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Efficacy of saffron (Crocus sativus) in the Treatment of Premenstrual Syndrome: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Premenstrual disorder (PMS) is perhaps the most widely recognized issues among women of reproductive age. The utilization of natural therapies or complementary medicine has grown in recent years, especially among women. This study aimed to determine the efficacy of saffron on the treatment of PMS.

Methods: Electronic searching of Medline, PubMed, Scopus, Cochrane, Embase, Web of science, SID and Google Scholar was performed up to Jan 2024. Inclusion criteria consist of both English and Persian, published, clinical trials using saffron as medical for treatment of PMS. In the long run Five CTs met the inclusion criteria. The quality of these trials was evaluated by two researchers who carried out the data extraction, using Oxford Center for Evidence Based Medicine checklist. A total of three RCTs were ultimately included in a meta-analysis. Statistical analysis were performed by Comprehensive Meta-analysis (CMA) Version 2.

Results: Qualitative analysis revealed that 8-12 week of treatment with saffron could be effective in reducing the symptoms and severity of PMS and it might cause fewer side effects than chemical medicines. Three studies were included in the quantitative analysis, which resulted in a mean difference of 0.63 with 95% confidence interval (CI) (1.18-0.07), implying that the effects of saffron on PMS were statistically significant (p=0.03).

Conclusion: Although saffron has a positive effect on PMS but interpretation of results is limited because of methodological flaws of the included studies so further trials are still needed to confirm the current findings.

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Introduction

Premenstrual syndrome is one of the most well-known issues among women of reproductive age which encompasses a vast array of physical, psychological, and emotional symptoms associated with the menstrual cycle in women (1-3). With periodic recurrences, that appears after ovulation and resolves within a few days of the onset of menstruation (the first weeks of the follicular phase) (4-6). Premenstrual dysphoric disorder (PMDD) is an extreme subtype of PMS that happens in 3–8% of ladies of reproductive age (Sepehrirad M 2016). The prevalence of PMS among women changes from 10% to 53%, contingent upon the population examined and diagnostic measures used. For instance, 10% of the participants in a Swiss Study experienced PMS. In a Japanese

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report, prevalence rates of moderate to severe PMS was 53% .In Iran, the prevalence of PMS is 67-78.4% (7-10). Etiology of this syndrome is multifactorial which is not totally characterized. At first, PMS is principally connected with diminished levels of progesterone in the luteal stage. Various etiologies depicted for PMS include abnormal neurotransmitter reactions to ordinary ovarian functions, hormonal irregularities, sodium maintenance, and nutritional deficiencies (11-14). Suggested Pharmacological treatments for this syndrome consist of: antidepressants (selective serotonin reuptake inhibitors, SSRIs) and other psychotropic agents, diuretics, progesterone, GnRh agonists, hormonal therapy such as estrogen therapy, combined oral contraceptives, pyridoxine, ethinyl estradiol and drospirenone, and synthetic androgen and gonadotropin inhibitors (15-18). Nonetheless, most women were detected to favor pharmaceutical proceeds containing dietary changes, work out, cognitive behavioral therapy, and complementary and alternative medicine (19). Studies recognized that patients with PMS attempt a wide scope of CAM cures including diet, yoga, massage, exercise, faith healing, hypnosis, herbs, acupuncture, meditation, homeopathy and vitamins/supplements (20-23). As noted, some herbal medicines such as Matricaria chamomile (24), Melissa officinalis (25), wheat germ (26), Soy Bean (27),Vitexagnus (28), Hypercom perforatum (29), Curcumin (30) can also be effective in treating this syndrome. Saffron plant is a dried stigma (string like pieces) of the flower Crocus sativus L., which has utilized as a kind of traditional herbal medicine (27). Saffron stigmas have four bioactive compounds that include Crocins, Crocetin, Picrocrocin, and Safranal. The crocin and crocetin are related to the color of saffron, and picrocrocin is responsible for the taste and safranal to the aroma of saffron. Its health-related properties are the result of all four of these compounds (31). Aside from its traditional usage and value, saffron has a long history of therapeutic application traversing more than 2,500 years (32). Saffron has been utilized in traditional medication for treating various diseases including cramps, asthma, menstruation issues, liver sickness, and pain (33, 34). Therapeutic properties of saffron are likely because of various compounds contained inside this spice, consist of crocetin, crocins, and safranal, which have been found to have strong antioxidant agents and radical scavenger properties and hence would give expanded assurance against an assortment of reactive oxygen species and proinflammatory cytokines. According evidence saffron has potential anticancerogenic (cancer-suppressing), anti-mutagenic (mutation-preventing), antioxidant, antidepressant, and memory-upgrading properties (27, 35-37). Since the symptoms of the syndrome disrupt everyday life, it is beneficial to distinguish the ways of treatment. In this regard several studies have been published examining saffron's potential to reduce these symptoms and improve health conditions in human participants, specifically with an emphasis on PMS (38-42). To the best of our knowledge, no systematic review and meta-analysis has been conducted on the efficacy of saffron for preventing or treating PMS symptoms. Hence the purpose of present study was to carry out a systematic and meta-analytic to sum up and fundamentally assess the evidence from randomized clinical trials (RCTs) that have examined the efficacy or effectiveness of saffron supplementation concerning results related to PMS.

