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Review Article

The efficacy of *Hypericum perforatum* L. for the treatment of premenstrual syndrome: A systematic review and meta-analysis

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Abstract

Objective: Premenstrual syndrome (PMS) occurs in the luteal phase of the menstrual cycle and is characterized by physical, behavioral, and psychological symptoms. *Hypericum perforatum* L. has shown promising therapeutic effects on this syndrome. This study aimed to systematically review the efficacy of *H. perforatum* on the treatment of PMS.

Materials and Methods: Scopus, PubMed, Web of Science, Cochrane Library, and regional databases (e.g., Magiran, IranDoc, and SID) were searched for studies published from 2000 to September 10, 2023. The randomized controlled clinical trials were included, and the risk of bias was assessed using the Verhagen tool. Heterogeneity was evaluated using the Q test and I^2 statistics. The pooled standardized mean difference (SMD) with a 95% confidence interval was calculated using fixed-effect or random-effects models.

Results: Nine randomized controlled trials involving 1,020 participants met the eligibility criteria and were included in the meta-analysis. *H. perforatum* was found to significantly reduce anxiety (SMD = -0.21, 95% CI: -0.37, -0.05), depression (SMD = -0.45, 95% CI: -0.74, -0.17), mood disturbances (SMD = -0.36, 95% CI: -0.66, -0.06) and behavioral symptoms (SMD = -0.43, 95% CI: -0.68, -0.19) compared to the placebo.

Conclusion: The meta-analysis showed that *H. perforatum* is more effective than a placebo in alleviating the psychological symptoms of PMS. However, there is a lack of high-quality evidence for some outcomes, highlighting the need for further research. Future studies should also focus on identifying and characterizing the plant's bioactive phytochemicals, which may lead to the development of novel, natural-based therapeutic agents.

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Introduction

Premenstrual syndrome (PMS) comprises cognitive, emotional, and physical symptoms affecting many women during the luteal phase of the menstrual cycle, typically resolving with menstrual bleeding (Sanchez, 2023). Premenstrual dysphoric disorder (PMDD), introduced in the DSM-IV, describes more severe symptoms, with specific diagnostic criteria (Reid and Soares 2018). The DSM-IV classifies premenstrual disorders based on their triggers such as exogenous progesterone or ovarian activity (Nappi, Cucinella et al. 2022). Causes of PMS and PMDD may include hormonal imbalances, neurochemical changes, and nutritional deficiencies (Afifi, Fahmy et al. 2017). Approximately 25% of women face mild to moderate symptoms while 5% experience severe PMDD (Nascimento, Gaab et al. 2020), and the symptoms include irritability, mood changes, anxiety, and physical discomfort. The DSM-5 requires at least five symptoms for PMDD diagnosis and suggests recording symptoms during the luteal phase using tools like the Daily record of severity of problems (DRSP) before the treatment (Yonkers and Simoni 2018).

The simultaneous occurrence of distressing symptoms in this syndrome disrupts daily functioning and reduces the quality of life of the affected women. Many women try medicinal and non-medicinal treatment options to alleviate these symptoms (Korelo, Moreira et al. 2022, Ahmadi, Khansary et al. 2023, Siminiuc and Ţurcanu 2023). Due to the unclear pathophysiology of the syndrome, various treatments are recommended, including bromocriptine, serotonin reuptake inhibitors (like fluoxetine), gonadotropin-releasing hormone analogs, and estrogen therapy (Takeda 2023). However, many women prefer the herbal treatments, complementary medicine, exercise, and dietary changes for their perceived benefits over synthetic drugs (Hofmeister and Bodden 2016, Siminiuc and Ţurcanu 2023). Among them, medicinal plants are often chosen for their affordability, availability, fewer side effects, and safety (Miranda 2021).

Hypericum perforatum (synonym: St. John's Wort, the Hypericaceae family) inhibits monoamine oxidase and serotonin reuptake, mechanisms implicated in PMS. *H. perforatum* has demonstrated efficacy in treating mild to moderate depression, whilst often called "natural fluoxetine" due to its similar mechanism and therapeutic properties (Gaster and Holroyd 2000, Nobakht, Akaberi et al. 2022). Its antidepressant effects stem from bioactive components like hypericin and hyperforin, which modulate neurotransmitter levels (serotonin, dopamine, and norepinephrine), while flavonoids (such as quercetin and luteolin) and tannin contents provide anti-inflammatory and antioxidant benefits, potentially alleviating the PMS (Mohagheghzadeh, Badr et al. 2023). The effectiveness of *H. perforatum* for the PMS has been assessed previously in three randomized, double-blind, placebo-controlled trials (Hicks, Walker et al. 2004, Pakgohar, Mehran et al. 2004, Pakgohar, Ahmadi et al. 2005). Two of these trials found that *H. perforatum* had a significant effect on the physical PMS (Pakgohar, Mehran et al. 2004, Pakgohar, Ahmadi et al. 2005). Hicks et al. found that *H. perforatum* (600 mg/day) did not significantly reduce the PMS compared to the placebo treatment (Hicks, Walker et al. 2004).

Given the prominence of meta-analytical studies and the conflicting results from previous research, the present study aimed to investigate the effects of *H. perforatum* on the PMS.

Materials and Methods

This systematic review was conducted following the guidelines of the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Parums 2021), and the study protocol was registered in

PROSPERO (Ref No: CRD42023456385, dated 2023/10/15).

The following steps were undertaken: (a) planning and developing a protocol, (b) registering the protocol in PROSPERO, (c) conducting a comprehensive literature search, (d) extracting data, (e) defining outcomes, (f) assessing risk of bias and quality, (g) devising a strategy for data analysis and effect measures, and (h) reporting the results (Shamseer, Moher et al. 2015).

Search strategy

We searched several online databases, including PubMed/MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Iranian databases such as Magiran, IranDoc, and SID. Potentially relevant publications were identified by reviewing the references of primary articles and examining the cited lists of eligible studies through Google Scholar. All relevant publications were assessed using predefined inclusion criteria. Initially, the search keywords were determined by reviewing relevant articles, consulting experts, and utilizing MeSH terms in PubMed, such as "*H. perforatum*" , "St. John's Wort" , "Premenstrual Syndromes" , and "Randomized Clinical Trial".

