes criminal behaviour, suicide attempts, work absences, hospital admissions and an increase in accidents. It influences women's feelings about themselves and others, and it co-occurs with a range of other problems, for example, anxiety, nutrition disorders and obesity.[8-10] Women with PMS complain of cyclical mastalgia (breast pain) that it leads to disturbances in sexual function and physical and social activities.[6,8,11] It was seen that in the luteal phase of women, menstrual migraine, headaches, depression, irritability, anxiety and nausea were increased.[12,13] Although the aetiology of PMS is unknown, the causative factors include hormonal imbalances, abnormalities in thyroid hormones, low serotonin levels, nutritional deficiencies and increased levels of inflammatory prostaglandins, cortisol, prolactin, β-endorphins and electrolytes.[14,15]

Many treatments for PMS have been tested over the years. These include non-pharmacological (dietary modification, dietary supplements and regular physical activity) and pharmacological treatments, which have varying outcomes.[16,17] As PMS is a persistent condition, we must pay attention to the side effects of medications.[18,19] Recent research demonstrates that herbal medicines are more acceptable to patients because they have fewer side effects.[18,19] The extract of *Hypericum perforatum* (perforan) has been shown to be effective through experimental investigations and clinical trials.[20,21] Since herbs can be safer and less expensive than chemical drugs, they are accepted more easily, and since women have the right to choose treatments that are affordable and have fewer side effects, we evaluate in this study the effect of perforan on the physical symptoms of PMS.

Materials and Methods

This study is a two-blind clinical trial that was conducted to evaluate the effect of perforan on the physical symptoms of PMS. The study was conducted on students living in Isfahan university residence halls and included all unmarried students who were dormitory residents during the study period.

Data were collected using a questionnaire including two sections: demographic characteristics and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) that includes eight physical symptoms and five behavioural symptoms of PMS: breast tenderness or swelling, headaches, back pain, abdominal pain, weight gain, swelling of the extremities, gastrointestinal disorders, feeling exhausted, lack of energy, sleep disorders, difficulty concentrating and appetite disorders.

The inclusion criteria were predefined as follows: regular menstrual cycles (arriving every 24–35 days) and being single. Exclusion criteria included unwillingness to remain in the study, drug allergies or side effects, physical and psychiatric symptoms resulting from endocrine disorders, severe PMS, taking any drugs or herbal medicines, having physical illnesses such as endocrine disorders, taking medication for PMS, consumption of alcohol, having relatives death history in the last 3 months and having had surgery in the last 3 months.

The sample size was calculated based on a study power of 80%, an alpha error of 5% and minimal difference between the two groups. In the first stage of the study, only 250 students from the 500 who were invited to participate returned the DSM-IV form. Following exclusion of participants with incomplete forms (n = 120), 130 students had completed the DSM-IV form at baseline. In the second stage of the study, participants were issued with a form for completion over a period of 2 months. This form was a daily schedule listing 13 symptoms that could be experienced on days 1–35 of the menstrual cycle. The individuals were advised not to use any drugs (including vitamins) during this time and were also advised to avoid caffeine and salt during the premenstrual period. The form was filled out in this way: absence of symptoms, 0 points; mild symptoms with no interference with daily activities, 1 point; moderate symptoms that may interfere with daily activities, 2 points; and severe symptoms that interfere with daily tasks such as attending class or using painkilling drugs, 3 points. A student had PMS if they had at least five symptoms in the period from a week before her menstruation until 3 days after. To analyse the severity of physical and behavioural symptoms of PMS, the total scores of 13 symptoms from 1 week pre-menstruation until 3 days after were added together. Then, the cases were classified as follows: lack of physical and behavioural symptoms of PMS (score = 0), mild physical and behavioural symptoms of PMS (1–130), moderate physical and behavioural symptoms of PMS (131–260) and severe physical and behavioural symptoms of PMS (>260). In enrolment phase, from 130 individuals who completed the daily symptoms and having inclusion criteria, 30 individuals excluded due to severe PMS or lack physical symptoms (n = 30) and finally 100 individuals entered to study. In the third stage of the study, the individuals were randomly assigned to two groups of 50 students, one taking perforan 280 mg/day and the other a placebo. The participants took these medicines over three menstrual cycles. During the first cycle, drugs were taken on each day of the cycle. During the second and third cycles, drugs were taken daily in the period starting 8 days before menstruation and finishing 2 days afterwards. The participants recorded any symptoms experienced during the total study period on a daily basis using the daily symptoms form. Seven students were excluded due to fear of dependence in the perforan group (n = 2) and gastrointestinal complications in the placebo group (n = 5) during the study period [Figure 1]. Written informed consent was taken from all eligible participants. Participation in the study was voluntary. The study protocol was approved by the Ethics Committee of Tehran University

