

Comparison of Saffron versus Fluoxetine in Treatment of Women with Premenstrual Syndrome: A Randomized Clinical Trial Study

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Abstract

Background: Premenstrual syndrome (PMS) is a set of physical and psychological symptoms such as mood disability, breast tenderness, food craving, fatigue, and depression. Fluoxetine and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) usually are being administered for these patients. This study aimed to evaluate the effect of saffron plant in terms of its anti-inflammatory and anti-depressant effects compared to fluoxetine.

Materials and Method: This study was a three-blind clinical trial that was carried out on working women and their relatives. Firstly, 164 patients with the premenstrual syndrome were selected, and they were randomly divided into two 82-person groups, including those who received fluoxetine and those who received saffron. Next, both groups were treated for two months. The data were collected in two stages through a self-designed questionnaire (on day 5 of menstrual cycle) and validated questionnaires of PRISM and Beck at the end of the period.

Results: It was indicated that similar to fluoxetine, the use of saffron in PMS reduced the symptoms such as abdominal bloating, depression, and mood swing, but the latter could better relieve the breast and abdominal pain than fluoxetine.

Conclusion: It was concluded that 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.

Keywords: Saffron, fluoxetine, premenstrual syndrome.

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Introduction

PMS is a type of mild to moderate neuropsychological disorder. Although its mild type occurs in 90% of cases, it is argued that its severe type occurs only in 5% of cases. PMS is a collection of physical, psychological and emotional symptoms associated with the menstrual

cycle in women. The syndrome begins 7 to 10 days before the start of menstruation, and it must be recorded in 2 consecutive cycles. It is associated with a set of physical and psychological symptoms such as mood swings, sensitization of breast, food craving, fatigue, irritability and depression¹. It is estimated that three women (out of 4 women) will experience this syndrome in their menstrual cycle. Some women experience this syndrome at the age of 20, but others suffer from this problem in their late 30s and 40s²⁻⁵.

Serotonin Reuptake Inhibitors (SSRIs), including Fluoxetine (Prozac, Sarafem), Paroxetine (Paxil, Pexeva), Sertraline (Zoloft), etc usually are recommended for the treatment of PMS. These drugs have been effective in improving symptoms such as fatigue, food cravings, and sleep disorders, and they are among the first choices to treat severe types of PMS⁶.

Moreover, the consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), diuretics as well as life style changes are suggested for these patients^{7, 8}. Some herbal medicines can also be effective in treating this syndrome. Saffron plant is one of these herbal medicines that is characterized by some anti-inflammatory and anti-depressant effects and, thus, it can be useful in treating this syndrome. Since the symptoms of the syndrome disrupt everyday life, it is beneficial to identify the ways of treatment, straightforward, harmless, and accessible treatments^{1-6, 9}. Saffron has known anti-nociceptive, relaxing and anti-inflammatory effects as well as anti-depressant effect on humans and animals¹⁰⁻¹², it was attempted to examine the impact of this Iranian traditional and valuable herb in comparison with fluoxetine as a relatively well-known drug in the treatment of psychiatric disorders and even PMS. The purpose of this study was to reduce the complications of chemical medicines and medicinal herbs.

Materials and Method

This study was an interventional three-blind trial) This means that the patient, physician, and statistical analyst did not know the contents of the capsules (that was carried out on women employed in Deputy of Health of Sabzevar University of Medical Sciences, Occupational Medicine Center as well as their relatives. Regarding this, 164 employees who had approved a PMS based on two previous menstrual cycles and Hamilton Test were randomly selected, and written consents were obtained from them. Treatment included 20 mg capsules

