Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2016, 5, 11:333-340

Comparison of the effect of omega-3 fatty acids and perforan (*Hypericum perforatum*) on severity of premenstrual syndrome (PMS): a randomized trial

Masoomeh kheirkhah[1], Roya Gholami[2], Sima Younesi Ghare-shiran[3] and Hanieh Abbasinia[4]*

[1]M Sc, Masoomeh kheirkgah, PHD Medical education and MSc Midwifery Assistant professor Iran University of Medical Sciences, Tehran, Iran.
[2]M Sc, Faculty member, Department of Midwifery, School of Nursing and Midwifery, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Islamic Republic of Iran.
[3]M Sc, Head of ward, Zaeem hospital maternity ward, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran
[4]M Sc, Department of Midwifery and Reproductive Health, School of Nursing and Midwife, Arak University of Medical Sciences, Tehran, Iran.
** Correspondence to Hanieh Abbasinia. email: kobraabbasinya@yahoo.com*

ABSTRACT

Premenstrual syndrome (PMS) encompasses a wide variety of cyclic and recurrent physical, emotional, and behavioral symptoms that occur before menstruation and has negative impact on activities of daily living, social activities, sexual functioning and quality of life. The aim of the present study was to compare the effect of omega-3 fatty acid and perforan (Hypericum perforatum) on severity of premenstrual syndrome (PMS). This study is a triple-blind clinical trial that was carried out across three groups with 150 students after considering inclusion and exclusion criteria. The subjects of this study were randomly divided into three groups include omega-3 fatty acid group, perforan group and control (placebo) group. Every subject in this study took drugs during three subsequent cycles so they took capsules daily in the first cycle for one month and in the second and third cycles they took them from eight days before menstruation to two days after and recorded the severity of premenstrual syndrome questionnaire. Statistical analyses were performed using SPSS version 17. The repeated measures ANOVA, chi-square and Wilcoxon tests were used to compare mean differences in three groups. The data showed that there were no significant differences between 3 groups before the intervention but 1, 2 and 3 months after consumption of perforan and omega-3 capsules, the severity of PMS was significantly lower than that in control group ($p<0.001$). perforan and omega-3 significantly reduce the severity of PMS.

Key words: Omega-3 fatty acid, perforan (Hypericum perforatum), premenstrual syndrome (PMS).

Quick points:

- *The mean scores for PMS were similar in three groups (omega-3 fatty acid group, perforan group and control (placebo) group) prior to the intervention.*
- *There was a substantial difference between these groups in mean scores for PMS, one, two and three months after the intervention. Results showed that the difference was caused by the difference between the placebo and drug groups.*
- *A significantly and similarly decreased PMS severity mean scores was observed during treatment cycles in both treatment groups (omega-3 fatty acid group and perforan group), but it did not change in placebo group.*
- *The mean scores for severity of mood symptoms, physical symptoms and behavioral symptoms were similar in three groups prior to the intervention, but there was a significant difference between these groups in mean scores for severity of these symptoms, one, two and three months after the intervention. The difference was caused by the difference between the placebo and drug groups.*
- *Success rates in both treatment groups were similar and we did not see any difference between two treatment groups PMS mean score, one, two and three months after the intervention.*

INTRODUCTION

Premenstrual syndrome (PMS) encompasses a wide variety of cyclic and recurrent physical, emotional, and behavioral symptoms that occur before menstruation (1) and has negative impact on activities of daily living(2), interpersonal relationships, social activities, leisure activities, sexual functioning, occupation and quality of life(3). The prevalence of PMS has been reported in 20 to 32 % of premenopausal and 30-40% of the reproductive female

population(4). Although some surveys have suggested that over 80% of women report PMS, when strict diagnostic criteria are applied; the prevalence of severe PMS is estimated to be about 2-6% in women of reproductive age(5).

