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ORIGINAL INVESTIGATION

Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo-controlled trial

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Abstract
Rationale Saffron (*Crocus sativus* L.) has shown aphrodisiac effects in some animal and human studies.
Objectives To assess the efficacy and tolerability of saffron in fluoxetine-related sexual dysfunction.
Methods This was a 4-week randomized double-blind placebo-controlled study. Thirty-six married male patients with major depressive disorder whose depressive symptoms had been stabilized on fluoxetine and had subjective complaints of sexual impairment entered the study. The patients were randomly assigned to saffron (15 mg twice per day) or placebo for 4 weeks. International Index of Erectile Function scale was used to assess sexual function at baseline and weeks 2 and 4.
Results Thirty patients finished the study. Baseline characteristics as well as baseline and final depressive symptoms scores were similar between the two groups. Effect of time × treatment interaction on the total score was significant [Greenhouse–Geisser-corrected, F (1.444, 40.434)=6.154, P=0.009]. By week 4, saffron resulted in significantly greater improvement in erectile function (P<0.001) and intercourse satisfaction domains (P=0.001), and total scores (P<0.001) than the placebo group. Effect of saffron did not differ significantly from that of placebo in orgasmic function (P=0.095), overall satisfaction (P=0.334), and sexual desire (P=0.517) domains scores. Nine patients (60%) in the saffron group and one patient (7%) in the placebo group achieved normal erectile function (score>25 on erectile function domain) at the end of the study (P value of Fisher's exact test=0.005). Frequency of side effects were similar between the two groups.
Conclusions Saffron is a tolerable and efficacious treatment for fluoxetine-related erectile dysfunction.

Keywords *Crocus sativus* · Erectile dysfunction · Fluoxetine · Saffron · Sexual dysfunction · SSRI

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Introduction

Sexual dysfunction is one of the most common causes of discontinuation of selective serotonin reuptake inhibitors (SSRIs) (Waldinger and Olivier 1998; Fava and Rankin 2002). All phases of sexual function (desire, arousal, and orgasm) can be affected by SSRIs, and all SSRIs can cause sexual impairment (Fava and Rankin 2002). As SSRIs gain more popularity by psychiatrists, the number of patients who are prescribed with these agents and thus the number of patients who experience sexual side effect increases. Reported frequencies of SSRI-induced sexual dysfunction have been between 7% and 70% (Fava and Rankin 2002; Hensley and Nurnberg 2002; Montejo-Gonzalez et al. 1997; Williams et al. 2006, 2010). Moreover, SSRIs were more likely to cause sexual dysfunction in men in some studies (Hensley and Nurnberg 2002; Williams et al. 2006).

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Several therapeutic modalities have been proposed for treatment of SSRI-related sexual impairment. While phosphodiesterase-5 inhibitors (Taylor et al. 2005; Damis et al. 1999) (such as sildenafil) and bupropion (Demyttenaere and Jaspers 2008) are the most widely studied agents, several other medications such as cyproheptadine (Aizenberg et al. 1995), amantadine (Shrivastava et al. 1995), yohimbine (Hollander and McCarley 1992), buspirone (Landen et al. 1999), mirtazapine(Atmaca et al. 2011; Michelson et al. 2002; Ozmenler et al. 2008), loratadine (Aukst-Margetic and Margetic 2005), and Gingko biloba (Taylor et al. 2005) have been used for treatment of SSRI-induced sexual impairment with inconsistent success rates. Some of these agents are associated with significant side effects, and some may even exacerbate depression and anxiety (DeBattista et al. 2005; Hollander and McCarley 1992; Feder 1991).