of fluoxetine in the control group and 30 mg capsules of saffron in the intervention group. The capsules were identical in appearance. The treatment allocation was randomly divided into two 82-person groups, and the drug packages were provided to patients by a person who did not know the contents of the drug packages. The two groups were treated in parallel. The duration of the treatment was two months, and the forenamed drugs should be taken daily from day 14 to day 28 of the menstrual cycle (within 14 days of the follicular phase). During the last 5 days of each cycle, the researchers attempted to record the concerned data using a self-designed checklist. During the treatment period, it was attempted to make sure that each patient made use of the prescribed drugs and that no associated drugs were used accordingly and no displacement occurred between the two groups. Furthermore, patients were reminded that they could contact the researchers if they had any new drug-related problems. It was also stipulated that if severe symptoms of depression occurred, which coerced the patients to use other drugs accordingly, the patients would be excluded from the study. Besides, if patients in the intervention group were obliged to use fluoxetine for some reason, these matters would be considered when analyzing the control group. At the end of each treatment period, it was attempted to make use of Beck Anxiety Inventory in order to determine the severity of anxiety and depression among patients. This questionnaire was a 21-point scale in which the patient chose one of four options in each item, and it indicated the severity of his/her anxiety. Four options of each question were scored in a four-part range from 0 to 3. Each test item described one of the common symptoms of anxiety (mental, physical and panic symptoms). The maximum score of this questionnaire was 63, and it was indicated that scores located between 0 and 7 were normal, scores located between 8 and 15 were mild, scores located between 16 and 25 were medium, and scores located between 26 and 63 were severe thereof. In addition, Visual Analogue Scales (VAS) was used to assess the severity of abdominal and breast pain (scores less than 3 showed mild abdominal pain, scores located between 4 and 7 indicated medium abdominal pain and scores located between 8 and 10 showed severe abdominal pain). In examining the amount of abdominal bloating, the patients were asked to measure their abdominal circumference (actually, patients were trained accordingly) (0-1 cm= unchanged, 1-2 cm = mild, 2-3 cm = medium and 3-4 cm = severe). Finally, the data were analyzed through Chi-square Test using

Results

In this study, 164 people participated (each group was 82 individuals). The mean age of the patients was 35.5 ± 13 years (Range: 26-45). After comparing the two groups, it was shown that the age distribution was similar in both groups (the age distributions in the intervention and control groups were 36.5 ± 10 and 34 ± 5.30 years old, respectively). It should be noted that all patients were married.

Having examined the abdominal pain using the Visual Analogue Scales, it was found that there was no significant difference in the improvement of abdominal pain in the two groups ($P > 0.05$). Having compared the severe to moderate abdominal pain, there was a significant difference between the two groups at the end of the first month ($p = 0.01$) and the second month ($p = 0.03$) (Table 1).

* Given the anxiety level, it was declared that there was no significant difference in the reduction of anxiety level between the two groups ($P > 0.05$). Having compared the severe to moderate anxiety, it was indicated that despite significant reduction in anxiety level after taking drugs, notably saffron, there was not a significant difference between the two groups at the end of the first month ($p = 0.83$) and the second month ($p = 0.09$) (Table 2).

Comparing the breast pain in saffron group with fluoxetine, it was indicated that there was a significant difference between the two groups at the end of the first month ($p = 0.0001$), but there was not a significant difference between the two groups at the end of the second month ($p = 0.014$) (Table 3).

It was shown that there was no significant difference between the two groups according to depression ($P > 0.05$) (Table 4).

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 ($P > 0.05$) (Table 5).

The side effects of saffron were not observed during the study.

Registration Number in the Clinical Practice Center of the Ministry of Health and Medical Education: IRCT

Discussion

PMS is a collection of physical, psychological and emotional symptoms associated with menstrual cycle in women. The syndrome begins 7 to 10 days before the start of menstruation, and it must be recorded in 2 consecutive cycles. Although its mild type occurs in 90% of cases, it is argued that its severe type occurs only in 5% of cases. It is associated with a set of physical and psychological symptoms such as mood swings, sensitization of breast, food craving, fatigue, irritability and depression¹. It is estimated that three women (out of 4 women) will experience this syndrome in their menstrual cycle. Some women experience this syndrome at the age of 20, but others suffer from this problem in their late 30s and 40s^{2,3}. Many medicines are proposed to treat this syndrome, and some herbal medicines have been effective in treating this syndrome. Saffron plant is one of these herbal medicines that is characterized by some anti-inflammatory and anti-depressant effects and, thus, it can be effective in treating this syndrome. Since the symptoms of the syndrome disrupt everyday life, it is beneficial to identify the ways of treatment, especially simple, harmless and accessible treatments¹⁻⁷. Considering the known anti-nociceptive, relaxing and anti-inflammatory effects of saffron extract as well as its anti-depressant effect on humans and animals¹⁰, it was attempted to examine the effect of this Iranian traditional and valuable herb in comparison with fluoxetine as a relatively well-known drug in the treatment of psychiatric disorders and even PMS.