PMS cause criminal behavior, suicide attempt, work absences, hospital admissions and increase in accidents(6). It influence on person's feeling about herself and others and it comes with problems for example, anxiety, nutrition disorders and overweight(7). The women with PMS complain of cyclical mastalgia (breast pain)(8), menstrual migraine(9), sleep problems(10), stress and depression(11). Mastalgia occurring during the luteal phase(12) and leads to disturbance of the sexual function, physical and social activities(13). It was seen that in women with menstrual migraine the headaches, depression, irritability, anxiety and nausea will increase in the luteal phase (14, 15). Though the etiology of PMS is unknown(16), The causative factors include hormonal imbalances, abnormalities in thyroid hormones, low serotonin levels, nutritional deficiencies, increased inflammatory prostaglandins, cortisol, prolactin, β-endorphins and electrolytes(17). Many treatments for PMS have been tried over the years. These treatments include non-pharmacological (dietary modification, dietary supplement and regular physical activity) and pharmacological and they have varying outcomes (13, 18).

While PMS is a persistent condition(19), we must pay attention to side effects of medications(20). Recent research demonstrates that herbal medicines have been known as acceptable treatment because they have fewer side effects(21). Hypericum perforatum (perforan) is a plant that its extract has a great effect(22). Its effectiveness is proven through experimental investigations and clinical trials(23). Hypericum perforatum has traditionally been used to treat many diseases, especially depression over 2000 years ago (22, 24). Perforan prevent amino oxidize activity and reuptake of norepinephrine, serotonin and dopamine(25). Perforan is a good treatment for mild depression, fatigue, nervous depression, menopausal symptoms and PMS(26, 27). It is the most successful herbal antidepressants and reduces the symptoms of PMS at least 50 percent(28).

On the other hand, good nutrition is important for balance and mental health as well as physical health. In some countries poor nutrition is a factor for diseases(29, 30). Studies have shown that fat as a source of energy helps the body absorb vitamins and adequate fat intake is essential to growth and health(31). The body can make all fatty acids except two unsaturated fatty acid: linoleic acid (n-6) and alpha- linolenic acid (n-3)(32). Researchers have shown an abnormal metabolism of essential fatty acids in women with PMS(33). Omega-3 fatty acids produce anti-inflammatory prostaglandins: prostaglandin E1 and thromboxane A3 that reduce myometrial contractions, vasoconstriction and ischemia. This phenomenon reduces pain, nausea and vomiting (34-36). Omega-3 fatty acids significantly reduce mood disorders and improve mental health(37). Some epidemiological studies have shown the relationship between low levels of omega-3 fatty acids and an increased risk of depression(38).

There are a few studies about the effect of omega-3 fatty acids and perforan on severity of PMS and previous research did not compare omega-3 fatty acids with perforan. Since herbs and supplements can be safer and less expensive than chemical drugs and they are more accepted, and women have the right to have too many choices and choose something that is more affordable and has fewer side effects, we compared the effect of omega-3 fatty acids and perforan on severity of PMS.

MATERIALS AND METHODS

This study is triple-blind clinical trial that was conducted to compare the effect of omega-3 fatty acids and perforan on severity of PMS. University internal review board approval and ethics committee approval were obtained before the start of the research project. The study was conducted on students living in Isfahan university residence halls and included all unmarried students who were dormitory resident during the study period. Data was collected by using a questionnaire including 2 sections: demographic characteristics and statistical manual of mental disorders form (DSM-IV) that includes 19 symptoms of PMS (irritability, restlessness, impatience, anger, fear, depression, sadness, crying for no reason, loneliness, physical symptoms such as breast tenderness or swelling, headaches, back pain, abdominal pain, weight gain, swelling of the extremities, gastrointestinal disorders, behavioral symptoms include fatigue, lack of energy, sleep problems, difficulty in concentrating and appetite disorders). The inclusion criteria were predefined as follows: having regular menstrual cycles (arriving every 24-35 days), being single, not to take any drugs and herbal medicines, having no physical illness such as endocrine disorders, not to take medication for PMS, no alcohol consumption, having no history of relative dies in the last three months and having no surgery in the last three months. Exclusion criteria included: unwillingness to remain in the study, drug allergy or side effect, recognizing physical and psychiatric symptoms of any endocrine disorders and severe premenstrual syndrome. At the first stage of study, from among 700 students who were invited to participate in the study only 350 returned the