Selection criteria

The studies were considered eligible for inclusion if they met the following criteria:

1. Study design: Randomized controlled trials (RCTs).
2. Population: Individuals diagnosed with premenstrual syndrome (PMS) who have regular menstrual cycles.
3. Language: No language restrictions applied.
4. Intervention: *H. perforatum* used alone or in combination with other herbal medicines.
5. Control group: Placebo
6. Outcomes: Evaluation of physical and mental symptoms of PMS.
7. Time frame: Studies published from 2000 until September 10, 2023.

Exclusion criteria included conference proceedings, protocols, descriptive-analytical studies, animal studies, systematic reviews, and guideline reports. Participants who had used hormonal or antidepressant drugs in the past few months, had chronic diseases (e.g., diabetes), mental illness, irregular menstrual cycles, experienced significant stressful life events in the last three months, or were suffering bone and joint diseases were also excluded.

Data extraction

All articles retrieved from the databases or through manual searches were imported into EndNote X20. After removing duplicates, two researchers (L.B and S.M) independently reviewed the titles and abstracts for potential eligibility based on the inclusion criteria. The full texts of potentially eligible studies were independently reviewed by both authors (L.B and S.M) to determine final eligibility.

The following information was extracted from the studies: the name of the first author, year of publication, country, target group, type of intervention, sample size, desired outcome, measurement scale, study results, and conclusion (Table 1). Data extraction was conducted independently by two researchers (LB and SM), with any disagreements resolved by a third researcher (P.A).

Quality assessment

To assess the quality of the studies, the tool developed by Verhagen et al. in 1998 was used (Verhagen, De Vet et al. 1998). This tool consists of nine questions, each with two response options (A and B). The scores of 1 and 0 were assigned for "yes" and "no" responses, respectively.

The quality assessment of the selected studies was performed independently by two researchers (L.B and S.M) using the Verhagen tool. The results from both researchers were then compared in a face-

to-face meeting. Any disagreements were resolved by a third researcher (P.A). Based on their scores, the studies were categorized into two groups: high-quality (scores 6-9) and low-quality (scores 1-5). The Verhagen tool was utilized for assessing the risk of bias, as it highlights key bias areas, including selection, performance, and detection bias, enabling a detailed evaluation of the studies included. Its practical application and established use in related research on similar interventions further justify our choice, ensuring a comprehensive and context-specific assessment of bias.

Statistical analysis

The outcomes of this study included both physical and psychological symptoms of PMS. Data analysis was conducted using STATA software (version 17). The standardized mean differences were used as the effect size for comparing the two groups. Necessary information from the included studies included mean, standard deviation, and sample size for each group.

Heterogeneity was assessed using Cochrane's Q test (with a low *p*-value indicating significant heterogeneity) and the I^2 index (where $I^2 < 40\%$ indicated low heterogeneity, and $I^2 > 75\%$ indicated high heterogeneity). When heterogeneity was present, a random-effects meta-analysis based on the Der Simonian-Laird method was employed; otherwise, a fixed-effect model was used. The publication bias was evaluated using the regression-based Egger test.

Ethical considerations

The present study was conducted in strict accordance with ethical research standards. The primary data sources were the existing studies, meaning that no direct human or animal subjects were involved in our analysis. We ensured that all the studies included had received appropriate ethical approval from their respective institutional review boards or ethics committees.

Results

A total of 316 primary articles were initially identified across all databases. After removing duplicates using the EndNote software, 167 studies remained; their titles and abstracts were then screened by two researchers, leading to the exclusion of irrelevant articles and leaving 34 studies. The full texts of these 34 studies were then independently assessed by the two researchers (LB and S.M). In addition to removing irrelevant studies that did not meet our inclusion criteria, three studies were also excluded due to the lack of desired outcome. A total of nine articles were ultimately included in the meta-analysis (Figure 1).

Study characteristics

The results of this study included 9 articles with a total sample size of 1,020 participants (Figure 1). One trial was excluded from the analysis due to insufficient extractable data (Salehi, Momeni et al. 2013). The meta-analysis included studies with sample sizes ranging from 30 to 170 participants. Of the included studies, seven were conducted in Iran (Pakgohar, Ahmadi et al. 2005, Ghazanfarpour, Kaviani et al. 2011, Tadayon-Najafabadi, Siyahpooshan et al. 2011, Kheirkhah, Abassinia et al. 2013, Salehi, Momeni et al. 2013, Kheirkhah, Gholami et al. 2016, Ghazanfarpour, Abdolahian et al. 2017), two in the UK (Hicks, Walker et al. 2004, Canning, Waterman et al. 2010), and one in Korea (Ryoo, Chun et al. 2010). Additionally, three studies were classified as low quality, while seven were classified as high quality (Table 2). Of the included studies, nine utilized a placebo as the control group, and two studies used vitamin E and vitamin B6 as controls (Salehi, Momeni et al. 2013, Ghazanfarpour, Abdolahian et al. 2017).

All interventions were administered individually, with only one study incorporating Vitagnos as part of the treatment (Salehi, Momeni et al. 2013) (Table 1). In eight studies, *H. perforatum*

was used in the form of tablets (Ghazi-Jahani 2004, Hicks, Walker et al. 2004, Canning, Waterman et al. 2010, Tadayon-Najafabadi, Siyahpooshan et al. 2011, Salehi, Momeni et al. 2013, Kheirkhah, Gholami et al. 2016, Ghazanfarpour, Abdolahian et al. 2017, Khademi, Abbassinya et al. 2020), in one study in the form of drops (Pakgohar, Ahmadi et al. 2005), and in one study in the form of capsules (Kheirkhah, Abassinia et al. 2013).

In eight studies, the drug was used for two cycles (Hicks, Walker et al. 2004, Pakgohar, Ahmadi et al. 2005, Canning, Waterman et al. 2010, Ryoo, Chun et al. 2010, Ghazanfarpour, Kaviani et al. 2011, Tadayon-Najafabadi, Siyahpooshan et al. 2011, Kheirkhah, Abassinia et al. 2013, Salehi, Momeni et al. 2013, Ghazanfarpour, Abdolahian et al. 2017), whereas in 2 studies, it was used for three cycles (Kheirkhah, Gholami et al. 2016, Khademi, Abbassinya et al. 2020).

The prescribed doses of the drug varied across the studies, ranging from 280 mg to 900 mg. None of the studies reported any side effects associated with the treatment.