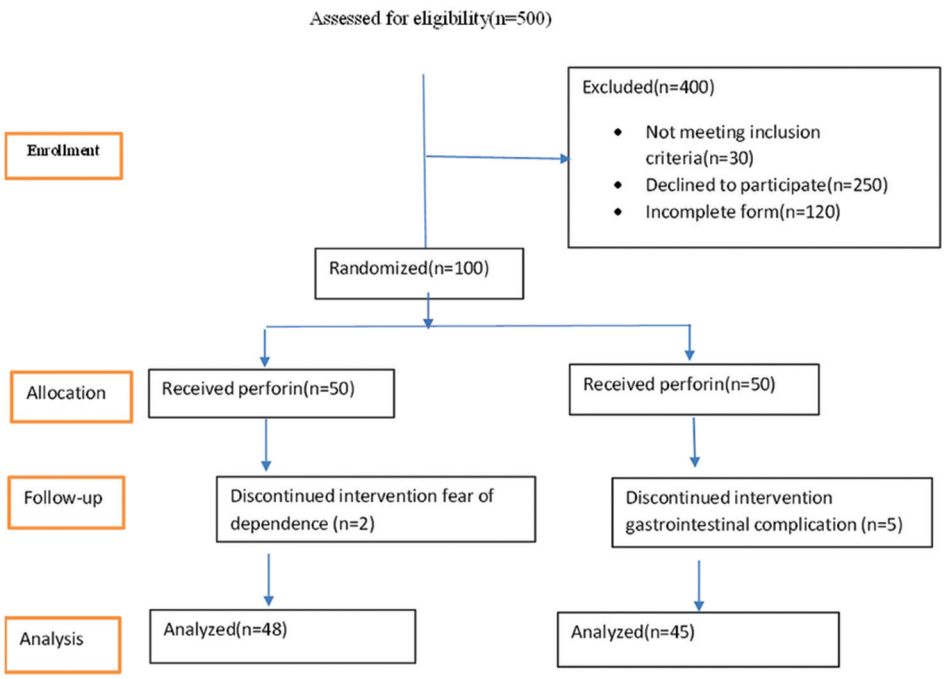

Figure 1: Flow diagram of the study group (consort 2010).

of Medical Sciences and registered with the Iranian Registry Clinical Trial Center.

Finally, the forms were collected, and the severity of symptoms was measured and analysed separately for each group. We used descriptive statistics to describe the demographic characteristics of the sample and used the repeated measures ANOVA test for quantitative variables, the Chi-squared test for relationships between categorical variables and the independent *t*-test to compare the mean scores of each group in each cycle. The normally distributed population was tested using the Kolmogorov–Smirnov test. Scheffe's *post hoc* test in repeated measures ANOVA test was used for two-by-two comparisons. All data analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Results

Confounding factors that were controlled through randomisation included age, age at menarche, length of menstrual cycle, duration of menstrual bleeding and body mass index. The two groups demonstrated similarities in all of these parameters [Table 1].

The mean scores for physical and behavioural symptoms of PMS were similar in the two groups before the intervention, but there was a substantial difference between these groups in mean scores for physical and behavioural symptoms of PMS, 1, 2 and 3 months after the intervention. Scheffe's test showed that this difference was due to the difference between the placebo and drug groups [Table 2].

A significant and similarly decreased mean PMS severity score was observed during treatment cycles in the treatment group, but it did not change in the placebo group [Figure 2]. Repeated measurement tests showed a significant difference between the two groups ($P < 0.001$).