DSM-IV form and following exclusion of participants with incomplete form (n = 170) resulted in 180 students who were completed DSM-IV at baseline. At the second stage of study, a form that was a daily schedule including 19 symptoms that experienced on days 1 to 35 on menstrual cycle were given to them for two months. The subjects were advised not to use any drugs even vitamins during this time and also caffeine and salt during the premenstrual period. The form was filled out in this way: absence of symptoms -0 points, mild symptoms which have no interfere with activities -1 points, moderate symptoms that may interfere with daily activities -2 points and severe symptoms that interfere with daily tasks such as class absence or use of painkilling drugs -3 points. A student had PMS if she had at least five symptoms for a week before her menstruation until 3 days after. To analyze the severity of PMS, the total scores of 19 symptoms from a week before menstruation until 3 days after were added together. Then the cases were classified as: lack of PMS symptoms (0 scores), mild PMS (1-190 scores), moderate PMS (191-380 scores) and severe form of PMS (381-570 scores). At these stage, from among 180 subjects who were completed daily symptoms form following exclusion of participants with severe or lack of PMS (n = 30) resulted in 150 subjects. At the third stage of study these subjects randomly (random assignment) divided into three groups (omega-3 fatty acid - 2000 mg per day, perforan -280 mg per day and placebo -2000 mg per day) and each group contains 50 students. Enough information was given subjects for taking drugs for three cycles. Thus, they take them for all days of the first menstrual cycle, and from 8 days before mensturation until 2 days after it for the next 2 months. Subjects recorded any symptoms experienced during the total study period on a daily basis using the daily symptoms form. 9 students were excluded due to weight gain and obesity in omega-3 fatty acid group (n=2), fear of dependence in perforan group (n=2) and gastrointestinal complications in placebo group (n=5) during the study period. Finally, the forms were collected and severity of symptoms were measured and analyzed separately for each group. We used descriptive statistics to describe the demographic characteristics of the sample, repeated measures ANOVA test for quantitative variables, chi-square test for relationships between categorical variables and Wilcoxon test for ranked variables. Normally distributed population was tested using Kolmogrov-Smirnov (k-s) test. All data analysis was performed using SPSS version 17.

RESULTS

Confounding factors that controlled through randomizing included: age, age at menarche, length of the menstrual cycle, duration of menstrual bleeding and body mass index.

Three groups were similar in age, age at menarche, length of the menstrual cycle, duration of menstrual bleeding and body mass index (table 1).

able1: Comparison of demographic and obstetrical characteristics among three groups using one-way ANOVA test

Variable	Omega-3 fatty acid N=48 Mean±SD	Perforan N=48 Mean±SD	Placebo N=45 Mean±SD	P.value
Age (years)	22.5±3.33	22.4±3.34	22.4±3.67	P=0.97
Age at menarche (years)	13.56±1.39	13.70±1.30	13±1.22	P=0.26
Length of the menstrual cycle (days)	27.33±2.32	27.62±2.59	26.93±2.41	P=0.39
Duration of menstrual bleeding (days)	6.04±1.42	6.14±1.57	5.97±1.43	P=0.85
Body mass index (kg/m^2)	20.83±3.18	20.72±2.56	21.30±3.59	P=0.64

The mean scores for PMS were similar in three groups prior to the intervention, but there was a substantial difference between these groups in mean scores for PMS, one, two and three months after the intervention. Scheffe's test showed that the difference was caused by the difference between the placebo and drug groups (Table 2).

Table2: Comparison of the mean scores for PMS among three groups using one-way ANOVA and Kruskal-Wallis tests.

Treatment cycles	Omega-3 fatty acid Mean±SD	Perforan Mean±SD	Placebo Mean±SD	P.value
prior to the intervention	106.32±45.63	119.63±45.66	109.94±42.75	P=0.32
1 month after the intervention	73.30±27.63	74.30±31.63	110.58±42.77	P<0.001
2 months after the intervention	70.36±26.91	71.64±30.46	110.66±43.02	P<0.001
3 months after the intervention	58.75±23.27	59.55±27.28	110.72±43.05	P<0.001