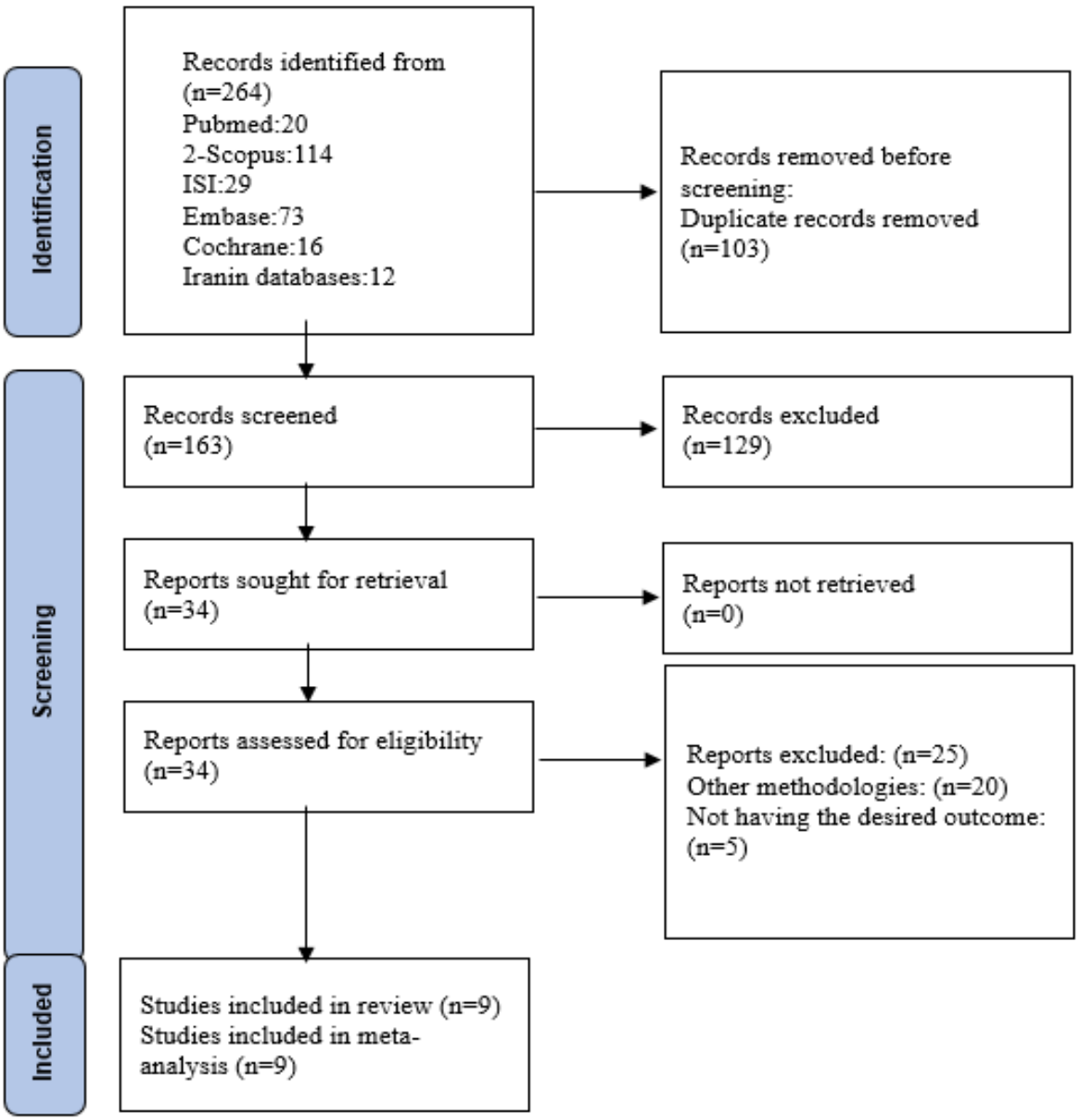

Figure 1. PRISMA 2020 flow diagram for systematic reviews

Table 1. Characteristics of all studies included in this study

First author, Year, Ref	Type of Study - Sample size	Intervention group	Instructions of Intervention and control group	Control group	Measuring tools	Outcomes
Khademi et al (2020) Iran [30]	RCT Intervention group=48 Control group= 45	*Hypericum perforatum* L.	daily in the first cycle- 8 days pre-menstruation to 2 days post-menstruation for second and third cycles	placebo	PMS questionnaire	The severity of physical and behavioral symptoms of PMS was significantly lower in the performance group than in 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 ($p < 0.001$).
STEPHEN et al (2013) UK [16]	RCT Intervention group=61 Control group= 64	*Hypericum perforatum* L. (St. John's Wort)	one week before menstruation 2 times a day 2 consecutive cycles	placebo	VAS	After averaging the effects of treatment over both treatment cycles it was found that there was a trend for SJW to be superior to placebo. However, this finding was not statistically significant.
Kirkham et al (2016) Iran [25]	RCT Intervention Group1=70 Intervention Group2=70 Control group= 70	*Hypericum perforatum* L.	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	placebo	PMS questionnaire	The data showed that there were no significant differences between the 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 the control group ($p<0.001$). perform and omega-3 significantly reduce the severity of PMS
Jung-Gum Ryoo et al (2010) Korea [29]	RCT Intervention group=16 Control group= 14	*Hypericum perforatum* L. (St. John's Wort)	one week before menstruation 2 times a day 2 consecutive cycles	placebo	(VAS)	Compared to the placebo group, the SJW group exhibited no significant differences in VAS, total PAF, or BDI. However, the groups differed significantly ($p<0.05$) on three PAF subtype scores: emotional lability, hostility/anger, and impulsivity
Ghazanfarpour et al (2011) Iran [27]	RCT Intervention group=85 Control group= 85	*Hypericum perforatum* L. (St John's wort)	one week before menstruation1 times a day2consecutive cycles	placebo	General Health Questionnaire	Those receiving *H. perforatum* had significantly lower PMS scores compared with the baseline (Pb0.001) and the control group (Pb0.001). The biggest improvements in score occurred for crying (71%) and depression (52%) in the study group. More participants from the study group than the control group dropped out because of adverse events (p=0.02)
Ghazanfarpour et al (2017) Iran [26]	RCT Intervention group=79 Control group= 78	*Hypericum perforatum* L.	one week before menstruation1 times a day2consecutive cycles	placebo	questionnaires	The mean total score decreased from 34.47 ± 6.82 to 20.68 ± 5.72 (40%) in the performance group, from 33.93 ± 6.95 to 20.92 ± 5.26 (38%) in the vitamin B6 and from 33.86 ± 6.16 to 23.90 ± 6 (29%) in the control group. The mean total score demonstrated a statistically significant decrease in the three arms compared to the baseline ($p < 0.001$). Also, the comparison of the three groups showed a significant difference at terminal weeks ($p < 0.002$).
Canning et al (2010) UK [28]	RCT crossover Intervention group=36 Control group= 36	*Hypericum perforatum* L.	one week before menstruation1 times a day 2consecutive cycles	placebo	Aggression Questionnaire and Barratt Impulsiveness Scale	*Pericum perforatum* was statistically superior to placebo in improving physical and behavioral symptoms of PMS ($p < 0.05$). There were no significant effects of *Hypericum perforatum* compared with placebo treatment for mood- and pain-related PMS symptoms ($p > 0.05$). Plasma hormone (FSH, LH, estradiol, progesterone, prolactin, and testosterone) and cytokine (IL-1b, IL-6, IL-8, IFNg, and TNFa) levels, and weekly reports of anxiety, depression, aggression, and impulsivity, also did not differ significantly during the Hypericum perforatum and placebo cycles ($p >0.05$).

