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Research paper

The effect of *Crocus sativus* (saffron) on the severity of premenstrual syndrome

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ABSTRACT

Introduction: Premenstrual syndrome is one of the most common problems for women during their reproductive age and has wider impacts affecting their family and their work. Herbal products are a suggested way of treating the syndrome. This research was carried out to identify whether saffron could have an effect on the severity of premenstrual syndrome among female students.

Methods: This randomized triple-blind controlled clinical trial was carried out with 78 students aged 18–35 years residing in university accommodation. The intervention group received capsules containing 30 mg of dried extract of saffron stigma once a day and the control group received placebo capsules for two menstrual cycles. The data gathering instrument consisted of questionnaire, the DASS21 scale, and premenstrual symptoms assessment form.

Results: At the beginning of the study, the two groups did not differ significantly in terms of their mean severity of PMS ($P=0.81$). At the end of the study, the changes of the mean severity of PMS were significantly different compared with those in the beginning: $P < 0.001$ for the intervention group, and $p = 0.04$ for the control group. In total, the two groups had significant differences in terms of changes in the mean severity of PMS over time ($P < 0.001$).

Conclusion: The results of this study suggest that saffron reduces the severity of PMS symptoms, but in order to prove its effectiveness for the treatment of this syndrome, further research is warranted.

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1. Introduction

Premenstrual syndrome (PMS) is one of the most common problems of women during their reproductive age [1–4]. PMS is a collection of physical, psychological, and behavioral symptoms that occur during the luteal phase of every menstrual cycle and

disappear quickly in a few days' time (7–14 days) after the beginning of menstrual bleeding [5,6]. Around 80–90% of women experience it before menstrual bleeding [7,8]. Premenstrual dysphoric disorder (PMDD) is known as the severe type of PMS which leads to the impairment of the individual's daily activities. It is observed in 3–5% of women [7,9].

PMS is prevalent in Iran such that according to the results of the study done by Delara et al., 99.5% of adolescent girls reported at least one of these symptoms, and among these, 66.3% had mild symptoms, 31.4% had moderate symptoms, and 2.3% had severe symptoms [10].

In various studies, more than 100 different physical and psychological signs and symptoms related to the syndrome have been reported [11]. The most common physical symptoms are

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fatigue; headaches; bloating; breast tenderness and swelling; edema; weight gain; and skin rash, respectively. The most common emotional signs are irritability, anxiety, anger and depression respectively. Individuals suffering from this syndrome may experience one or more of the above-mentioned problems [12,13].

Premenstrual syndrome leads to an increase in suicides, accidents, unemployment, and absenteeism from work and school, poor academic performance, and acute psychiatric problems compared to men. PMS is one factor that makes women more prone to depression especially in premenstrual, postpartum, and climacteric periods. The results of studies in various countries show that premenstrual symptoms are more prevalent and more severe among women at a higher educational level compared with uneducated women. This fact points to the possibility of a relationship between stress and PMS [14–18]. Furthermore, child abuse and domestic violence have also been reported in families with members suffering from PMS. Thus, this syndrome affects not only the individual herself, but the family and other members of the community [19].

The pathogenesis of PMS is complicated and multifactorial. It has not been identified fully so far and may be due to the effect of progesterone on neurotransmitters such as serotonin, opioids, catecholamines, or GABA. It may also be due to increased prolactin levels, increased sensitivity to the effects of prolactin, insulin resistance, sensitivity to endogenous hormones, hypothalamic–pituitary–adrenal axis function abnormalities, nutritional deficiencies, glucose metabolism changes, or fluid and electrolyte imbalance [4,15,20–22].

There are numerous pieces of evidence pointing to changes in serotonergic conductivity of the central nervous system in PMDD and PMS. This relationship has been confirmed by the positive therapeutic effects of serotonergic inhibitors in women suffering from PMS/PMDD [23,24] such that fluoxetine and sertraline have been recognized as effective in the treatment of physical and psychological signs, the improvement of job performance, and the quality of life of women suffering from the syndrome [13,25–27].

Nowadays, the use of complementary medicine and herbal products has gained a lot of popularity in the treatment of conditions such as menopausal symptoms, dysmenorrhea, and premenstrual syndrome [28–31].