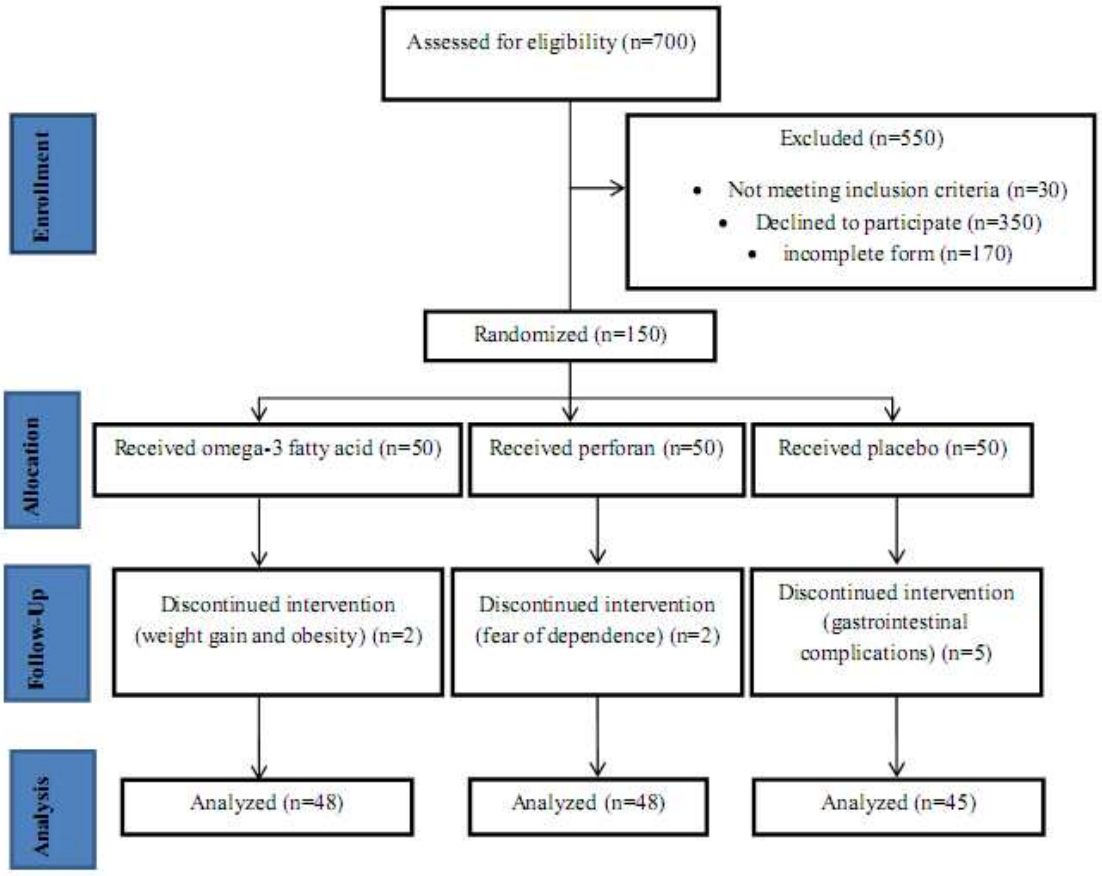
A significantly and similarly decreased PMS severity mean scores was observed during treatment cycles in both treatment groups, but it did not change in placebo group.

The mean scores for severity of mood symptoms, physical symptoms and behavioral symptoms were similar in three groups prior to the intervention, but there was a significant difference between these groups in mean scores for severity of these symptoms, one, two and three months after the intervention. Scheffe's test showed that the difference was caused by the difference between the placebo and drug groups (Table 3).

Table3: Comparison of the mean scores for severity of mood, physical and behavioral symptoms among three groups using one-way ANOVA and Kruskal-Wallis tests