Table 1 continued

Pak Gohar et al (2005) Iran [17]	RCT Intervention group=35 Control group= 35	*Hypericum perforatum* L.	one week before menstruation 2 times a day 2 consecutive cycles	placebo	Daily status registration form	The reduction in the severity of premenstrual syndrome symptoms after taking Hyperan is 45.46% and in the placebo group, it is 1.18%. The result of the t-test shows that there is a significant difference between the reduction in the severity of symptoms between the two groups (p=0.000).
Kheirkhah et al. (2013) Iran [24]	RCT Intervention group=48 Control group= 45	*Hypericum perforatum* L.	daily in the first cycle- 8 days pre-menstruation to 2 days post-menstruation for second and third cycles	placebo	questionnaire	The results showed a reduction of symptoms in the treatment drug group compared to the placebo. So the mean severity was reported at 23.64 in the Perforan group, and 46.37with (p=0.001) in the placebo group.

RCT: Randomized Controlled Trial; SJW: St. John's Wort (*Hypericum perforatum* L.); PMS: Premenstrual Syndrome; VAS: Visual Analogue Scale; PAF: Premenstrual Assessment Form; BDI: Beck Depression Inventory; GHQ: General Health Questionnaire; AQ: Aggression Questionnaire; BIS: Barratt Impulsiveness Scale; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; IL-1β: Interleukin 1 beta; IL-6: Interleukin 6; IL-8: Interleukin 8; IFN-γ: Interferon gamma; TNF-α: Tumor Necrosis Factor alpha.

Table 2. Risk of bias assessment

First author(year)	Question1	Question2	Question3	Question4	Question5	Question6	Question7	Question8	Question9	Total
Khademi (2020)	1	0	1	1	1	0	1	1	0	6
STEPHEN (2004)	1	0	0	1	1	0	1	1	0	5
Kheirkhah (2016)	1	0	1	1	1	0	1	1	0	6
Jung-Gum Ryoo (2010)	1	0	1	1	1	0	1	1	0	6
Ghazanfarpour (2011)	1	0	1	1	1	0	1	1	0	6
Ghazanfarpour et al (2017)	1	0	1	1	1	0	1	1	0	6
Canning (2010)	1	0	0	1	1	0	1	1	0	5
Pak Gohar (2005)	1	0	1	1	1	0	1	1	0	6
Kheirkhah M (2013)	1	0	1	1	1	0	1	1	0	6

The effect of *Hypericum perforatum* L. on anxiety

Figure 2 presents the results from five primary studies comparing anxiety levels between the *H. perforatum* and placebo groups. The pooled standardized mean difference (SMD) was -0.21 (95% CI: -0.37, -0.05). Given that I^2 = 0.00% and the studies were homogeneous, a fixed-effect model was applied. The analysis indicated that anxiety levels were significantly lower in the *H. perforatum* group compared to the control group. The Egger test (beta = -0.99, p=0.565) revealed no significant publication bias.

The effect of performance on depression

Figure 3 illustrates the combined results from five primary studies comparing *H. perforatum* with a placebo. The pooled standardized mean difference (SMD) was -0.45 (95% CI, -0.74 to -0.17). Due to a heterogeneity index of I^2 = 62.72%, indicating variability among the studies, a random-effects model was employed. The analysis demonstrated that depression levels were significantly lower in the *H. perforatum* group compared to the placebo group. The Egger test (beta= 1.62, p=0.500) revealed no significant publication bias.