Saffron is an herbal product used as antispasmodic, sedative, aiding digestion, carminative, diaphoretic, mucokinetic, stimulating sexual desire, soothing pain, easing menstruation, exhilarating, and dispelling gloom [32,33]. In addition, the results of recent experimental studies and clinical trials demonstrate that saffron is effective in the treatment of mild to moderate depression [32,34–37] and its anti-depressant effect is through a serotonergic mechanism [38]. The safranal and crocin of saffron both have antidepressant effects. It is likely that crocin exerts its antidepressant effects by inhibiting norepinephrine and dopamine reuptake. Safranal does the same through inhibiting serotonin reuptake [33,39].

Noorbala et al. report that the consumption of 30-mg saffron capsules (BD) is as effective as the consumption of 20-mg fluoxetine capsules for six weeks in the treatment of mild to moderate depression [37]. Akhoundzadeh et al. have reported that the consumption of 30-mg saffron capsules for a period of six weeks has been effective on the treatment of mild to moderate depression compared to that of a placebo [36]. In another study, Akhoundzadeh et al. compared the therapeutic effects of the consumption of 30-mg saffron capsules (TDS) with those of 100-mg imipramine capsules on the treatment of mild to moderate depression for six weeks and concluded that the effects of saffron capsules are similar to those of imipramine [35]. Also, Akhoundzadeh et al. reported that the therapeutic effects of 15-mg saffron capsules (in the morning and in the evening) for outpatients

suffering from mild to moderate depression are similar to those of 10-mg fluoxetine capsules (in the morning and in the evening) for a period of eight weeks [34].

Fukui et al. carried out a research with the aim of determining the effect of saffron odor on premenstrual syndrome (PMS), dysmenorrhea, and irregular menstruation. They exposed 35 women with a normal sense of smell to saffron odor for 20 min and demonstrated the increase in cortisol levels, decrease in levels of 17- β estradiol, and the reduction of the STAI score (State-Trait Anxiety Inventory) in both the follicular and the luteal phases. They confirmed the physiological and psychological effects of saffron odor on women [32]. A clinical trial carried out by Agha-Hosseini et al. investigated the effectiveness of saffron on reducing the intensity of PMS on 50 women aged 20–45 who suffered from PMS. Oral consumption of 15 mg of saffron twice a day for two menstrual cycles led to a decrease in 50% of the severity of PMS symptoms in 75% of individuals and a decrease in 50% of depression symptoms in 60% of individuals in the intervention group [38].

Since there is an overlap between the symptoms of depression and those of PMS, and given the importance of the syndrome in the development of personal and social problems, this research was carried out with the aim of specifying the effect of saffron on the severity of PMS in female students.

2. Materials and methods

This randomized triple-blind controlled clinical trial was carried out on female students suffering from premenstrual syndrome residing in the dormitory of Lorestan University of Medical Sciences in the city of Khorramabad. The research data were gathered during May 2013 for a period of nine months.

The inclusion criteria in the study were as follows: being 18–35 years of age; being single, being Iranian and residing in the dormitory; having regular menstrual cycles; having 21- to 35-day intervals between two menstrual cycles, having a menstrual bleeding duration of 3–10 days, and consenting to participate in the study. The exclusion criteria for the study consisted of having a record of regular physical exercise during the three months before the beginning of the study; having a physical education course during the study; being on a special diet (vegetarianism, raw eating, hydrotherapy, etc.); consuming alcohol, narcotics, or smoking; having a history of ovarian cyst or gynecological surgeries; having a history of underlying conditions leading to PMS (heart diseases, respiratory diseases, kidney diseases, high blood pressure, asthma, diabetes, epilepsy, migraine, thyroid diseases, anemia, psychiatric illness, etc.); taking any type of drug regularly before and during the study; using therapeutic measures to prevent premenstrual problems during the three months before the study and during it; being stressed, anxious or depressed as indicated by DASS21 test; and having undergone an adverse experience or a disaster during the three months before and during the study.

