HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2013; **28**: 54–60.
Published online 20 December 2012 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2282

Saffron for treatment of fluoxetine-induced sexual dysfunction in women: randomized double-blind placebo-controlled study

Ladan Kashani[1], Firoozeh Raisi[2], Sepideh Saroukhani[2], Hamid Sohrabi[2], Amirhossein Modabbernia[2], Abbas-Ali Nasehi[2], Amirhossein Jamshidi[2], Mandana Ashrafi[2], Parisa Mansouri[2], Padideh Ghaeli[2] and Shahin Akhondzadeh[2]*

[1]*Infertility Ward, Arash Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[2]*Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[3]*Division of Herbal Medicine, Food and Drug Organization, Ministry of Health, Treatment and Medical Education, Tehran, Iran*

Objective Saffron (*Crocus sativus* L.) has shown beneficial aphrodisiac effects in some animal and human studies. The aim of the present study was to assess the safety and efficacy of saffron on selective serotonin reuptake inhibitor-induced sexual dysfunction in women.
Methods This was a randomized double-blind placebo-controlled study. Thirty-eight women with major depression who were stabilized on fluoxetine 40 mg/day for a minimum of 6 weeks and had experienced subjective feeling of sexual dysfunction entered the study. The patients were randomly assigned to saffron (30 mg/daily) or placebo for 4 weeks. Measurement was performed at baseline, week 2, and week 4 using the Female Sexual Function Index (FSFI). Side effects were systematically recorded.
Results Thirty-four women had at least one post-baseline measurement and completed the study. Two-factor repeated measure analysis of variance showed significant effect of time × treatment interaction [Greenhouse–Geisser's corrected: $F(1.580, 50.567) = 5.366$, $p = 0.012$] and treatment for FSFI total score [$F(1, 32) = 4.243$, $p = 0.048$]. At the end of the fourth week, patients in the saffron group had experienced significantly more improvement in total FSFI ($p < 0.001$), arousal ($p = 0.028$), lubrication ($p = 0.035$), and pain ($p = 0.016$) domains of FSFI but not in desire ($p = 0.196$), satisfaction ($p = 0.206$), and orgasm ($p = 0.354$) domains. Frequency of side effects was similar between the two groups.
Conclusions It seems saffron may safely and effectively improve some of the fluoxetine-induced sexual problems including arousal, lubrication, and pain. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—*Crocus sativus* L.; fluoxetine; saffron; sexual dysfunction; SSRI; women

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are frequently associated with sexual dysfunction and can affect all phases of sexual function (desire, arousal, and orgasm) (Lane, 1997; Montejo-Gonzalez *et al*., 1997; Hensley & Nurnberg, 2002; Serretti & Chiesa, 2009, Montejo *et al*., 2011). Increasing the use of these agents in affective and anxiety disorders has resulted in increasing the number of patients suffering from SSRI-induced sexual dysfunction (Hensley & Nurnberg, 2002). Women are at higher risk for mood and anxiety disorders as well as many other psychiatric disorders in which SSRIs are commonly being used (Hensley & Nurnberg, 2002). Thus, women are more exposed to SSRIs and might therefore be more likely to experience the sexual side effects of these drugs. It has been reported that severity of sexual dysfunction is generally higher in women (Hensley & Nurnberg, 2002). All SSRIs including commonly used fluoxetine can cause sexual dysfunction (Sidi *et al*., 2012).

Several strategies have been used to treat or decrease the sexual side effects of SSRIs. Several agents such as sildenafil (Gupta *et al*., 1999), buspirone (Landen *et al*., 1999), cyproheptadine (Aizenberg *et al*., 1995), bupropion (Clayton *et al*., 2001), and amantadine (Woodrum & Brown, 1998) have been used for treatment of SSRI-induced sexual dysfunction with variable success rates. Many of these agents are associated with significant side effects, and some are even associated with reversal of antidepressant or anti-anxiety effects of SSRIs (Feder, 1991).