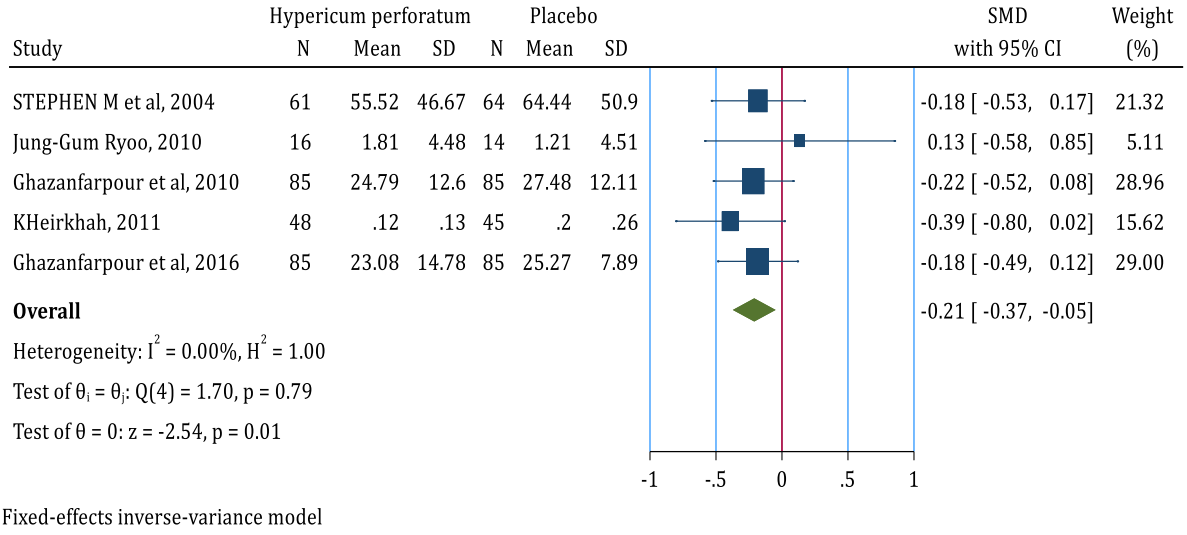

Figure 2. Forest plot of effects of interventions on anxiety

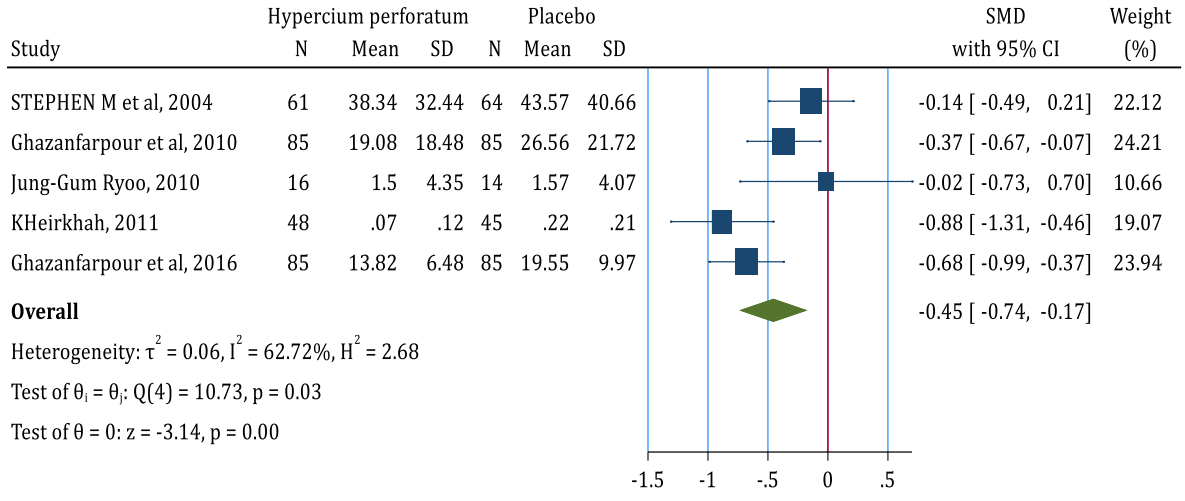

Figure 3. Forest plot of effects of interventions on depression

The effect of *Hypericum perforatum* L. on mood

Figure 4 displays the results from two primary studies comparing the effects of *H. perforatum* with placebo on mood. The pooled SMD was -0.36 (95% CI: -0.66, -0.06), indicating that mood was significantly improved in the *H. perforatum* group compared to the control group. With I^2 = 71.84 %, the studies were not highly heterogeneous, allowing the use of a fixed-effect model; while, the Egger test (beta = 8.80, p = 0.422) showed no significant publication bias.

The effect of *Hypericum perforatum* L. on behavioral

Figure 5 indicates the results from three primary studies comparing the effects of *H. perforatum* and placebo on behavioral symptoms. The pooled SMD was -0.43 (95% CI: -0.68, - 0.19), suggesting a significant difference in behavioral levels between the *H. perforatum* and the control groups. Due to the high heterogeneity (I^2 = 45.74%), a random-effects model was employed. The Egger test (beta = 25.38, p = 0.005) revealed significant publication bias.

The effect of *Hypericum perforatum* L. on craving

Figure 6 illustrates the results from three primary studies comparing the effect of *H. perforatum* and placebo on craving. The pooled SMD was -0.56 (95% CI: -0.99, -0.13), indicating that craving was significantly reduced in the *H. perforatum* group compared to the control group. Given the high heterogeneity (I^2 = 80.88%), a random-effects model was applied. The Egger test (beta = 34.38, p = 0.001) revealed significant publication bias.