This study was an interventional three-blind trial that was carried out on 164 women as well as their relatives. The most common age group afflicted with the PMS was those patients aged 16 to 45 years old. Compared to fluoxetine, it was indicated that if patients consumed saffron, their symptoms of abdominal and breast pain were alleviated better and more efficiently. However, there was no significant difference between the two groups in terms of reduction in anxiety level.

Mokhber et al. (2004) reported that the improvement in symptoms of depression, emotional dysfunction, appetite changes, lack of self-control, decreased interest in doing activities, concentration disorders, and sleep changes were significantly higher in fluoxetine-treated patients¹³. They also evaluated the improvement of physical symptoms and tiredness and asserted that there

was no significant difference between placebo and fluoxetine¹³.

In our study, the intake of fluoxetine and saffron alleviated the depression and anxiety symptoms, but there was no significant difference between them. Moreover, the present study indicated that, compared to fluoxetine, saffron could better alleviate the symptoms of abdominal and breast pain.

Besides, Agha-Hosseini et al.¹⁴ found that, compared to placebo, saffron significantly improved the symptoms of PMS (up to 50%). Similarly, the present study showed that saffron could significantly alleviate the symptoms of PMS (i.e., depression, abdominal bloating, abdominal pain, breast pain, and anxiety).

Kashani et al. (2017) reported that saffron acted similar to fluoxetine in alleviating depression¹⁵. They also found that saffron is a safe alternative medication for improving depressive symptoms of postpartum depression. Similarly, the results of the present study confirmed this anti-depressant effect of saffron.

One of the strengths of this study was to investigate the effects of saffron on patients who were all married. Inevitably, this homogenization reduced the impact of

interfering factors.

Accordingly, it can be argued that the administration of saffron in the follicular phase of menstruation has a better effect on alleviating the severity of symptoms of the PMS than fluoxetine.

Considering the fact that pharmaceutical drugs and chemicals poisoning are common in Iran¹⁶⁻¹⁹, considering traditional plant may be a better option in the PMS.

Conclusion

It was concluded that 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.

Conflict of Interests: None.

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Ethical Clearance: This study was approved by the ethics committee of Sabzevar university of medical sciences.

Table 1. Frequency of patients with moderate to severe abdominal pain.

Abdominal pain (medium-severe)	The end of first month	The end of second month
Fluoxetine	64 patients	9 patients
Saffron	47 patients	0 patient

Table 2. Frequency of patients with moderate to severe mood swing.

Mood swing	The end of first month	The end of second month
Fluoxetine	74 patients	44 patients
Saffron	71 patients	0 patient

Table 3: The comparison of breast pain measured by Visual Analogue Scales (VAS) in two groups.

Breast pain	The end of first month	The end of second month
Fluoxetine	73 patients	27 patients
Saffron	32 patients	0 patient

Table 4. Frequency of patients with depression (moderate to severe) diagnosed by the physician.

Depression	The end of first month	The end of second month
Fluoxetine	28 patients	0 patients
Saffron	28 patients	0 patient

Table 5. Frequency of patients with moderate to severe abdominal bloating.