Saffron (*Crocus sativus* L.) and its extract are used as a medicinal plant in traditional medicine. Several controlled and uncontrolled studies have shown its beneficial antidepressant and anti-dementia effects (Akhondzadeh *et al*., 2004; Akhondzadeh *et al*., 2005; Akhondzadeh Basti *et al*., 2007; Agha-Hosseini

*Correspondence to: S. Akhondzadeh, PhD, Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran 13337, Iran. Tel: 98-21-88281866; Fax: +98-21-55419113. E-mail: s.akhond@neda.net

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Received 29 July 2012
Accepted 9 November 2012

et al., 2008; Akhondzadeh, *et al*., 2010a,2010b). There are also many less studied claims about the other effects of saffron. Two important components of saffron are crocin and safranal. Some animal and human studies have shown the beneficial effects of saffron and particularly its crocin component on sexual function (Hosseinzadeh *et al*., 2008; Shamsa *et al*., 2009). We have recently shown the beneficial effects of saffron on SSRI-induced sexual dysfunction in men (Modabbernia *et al*., 2012).

We hypothesized that saffron could improve sexual dysfunction in female patients who were being treated with an SSRI. The aim of the present study was to assess the effect of saffron on fluoxetine-induced sexual side effects in women with major depressive disorder.

METHODS

Trial design

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted in three centers (two private clinics and one hospital outpatient clinic) in Tehran, Iran (Registration number: IRCT138711121556N3, http://www.irct.ir/searchresult.php?id=1556&number=3).

Participants

Participants were married women aged 18–45 years with diagnosis of major depressive disorder based on DSM-IV criteria who were being treated with fluoxetine and had responded to antidepressant treatment (50% drop in depression score). The patients who had subjective feeling of sexual dysfunction while on fluoxetine were eligible for the trial. All patients were on fluoxetine at a stable dose of 40 mg/day for at least 6 weeks prior to entry and before that they did not have any sexual dysfunctions. A minimum score of 16 on the Female Sexual Function Index (FSFI) at baseline was required (Rosen *et al*., 2000). Exclusion criteria were other DSM axis disorders, medical comorbidites that could underlie sexual symptoms, using other psychotropic agents within 1 month of recruitment, substance abuse within 6 months of recruitment, other serious or life-limiting disease, pregnancy, and lactation.

The patients and their legally authorized representatives signed an informed consent form. All patients were free to withdraw from the study at any time. The protocol was approved by the Institutional Review Board of Tehran University of Medical Sciences (Grant no: 8780). The study was conducted in agreement with the Declaration of Helsinki and its subsequent revisions and was in accordance with local Institutional Review Board recommendations.

Study settings

The study was conducted in an outpatient clinic of the Roozbeh Psychiatric Hospital, a tertiary psychiatric referral center affiliated with Tehran University of Medical Sciences, Tehran, Iran, and two additional private outpatient clinics from February 2009 to February 2010.

Interventions

The participants randomly received saffron capsule 15 mg twice a day or placebo for 4 weeks. All patients were under treatment with fluoxetine 40 mg daily, and their depressive symptoms had been stabilized.

The saffron used in this study was donated by Green Plants of Life Co. (IMPIRAN; Tehran, Iran) and was identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The stigma's extract was prepared as follows: 120 g of dried and milled petal was extracted via 1800 mL ethanol (80%) by percolation procedure in three steps; subsequently, the ethanol extract was dried by evaporation in a temperature between 35 and 40 °C. Each capsule had dried extract of petal of *Crocus sativus* (15 mg), lactose (filler), magnesium stearate (lubricant), and sodium starch glycolate (disintegrant). Crocin value is expressed as direct reading of the absorbance at about 440 nm. Each capsule had 1.65–1.75 mg crocin.

Outcomes

Female Sexual Function Index was used to assess sexual function at baseline and weeks 2 and 4. FSFI is a self-report questionnaire, which consists of 19 questions comprising six domains (Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain) (Rosen *et al*., 2000). Higher scores on the questionnaire and its domains show better sexual function.

Primary outcome measures were the difference in the score change of FSFI total score from baseline to week 4 between the placebo and saffron groups. Secondary outcome measures were the difference in the subscale scores change (on FSFI) between the two groups. Depressive symptoms were assessed using Hamilton Depression Rating Scale (HDRS) at baseline and week 4.

Adverse events were systematically recorded during the course of the trial using a side-effect checklist.

Sample size

Assuming a difference of 5 on the FSFI total score, and standard deviation (SD) of 5, power of 80%, and two-sided significance of 0.05, a sample size of 32 was calculated. Thus, our final sample size of 34 was able

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DOI: 10.1002/hup

to detect a clinical difference of 5 on the FSFI with a power of 83%.