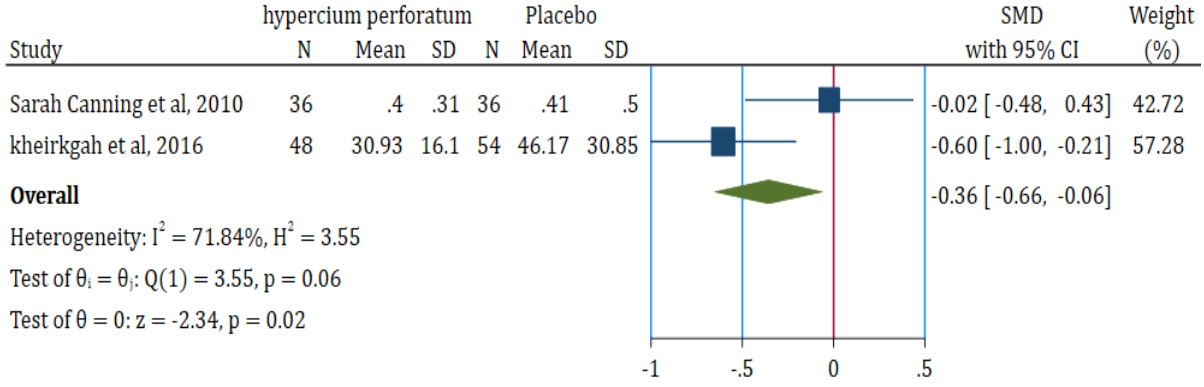

Figure 4. Forest plot of effects of interventions on mood

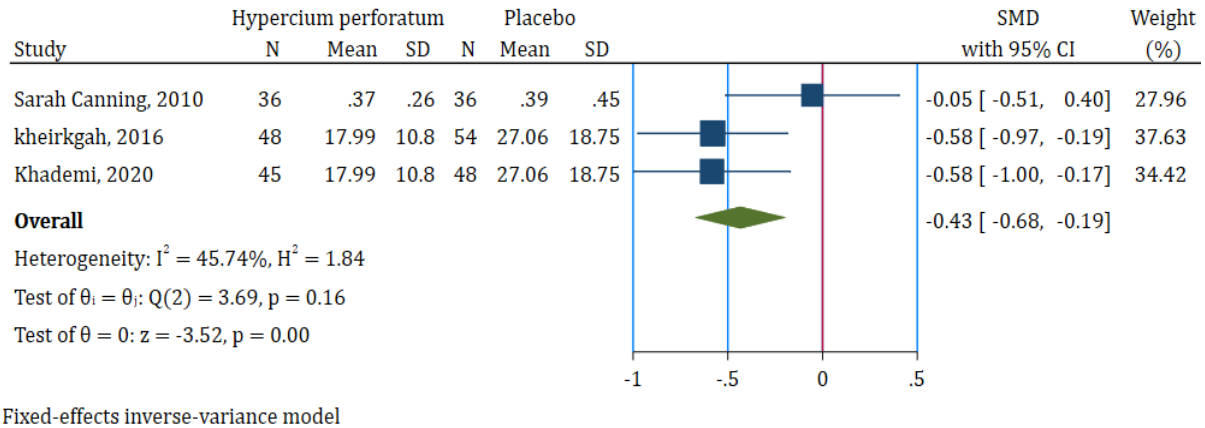

Figure 5. Forest plot of effects of interventions on behavioral symptoms

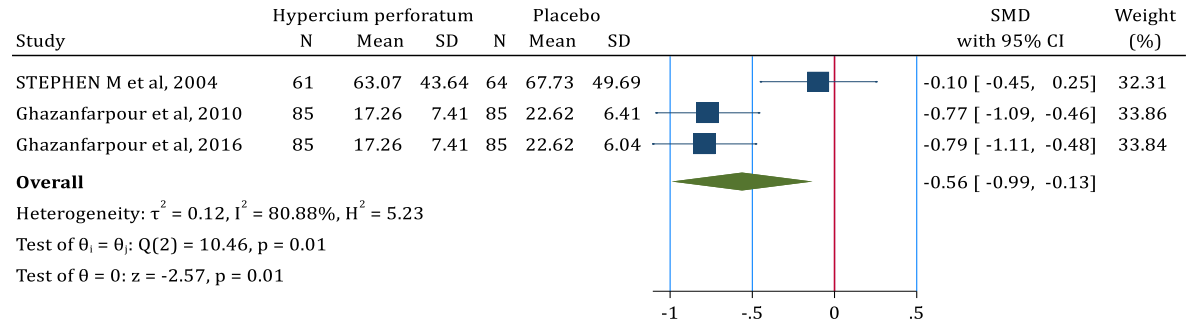

Figure 6. Forest plot of effects of interventions on craving

The effect of *Hypericum perforatum* L. on hydration

Figure 7 presents the results from four primary studies comparing the effects of *H. perforatum* and placebo on hydration. The pooled SMD was -0.09 (95% CI: -0.27, 0.08), indicating that hydration levels in the *H. perforatum* group were not significantly different from those in the control group. With an I² of 12.28%, indicating low heterogeneity, a fixed-effect model was applied. The Egger test (beta=2.97, p=0.094) suggested no significant publication bias.

The effect of *Hypericum perforatum* L. on physical activity

Figure 8 illustrates the results from four primary studies comparing the effects of *H. perforatum* and placebo on physical activity. The pooled SMD was -0.32 (95% CI: -0.93, 0.28), suggesting no significant difference in physical activity levels between the *H. perforatum* and control groups. Due to an I² value of 86.75%, indicating high heterogeneity, a random-effects model was used. The Egger test (beta=-3.22, p=0.846) indicated no significant publication bias.

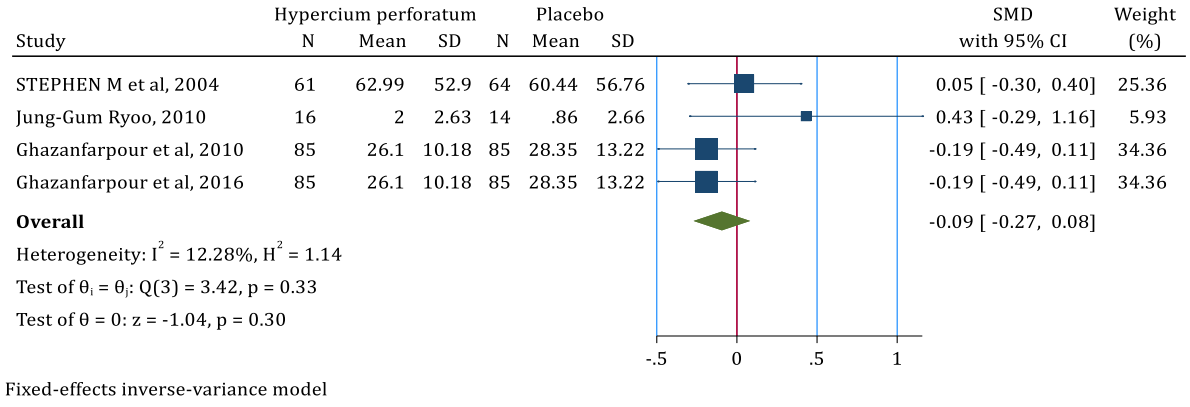

Figure 7. Forest plot of effects of interventions on hydration

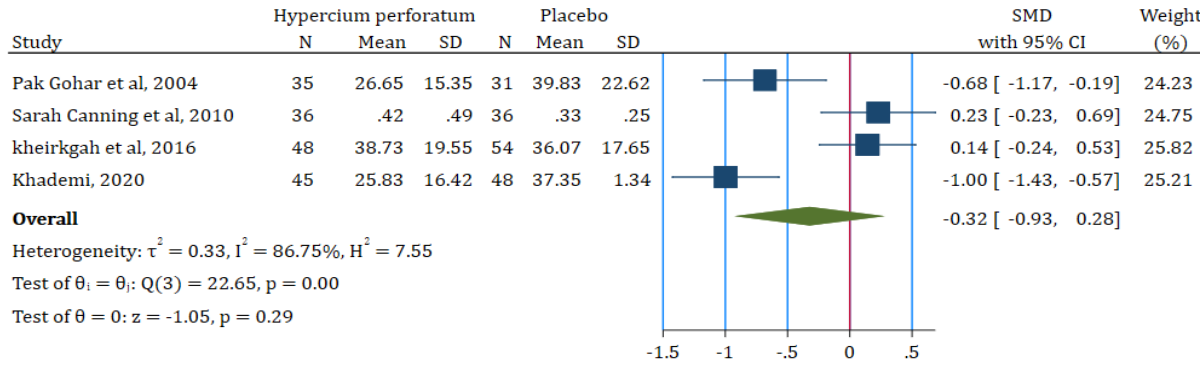

Figure 8. Forest plot of effects of interventions on physical activity

Discussion

The present study aimed to evaluate the efficacy of *H. perforatum* on the treatment of PMS. The results indicated that *H. perforatum* significantly outperforms placebo in alleviating psychological symptoms of PMS including anxiety, depression, mood disturbances, and behavioral symptoms. However, it did not show significant improvements in cravings, hydration, or physical activity.