The mean scores for the severity of physical and behavioural symptoms were similar in the two groups before the

Table 1: Comparison of demographic and obstetrical characteristics among two groups using independent *t*-tests

Variable	Mean±SD		*P*
	Perforan (*n*=48)	Placebo (*n*=45)	
Age (years)	22.4±3.34	22.4±3.67	0.52
Age at menarche (years)	13.70±1.30	13±1.22	0.28
Length of the menstrual cycle (days)	27.62±2.59	26.93±2.41	0.39
Duration of menstrual bleeding (days)	6.14±1.57	5.97±1.43	0.31
Body mass index (kg/m^2)	20.72±2.56	21.30±3.59	0.14

SD: Standard deviation

Table 2: Comparison of the mean scores for physical and behavioural premenstrual syndrome of two groups using independent *t*-tests

Treatment cycles	Mean±SD		*P*
	Perforan	Placebo	
Before the intervention	41.61±23.44	38.19±29.31	0.74
1 month after the intervention	24.55±16.64	38.19±19.32	<0.001
2 months after the intervention	24.30±15.67	38.27±19.34	<0.001
3 months after the intervention	23.61±15.60	38.39±19.29	<0.001

SD: Standard deviation

intervention, but there was a significant difference between these groups in mean scores for the severity of these symptoms, 1, 2 and 3 months after the intervention. Scheffe's test showed that the difference was caused by the difference between the placebo and the drug groups [Table 3]. Moreover, the success rates in the treatment groups were not similar. Perforan significantly reduced the physical and behavioural symptoms of PMS [Table 4].

Discussion

H. perforatum has been used to treat many diseases for 2000 years, especially depression.[22-24] Perforan prevents amino oxidase activity and reuptake of norepinephrine, serotonin and dopamine.[25] Perforan is an effective treatment for mild depression, fatigue, nervous depression, menopausal symptoms and PMS.[21,26] Our study shows that perforan significantly alleviates the physical and behavioural symptoms of PMS. Some studies have reported that factors such as age,[27] age at menarche,[24] length of menstrual cycle, duration of menstrual bleeding[28] and body mass index[22] are involved in the occurrence of PMS; we controlled for all of these parameters through randomisation.

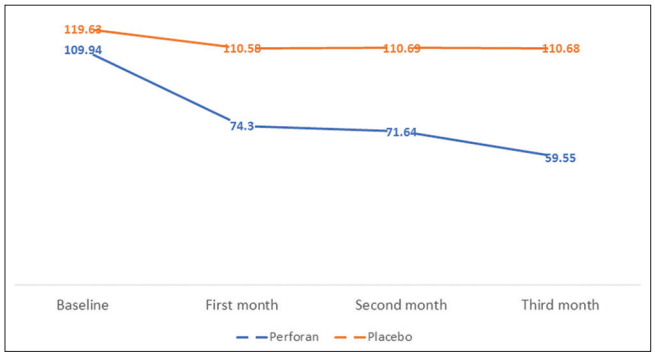

Figure 2: The trend of premenstrual syndrome severity mean scores comparing two study groups.

Table 3: Comparison of the mean scores for severity of physical and behavioural symptoms of two groups using independent *t*-tests

Treatment cycles	Symptom	Mean±SD		*P*
		Perforan	Placebo	
Before the innervation	Physical	19.55±38.05	36.07±18.65	0.70
	Behavioural	19.04±32.83	18.75±27.06	0.18
1 month after the intervention	Physical	25.83±16.42	37.35±17.34	<0.001
	Behavioural	17.99±10.80	27.06±18.75	0.01
2 months after the intervention	Physical	23.46±16.55	36.62±17.65	<0.001
	Behavioural	15.38±10.02	27.06±18.75	0.002
3 months after the intervention	Physical	23.15±16.24	36.71±17.65	<0.001
	Behavioural	13.85±9.43	27.08±18.75	<0.001

SD: Standard deviation

Table 4: Comparison of the mean scores for physical and behavioural premenstrual syndrome of two treatment groups using independent *t*-test

Treatment cycles	Mean±SD		*P*
	Perforan	Placebo	
Before the intervention	90.32±25.63	93.63±40.66	0.17
1 month after the intervention	73.30±27.63	94.30±40.63	<0.001
2 months after the intervention	70.36±26.91	93.64±40.46	<0.001
3 months after the intervention	58.75±23.27	93.55±27.28	<0.001

SD: Standard deviation

H. perforatum is statistically superior to placebo in its ability to improve the physical and behavioural symptoms of PMS.[21] Another study demonstrated that using *H. perforatum*, the physical symptoms were significantly reduced in both the groups. In accordance with the results reported by Ghazanfarpour *et al*.,[29] Ryoo *et al*.,[30] Pakgohar *et al*.[23] and Hicks *et al*.,[31] we observed that perforan significantly reduces PMS.