Treatment cycles	symptom	Omega-3 fatty acid Mean±SD	Perforan Mean±SD	Placebo Mean±SD	P.value
prior to the intervention	**Mood**	43.28±25.49	48.05±24.67	46.18±30.86	P=0.68
	Physical	37.06±19.92	38.73±19.55	36.07±17.65	P=0.85
	Behavioral	25.97±20.44	32.83±19.04	27.06±18.75	P=0.18
1 month after the intervention	**Mood**	30.46±17.58	30.93±16.10	46.17±30.85	P=0.02
	Physical	24.05±13.43	25.38±17.42	37.35±17.34	P<0.001
	Behavioral	18.33±11.50	17.99±10.80	27.06±18.75	P=0.02
2 months after the intervention	**Mood**	32.79±18.96	31.80±16.87	46.91±31.30	P=0.05
	Physical	21.21±12.38	24.46±16.55	36.62±17.65	P<0.001
	Behavioral	16.35±10.79	15.38±10.02	27.06±18.75	P=0.003
3 months after the intervention	**Mood**	24.09±14.90	22.54±13.48	46.91±31.30	P<0.001
	Physical	19.25±11.76	23.15±16.24	36.71±17.65	P<0.001
	Behavioral	13.85±10.44	13.85±9.43	27.06±18.75	P<0.001

Figure1: flow diagram of the study group



Success rates in both treatment groups were similar and we did not see any difference between two groups PMS mean score, one, two and three months after the intervention (Table 4).

Table4: Comparison of the mean scores for PMS among two treatment groups using independent t-test

Treatment cycles	Omega-3 fatty acid Mean±SD	Perforan Mean±SD	P.value (95% Confidence Invervals)
prior to the intervention	106.32±45.63	119.63±45.66	P=0.15 (-31.82-5.19)
1 month after the intervention	73.30±27.63	74.30±31.63	P=0.86 (-12.1-10.1)
2 months after the intervention	70.36±26.91	71.64±30.46	P=0.82 (-12.93-10.36)
3 months after the intervention	58.75±23.27	59.55±27.28	P=0.91 (-10.94-9.76)

DISCUSSION

Our study shows that omega-3 fatty acids and perforun significantly reduce the premenstrual symptoms and omega-3 fatty acids did not differ in effectiveness from perforun.

Some studies have reported that factors like: age(39), age at menarche(40), length of the menstrual cycle, duration of menstrual bleeding(39) and body mass index(41) are involved in the occurrence of PMS, we have controlled all of them through randomizing.

There are various hypotheses for the biological action of omega-3 fatty acid that leads to decreased PMS severity. Prior to menstruation we can see an increase in the level of arachidonic acid in the uterus and at the same time, cyclooxygenase, prostaglandin E2, prostaglandin F2α and leukotriene B4 which have role in inflammation, produce from arachidonic acid(42). Also arachidonic acid induces an increase in ischemia, myometrial contractions, menstrual cramps and gastrointestinal symptoms such as nausea, vomiting and flatulence (34). Omega-3 fatty acid contains alpha-linolenic acid that increases production of eicosapentaenoic and docosahexaenoic(43); both of these are eicosanoids precursors that compete with prostaglandin synthesis. Omega-3 fatty acids produce anti-inflammatory prostaglandins: prostaglandin E1 and thromboxane A3 that reduce myometrial contractions, vasoconstriction and ischemia. This phenomenon reduces pain, nausea and vomiting(44, 45). In this study, we found a significantly decreased PMS severity mean score during treatment cycle in Omega-3 fatty acid group. This is in line with the findings from Tofighiyan(46), Sohrabi(47), Kashanian(48), Fontani(49), Sampalis (50) and Deutch(51) works.

Perforan has traditionally been used to treat many diseases, especially depression (22, 24). Perforan prevent amino oxidize activity and reuptake of norepinephrine, serotonin and dopamine(25). Similar to results reported by Sabet-Birjandi(52), Ghazanfarpure(27), Ryoo (53), canning(54), Pakgohar(55) and Hicks(56), we observed that perforun significantly reduce the PMS.

As mentioned, omega-3 fatty acids did not differ in effectiveness from perforun. According on our investigation, no work has been found comparing the effect of omega-3 fatty acid and perforan on severity of PMS to this time.

The present study has a limitation. Although the researcher tried to call the students once a week during the study period and ensured that drugs are used correctly, they may not take the drugs and this was out of our control.

Despite this possible limitation, there are certain important aspects of the design of this study that may have enhanced the accuracy of the study. These include being triple-blind that reduce the bias to the extent possible and having a control group that enabled us to find out if the treatments really had effect.

