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Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial

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Objective The aim of this double-blind and placebo-controlled trial was to investigate whether saffron (stigma of *Crocus sativus* L.) could relieve symptoms of premenstrual syndrome (PMS).

Design Double-blind, randomised and placebo-controlled trial.

Setting Departments of Gynaecology/Obstetrics and Psychiatry, Tehran and Zanjan University of Medical Sciences.

Population Women aged 20–45 years with regular menstrual cycles and experience of PMS symptoms for at least 6 months were eligible for the study.

Method Women were randomly assigned to receive capsule saffron 30 mg/day (15 mg twice a day; morning and evening) (group A) or capsule placebo (twice a day) for a two menstrual cycles (cycles 3 and 4).

Main outcome measures The primary outcome measure was the Daily Symptom Report, and secondary outcome measure was the Hamilton Depression Rating Scale.

Results In this trial, 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.

Conclusion The results of this study indicate the efficacy of *C. sativus* L. in the treatment of PMS. However, a tolerable adverse effects profile of saffron may well confirm the application of saffron as an alternative treatment for PMS. These results deserved further investigations.

Keywords *Crocus sativus*, premenstrual dysphoric disorder, premenstrual syndromes, saffron.

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Introduction

Premenstrual syndromes (PMSs) are among the most common health problems reported by women, affecting 20–40% of women of reproductive age. Premenstrual dysphoric disorder (PMDD) is a severe subtype of PMS that occurs in 3–8% of women of reproductive age.[1] It is characterised by severe mood and behavioural changes. The hallmark of PMDD is its cyclical luteal phase-related nature.[2] The aetiology of the syndrome is multifactoral and not fully defined. Initially, a great role in the aetiology was attributed to decreased levels of progesterone in the luteal phase.[2] There is abundant evidence pointing to changes in serotonergic conductivity in the central nervous system in PMS/PMDD. Thus, the symptoms of PMS/PMDD are suggested to be partly associated with disturbed serotonergic conductivity. This possibility is confirmed by the positive therapeutic effect of serotonergic inhibitors in women suffering from PMS/PMDD.[3,4] A review of the literature shows that the majority of the data point to fluoxetine as an effective drug, followed by sertraline, citalopram, paroxetine and clomopramine. Both fluoxetine and sertraline have been shown to be effective in treating physical symptoms and psychosocial functioning, work performance and quality of life in women with PMS/PMDD.[5–8] An American telephone survey suggested that up to 80% self-medicating sufferers use complementary remedies.[9] It has

been reported that herbal medicine is useful in relieving the symptoms of PMS.[10–12] In addition, a number of recent experimental studies and clinical trials have been indicated that saffron is effective in the treatment of mild to moderate depression.[13–15] It has been suggested that serotonergic mechanism is involved in the antidepressant effect of saffron. As a therapeutically plant, saffron (dried stigma of *Crocus sativus* L. that belongs to the Iridaceae family) is considered an excellent stomach ailment and an antispasmodic, helps digestion and increases appetite. It also relieves renal colic, reduces stomachaches and relieves tension. In Persian tradition medicine, it is used for depression. Recent studies indicate its potential as an anticancer agent and memory enhancer.[13–15] The aim of this double-blind and placebo-controlled trial was to investigate whether saffron could relieve symptoms of PMS.

Methods

This was a randomised and double-blind clinical trial. The trial was conducted between December 2005 and April 2007.

Participants

Women aged 20–45 years with regular menstrual cycles and experience of PMS symptoms (according to the current diagnostic criteria proposed by the American College of Obstetrics and Gynecology)[16] for at least 6 months were eligible for the study. The exclusion criteria were as follows: pregnancy or lactation, menstrual cycle irregularity, unstable medical illness, seizure disorder within the past year, history of multiple drug reaction, menstrual cycle length shorter than 24 days or longer than 35 days, major psychiatric disorder, suicidal ideation or intent, use of psychoactive drugs, investigational drugs or specific medication for PMS in the past 2 month, hormonal method of contraception and history of substance abuse in the previous 6 months.

The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions[17] and approved by institutional review board. Written informed consents were obtained before entering into the study. Women were recruited through an advertisement. Although all participants had been diagnosed with PMS by their gynaecologist, they were interviewed again for two menstrual cycles (premenstrual stage) before medication started to complete baseline Daily Symptom Ratings Report and Hamilton Depression Rating Scale and reconfirmation for diagnosis of PMS.

Intervention

The stigma of *C. sativus* in this study was identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The stigma's extract was prepared as follow: 120 g of dried and milled petal was extracted with 1800 ml ethanol (80%) by percolation procedure in three steps, then the ethanolic extract was dried by evaporation in temperature between 35–40°C. Each capsule had dried extract of petal of *C. sativus* (15 mg), lactose (filler), magnesium stearate (lubricant) and sodium starch glycolate (disintegrant).