Materials and methods

This systemic review and meta-analysis, was designed and reported using a checklist of items in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher, Liberati et al.)" statement (Moher, Liberati et al. 2014). The systematic electronic search was done on the databases of the MEDLINE, PubMed, web of science, Embase, Scopus, the Cochrane Central Register Trials inception, Google Scholar as well as Persian databases such as SID, Iran Medex, and Magiran up to Jan 2024 to evaluate the efficacy of saffron in the treatment of PMS.

We searched the Cochrane Sexual and Reproductive Health Editorial Base, Cochrane Gynecology and Fertility Highlights, IRCT[1] and ICTRP[2] to seek any relevant review, RCT or RCTs in progress, as well as PROSPERO[3] for SR protocols at https://www.crd.york. ac.uk/Prospero/. We contacted the Protocol authors for a pre-publication version of RCTs. Additionally; we searched the reference lists of retrieved studies. No determined limitation was considered and the search keywords were premenstrual syndrome OR PMS OR Dysmenorrhea AND Crocus sativus OR saffron. To be included in the review, the chosen articles expected to meet the accompanying criteria: All of the in-Vivo studies, Reproductive age women diagnosed with PMS, Randomized Controlled Trials (RCTs), Interventions consist of Saffron, Comparisons could consist of a placebo or any other interventions. Outcome measures include, Primary outcomes: Change of symptoms by Daily Symptom Record (DSR) and visual analogue scale (Fabiyi, Rankin et al.) the following issues were considered for Secondary outcomes: Adverse events, Dysmenorrhea, Hamilton Depression Rating Scale.

Five studies assessed the effect of saffron medicine on PMS and Dysmenorrhea. Figure 1 shows the process of selection of articles for this systematic review. The process of the search and selection of RCTs is shown in **Figure1.** The data extraction and the quality

[1] Iranian Registry of Clinical Trials

[2] International Clinical Trials Registry Platform

[3] The International Prospective Register of Systematic Reviews

assessment of the included trials were carried out by two separate individuals according to a predefined checklist, consist of; first author, year of publication, design, sample size, duration of treatment, dosage and outcome values for both the intervention and the control groups with the mean and standard deviation of pre- and post-treatment or mean difference from the baseline (Table 1).

Table1. Characteristics of five randomized controlled trials included in systematic review.