Saffron (*Crocus sativus* L.) is widely used as a spice and a medicinal plant in Iran as well as India, Greece, Spain, and Italy (D'Agostino et al. 2007). Most evidence-based studies on saffron have focused on its effect on central nervous system disorders and particularly on depression and dementia (Akhondzadeh Basti et al. 2007; Moshiri et al. 2006; Akhondzadeh et al. 2010a, b). In folk medicine, there is a widely held belief that saffron might have aphrodisiac effects. Recently, some animal and human studies have shown beneficial effect of saffron and particularly its crocin component on sexual function (Shamsa et al. 2009; Hosseinzadeh et al. 2008). In a study on male rats, the aphrodisiac effect of saffron was shown by its beneficial effect on several aspects of sexual function measures including mounting, intromission, and erection frequencies and mounting, intromission, and ejaculation latencies (Hosseinzadeh et al. 2008). The effect of saffron on SSRI-induced sexual dysfunction has not been studied yet.

We hypothesized that saffron would show beneficial effect on SSRI-induced sexual impairment of male patients. The goal of the present study was to assess the tolerability and efficacy of saffron in the treatment of fluoxetine-induced sexual dysfunction in men with major depressive disorder (MDD).

Patients and methods

Trial design

This was a 4-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted in one hospital outpatient clinic in Tehran, Iran from February 2009 to December 2011. The trial was registered in Iranian Registry of Clinical Trials (Registration number: IRCT138711121556N3, http://www.irct.ir/searchresult.php?id=1556&number=3)

Participants

The participants were married male aged 18–45 who had MDD based on *DSM-IV* criteria and were under treatment with fluoxetine. The patients who had subjective feeling of sexual dysfunction following the start of fluoxetine were eligible for the trial. The subject feeling of sexual dysfunction should be accompanied by a score <25 on the erectile function domain of International Index of Erectile Function scale (IIEF). The sexual side effects should be treatment-emergent (i.e., either emerging after onset of fluoxetine treatment, or being significantly worsened following treatment with fluoxetine) as stated in the study by Baldwin et al. (2008). All patients had been treated with fluoxetine at a dose of 40 mg/day for a minimum of 6 weeks prior to entry. Exclusion criteria were other psychiatric disorders, taking other psychotropic medications within 4 weeks of screening visit, substance abuse within 6 months of recruitment, and other serious or life-limiting conditions.

All participants were free to withdraw from the trial at any time. The study protocol was approved by the Institutional Review Board of Tehran University of Medical Sciences (grant no: 8140). The trial was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. All participants and their legally authorized representatives signed an informed consent.

Interventions

The patients were randomly assigned to receive saffron capsule 15 mg twice per day or placebo (with the same appearance and taste as saffron capsule) twice per day for 4 weeks. Patients should have been stabilized on fluoxetine 40 mg/day for at least 6 weeks prior to entry.

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 similar to our previous studies (Akhondzadeh et al. 2010b; Agha-Hosseini et al. 2008) was prepared as follows—120 g of dried and milled stigmas was extracted with 1,800 ml ethanol (80%) by percolation procedure in three steps. Subsequently, the ethanol extract was dried by evaporation at a temperature of 35–40°C. Each capsule contained dried extract of saffron (15 mg), lactose (filler), magnesium stearate (lubricant), and sodium starch glycolate (disintegrant). The extract was standardized based on crocin which is the most important component of saffron. Spectrophotometry was used to determine crocin values in each capsule. Crocin value is expressed as direct reading of the absorbance at about 440 nm. Each capsule had 1.65–1.75 mg crocin.

Outcomes

Sexual function was assessed using IIEF scale at baseline and weeks 2 and 4 (Rosen et al. 1997). IIEF is a self-report instrument with 15 questions measuring sexual function on a 5–6-Likert-type scale. The IIEF has five domains that are relevant to male sexual function (namely erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). Higher scores on the instrument and its domains correspond to better sexual function. A definition has recently been proposed for minimal clinically important difference (MCID) for the erectile function domain of IIEF. For mild to moderate erectile dysfunction (score 17–25) a MCID of 2.8 and for moderate erectile dysfunction (score 11–16) a MCID of 7.2 have been defined (Rosen et al. 2011). Moreover, those with erectile function domain score of >25 are considered to have normal erectile function(Cappelleri et al. 1999).