In order to produce capsules containing dried extract of saffron stigma, the required saffron was first bought from Saharkhiz Saffron Company in Iran. Then, it was prepared through percolation procedure with 80% ethanol: to prepare an 80% hydroalcoholic solution, 800 mL of 96% ethanol was poured into a 1000-mL graded cylinder. After adding distilled water, the volume of the solution reached 960 mL. Then, we ground 120 g of saffron stigma and fed it to the percolating device. It was then decocted at three stages. We entered the extract collected at the percolation stage into the vacuum distillation device for condensation. It was afterwards condensed in a 35–40 °C temperature. In order to prepare 30-mg saffron stigma capsules, the condensed extract was turned into granules using lactose powder. Using a capsule filling machine, 30-mg capsules containing saffron extract were prepared.

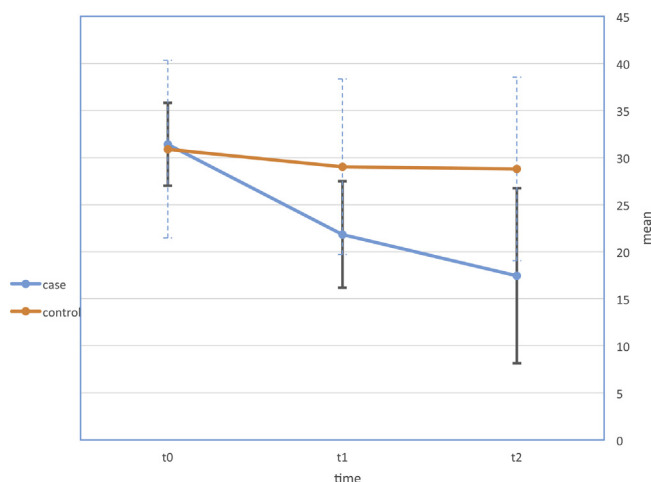
Placebo capsules contain 30 mg of lactose powder and were prepared under the supervision of pharmacist. Saffron capsules and placebo were packed the same appearance (dark red coverage) and the producer of packing was in such a form that the smell of saffron was not dispersed and was determined codes can only be identified by the manufacturing pharmaceutical company. Participants, researchers and statistical analyst were not informed from codes until the end of analysis process of data. In this way triple blinding of study was secured (Graph 1).

In the study, 88 students met the inclusion criteria for the study. They gave their written informed consent and were then, randomly assigned to the intervention and control groups. During the study, five participants from the intervention group and five participants from the control group had to be excluded from the study as they did not meet the exclusion criteria. Eventually, 78 people (39 participants in each group) were studied (Fig. 1) [40].

Data gathering instruments in the research consisted of (1) participant selection form, (2) questionnaire about menstrual record and food habits, (3) vital signs, height, and weight registration form, (4) questionnaire about the exclusion criteria during and at the end of the study. The participant selection form consisted of three sections: (a) the personal and medical information questionnaire, (b) the simultaneous determination of stress, anxiousness, and depression scale (DASS21), and (c) the shortened premenstrual assessment form (SPAF).

The shortened premenstrual assessment form (SPAF) is a standard form with ten items: (1) pain, tenderness, enlargement, or swelling of the breasts, (2) feeling of inability to perform common tasks, (3) feeling of being under pressure, (4) nervousness, irritability or moodiness, (5) feeling of sadness or depression, (6) back pain, (7) muscle or joint pain, or muscle stiffness, (8) heaviness, discomfort or pain in the abdomen, (9) swelling and puffiness, and (10) bloating. The form has been graded on a six-point scale. Number 1 indicates absence of the sign, and numbers 2–6 indicate minimal, mild, moderate, severe and extremely severe degrees, respectively. The range of the scores varies from 10 to 60 [41–44].

The validity of the Shortened Premenstrual Assessment Form (SPAF) has been approved by Pires and Calil [44,45]. In this study, after the translation of the form into Persian, the content validity method was used to confirm its validity. The reliability of the SPAF form has been confirmed by Rozen with $\alpha = 95\%$ [44]. In this study, it was confirmed by test-retest method with $r = 0.92\%$. This form has been used in many studies [32,46–51].



Graph 1. Comparison of the mean severity of PMS in the beginning, one month and two months after intervention in each group.
Error bar : mean \pm SD.