No	1	2	3	4	5
Author, Year	**Nemat-Shahi** et al. (58),	Agha-Hosseini et al.(2008) (2007). Iran	Pirdadeh et al. (2015), Iran Iran Beiranvand et al.	**Rajabi** et al. (58),	Azimi and Abrishami (2016)), Iran
Design	RCT	RCT	RCT	RCT	RCT
Duration ,(wk.)	8	8	8	8	for three consecutive menstrual cycles
Age (/Y)	26-45	20 to 45	18 to 35	20–45	
Intervention mg	30 mg capsules of saffron	Saffron capsule 30 mg	saffron capsules, 30-mg	fluoxetine 20 mg, saffron 15 mg	Saffron capsules 30 mg.:Mefenamic acid capsules 250 mg
Type of control	fluoxetine 20 mg capsules	placebo capsule	Placebo capsules	Placebo capsules	Placebo capsules
Participants Intervention	N= 82	N=24	N=39	N=40 N=40	N=60, N=60
Participants control	N=82	N=23	N=39	N=40	N=60
Baseline comparability	Yes	Yes	Yes	Yes	Yes
Dropouts (56)	0%	6%	11%	0%	4/5%
Tools	Demographic questionnaire Visual Analogue Scales (57) Beck Anxiety Inventory	Daily Symptom Report for PMS Hamilton Depression Rating Scale	personal and medical information questionnaire the simultaneous determination of stress,	Daily record of severity of problems (DRSP) Hamilton questionnaires	VAS
blinding method	three-blind	Double-blind	triple-blind	single -blinded	double-blind
Adverse effects	There was no side effects	Appetite changes Headache Sedation Nausea Hypomania (None of adverse effects were severe)	increased appetite, loss of appetite, sedation, nausea, headache, and euphoria	Gastrointestinal symptoms Insomnia Increased menorrhagia	mild pruritus and red skin
Outcome(s)	The use of medicinal herbs such as saffron could be effective in reducing. the symptoms and they might cause fewer side effects than chemical drugs	saffron was found to be effective in relieving Symptoms of PMS. A significant difference was observed in efficacy of saffron in cycles 3 and 4 in the Total Premenstrual Daily Symptoms and Hamilton Depression Rating Scale Rating Scale	saffron reduces the severity of PMS symptoms	saffron was an efficacious herbal agent for the treatment of PMDD with minimal adverse effects	the effect of saffron in reducing pain is more than mefenamic acid and far more than placebo

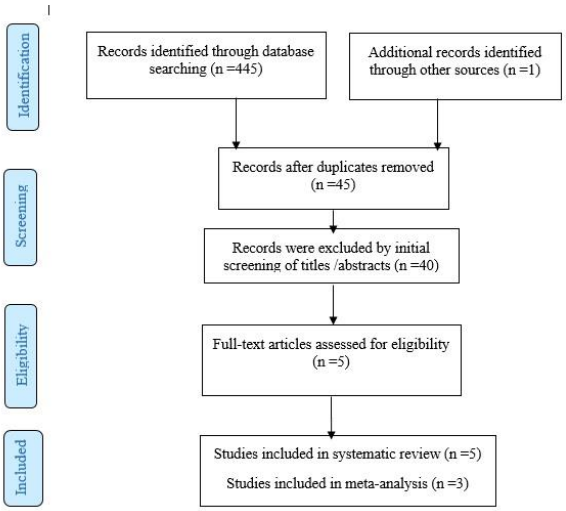
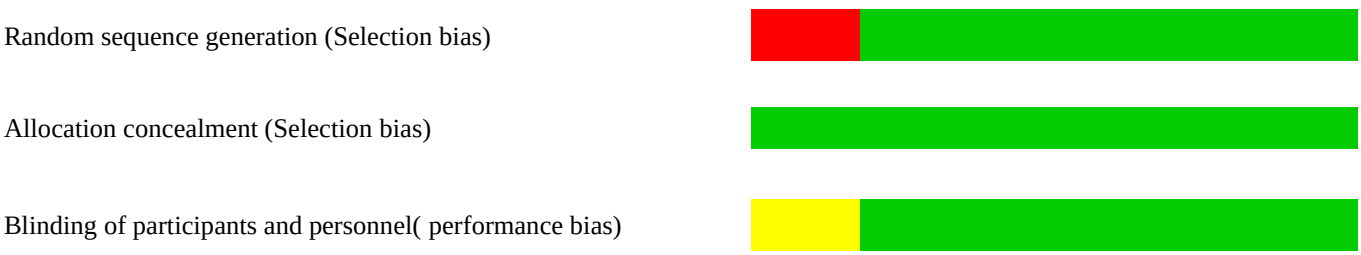