According to this study omega-3 fatty acids and perforun significantly reduce the PMS. The cause of PMS is unknown and some people with this syndrome do not respond to conventional treatments, so new method is suggested in these cases. Herbal medicines and supplements have been known as acceptable treatment because they are affordable and have fewer side effects(21).

Acknowledgements
We express our deep gratitude toward all dear colleagues and subjects taking part in this study for their sincerely cooperation. We are also thankful of 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.

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. Gynecological Endocrinology. 2013;29(2):169-72.
[2] Marván M, Vázquez-Toboada R, Chrisler JC. Ambivalent sexism, attitudes towards menstruation and menstrual cycle-related symptoms. International Journal of Psychology. 2014;49(4):280-7.
[3] O'Brien S, Rapkin A, Dennerstein L, Nevatte T. Diagnosis and management of premenstrual disorders. Bmj. 2011;342:d2994. PubMed PMID: 21642323.
[4] Direkvand-Moghadam A, Sayehmiri K, Delpisheh A. Epidemiology of premenstrual syndrome (PMS)-A systematic review and meta-analysis study. Journal of clinical and diagnostic research: JCDR. 2014;8(2):106.
[5] Awanish Kumar Pandey, Poonam Tripathi, Shambaditya Goswami, Rishabh Dev Pandey. Prevalence of psychological and physical symptoms of pre-menstrual syndrome in female students. Archives of Pharmacy Practice 2013;4(1):47-9.
[6] Fritz MA & Speroff L. Clinical Gynecologic Endocrinology and Infertility. 8th edition. . Philadelphia, Pa, USA: Wolters Kluwer Health/Lippincott Williams & Wilkins. 2011.
[7] Craner J, Sigmon S, Martinson A, McGillicuddy M. Perceptions of health and somatic sensations in women reporting premenstrual syndrome and premenstrual dysphoric disorder. The Journal of nervous and mental disease. 2013 Sep;201(9):780-5. PubMed PMID: 23995034.
[8] Kloss, Beth A.; Marcom, Lisa A.; Odom, Ann M.; Tuggle, Courtney L.; Weatherspoon, Deborah. PMS Treatment Through the Use of CAM. International Journal of Childbirth Education. 2012;27(3):60.
[9] MacGregor EA. Classification of perimenstrual headache: clinical relevance. Current pain and headache reports. 2012 Oct;16(5):452-60. PubMed PMID: 22653664.
[10] Gupta R, Lahan V, Bansal S. Subjective sleep problems in young women suffering from premenstrual dysphoric disorder. North American journal of medical sciences. 2012 Nov;4(11):593-5. PubMed PMID: 23181235. Pubmed Central PMCID: 3503382.
[11] Watanabe K, Shirakawa T. Characteristics of Perceived Stress and Salivary Levels of Secretory Immunoglobulin A and Cortisol in Japanese Women With Premenstrual Syndrome. Nursing and midwifery studies. 2015;4(2).
[12] Lewis EI & Rapkin AJ. Treatment of premenstrual dysphoric disorder. Women's Health. 2013;9(9):537-56.
[13] Rapkin AJ & Mikacich JA. Premenstrual Dysphoric Disorder and Severe Premenstrual Syndrome in Adolescents. Pediatric Drugs. 2013; 15(3):191-202.
[14] MacGregor EA. Migraine Management During Menstruation and Menopause. CONTINUUM: Lifelong Learning in Neurology. 2015;21(4, Headache):990-1003.
[15] Shuster LT, Faubion SS, Sood R, Casey PM. Hormonal manipulation strategies in the management of menstrual migraine and other hormonally related headaches. Current neurology and neuroscience reports. 2011 Apr;11(2):131-8. PubMed PMID: 21207200.
[16] Ibrahim Karaca SK, Emrah Toz, Mehmet Adiyeke, and Mehmet Tunç Canda. Treatment of Premenstrual Syndrome with Progesterone in Women with Polycystic Ovary Syndrome. Gynecology & Obstetrics. 2013;3(3):1000151.
[17] Verma RK, Chellappan DK, Pandey AK. Review on treatment of premenstrual syndrome: from conventional to alternative approach. Journal of basic and clinical physiology and pharmacology. 2014;25(4):319-27.
[18] Chocano-Bedoya PO, Manson JE, Hankinson SE, Willett WC, Johnson SR, Chasan-Taber L, et al. Dietary B vitamin intake and incident premenstrual syndrome. The American journal of clinical nutrition. 2011 May;93(5):1080-6. PubMed PMID: 21346091. Pubmed Central PMCID: 3076657.
[19] Klatzkin RR, Bunevicius A, Forneris CA, Girdler S. Menstrual Mood Disorders are Associated with Blunted Sympathetic Reactivity to Stress. Journal of Psychosomatic Research. 2013.
[20] Rountree R, Martin LC, Cooper R, Hart J, Yarnell E, Abascal K, et al. Clinical Roundup: How Do You Treat Stress in Your Practice? Part 2. Alternative and Complementary Therapies. Alternative and Complementary Therapies. 2011;17(3):181-7.
[21] Lust J. The Herb Book: The Most Complete Catalog of Herbs Ever Published: Courier Corporation; 2014.
[22] Gautam RK, Dixit PK, Mittal S. Herbal Sources of Antidepressant Potential: A Review. International Journal of Pharmaceutical Sciences Review and Research. 2013;18(1):86-91.
[23] Gomez del Rio M, Sánchez-Reus M, Iglesias I, Pozo M, Garcia-Arencibia M, Fernandez-Ruiz J, et al. Neuroprotective properties of standardized extracts of Hypericum perforatum on rotenone model of parkinson’s