In order to collect data, the researcher went to the dormitory and after acquiring the students' written consent, distributed the questionnaire about their personal and medical information (including the inclusion criteria and the exclusion criteria from the study) among the students. After the completion of the forms by the students and their checking by the researcher, if they had the criteria for being included in the study, they were given the simultaneous stress, anxiety and depression form (DASS21) one week after menstrual bleeding had stopped to exclude individuals suffering from stress, anxiety and depression disorders. If they did not have the symptoms, they would be given the SPAF form to diagnose PMS to be filled out by them one week before the next menstruation for two menstrual cycles (before intervention). All individuals who had at least five of the ten symptoms during the week before the next menstrual period (provided that at least one of those symptoms was among the four initial symptoms) were chosen as participants and the severity of their PMS was measured according to the sum of the scores of syndrome severity. At the last stage, the form about menstruation history and eating habits (including age at menarche; menstrual pain severity; impairment of daily activities due to premenstrual problems; previous treatments and the effect of previous treatments on premenstrual problems; the number of meals; and the amount of tea and sweet drinks consumed) and the vital signs, weight and height form were filled out by the research unit and the researcher, respectively.

Before prescribing the drug, the researcher provided the participants with necessary explanations about the type of medication; the duration of medication; and the dosage and the side effects of the drug. Random allocation to one of the two groups was performed in a ratio of 1:1 within balanced blocks of two. For every two participants, one was allocated to saffron and other to the placebo group; the sequence varied randomly. The intervention group received 30-mg capsules containing dried extract of saffron stigma (produced by Khorraman Pharmaceutical Company) once a day, and the control group received a placebo once a day with lunch for a period of two menstrual cycles. After the consumption of the drug, at the end of each menstrual cycle (one month and two months after the intervention), the research units filled out the form about the exclusion criteria and if they did not have those criteria, the severity of PMS symptoms would be measured in all of them using the SPAF scale again. It was then compared with the results at the beginning of the study.

Data analysis was carried out using Chi-square test, Mann-Whitney, *t*-test, ANOVA repeated measures, and Tukey's test to compare the two groups in terms of pain severity at different times using SPSS software. $P < 0.05$ was considered as the level of statistical significance.

3. Results

Using the independent *t*-test it was showed that participants did not have any significant difference in terms of age, body mass index (BMI), age at menarche, duration of menstrual cycle, and duration of bleeding in a menstrual cycle (Table 1). Also, using Chi-square and Mann-Whitney tests, the intervention and the control groups were homogeneous in terms of the number of daily meals ($p = 0.06$), the amount of tea or coffee consumed ($p = 0.97$), the amount of sweet drinks consumed ($p = 0.58$), disruption of daily activities due to premenstrual problems ($p = 0.64$), use of previous treatment measures ($p = 0.35$), types of previous treatments ($p = 0.52$), effectiveness of previous treatments for premenstrual problems ($p = 0.51$), and vital signs ($p > 0.05$).

At the beginning of the study, the two groups were not statistically significantly different in terms of dysmenorrhea. In other words, using the Chi-square test, at the beginning of the