Figure 1. PRISMA Flow Diagram of study selection progress.

Two reviewers using Oxford Center for Evidence Based Medicine checklist (Table 2) independently rated the quality of RCTs (14). This tool assess Internal Validity: comprising of six general inquiries regarding the method of patients assignment, comparability and matching of groups, equality of allocated treatment, losses to follow-up and intention-to-treat analysis, blindness and effect size which was replied with three alternatives Yes , No and Unclear. This tool has been designed in two sections to evaluate internal and external validity. in this review, Internal validity was examined by six general questions containing the way of patient's assignment, similarity, and matching of groups, equality of allocated treatment, losses to follow-up and intention-to-treat analysis, blindness and effect size which was assessed with three answers of Yes, No and Unclear. Risks of bias assessment are shown in figure 2 and table2. All statistical analyses were done by Comprehensive Meta-analysis Version 2 (Biostat, Englewood, NJ, USA).

Table 2. Risk of bias summary: Systematic review. Author's judgments of risk of bias item for each included study

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Did the analysis include an intention to treat analysis?
Nemat-Shahi et al. 2020	+	+	+	+	-	+	?
Rajabi et al.2020	-	+	?	?	+	+	?
Agha-Hosseini et al. 2008	+	+	+	-	-	+	+
PirdadehBeiranvand etal. 2015	+	+	+	+	-	+	?
Azimi and Abrishami	+	+	+	-	-	+	?



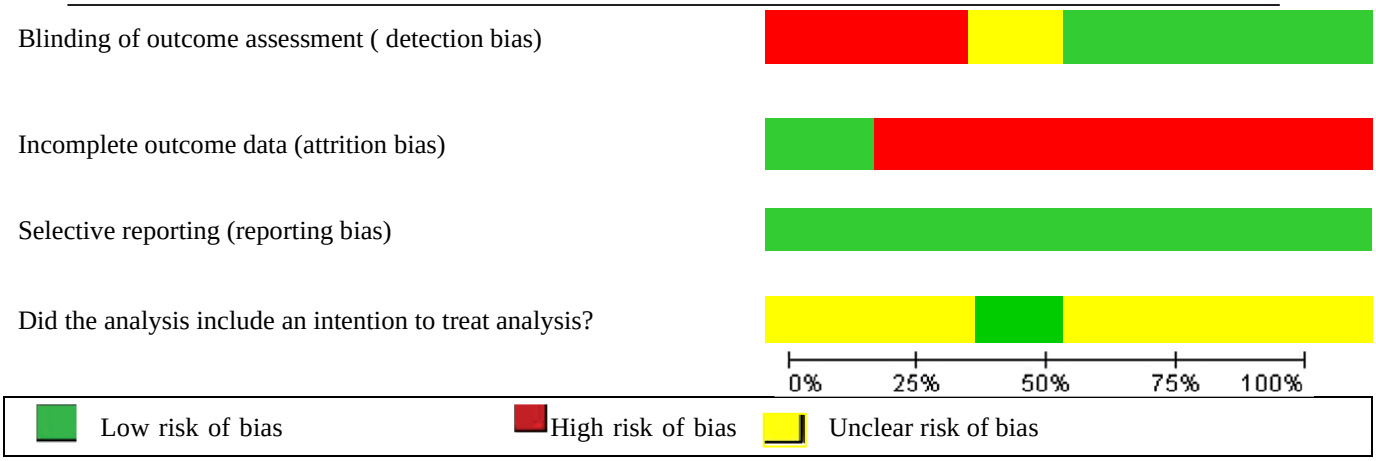


Figure 2. Risk of bias graph: Systematic review. Author's judgments of risk of bias presented as percentages across all included studies.