disease. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2013;12(5):665-79.
[24] El-Alfy AT, Abourashed EA, Matsumoto RR. Nature against depression. Current medicinal chemistry. 2012;19(14):2229-41. PubMed PMID: 22414105.
[25] Negi PS. Plant extracts for the control of bacterial growth: efficacy, stability and safety issues for food application. International journal of food microbiology. 2012 May 1;156(1):7-17. PubMed PMID: 22459761.
[26] Canning S, Waterman, M Orsi N, Ayres J, Simpson N, Dye L. The Efficacy of Hypericum perforatum (St Johns Wort) for the Treatment of Premenstrual Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. CNS drugs. 2010;24(3):207-25.
[27] 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 Diseases Journal. 2013;1(2):67-73.
[28] 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(7):275-8.
[29] Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. The Journal of nutritional biochemistry. 2013;24(5):725-43.
[30] Thoits PA. Self, identity, stress, and mental health. Handbook of the sociology of mental health: Springer. 2013;2013: 357-77.
[31] Simpson JL, Bailey LB, Pietrzik K, Shane B, Holzgreve W. Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficienty or excess. Part II-Vitamin D, Vitamin A, Iron, Zinc, Iodine, Essential Fatty Acids. Journal of Maternal-Fetal and Neonatal Medicine. 2011;24(1):1-24.
[32] Turner N, Mitchell TW, Else PL, Hulbert AJ. The ω-3 and ω-6 fats in meals: A proposal for a simple new label. Nutrition. 2011;27(6):719-26.
[33] Dante G, Facchinetti F. Herbal treatments for alleviating premenstrual symptoms: a systematic review. Journal of psychosomatic obstetrics and gynaecology. 2011 Mar;32(1):42-51. PubMed PMID: 21171936.
[34] Raatz SK, Young LR, Picklo MJ, Sr., Sauter ER, Qin W, Kurzer MS. Total dietary fat and fatty acid content modifies plasma phospholipid fatty acids, desaturase activity indices, and urinary prostaglandin E in women. Nutr Res. 2012 Jan;32(1):1-7. PubMed PMID: 22260857.
[35] Rocha Filho EA, Lima JC, Pinho Neto JS, Montarroyos U. Essential fatty acids for premenstrual syndrome and their effect on prolactin and total cholesterol levels: a randomized, double blind, placebo-controlled study. Reprod Health. 2011;8(2).
[36] Pepper-Yowell A, Wang S, Byelashov O, Sellers M, Harris T, Ballou M. All omega 3 fatty acids decrease macrophage prostaglandin E2 and inflammatory cytokine production (1034.16). The FASEB Journal. 2014;28(1 Supplement):1034.16.
[37] Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Molecular psychiatry. 2012 Dec;17(12):1272-82. PubMed PMID: 21931319. Pubmed Central PMCID: 3625950.
[38] Su K-P, Lai H-C, Yang H-T, Su W-P, Peng C-Y, Chang JP-C, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. Biological psychiatry. 2014;76(7):559-66.
[39] Zamani M, Neghab N, Torabian S. Therapeutic effect of Vitex agnus castus in patients with premenstrual syndrome. Acta Medica Iranica. 2012;50(2):101-6.
[40] 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 and quality of life outcomes. 2012;10(1):1.
[41] Bertone-Johnson ER, Whitcomb BW, Rich-Edwards JW, Hankinson SE, Manson JE. Premenstrual Syndrome and Subsequent Risk of Hypertension in a Prospective Study. American journal of epidemiology. 2015;182(12):1000-9.
[42] Shoeb M, Yadav UC, Srivastava SK, Ramana KV. Inhibition of aldose reductase prevents endotoxin-induced inflammation by regulating the arachidonic acid pathway in murine macrophages. Free radical biology & medicine. 2011 Nov 1;51(9):1686-96. PubMed PMID: 21856412. Pubmed Central PMCID: 3188329.
[43] Salem Jr N, Eggersdorfer M. Is the world supply of omega-3 fatty acids adequate for optimal human nutrition? Current Opinion in Clinical Nutrition & Metabolic Care. 2015;18(2):147-54.
[44] Burri L, Hoem N, Banni S, Berge K. Marine omega-3 phospholipids: metabolism and biological activities. International journal of molecular sciences. International journal of molecular sciences. 2012; 13(11):15401-19.