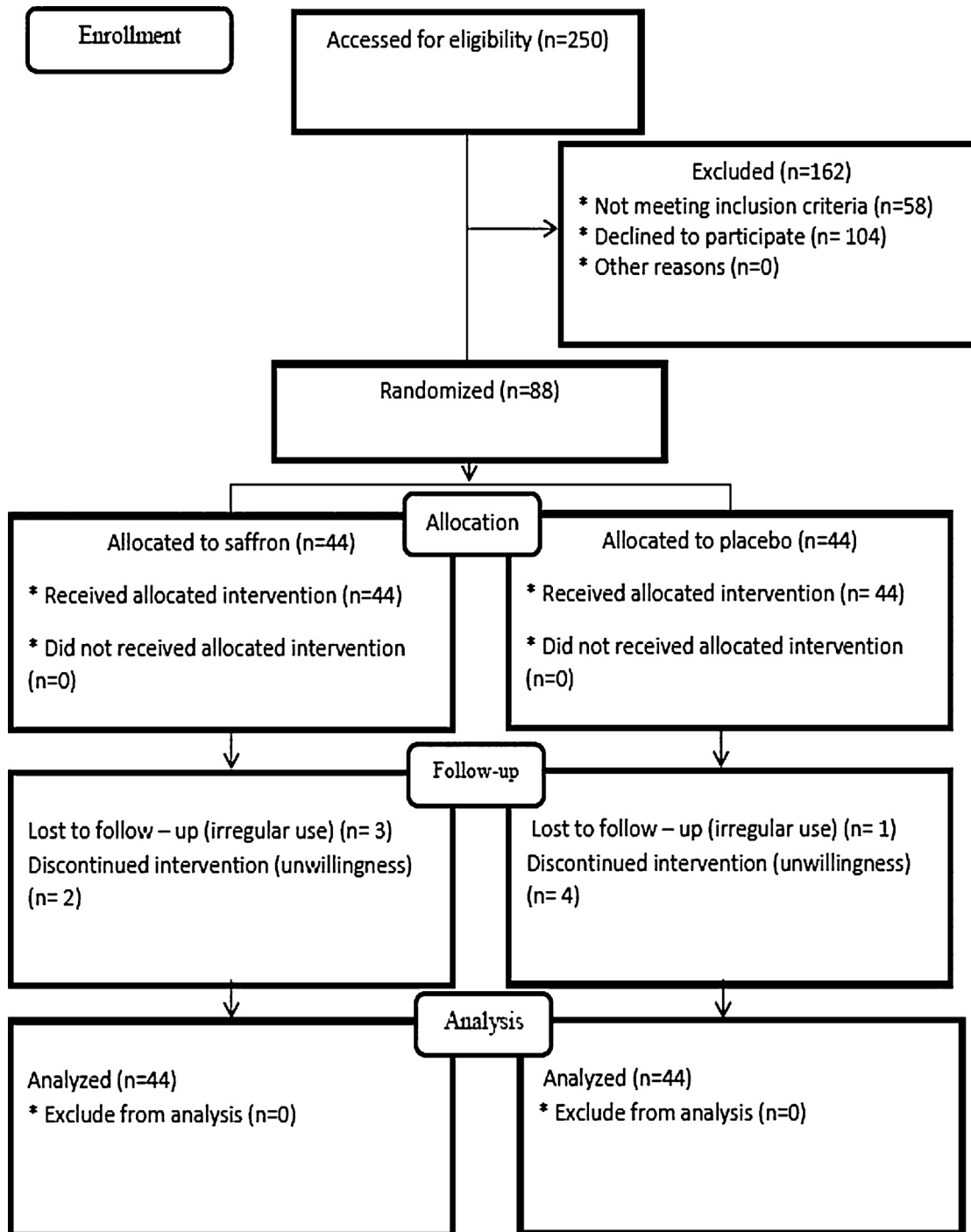


Fig. 1. Flow diagram of participants.

Table 1
The comparison of the mean age, bmi, and menstrual history of the units of the study in each group.

	Group		t	P Value
	Intervention (n = 39) mean ± SD	Control (n = 39) mean ± SD		
Age (Years)	21.03 ± 2.12	20.46 ± 1.35	1.4	0.166
BMI (kg/m ²)	22.45 ± 2.56	22.60 ± 2.51	-0.27	0.79
Age at menarche (Years)	13.44 ± 1.33	13.41 ± 1.18	0.09	0.929
Duration of menstrual cycle (Days)	27.67 ± 2.76	27.72 ± 2.70	-1.7	0.619
Duration of menstrual bleeding (Days)	6.74 ± 8.35	5.38 ± 1.29	1	0.32

Table 2

Comparison of the severity of dysmenorrhea in the intervention and the control groups.

Group	Severity of dysmenorrhea				Total
	None	Mild	Moderate	Severe	
Intervention	1 (2.6%)	9 (23.1%)	10 (25.6%)	19 (48.7%)	39 (100%)
Control	3 (7.7%)	7 (18%)	13 (33.3%)	16 (41%)	39 (100%)
Total	4 (5.1%)	16 (20.5%)	23 (29.5%)	35 (44.9%)	78

p* value = 0.6.Table 3**

Comparison of the mean severity of PMS before and after the intervention in each group.