Women were randomised to receive *C. sativus* or placebo in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes in each participant's file until the point of analysis of data. In this double-blind, women were randomly assigned to receive capsule of *C. sativus* 30 mg/day (15 mg twice a day; morning and evening) (group A) or capsule placebo (twice a day) for two menstrual cycles (cycles 3 and 4). This daily dose of *C. sativus* was considered based on our previous studies regarding antidepressant effect of *C. sativus* in the treatment of mild to moderate depression.[13–15] The randomisation and allocation process was performed by the principal investigator of the trial (S.A.) who was not involved in the process of treatment and measurements. Three women dropped out over the trial, one from saffron group and two from placebo group.

Measurements

The primary outcome measure was the Daily Symptom Report, a checklist of 17 premenstrual symptoms rated from 0 to 4 according to their severity throughout the menstrual cycle and consists four subscale including mood (anxiety, irritability, depression, nervous tension, mood swings and out of control), behaviour (poor coordination, insomnia, confusion, headache, crying and fatigue), pain (aches, cramps and tender breasts) and physical (food craving and swelling) subscale.[18] Secondary outcome measure was Hamilton Depression Rating Scale (17-item).[19] All women expressing interest in participating in the trial underwent a preliminary screening interview by telephone, and those fulfilling the inclusion criteria were sent an information pack and Daily Symptom Ratings forms to be maintained for two menstrual cycles. A provisional diagnosis of PMS was made if the Total Premenstrual Daily Symptom Ratings score (over 6 days prior to the onset of menstruation) was at least 50 and at least 30% higher than the total postmenstrual Daily Symptom Ratings score (days 5–10 with day 1 being the first day of menstruation). These women were subsequently invited to a clinical screening visit mid-cycle, where a psychiatrist confirmed the existence of PMS and excluded women with a major physical or psychiatric disorder or substance abuse in the previous 6 months. Those invited to the study gave informed consent. Participants returned for a second visit at the end of cycle 2 (premenstrual stage—as close as possible to 2 days prior to the onset of menstruation) to complete baseline measures of the Hamilton Depression Rating Scale and were randomised in the two treatment groups. Daily Symptom Ratings were completed throughout the duration of the trial (menstrual cycles 1–4 by women). Participants returned for two more visits (at the premenstrual stage of cycles 3 and 4) for assessing

Hamilton Depression Rating Scale by psychiatrist. The effect of treatment was assessed by comparing the baseline (cycle 2) Premenstrual Daily Symptom Ratings and Hamilton Depression Rating Scale scores with the premenstrual scores after one and two cycles of treatment with intervention (cycles 3 and 4).

Statistical analysis

A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and the three monthly measurements during treatment as the within-subjects factor (time) were considered. To compare the two groups at baseline and the outcome of two groups at the end of the trial, an unpaired Student's *t* test with a two-sided *P* value was used. Results are presented as mean ± SD. Differences were considered significant with $P < 0.05$. To consider, $\alpha = 0.05$ and $\beta = 0.2$, the final difference between the two groups, at least score of 5 on the Daily Symptom Report, S = 5 and power = 0.8 (according to the pilot study of this research), the sample size was calculated for at least 15 in each group. Intention-to-treat analysis with the last observation carried forward procedure was performed.

Results

Seventy-eight women were screened for the study and 50 were randomised to trial medication (25 women in each group) (Figure 1). No significant differences was identified between women randomly assigned to the group A or B condition with regard to basic demographic data, including age, marital status and level of education (Table 1). Three women dropped out over the trial (one from the saffron and two from the placebo group) due to withdraw consent (they were convinced by their family that withdraw from the research project).

Total Premenstrual Daily Symptoms

The mean ± SD scores of two groups of women are shown in Figure 2. There were no significant differences between the two groups in month 2 (baseline, cycle 2) on the Total Daily Symptom Ratings ($t = 0.69$, $df = 48$, $P = 0.48$). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor (Greenhouse-Geisser corrected: $F = 11.13$, $df = 1$, $P = 0.002$). A responder was defined as a woman showing 50% reduction in severity of symptoms. The number of responder was 19 (76%) in the saffron group and 2 (8%) in the placebo group ($P < 0.0001$; number needed to treat = 1.47). The behaviour of the two treatment groups was not homogeneous across time (groups-by-time interaction, Greenhouse-Geisser corrected: $F = 53.09$, $df = 1.55$, $P < 0.0001$). In addition, a one-way repeated measures analysis of variance showed a significant effect of saffron on the Total Daily Symptom Ratings ($P < 0.0001$). In saffron group, *post hoc* comparisons showed a significant change from cycle 3. A significant difference between cycles 3 and 4 was observed in the saffron group ($P < 0.001$). The difference between the two protocols was significant at the endpoint (cycle 4) ($t = 5.92$, $df = 48$, $P < 0.001$).