PMS symptoms are influenced by various biological factors, with growing evidence highlighting the critical role of serotonin in the disorder's pathogenesis (Hofmeister and Bodden 2016). Selective serotonin reuptake inhibitors (SSRIs) have been shown to effectively reduce both psychological and physical symptoms of PMS within a few days (Ayhan, Altuntaş et al. 2021). *H. perforatum* increases serotonin levels in the brain and enhances the density of 5-HT1A and 5-HT2A receptors in the frontal cortex (Crupi, Abusamra et al. 2013). Several studies have suggested that *H. perforatum* may be effective for treating mild depression, but it is less effective for severe forms of the condition (Laakmann, Schüle et al. 1998, Shelton, Keller et al. 2001). Therefore, the observed beneficial effects of *H. perforatum* on the psychological symptoms of PMS in this study could be attributed to increased serotonin synthesis.

Additionally, evaluation of the biomarkers associated with serotonin production may reveal an increase in proinflammatory cytokines (Barcikowska, Rajkowska-Labon et al. 2020). During the luteal phase, cytokine levels rise, which are commonly associated with PMS (Bertone-Johnson, Ronnenberg et al. 2014). *H. perforatum* inhibits the production of proinflammatory cytokines; theoretically, this inhibition could positively impact PMS by reducing proinflammatory cytokine levels during the luteal phase (Canning, Waterman et al. 2010).

Furthermore, *H. perforatum* may be effective for the treatment of PMS when used as an adjuvant therapy alongside other medications, but it appears insufficiently potent to produce a therapeutic effect when used alone (Russo, Scicchitano et al. 2014). Future research should incorporate qualitative methods to better understand the experiences of women undergoing treatment with *H. perforatum* and placebo. This approach could shed light on how psychological and social factors—such as life circumstances, relationships, and coping mechanisms—affect the PMS and their treatment responses.

Additionally, the RCTs included in this study have several methodological limitations. Most of the studies possessed small sample sizes and short treatment durations. The variability in the PMS presentation and the different cultural perceptions of premenstrual symptoms across diverse populations indicate the need for further trials before concluding that this herb alone is an effective treatment.

All studies included in this systematic review used retrospective criteria for PMS diagnosis. To reduce the impact of confounding variables, it is crucial to adhere strictly to entry and exclusion criteria. Therefore, women who meet the PMS criteria based on retrospective reports should validate their symptoms by completing prospective daily ratings for two consecutive menstrual cycles before recruitment.

In most of the studies included, the control group was given a placebo. The placebo response can significantly affect the outcomes of the PMS research (Nascimento, Gaab et al. 2020). Therefore, it is essential to use appropriate control groups, and where possible, implement effective blinding procedures. Trials should also be of sufficient duration to allow any initial placebo response to diminish, ensuring a more accurate assessment of the treatment's true effects. Introducing a placebo phase before starting the actual treatment could help mitigate the initial placebo response. Additionally, employing validated outcome measures in all clinically

relevant trials is crucial for obtaining reliable results.

Although this study highlights some of the evidence on the effectiveness of *H. perforatum* in treating premenstrual syndrome, limitations such as small sample size, variability in PMS diagnostic criteria, and differences in formulations, doses of *H. perforatum*, and quality of evidence should be considered in interpreting the findings, and further research in this area is warranted.

Our findings suggest that *H. perforatum* may primarily benefit the psychological symptom domains associated with premenstrual syndrome (PMS). However, due to the limited number and quality of available studies, these results should be interpreted with caution, highlighting the need for further research in this area. More high-quality trials are necessary to confirm these effects.

Conflicts of interest

The authors declare that they have no competing interests.

References

Afifi, O. A.-W., N. M. Fahmy, A. A. Omran and S. O. Abd-Elmoniem (2017). "Effect of self-feet reflexology on relieving premenstrual syndrome." Menoufia Nurs. J. 2(2): 1-16.

Ahmadi, M., S. Khansary, H. Parsapour, A. Alizamir and A. Pirdehgha) 2023)" .The Effect of Zinc Supplementation on the Improvement of Premenstrual Symptoms in Female University Students: a Randomized Clinical Trial Study." Biol. Trace Elem. Res.

Ayhan, İ., İ. Altuntaş, İ. Üzümcü and O. Erbaş (2021)" .Premenstrual syndrome mechanism in the brain." D J Med Sci,7(2): 213-224.

Barcikowska, Z., E. Rajkowska-Labon, M. E. Grzybowska, R. Hansdorfer-Korzon and K. Zorena (2020). "Inflammatory markers in dysmenorrhea and therapeutic options." Int J Environ Res Public Health.17(4): 1191.

Bertone-Johnson, E., A. Ronnenberg, S. Houghton, C. Nobles, S. Zagarins, B. Takashima-Uebelhoer, J. Faraj and B. Whitcomb (2014). "Association of inflammation markers with menstrual symptom severity and premenstrual syndrome in young women." Hum Reprod. 29(9): 1987-1994.

Canning, S., M. Waterman, N. Orsi, J. Ayres, N. Simpson and L. Dye (2010). "The efficacy of Hypericum perforatum (St John's wort) for the treatment of premenstrual syndrome: a randomized, double-blind, placebo-controlled trial." CNS drugs 24: 207-225.

Crupi, R., Y. A. Abusamra, E. Spina and G. Calapai (2013). "Preclinical data supporting/refuting the use of Hypericum perforatum in the treatment of depression." CNS Neurol Disord Drug Targets. 12(4): 474-486.

Gaster, B. and J. Holroyd (2000). "St John's wort for depression: a systematic review." Arch. Intern. Med. 160(2): 152-156.

Ghazanfarpour, M., S. Abdolahian, T. Khadivzadeh and M. Kaviani (2017). "Hypericum perforutum and Vitamin B6 as a Treatment for Premenstrual Syndrome." jundishapur J. Nat. Pharm. Prod.12(2).

Ghazanfarpour, M., M. Kaviani, N. Asadi, F. Ghaffarpasand, S. Ziyadlou, H. R. Tabatabaee and M. Dehghankhalili (2011). "Hypericum perforatum for the treatment of premenstrual syndrome." Int J Gynaecol Obstet. 113(1): 84-85.