Abdominal bloating	The end of first month	The end of second month
Fluoxetine	34 patients	4 patients
Saffron	27 patients	1 patient

References

- Speroff, L., Glass, R. H., Kase, N., and Seifer, D. (2001). Clinical gynecologic endocrinology and infertility: text and self-assessment and study guide on CD-ROM (translated by Hanieh Zokayi, Shaqayeq Rashidi and Leila Zahedi, 2001). Tymorzadeh, 473-482.
- Maj, M. (2012). Development and validation of the current concept of major depression. *Psychopathology*, 45(3): 135-146 [PubMed: 22399134].
- Farzaneh E, Mehrpour O, Alfred S, Moghaddam HH, Behnoush B, Seghatoleslam T. Self-poisoning suicide attempts among students in Tehran, Iran. *Psychiatr Danub*. 2010 Mar;22(1):34-8.
- Karrari P, Mehrpour O, Afshari R, Keyler D. Pattern of illicit drug use in patients referred to addiction treatment centres in Birjand, Eastern Iran. *J Pak Med Assoc*. 2013 Jun;63(6):711-6.
- Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003 Jun 18;289(23):3095-105.
- Olfson, M, Marcus S, Druss B, Elinson L, Tanielian T, Pincus H. National trends in the outpatient treatment of depression. *JAMA*. 2002; 287(2):203-209
- Ferguson, J. SSRI antidepressant medications: adverse effects and tolerability. *Prim Care Companion. J Clin Psychiatry*. 2001; 3(1):22-27.
- Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. *Eur Neuropsychopharmacol*. 2011; 21(12):841-860 [PubMed: 21601431].
- Williams J. J, Rost K, Dietrich A, Ciotti M, Zyzanski S, Cornell J. Primary care physicians' approach to depressive disorders. Effects of physician specialty and practice structure. *Arch Fam Med*. 1999; 8(1):58-67.
- Mehrpour O, Farkhondeh T, Ravanbakhsh M, Ebrahimi A, Samarghandian S. Saffron, Organ Toxicity and Clinical Complications: A Review. *J Neyshabur Univ Med Sci*. 2018 ; 6(3): 76-86.
- Hemmati M, Zohoori E, Mehrpour O, Karamian M, Asghari S, Zarban A, Nasouti R. Anti-atherogenic potential of jujube, saffron and barberry: anti-diabetic and antioxidant actions. *EXCLI J*. 2015 Aug 4;14:908-15.
- Hoshyar R, Hosseinian M, Naghandar MR, Hemmati M, Zarban A, Amini Z, et al. Anti-Dyslipidemic Properties of Saffron: Reduction in the Associated Risks of Atherosclerosis and Insulin Resistance. *Iran Red Crescent Med J*. 2016; 18:1-8.

13. Mokhber, N., Fayyazi Bordbar, M. R., and Javidi, K. The effects of fluoxetine treatment on premenstrual dysphoric syndrome. *Fundamentals of Mental Health Journal*.2004; 23, 24: 111-115.
14. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR, Akhondzadeh S. *Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG*. 2008 Mar;115(4):515-9.
15. Kashani L, Eslatmanesh S, Saedi N, Niroomand N, Ebrahimi M, Hosseinian M, Foroughifar T, Salimi S, Akhondzadeh S. Comparison of Saffron versus Fluoxetine in Treatment of Mild to Moderate Postpartum Depression: A Double-Blind, Randomized Clinical Trial. *Pharmacopsychiatry*. 2017 Mar;50(2):64-68.
16. Mehrpour O, Dolati M, Soltaninejad K, et al. Evaluation of histopathological changes in fatal aluminum phosphide poisoning. *Ind J Forensic Med Toxicol* 2008; 2: 34-36.
17. Ghaderi A, Vahdati-Mashhadian N, Oghabian Z, Moradi V, Afshari R, Mehrpour O. Thallium exists in opioid poisoned patients. *Daru*. 2015 Aug 1;23:39.
18. Hayatbakhsh MM, Oghabian Z, Conlon E, Nakhaee S, Amirabadizadeh AR, Zahedi MJ, Darvish Moghadam S, Ahmadi B, Soroush S, Aaseth J, Mehrpour O. Lead poisoning among opium users in Iran: an emerging health hazard. *Subst Abuse Treat Prev Policy*. 2017 Oct 5;12(1):43.