Randomization, allocation concealment, and blinding

A computerized random number generator was used to randomize the participants in a 1:1 ratio, to receive either saffron or placebo in addition to their standard treatment. Allocation was concealed using sequentially numbered, sealed, and opaque envelopes. The patients, the physician who prescribed the medications and assessed the patients, and the statistician were blind to allocation. Randomization, allocation, and interviewing were carried out by separate persons.

Table 1. Baseline characteristics of the patients

Variable	Saffron ($n=17$)	Placebo ($n=17$)
Age, year, mean ± SD	34.7 ± 4.7	36.0 ± 6.1
Smoking, *n* (%)	4 (20)	3 (15)
Weight, kg, mean ± SD	68.1 ± 6.4	70.1 ± 7.1
Height, cm, mean ± SD	161.2 ± 8.2	163.1 ± 6.8
Baseline HDRS score, mean ± SD	9 ± 1.3	8.9 ± 0.7
Baseline FSFI, Total, mean ± SD	20.42 ± 3.79	20.35 ± 3.84
Baseline FSFI, Desire, mean ± SD	2.96 ± 1.09	2.79 ± 0.89
Baseline FSFI, Arousal, mean ± SD	3.07 ± 0.76	2.68 ± 1.28
Baseline FSFI, Lubrication, mean ± SD	4.57 ± 1.01	4.11 ± 1.38
Baseline FSFI I, Orgasm, mean ± SD	2.89 ± 1.09	2.28 ± 1.38
Baseline FSFI, Satisfaction, mean ± SD	3.98 ± 1.32	3.48 ± 1.67
Baseline FSFI I, Pain, mean ± SD	3.57 ± 1.26	4.09 ± 1.53

HDRS, Hamilton Depression Rating Scale; FSFI, Female Sexual Dysfunction Index.

Statistical analysis

IBM SPSS Statistic 19.0.0 (IBM Corporation, Armonk, NY, USA) was used to analyze the data. Continuous and categorical variables were reported as mean (± SD) and number (%), respectively. Two-factor repeated measure analysis of variance (ANOVA) was used for comparison of the score changes between the two groups. In repeated measure analysis, we reported the results of Greenhouse–Geisser correction whenever Mauchly's test of sphericity was significant. To compare the score reduction between the two treatment groups, unpaired *t*-test was used. Cohen's *d* effect sizes were calculated by dividing the mean difference of score change in the two groups by their pooled standard deviation. Fisher's exact test or Chi-square test was used for comparison of proportions between the two groups. A p value of <0.05 was considered statistically significant. All analyses were based on the intention-to-treat sample and were performed using Last Observation Carried Forward procedure.

RESULTS

Participants

Of 50 patients who were screened for eligibility criteria, 38 eligible patients were randomly assigned to saffron ($n=19$) or placebo ($n=19$). Table 1 summarizes baseline characteristics of the study participants. Thirty-four patients (17 in each group) had at least one post-baseline measurement and entered the final analysis (Figure 1).