Results

Finally, out of 446 articles, five clinical trial studies were included in the study after review and during different stages of screening. These five clinical trial studies were conducted in Iran between 2008 and 2020. A total of 549 people participated in these studies as an intervention group and a control group. Saffron was administered orally in these studies. Nemat-Shahi et al. conducted a randomized, three-blinded clinical trial to the comparison of Saffron versus Fluoxetine in the Treatment of Women with Premenstrual Syndrome for two months (The end of the first month, the end of the second month). 164 Participants were randomly divided into two groups, the intervention group (n=82) received saffron, and the control group received fluoxetine (n=82). It was found that there was no significant difference in the improvement of abdominal pain in the two groups (P>0/05). There was a significant difference between the two groups at the end of the first month (p = 0.01) and the second month (p =0.03) associated with severe to moderate abdominal pain. It was declared that there was no significant difference in the reduction of anxiety levels between the two groups (P>0.05). It was indicated that there was not a significant difference between the two groups at the end of the first month (p = 0.83) and the second month (p =0.09). It was indicated that there was a significant difference between the two groups at the end of the first month (p = 0.0001), related to breast pain but there was not a significant difference between the two groups at the end of the second month (p = 0.014) (41). It was shown that there was no significant difference between the two groups according to depression (P>0/05). In the study of mild, medium, and severe abdominal bloating, there was no significant difference between the two groups at the end of the first and second months (P>0/05) (41). Rajabi et al. in randomized, single -blinded, clinical trial, compared saffron with fluoxetine for PMS management. This study included 120 cases with PMS for 8 weeks. The intervention group (n=40) received saffron, 15 mg twice daily and the control group (n=40) received placebo capsules containing starch similar in shape, color, and size. Results of study revealed significant improvement in all of the treatment approaches in terms of DRSP and Hamilton assessments (P < 0.001). Although DRSP assessments showed remarkable superiority of saffron to placebo (P = 0.027), Hamilton evaluations showed insignificant differences among the three interventions (P > 0.05). Fluoxetine posed a significantly higher rate of adverse effects as compared to the other agents (P = 0.01) (42).

In another report by Agha-Hosseini et al. in 2008, represented considerable symptoms improvement following the treatment either with placebo or saffron prescribed in 30 mg daily doses divided into two 15 mg capsules. The comparison of placebo with saffron showed remarkable superiority of saffron in both DRSP (t = 5.92, df = 48, P < 0.001) and Hamilton scoring systems (t = 8.99, df = 48, P < 0.001) (38). Beiranvand et al. conducted a randomized triple-blind controlled clinical trial on females resenting from PMS. They prescribed 30 mg of extracted saffron once daily for two menstrual cycles versus placebo, and eventually found significant improvement in the severity of PMS symptoms for both of the groups (P = 0.04), while the comparison of the cases and controls revealed the significant superiority of saffron to placebo (P < 0.001) (40). Azimi and Abrishami (2016) performed a randomized double-blind clinical trial on 180 female students, diagnosed with primary dysmenorrhea. The participants were assigned in to three groups, Group I received Mefenamic acid 250 mg capsules. Group II received Saffron 30 mg capsules and group III received Placebo capsules, in which received three capsules per day for three days during three consecutive menstrual cycles. In Saffron Group, 4 (2.2%) left the study due to the need for concomitant pain killers, and one patient (0.6%) left the study due to sensitivity to saffron (mild pruritus and red skin, which was resolved after saffron was discontinued without any treatment). Data were analyzed by repeated measure ANOVA test. In saffron group VAS was reduced from 6.8 to 3.6, 3.4, and 3 in 3 consecutive months. This effect was significantly

greater than Mefenamic acid and placebo (P=0.0001) (39).