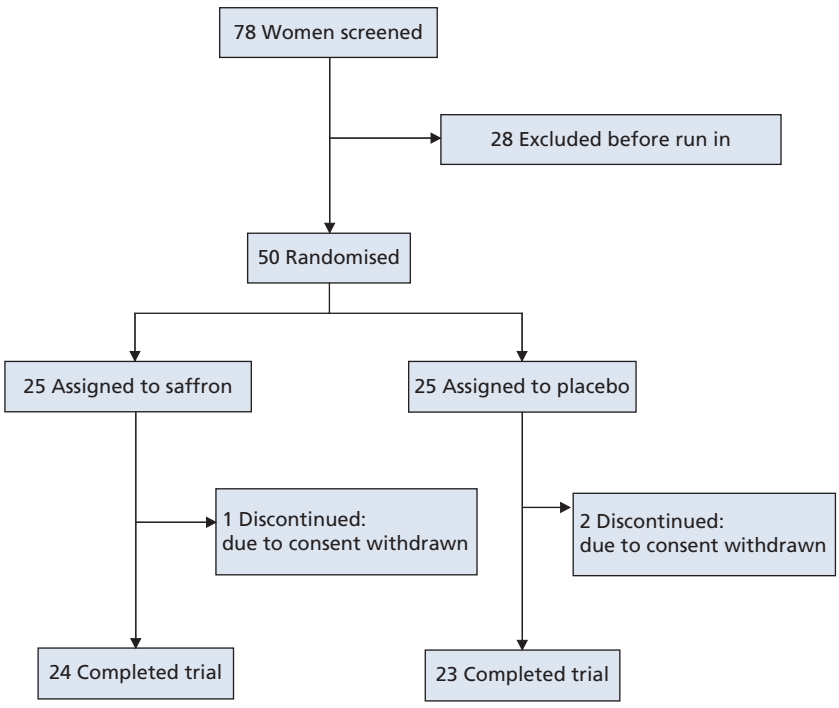

Figure 1. Trial profile.

Table 1. Baseline data

	Saffron group	Placebo group	*P*
Age (mean ± SD)	35.10 ± 7.79 (years)	33.45 ± 7.61 (years)	NS
Marital status	Single: 20 Married: 8 Divorced: 2	Single: 21 Married: 7 Divorced: 2	NS
Level of education	Under diploma: 6 Diploma: 10 Higher diploma: 9	Under diploma: 5 Diploma: 10 Higher diploma: 10	NS

NS, nonsignificant.

Hamilton Depression Rating Scale

The mean ± SD scores of two groups of women are shown in Figure 3. There were no significant differences between the two groups in month 2 (baseline, cycle 2) on the Hamilton Depression Rating Scale scores (t = 1.24, df = 48, P = 0.21). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor (Greenhouse-Geisser corrected: F = 87.36, df = 1, P = 0.001). A responder was defined as a woman showing 50% reduction in severity of symptoms. The number of responder was 15 (60%) in the saffron group and 1 (4%) in the placebo group (P < 0.0001; number needed to treat = 1.78). The behaviour of the two treatment groups was not homogeneous across time (groups-by-time interaction, Greenhouse-Geisser corrected: F = 43.16, df = 1.63, P < 0.0001). In addition, a one-way repeated measures analysis of variance showed a significant effect of saffron on Hamilton Depression Rating Scale (P < 0.0001). In saffron group, *post hoc* comparisons showed a significant change from cycle 3. A significant difference between cycles 3 and 4 was observed in the saffron group (P < 0.001). The difference between the two protocols was significant at the endpoint (cycle 4) (t = 8.99, df = 48, P < 0.001).

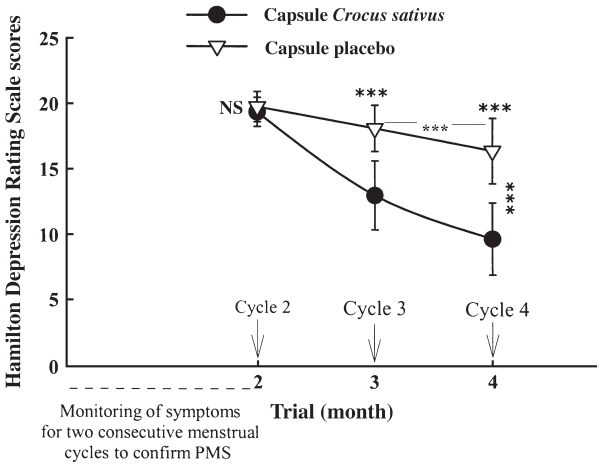

Figure 3. Mean ± SD scores of two groups of women on the Hamilton Depression Rating Scale scores. NS, nonsignificant and ***P < 0.001. The horizontal symbols (***) were used to express statistical significance versus their respective baseline value and vertical symbols (***) were used for between-group comparisons.