Ghazi-Jahani, B. (2004). "Translation of clinical gynecologic endocrinology and infertility." Persian. Leon Speroff. Tehran: Golban Publications 13.

Hicks, S. M., A. F. Walker, J. Gallagher, R. W. Middleton and J. Wright (2004). "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. 10(6): 925-932.

Hofmeister, S. and S. Bodden (2016). "Premenstrual syndrome and premenstrual dysphoric disorder." AFP. 94(3): 236-240.

Khademi, N., H. Abbassinya, F. Heshmat, M. Naafe and A. Mohammadbeigi (2020). "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." AHB. 10(3): 110-114.

Kheirkhah, M., K. Abassinia, F. Jahdi, F. Hosseini and M. Hassani (2013" .(The effect of perforan on the mood symptoms of premenstrual syndrome." Adv Nurs Midwifery. 11(3): 0-0.

Kheirkhah, M., R. Gholami, S. Y. Ghare-shiran and H. Abbasinia (2016). "Comparison of the effect of omega-3 fatty acids and perforan (Hypericum perforatum) on severity of premenstrual syndrome (PMS): A randomized trial." Int J Med Res Health Sci. 5(11): 333-340.

Korelo, R. I. G., N. B. Moreira, B. A. de Carvalho Miguel, C. d. G. da Cruz, N. S. P. de Souza ,R. M. B. de Macedo and R. B. S. Gallo (2022). "Effects of Auriculotherapy on treatment of women with premenstrual syndrome symptoms: A randomized, placebo-controlled clinical trial." Complement. Ther. Med. 66: 102816.

Laakmann, G., C. Schüle ,T. Baghai and M. Kieser (1998). "St. John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy." Int. Pharmacopsychiatry 31(S 1): 54-59.

Miranda, J. J. M. (2021). Medicinal plants and their traditional uses in different locations. Phytomedicine, Elsevier: 207-223.

Mohagheghzadeh, A., P. Badr, A. Mohagheghzadeh and S. Hemmati (2023). "Hypericum perforatum L. and the underlying molecular mechanisms for its choleretic, cholagogue, and regenerative properties." Pharma. 16(6): 887.

Nappi, R. E., L. Cucinella, D. Bosoni, A. Righi, F. Battista, P. Molinaro, G. Stincardini, M. Piccinino, R. Rossini and L. Tiranini (2022). "Premenstrual syndrome and premenstrual dysphoric disorder as centrally based disorders." Endocr.3(1): 127-138.

Nascimento, A. F., J. Gaab, I. Kirsch, J. Kossowsky, A. Meyer and C. Locher (2020). "Open-label placebo treatment of women with premenstrual syndrome: study protocol of a randomised controlled trial." BMJ open 10(2): e032868.

Nobakht, S .Z., M. Akaberi, A. H. Mohammadpour, A. T. Moghadam and S. A. Emami (2022). "Hypericum perforatum: Traditional uses, clinical trials, and drug interactions." Iran. J. Basic Med. Sci. 25(9): 1045.

Pakgohar, M., M. Ahmadi, A. Mehran and S. Akhondzadeh (2005). "Effect of Hypericum perforatum L. for treatment of premenstrual syndrome." Plants and J. Med. 4(15): 33-42.

Pakgohar, M., A. Mehran, M. Salehi Sour Moghi, S. Akhondzadeh and M. Ahmadi (2004). "Comparison of hypericum perforatum and placebo in treatment of physical symptoms of premenstrual syndrome." Hayat 10(3): 31-37.

Parums, D. V. (2021). "Review articles, systematic reviews, meta-analysis, and the updated preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines." Medical science monitor: Int. J. Exp. Clin. Res. 27: e934475-934471.

Reid, R. L. and C. N. Soares (2018). "Premenstrual dysphoric disorder: contemporary diagnosis and management." JOGC. 40(2): 215-223.

Russo, E., F. Scicchitano, B. J. Whalley, C. Mazzitello, M. Ciriaco, S. Esposito, M. Patanè, R. Upton, M. Pugliese and S. Chimirri (2014). "Hypericum perforatum: pharmacokinetic, mechanism of action , tolerability, and clinical drug–drug interactions." Phytother. Res. 28(5): 643-655.

Ryoo, J.-G., S.-I. Chun, Y.-J. Lee and H.-S. Suh (2010). "The Effects of St. John's Wort on Premenstrual Syndrome in Single Women: A Randomized Double-Blind, Placebo-Controlled Study." Clin Psychopharmacol Neurosci. 8(1): 30-37.

Salehi, A., H. Momeni and A. Seraji (2013). "Comparison of the effects of Hypericum and Vitex agnus premenstrual syndrome compared with vitamin E: a randomized clinical trial. Complement. Med. Res. 3(1): 395-405.

Salehi, A., H. Momeni and A. Seraji (2013). "Comparison of the effects of Hypericum and Vitex agnus premenstrual syndrome compared with vitamin E: a randomized clinical trial". cmja 2013; 3 (1) :395-405
http://cmja.arakmu.ac.ir/article-1-148-en.html

Shamseer, L., D. Moher, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle and L. A. Stewart (2015). "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation." Bmj 349.

Shelton, R. C., M. B. Keller, A. Gelenberg ,D. L. Dunner, R. Hirschfeld, M. E. Thase, J.

Russell, R. B. Lydiard, P. Crits-Christoph and R. Gallop (2001). "Effectiveness of St John's wort in major depression: a randomized controlled trial." Jama 285(15): 1978-1986.

Siminiuc, R. and D. Ţurcanu (2023" .(Impact of nutritional diet therapy on premenstrual syndrome." Front. Nutr. 10: 1079417.

Tadayon-Najafabadi, M., A. Siyahpooshan and M. H. Haghighizadeh (2011). "Comparision the effect of Hypericum perforatum and vitamin B6 in the treatment of premenstrual syndrome." Zahedan J. Res. Med. Sci. 13(4).

Takeda, T. (2023). "Premenstrual disorders: Premenstrual syndrome and premenstrual dysphoric disorder." J. Obstet. Gynaecol. Res. 49(2): 510-518.

Verhagen, A. P., H. C. De Vet, R. A. De Bie, A. G. Kessels, M. Boers, L. M. Bouter and P. G. Knipschild (1998). "The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 51(12): 1235-1241.

Yonkers, K. A. and M. K. Simoni (2018). "Premenstrual disorders." Am J Obstet Gynecol. 218(1): 68-74.