Meta-analysis

Publication bias was assessed statistically using Egger's and Begg's tests at the first. P-values of the Egger's and Begg's tests were 0.0٠5 and 0.٢٩, respectively, due to the small number of articles, publication bias could not be evaluated validate, so the trim-and-fill method was used and it was seen that after adjusting for potential publication bias, the study results were not affected by publication bias (Figure 3). The heterogeneity of the measure of effects among the studies was assessed based on I^2, which was ٧5.8% ($p<0.026$). However, a Random effects model was applied to all calculations because there were some of the differences between the studies. All three studies were included in the meta-analysis, which resulted in a mean difference of 0.63 with 95% confidence interval (CI) (1.18-0.07), implying that the effects of saffron on PMS were statistically significant ($p<0.03$). The forest plot, the mean difference, its CI, the corresponding weight of each individual study, the pooled mean difference, and its CI, are shown in Figure 4, 5.

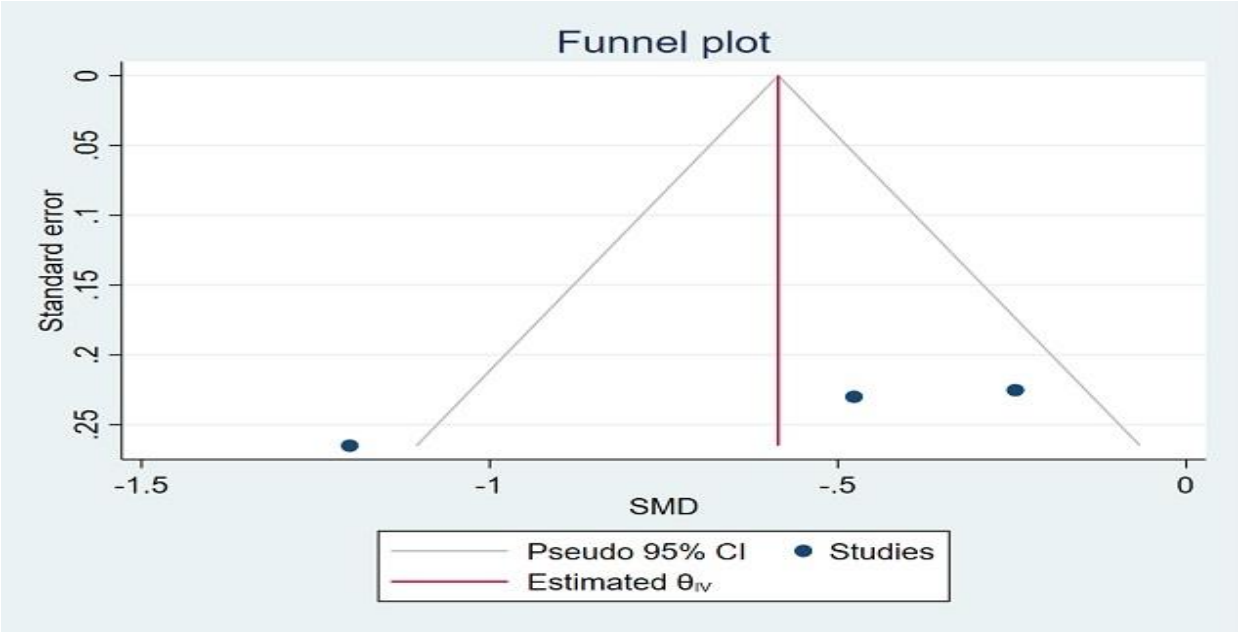


Figure 3. Funnel plot, X-axis is the natural logarithm of the mean difference and the y-axis is the standard error of the natural logarithm of means.