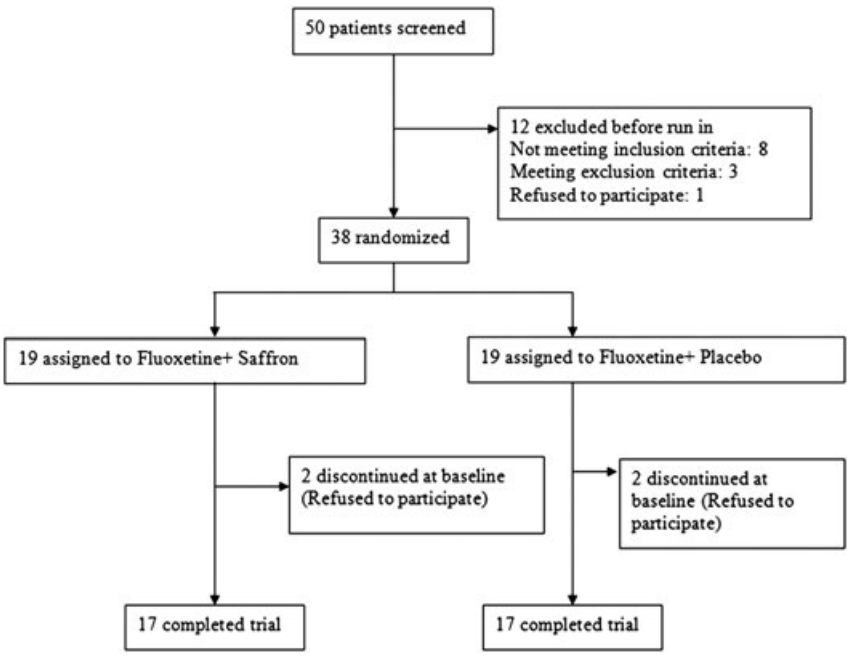

Figure 1. Flow diagram of the trial

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DOI: 10.1002/hup

There were no reports of serious adverse events during the course of the study. Baseline HDRS scores were similar between the two groups {mean difference [95% confidence interval (95% CI)] = 0.06 (−0.67 to 0.79), $t(32) = 0.164$, $p = 0.871$}. Final HDRS scores did not significantly differ between the two groups [mean difference (95% CI) = −0.29 (−0.84 to 0.25), $t(32) = -1.104$, $p = 0.278$].

Analysis of outcomes

Total Female Sexual Function Index score. There was no significant difference in baseline total FSFI score between the two groups [mean difference (95% CI) = 0.07(−2.73 to 2.59), $t(32) = -0.054$, $p = 0.957$]. Two-factor repeated measure ANOVA showed significant effect for time × treatment interaction [Greenhouse–Geisser's corrected: $F(1.580, 50.567) = 5.366$, $p = 0.012$], indicating that the effect of two treatment groups was significantly different across time. Effect of treatment was also significant [$F(1, 32) = 4.243$, $p = 0.048$] (Figure 2.).

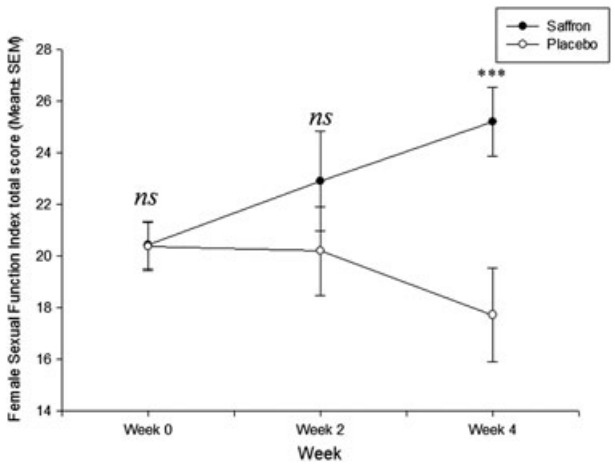

Figure 2. Results of repeated measure analysis of variance for Female Sexual Function Index total scores. ***p value < 0.001; *ns*, non-significant p values. p values represent results of unpaired t-test between the score change of the two groups at each time point

Desire subscale. There was no significant difference in baseline desire subscale scores between the two groups [mean difference (95% CI) = 0.18(−0.50 to 0.85), $t(32) = -0.533$, $p = 0.598$]. Two-factor repeated measure ANOVA showed significant effect for time [$F(2, 64) = 7.769$, $p = 0.001$] but not time × treatment interaction [$F(2, 64) = 1.042$, $p = 0.359$], indicating that the effect of two groups was not significantly different across time. Results of unpaired t-test showed no significant difference in the desire subscale score change from baseline to week 4 between the two groups (Table 2).

Arousal subscale. There was no significant difference in baseline arousal subscale scores between the two groups [mean difference (95% CI) = 0.39(−0.35 to 1.12), $t(32) = 1.073$, $p = 0.292$]. Two-factor repeated measure ANOVA showed significant effect for time treatment interaction [$F(2, 64) = 3.443$, $p = 0.038$], indicating that the effect of two groups was significantly different across time. Effect of time was not significant [$F(2, 64) = 0.729$, $p = 0.486$]. Change in the arousal subscale from baseline to week 4 was significant between the two groups (Table 2).

Lubrication subscale. There was no significant difference in baseline lubrication subscale scores between the two groups [mean difference (95% CI) = 0.46 (−0.39 to 1.30), $t(32) = 1.103$, $p = 0.278$]. Two-factor repeated measure ANOVA did not show significant effect for time × treatment interaction [Greenhouse–Geisser corrected: $F(1.673, 53.544) = 1.794$, $p = 0.181$],

Table 2. Comparison of changes in FSFI subscales scores from baseline between the two groups