As mentioned above, treatment with perforan differs in effectiveness from treatment with placebo. According to this study, perforan significantly reduces the physical and behavioural symptoms of PMS. However, the cause of PMS is unknown, and some people with this syndrome do not respond to conventional treatments, so a new method is suggested in these cases. Herbal medicines have been recognised as effective treatments because they are affordable and have fewer side effects.[27]

The present study has limitations. Although the researcher tried to call the students once a week during the study period and ensure that drugs were used correctly, the participants may have not taken the drugs (poor compliance). This was out of our control. Despite this limitation, there are certainly important aspects of the design of this study that may have enhanced the accuracy of the study. For example, the triple-blind design reduced bias to the maximum extent possible. Similarly, having a control group enabled us to find if the treatments were effective.

Conclusion

According to our results, perforan significantly reduces the physical and behavioural symptoms of PMS. Moreover, based on repeated measurement tests, a significant decrease was observed in the perforan treatment group regarding the PMS severity score. Therefore, it seems that perforan could be effective in reducing the physical and behavioural symptoms of PMS in patients. Nevertheless, future studies should be performed to confirm these results.

Acknowledgements

We express our deep gratitude towards all dear colleagues and individuals taking part in this study for their sincere cooperation. We are also thankful to the Deputy of Research and Technology of Tehran University of Medical Sciences for providing facilities and opportunities to conduct this study. This study was approved by the Ethical Committee