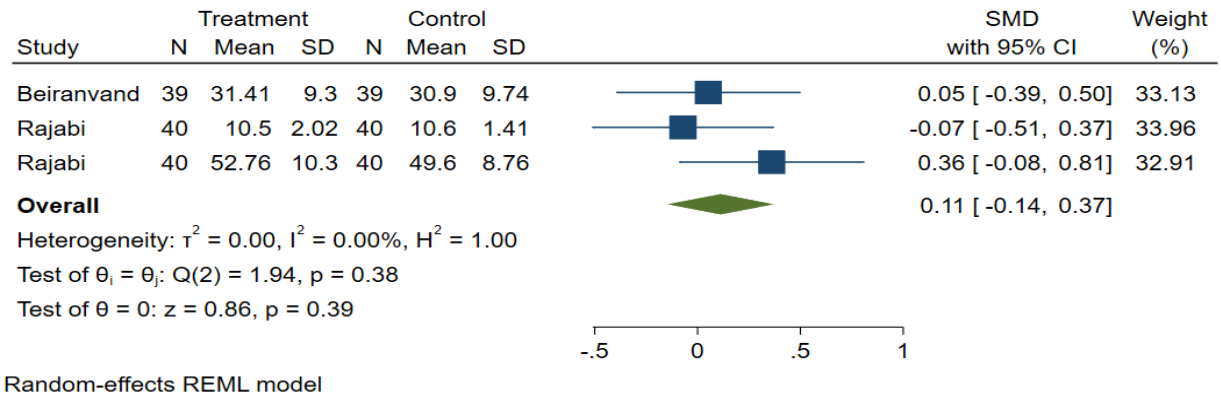


Figure 4. Effects of saffron on PMS (pretreatment). The horizontal lines denote the 95% CI, ■ point estimate (size of the square corresponds to its weight); ♦, combined overall effect of treatment.

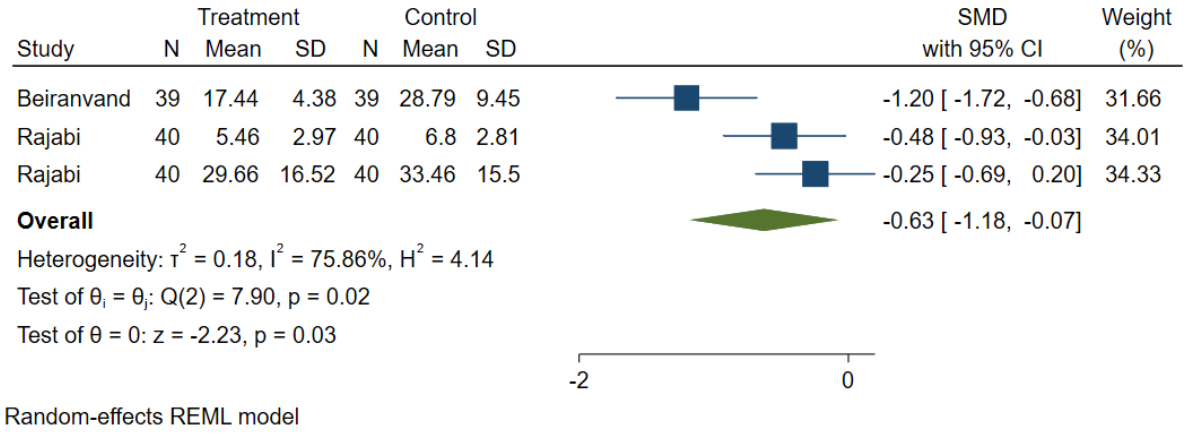


Figure 5. Effects of saffron on PMS (post treatment). The horizontal lines denote the 95% CI, ■ point estimate (size of the square corresponds to its weight); ♦, combined overall effect of treatment.