Week	Saffron group (mean ± SD)	Placebo group (mean ± SD)	Mean difference (95% confidence interval)	$t(32)$	p value	Cohen's d (95% confidence interval)
Baseline–week 2, Desire	−0.35 ± 0.77	−0.10 ± 0.53	−0.25 (−0.70 to 0.21)	−1.093	0.282	0.4 (−0.3 to 1.0)
Baseline–week 4, Desire	−0.67 ± 0.99	−0.32 ± 0.48	−0.35 (−0.90 to 0.19)	−1.320	0.196	0.4 (−0.2 to 1.1)
Baseline–week 2, Arousal	−0.41 ± 0.82	0.09 ± 0.61	−0.49 (−1.00 to 0.01)	−1.995	0.055	0.7 (−0.01 to 1.4)
Baseline–week 4, Arousal	−0.49 ± 0.84	0.23 ± 0.98	−0.72 (−1.36 to −0.08)	−2.308	**0.028**	0.8 (0.1 to 1.5)
Baseline–week 2, Lubrication	−0.30 ± 1.80	0.37 ± 2.19	−0.67 (−2.07 to 0.73)	−0.975	0.337	0.3 (−0.3 to 1.0)
Baseline–week 4, Lubrication	−0.46 ± 1.11	0.62 ± 1.68	−1.08 (−2.07 to −0.08)	−2.201	**0.035**	0.7 (0.05 to 1.4)
Baseline–week 2, Orgasm	−0.82 ± 1.33	−0.14 ± 0.96	−0.68 (−1.49 to 0.13)	−1.716	0.096	0.6 (−0.1 to 1.3)
Baseline–week 4, Orgasm	−0.92 ± 1.38	−0.52 ± 1.07	−0.40 (−1.26 to 0.46)	−0.941	0.354	0.3 (−0.3 to 1.0)
Baseline–week 2, Satisfaction	−0.40 ± 0.93	−0.07 ± 0.49	−0.33 (−0.85 to 0.19)	−1.292	0.346	0.4 (−0.2 to 1.1)
Baseline–week 4, Satisfaction	−0.23 ± 1.02	0.05 ± 0.74	−0.28 (−0.91 to 0.34)	−0.921	0.206	0.3 (−0.4 to 1.0)
Baseline–week 2, Pain	−0.38 ± 0.94	0.35 ± 1.04	−0.73 (−1.42 to −0.04)	−2.144	**0.040**	0.7 (0.03 to 1.4)
Baseline–week 4, Pain	−0.49 ± 0.73	0.85 ± 2.06	−1.34 (−2.42 to −0.26)	−2.532	**0.016**	0.9 (0.1 to 1.6)

FSFI, Female Sexual Dysfunction Index; Bold emphasis = $p < 0.05$.

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DOI: 10.1002/hup

indicating that the effect of two groups was not significantly different across time. Effect of time was not significant [Greenhouse–Geisser corrected: $F(1.673, 53.544) = 0.038$, $p = 0.941$]. Change in the lubrication subscale from baseline to week 4 was significant between the two groups (Table 2).

Orgasm subscale. There was no significant difference in baseline orgasm subscale scores between the two groups [mean difference (95% CI) = 0.61(−0.26 to 1.48), $t(32) = 1.436$, $p = 0.161$]. Two-factor repeated measure ANOVA showed significant effect of time [$F(2, 64) = 6.307$, $p = 0.003$] but not time × treatment interaction [$F(2, 64) = 1.385$, $p = 0.258$], indicating that the effect of two groups was not significantly different across time. Results of *t*-test showed no significant difference in improvement of the orgasm subscale scores between the two groups (Table 2).

Satisfaction subscale. There was no significant difference in baseline satisfaction subscale scores between the two groups [mean difference (95% CI) = 0.49 (−0.56 to 1.55), $t(32) = 0.956$, $p = 0.346$]. Two-factor repeated measure ANOVA did not show significant effect of time [$F(2, 64) = 1.563$, $p = 0.217$] or time treatment interaction [$F(2, 64) = 0.885$, $p = 0.418$], indicating that the effect of two groups was not significantly different across time. Results of *t*-test showed no significant difference in improvement of the satisfaction subscale scores between the two groups (Table 2).

Pain subscale. There was no significant difference in baseline pain subscale scores between the two groups [mean difference (95% CI) = −0.52(−1.49 to 0.46), $t(32) = -1.078$, $p = 0.289$]. Two-factor repeated measure ANOVA did not show significant effect for time [$F(1.319, 42.198) = 0.305$, $p = 0.646$], but it showed nearly significant effect for time × treatment interaction [$F(1.319, 42.198) = 3.094$, $p = 0.075$]. Change in the pain subscale from baseline to week 4 was significant between the two groups (Table 2).