of the university. The registered article number in IRCT is 201107262751N3.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Itsekson AM, Soriano D, Zolti M, Seidman DS, Carp HJ. Intradermal sex hormone desensitization for relief of premenstrual symptoms may improve the obstetric outcome of women with recurrent pregnancy loss. Gynecol Endocrinol 2013;29:169-72.
2. Marván ML, Vázquez-Toboada R, Chrisler JC. Ambivalent sexism, attitudes towards menstruation and menstrual cycle-related symptoms. Int J Psychol 2014;49:280-7.
3. O'Brien S, Rapkin A, Dennerstein L, Nevatte T. Diagnosis and management of premenstrual disorders. BMJ (Clinical research ed) 2011;342:d2994.
4. Ranjbaran M, Omani Samani R, Almasi-Hashiani A, Matourypour P, Moini A. Prevalence of premenstrual syndrome in Iran: A systematic review and meta-analysis. Int J Reprod Biomed (Yazd) 2017;15:679-86.
5. Delara M, Borzuei H, Montazeri A. Premenstrual disorders: Prevalence and associated factors in a sample of Iranian adolescents. Iran Red Crescent Med J 2013;15:695-700.
6. Lee Y, Im EO. Stress and premenstrual symptoms in reproductive-aged Women. Health Care Women Int 2016;37:646-70.
7. Naeimi N. The prevalence and symptoms of premenstrual syndrome under examination. J Biosci Med 2015;3:1-8.
8. Yoshimi K, Shiina M, Takeda T. Lifestyle factors associated with premenstrual syndrome: A cross-sectional study of Japanese high school students. J Pediatr Adolesc Gynecol 2019;32:590-5.
9. Shrestha DB, Shrestha S, Dangol D, Aryal BB, Shrestha S, Sapkota B, *et al*. Premenstrual syndrome in students of a teaching hospital. J Nepal Health Res Counc 2019;17:253-7.
10. Craner J, Sigmon S, Martinson A, McGillicuddy M. Perceptions of health and somatic sensations in women reporting premenstrual syndrome and premenstrual dysphoric disorder. J Nerv Ment Dis 2013;201:780-5.
11. MacGregor EA. Classification of perimenstrual headache: Clinical relevance. Curr Pain Headache Rep 2012;16:452-60.
12. Gupta R, Lahan V, Bansal S. Subjective sleep problems in young women suffering from premenstrual dysphoric disorder. N Am J Med Sci 2012;4:593-5.
13. Iida T, Chikamura C, Inoue K, Ito Y, Ishikawa H, Teradaira R, *et al*. Association of STAI and SDS scores with 8-hydroxydeoxyguanosine and serotonin levels in young women with depressive symptoms. J Neuropsychiatry Clin Neurosci 2011;23:E10.
14. Rapkin AJ, Mikacich JA. Premenstrual dysphoric disorder and severe premenstrual syndrome in adolescents. Paediatr Drugs 2013;15:191-202.
15. Zendehdel M, Elyasi F. Biopsychosocial etiology of premenstrual syndrome: A narrative review. J Family Med Prim Care 2018;7:346-56.
16. Shuster LT, Faubion SS, Sood R, Casey PM. Hormonal manipulation strategies in the management of menstrual migraine and other hormonally related headaches. Curr Neurol Neurosci Rep 2011;11:131-8.
17. Nakaya N, Sugano N, Nishi A, Tsukada K. Protein kinase in cultured plant cells. Biochim Biophys Acta 1975;410:273-8.
18. Jing Z, Yang X, Ismail KM, Chen XY, Wu T. Chinese herbal medicine for premenstrual syndrome. Cochrane Datab Syst Rev 2009;21:CD006414.
19. Gautam R, Dixit P, Mittal S. Herbal sources of antidepressant potential: A review. Int J Pharm Sci Rev Res 2013;18 Suppl 1:86-91.
20. Ghazanfarpour M, Ghaderi E, Kaviani M, Haddadian K. Comparison the efficacy of Hypericum perforatum and vitex agnus-castus in hot flushes: A double-blinded randomized controlled trial. Chronic Dis J 2013;1:67-73.
21. 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: A randomized, double-blind, placebo-controlled trial. CNS Drugs 2010;24:207-25.
22. Goodwin TM, Montoro MN, Muderspach L, Paulson R, Roy S. Management of Common Problems in Obstetrics and Gynecology. California: John Wiley & Sons; 2010.
23. Pakgohar M, Mehran A, Salehi Sour Moghi M, Akhondzadeh S, Ahmadi M. Comparison of hypericum perforatum and placebo in treatment of physical symptoms of premenstrual syndrome. J hayat 2004;10:31-7.
24. Zamani M, Neghab N, Torabian S. Therapeutic effect of Vitex agnus castus in patients with premenstrual syndrome. Acta Med Iran 2012;50:101-6.
25. Sarris J, Fava M, Schweitzer I, Mischoulon D. St John's wort (Hypericum perforatum) versus sertraline and placebo in major depressive disorder: Continuation data from a 26-week RCT. Pharmacopsychiatry 2012;45:275-8.
26. Sabet-Birjandi S, Tadayon-Najafabadi M, Siyahpooshan A, Haghighizadeh M. Ghazanfarpour M, Abdolahian S, Khadivzadeh T, Kaviani M. Hypericum perforutum and Vitamin B6 as a Treatment for Premenstrual Syndrome, Jundishapur J Nat Pharm Prod 2017;12:e34093.
27. Dadkhah H, Ebrahimi E, Fathizadeh N. Evaluating the effects of vitamin D and vitamin E supplement on premenstrual syndrome: A randomized, double-blind, controlled trial. Iran J Nurs Midwifery Res 2016;21:159-64.
28. Delara M, Ghofranipour F, Azadfallah P, Tavafian SS, Kazemnejad A, Montazeri A. Health related quality of life among adolescents with premenstrual disorders: A cross sectional study. Health Qual Life Outcomes 2012;10:1.
29. Ghazanfarpour M, Abdolahian S, Khadivzadeh T, Kaviani M. Hypericum perforutum and Vitamin B6 as a treatment for premenstrual syndrome. Jundishapur J Nat Pharm Prod 2017;12:e34093.
30. Ryoo JG, Chun SI, Lee YJ, Suh HS. The effects of St. John's wort on premenstrual syndrome in single women: A randomized double-blind, placebo-controlled study. Clin Psychopharmacol Neurosci 2010;8:30-7.
31. Hicks SM, Walker AF, Gallagher J, Middleton RW, Wright J. The significance of "nonsignificance" in randomized controlled studies: A discussion inspired by a double-blinded study on St. John's wort (*Hypericum perforatum L*.) for premenstrual symptoms. J Altern Complement Med 2004;10:925-32.