Discussion

Current systematic review and meta-analysis, assessed available literature regarding the effects of oral administration of saffron on symptoms of PMS in reproductive age women and to the best of our knowledge; this is the first study evaluating the impact of saffron on PMS symptoms.

Overall, the results revealed that 8-12 weeks of treatment with saffron could be effective in reducing the symptoms and severity of PMS and it might cause fewer side effects than chemical medicines.

The impact of saffron on abdominal pain (Visual Analogue Scales)

Overall, in different countries, including Iran, saffron is traditionally used for various purposes such as analgesia and anti-inflammatory (35). From all the present studies, one study has investigated the effect of saffron on abdominal pain. Some studies have examined the effect of saffron on abdominal pain. They reported a positive effect on abdominal pain in women with PMS (43) and on the severity of labor pain in primiparous women compared with placebo. Saffron reduced pain intensity compared with placebo (44).The proposed mechanism for the analgesic effect of saffron is to inhibit the release of prostaglandins and the presence of anthocyanin and flavonoid compounds (crocin and crocetin) (45).

The impact of saffron on Severity of dysmenorrhea

Two studies revealed the efficacy of saffron in reducing the severity of Primary Dysmenorrhea (39).In reviewing the clinical applications of saffron, it was reported that saffron alone or in combination with other plants can be effective in dysmenorrhea, although the type of compound used in these studies has been criticized (34).Primary dysmenorrhea is associated with increased prostaglandin secretion in the body (46). Hemshekhar, M et al (2012) report that in animal studies, crocin could inhibit some inflammatory mediators, including prostaglandin E-2 (PGE-2) (47).

The impact of saffron on Severity of PMS (DRSP)

Four studies reported useful impacts of saffron on Severity of PMS in all five subtypes of the questionnaire namely anxiety, depression, emotional, retention, and physical symptoms (38, 40-42). The fundamental constituents of saffron are coloring carotenoids, crocin, a bitter picrocrocin and its aroma-inducing chemical, safranal. Moreovr, crocetin is another carotenoid of saffron (48). Saffron and its constituents have been shown to alleviate a variety of neurological and inflammatory pains in different models. This effect may attribute to its positive effects on abdominal pain or other PMS symptoms (49).

The impact of saffron on Hamilton Depression Rating Scale (HDRS)

Two studies described useful impacts of saffron on Depression (38, 42). According to evidence, the serotonergic system has a significant role in the luteal phase. Besides, the effect of sex hormones on serotonin uptake, binding, turnover and transport has also been signified. So dysregulation of the serotonergic system has been suggested as a reason for the majority of PMS symptoms (50-52).

In association with Depression, it has been reported that saffron by means of a serotonergic mechanism demonstrates an antidepressant effect in the treatment of women with psychological signs such as depression (53-55).

Despite these basic outcomes, attention to alternative therapy of PMS, the mechanism of action and advantages of every treatment option like saffron must be completely investigated before its usage.

There are several limitations in the systematic review and meta-analysis, which should be addressed,

including small sample size and relatively short-term treatment duration, using only a fixed dose of saffron insufficient explanation of randomization method and blinding, and lack of Intent-To-Treatment (ITT) analysis. Also, the quality of some included studies was not optimal which may decrease the reliability of our results. Considering the above-mentioned limitations, there is a need to conduct well-designed trials to address these subjects.

Conclusion

Quantitative analysis showed that Saffron has a positive effect in treatment women with PMS symptom. But the interpretation of results of the current study is restricted because of methodological flaws and some heterogeneity among the included studies, so further trials with larger sample size and longer treatment duration are needed to affirm the present findings.

Authors' contributions

N.M, designed and directed the project. N.M and A.S drafted the first version of the manuscript. H.HM analyzed the data and verified the numerical results. N.M and A.S revised the manuscript. N.M and A.S critically reviewed the manuscript for important intellectual content. All authors approved the final version.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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