Clinical complications and adverse effects

Six adverse effects were observed over the trial. The difference between the saffron and placebo in the frequency of adverse effects was not significant (Table 2). None of adverse effects was severe. Appetite changes and headache occurred more in the saffron group, but it was not significant.

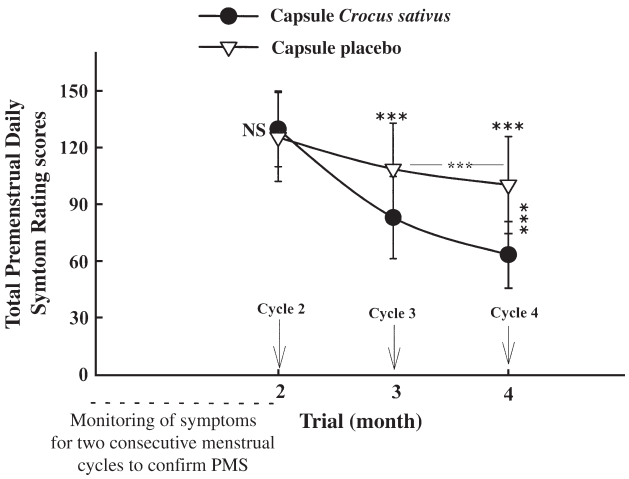

Figure 2. Mean ± SD scores of two groups of women on the Total Premenstrual Daily Symptoms scores. NS, nonsignificant and ***P < 0.001. The horizontal symbols (***) were used to express statistical significance versus their respective baseline value and vertical symbols (***) were used for between-group comparisons.

Discussion

PMS are a group of menstrually related, chronic and cyclical disorders characterised by emotional, behavioural and physical symptoms in the second half (luteal phase) of the menstrual cycle.[20] Several line of evidence point to a significant role of the serotonergic system in the course of the luteal

Table 2. Clinical complications and adverse effects were reported as number per group

Adverse effects	Saffron	Placebo	*P*
Decreased appetite	3	2	NS
Increased appetite	4	2	NS
Sedation	1	2	NS
Nausea	2	2	NS
Headache	3	2	NS
Hypomania	2	2	NS

NS, nonsignificant.

phase in women with PMS.[3] Moreover, the effect of sex hormones on serotonin uptake, binding, turnover and transport has also been indicated.[21] For this reason, it has been suggested that it is the dysregulation of the serotonergic system, which is responsible for the majority of PMS symptoms.[3] It has been reported that saffron through a serotonergic mechanism shows an antidepressant effect in the treatment of women with mild to moderate depression.[13–15] Moreover, there is an overlap between the symptoms of depression and those associated with PMS. In this small preliminary double-blind and placebo-controlled randomised trial, stigma of *C. sativus* at this dose was found to be effective in relieving symptoms of PMS. The clinical relevance of this finding was emphasised by the improvements seen in the Total Premenstrual Daily Symptoms and the Hamilton Depression Rating Scale. It has been reported that stigma of *C. sativus* has antidepressant effect by at least three clinical trials and serotonergic mechanism is involved in its antidepressant effect.[22] Therefore, the present study is in line with the previous reports that present serotonergic agents in the treatment of PMS.[6,7] A significant difference was observed in efficacy of saffron in cycles 3 and 4 in the Total Premenstrual Daily Symptoms and the Hamilton Depression Rating Scale. There were no significant differences in the two groups in terms of observed adverse effects. To the best of our knowledge, this study is the first clinical trial of saffron in the treatment of PMS, so it is not possible to draw any comparisons with others trials.[23] The limitations of the present study, including using only a fixed dose of saffron, the small number of participants and short period of follow up should be considered, and further research in this area in particular comparison with an active agent such as fluoxetine is needed.

Conclusion

The results of this study indicate the efficacy of *C. sativus* L. in the treatment of PMS. However, a tolerable adverse effects profile of saffron may well confirm the application of saffron as an alternative treatment for PMS. These results deserved further investigations.

Ethics approval

The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by institutional review board. Written informed consents were obtained before entering into the study.

Contribution to authorship

S.A. was the principal investigator and performed statistical analysis. L.K., M.A.-H., A.A. and H.R. were the trialist (gynaecologist). A.G. was the trialist (psychiatrist). All authors read and approved the final manuscript. ■

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