Group	Time			<i>F</i>	<i>P</i> value (changes in each group)	<i>P</i> value (group time)
	Before intervention mean ± SD	One month after intervention mean ± SD	Two months after intervention mean ± SD			
Intervention	31.41 ± 9.30	21.82 ± 5.64	17.44 ± 4.38	90.33	<0.001	<0.001
Control	30.90 ± 9.74	29.03 ± 9.33	28.79 ± 9.45	4.182	0.04	

study, the two groups were homogeneous in terms of the severity of dysmenorrhea (Tables 2 and 3).

At the beginning of the study, the mean severity of PMS was 31.41 ± 9.30 for the intervention group, and 30.90 ± 9.74 for the control group. Thus, the two groups were not significantly different in this regard ($p = 0.81$). At the end of the study, using repeated measures test, the difference in the severity of PMS symptoms over time in the intervention group ($p < 0.001$) and in the control group ($p = 0.04$) were statistically significant; also, due to the significance of time–group interaction, it was revealed that there is a significant difference between changes of the mean severity of PMS in the two groups over time ($p < 0.001$).

According to Chi-square test, the two groups were not significantly different in terms of side effects such as increased appetite, loss of appetite, sedation, nausea, headache, and euphoria ($p > 0.05$).

4. Discussion

The findings of the research demonstrated that the consumption of saffron reduced the severity of PMS symptoms in students suffering from the syndrome. In this regard, Agha-Hosseini et al. studied the effect of saffron in the treatment of premenstrual syndrome and concluded that 76% of women who had taken saffron reported a fifty-percent reduction in the severity of PMS symptoms at least, whereas such an effect was observed in only eight percent of women who has received placebo. Furthermore, a fifty-percent alleviation of depression symptoms in 60% of participants who had taken saffron was reported compared to that in 4% of people from the control group [38].

The existing evidence emphasizes the important role of serotonergic system during the luteal phase in women suffering from PMS. In addition, the impact of sexual hormones on the uptake, binding, turnover, and transportation of serotonin has been shown [52]. Based on the above reasons, it has been suggested that dysregulation of the serotonergic system, in other words a change in serotonin activity, is responsible for most PMS symptoms [23].

The safranal and crocin found in saffron apply their antidepressant effects through influencing the serotonergic system such that in several studies, the effectiveness of saffron in the treatment of women's mild to moderate depressions has been confirmed [35–37]. In the study done by Akhoundzadeh et al. with the aim of comparing the antidepressant effects of saffron and imipramine for depressed outpatients suffering from a mild to moderate depression during the six weeks of treatment, they did not differ, and both

protocols showed their significant effects since week one as compared with week zero [35].

The results of the study carried out by Azhari et al. with the aim of specifying the effects of edible saffron capsules on the severity of pain during the active phase of the first stage of labor, demonstrated that the mean severity of general pain was 85.9 ± 8.4 for the group receiving saffron, and 97.4 ± 2.9 for the placebo group. They show a significant difference ($p < 0.001$).

Saffron has various components like crocin, safranal, flavonoids, and carotenoids. In animal studies, the analgesic effects of the different components of saffron have been confirmed. Other components of saffron such as flavonoids, and carotenoids have antioxidant effects and through trapping free radicals like oxygen and superoxide radicals, prevent the production of prostaglandins [53]. Therefore, one of the mechanisms of pain reduction by saffron is related to its antioxidant property.

The muscle relaxant and antispasmodic properties of saffron have been mentioned in traditional medicine books [54]. They have also been confirmed by contemporary studies [55–57]. It has been reported that the effects of saffron are similar to those of diazepam and that like diazepam; it has anxiolytic, analgesic and muscle relaxant effects as a benzodiazepine [58,59].

Based on what was mentioned above and the results of the present study, saffron leads to a decrease in the severity of PMS symptoms and probably a better occupational and social performance of the individual.

Reliance on what the students said about their health and correct consumption of the drug; and the short follow-up period were the limitations of this study. Thus, carrying out more studies with bigger sample sizes, comparing saffron with other factors effective on PMS such as fluoxetine, and using different doses of saffron for longer periods of time is suggested to achieve more definitive results about the effectiveness and safety of saffron for alleviating PMS symptoms.

Conflict of interest

The authors declare no conflict of interest.

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This study has been approved by Lorestan University of Medical Sciences and registered in the clinical trial registration center of Iran with the code IRCT138807292618N1. We would also like to express our gratitude to the vice dean of research; Razi Herbal

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