Adverse events. Eight side effects were recorded during the course of the trial (Table 3). Frequency of side effects did not differ between the two groups.

Table 3. Frequency of adverse events in the two groups

Adverse events	Placebo ($n = 17$)	Saffron ($n = 17$)
Increased appetite (%)	1 (6)	2 (12)
Dizziness (%)	1 (6)	0
Sore throat (%)	1 (6)	0
Decreased appetite (%)	1 (6)	2 (12)
Headache (%)	2 (12)	1 (6)
Insomnia (%)	2 (12)	1 (6)
Sedation (%)	2 (12)	1 (6)
Nausea (%)	3 (18)	2 (12)

DISCUSSION

In line with our hypothesis, saffron was particularly effective in improving the arousal, lubrication, and pain domains of FSFI. Because the baseline data of our patients were similar between the two groups, the beneficial effect observed in the saffron group could be attributed to the aphrodisiac effect of saffron. The results of the present study support some previous studies assessing the effect of saffron on sexual dysfunction in men (Hosseinzadeh, *et al*., 2008; Shamsa, *et al*., 2009). Hosseinzadeh *et al*. (2008) studied the aphrodisiac effect of saffron, safranal, and crocin in rats. Following intraperitoneal injection of crocin, there was significant improvement in several sexual behavior-related parameters including mounting, intromission, and erection frequencies, and mount, intromission, and ejaculation latencies.

Importantly, saffron was as safe as placebo in our study. This supports findings on safety of saffron in other studies. SSRI-induced sexual dysfunction is an important cause of antidepressant discontinuation. Most medications that are used as remedy for SSRI-induced sexual dysfunction have specific side effects, and this may prevent their effective use in the clinical setting. Some such as cyproheptadine may even exacerbate mood symptoms, and some such as yohimbine may cause significant anxiety (Feder, 1991; Balon, 1993).

Interestingly, saffron was not effective in all domains of sexual dysfunction, suggesting that saffron might selectively regulate sexual behavior. The mechanism of aphrodisiac effect of saffron remains to be established. Several studies have also shown anti-inflammatory, antioxidative, neuroprotective, and antiepileptic effects of saffron (Hosseinzadeh & Younesi, 2002; Hosseinzadeh & Sadeghnia, 2005, 2007; Hosseinzadeh *et al*., 2009; Hosseinzadeh *et al*., 2012). Whether the underlying mechanisms of these effects can also explain the aphrodisiac effects of saffron needs further investigation.

Saffron significantly improved intercourse-related pain in the present study. Studies suggest that intercourse-related pain in women might be linked to the action of opioids and neuropeptides (Wilson *et al*., 2009). In a study in mice, Hosseinzadeh and Younesi (2002) showed the anti-nociceptive effects of saffron. They also showed that this effect was inhibited partially by naloxone. In a separate study, Hosseinzadeh and Jahanian (2010) showed the beneficial effect of

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DOI: 10.1002/hup

saffron on opioid withdrawal syndrome, further suggesting that saffron and its extracts might interact with the opioid system. Saffron might also be beneficial in dysmenorrhea (Nahid *et al*., 2009). Taken together, it seems that the advantageous effect of saffron on intercourse-related pain might be partially related to its effect on opioids.

Saffron has shown antidepressant properties in several trials (Akhondzadeh, *et al*., 2005; Noorbala *et al*., 2005). However, because the patients in the present study had been stabilized on fluoxetine and had minimal depressive symptoms, the antidepressant effect of saffron could not be evaluated.

The present study had some limitations. Short study duration might have limited the interpretation of the present study regarding long-term effects of saffron on sexual dysfunction. Although the sample size was relatively small, we were able to detect the significant effect of saffron on sexual dysfunction. Cultural factors might be responsible for relatively high drop-out rates in the present study even though the number and the cause of patient withdrawal were similar between the two groups, suggesting that the study results were not affected by drop-outs. In addition, different dosages of saffron should be investigated in future studies.

CONCLUSIONS

In summary, we showed that saffron had beneficial effects on sexual arousal, lubrication, and pain domains of sexual dysfunction in women with fluoxetine-related sexual dysfunction.

CONFLICT OF INTEREST

No competing financial interests exist.

ACKNOWLEDGEMENT

The present study was supported by a grant from Tehran University of Medical Sciences to Professor Shahin Akhondzadeh (Grant number: 8780).

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DOI: 10.1002/hup