[45] Harris WS, Jacobson T. Omega-3 fatty acids. Clinical Lipidology, A Companion to Braunwald's Heart Disease Philadelphia, PA: Saunders. 2009:326-38.
[46] Tofighiyan T, Kooshki A, Rakhshani MH. The Effects of Omega-3 Fatty Acids on Premenstrual Syndrome. Iranian Journal of Obstetrics, Gynecology & Infertility. 2013;15(32).
[47] Sohrabi N, Kashanian M, Ghafoori SS, Malakouti SK. Evaluation of the effect of omega-3 fatty acids in the treatment of premenstrual syndrome: "a pilot trial". Complement Ther Med. 2013;21(3):141-6.
[48] Sohrabi N, Kashanian M, Ghafoori SS, Malakouti SK. Evaluation of the effect of omega-3 fatty acids in the treatment of premenstrual syndrome:"a pilot trial". Complementary therapies in medicine. 2013;21(3):141-6.
[49] Fontani ,G Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. Cognitive and physiological effects of Omega3 polyunsaturated fatty acid supplementation in healthy subjects. European journal of clinical investigation. 2005;35(11):691-9.
[50] Sampalis F, Bunea R, Pelland MF, Kowalski O, Duguet N, Dupuis S. Evaluation of the effects of Neptune Krill Oil on the management of premenstrual syndrome and dysmenorrhea. Alternative medicine review : a journal of clinical therapeutic. 2003 May;8(2):171-9. PubMed PMID: 12777162.
[51] Deutch B, Jørgensen EB, Hansen JC. Menstrual discomfort in Danish women reduced by dietary supplements of omega-3 PUFA and B12 (fish oil or seal oil capsules). Nutrition Research. 2000;20(5):621-31.
[52] Sabet-Birjandi S, Tadayon-Najafabadi M, Siyahpooshan A, Haghighizadeh M. Comparision the effect of Hypericum perforatum and vitamin B6 in the treatment of premenstrual syndrome. Zahedan Journal of Research in Medical Sciences. 2011;13(4):1-5.
[53] 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.
[54] 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 Mar;24(3):207-25. PubMed PMID: 20155996.
[55] Pakgohar M, Mehran A, Salehi M, Sh A, Ahmadi M. Comparison of hypericum perforatum and placebo in treatment of physical symptoms of premenstrual syndrome. HAYAT. 2004;10(3).
[56] 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. Journal of Alternative & Complementary Medicine. 2004;10(6):925-32.