Primary outcome measures were the difference in the score change of IIEF from baseline to week 4 between the two study groups.

Secondary outcome measures were the difference in the IIEF domain scores change, as well as the difference in the proportion of patients who achieved MCID and normal erectile function between the two study groups. Hamilton depression rating scale (HDRS) was used to assess depression at baseline and week 4.

A side-effect checklist was used to assess the adverse events at each visit during the course of the study.

Sample size

Primary sample size of this study was 36 (18 in each group). Assuming a two-sided significance of 5%, our final sample size of 30 was capable of detecting a minimal difference of 5 and a standard deviation of 4 with a power of 93%.

Randomization, allocation concealment, and blinding

Randomization was done using a computer random number generator in a 1:1 ratio and block size of 4. Allocation concealment was achieved using successively numbered, opaque, and sealed envelopes. The patients, the psychiatrists who rated them and prescribed the study medications, and the statistician were blind to allocation. Random allocation and interviewing the patients were done by separate individuals.

Statistical analysis

Data analysis was done using IBM SPSS Statistic 19.0.0 (IBM Corporation). All analyses were based on the intention-to-treat sample and were done using last-observation-carried-forward algorithm. Mean (±standard deviation (SD)) and number (percentage) were used to report continuous and categorical variables, respectively. Mean differences were reported as mean difference (±95% confidence intervals, 95% CI). To compare the pattern of score change between the two groups across time (time×treatment interaction), two-factor repeated-measure analysis of variance (ANOVA) was used. In repeated-measure ANOVA, results of Greenhouse–Geisser correction for degrees of freedom was reported whenever Mauchly's test of sphericity was significant. Independent sample t test was used for comparison of the score change at each time point between the two groups. Effect sizes (Cohen's d) were calculated by dividing the mean difference of score change in the two treatment groups by their pooled standard deviation. Pearson chi-square and Fisher's exact test was used to compare proportions between the two groups. A P value of <0.05 was considered statistically significant.

Results

Participants

Fifty-four patients were screened for eligibility criteria, and 36 eligible participants randomly received saffron ($n=18$) or placebo ($n=18$). Table 1 shows baseline data of the patients. Thirty patients ($n=15$ in each group) had at least one post-baseline measurement, and a similar number of patients finished the study (Fig. 1). Baseline HDRS scores did not differ significantly between the two groups (mean difference (95%CI)=−0.3 (−1.1 to 0.5), $t(28)=-0.673$, $P=0.506$). Final HDRS scores were also similar between the two groups (mean difference (95% CI)=−0.4 (−1.0 to 0.2), $t(28)=-1.382$, $P=0.178$). The mean±SD age for the patients who dropped out of the study was 32.5±4.6 years which was not significantly different from the patients who remained in the study ($t(34)=1.595$, $P=0.119$). Most of the patients who dropped out of the study had a diploma degree which was not significantly different from the patients who finished the study ($\chi^2(2)=4.564$, $P=0.102$). However, the patients who dropped out were less likely to be smokers than the patients who finished the study with a trend toward significance ($\chi^2(1)=3.600$, $P=0.058$). During the study course, no change was made in the medication type or dosage.

Analysis of outcomes

Total score

There was no significant difference in baseline total IIEF score between the two groups (mean difference (95% CI)= 6.1(−3.0 to 15.2), $t(28)=1.381$, $P=0.178$). Two-factor repeated-measure ANOVA showed significant effect for time×treatment interaction [Greenhouse–Geisser-corrected,

Table 1 Baseline characteristics of the patients

Variable	Saffron (n=15)	Placebo (n=15)
Age, years (mean±SD)	36.6±8.3	40.5±9.4
Smoking, *n* (%)	10 (67%)	12 (80%)
Educational level, *n* (%)	Under diploma[a]=4(27%), diploma=6(40%), over diploma=5(33%)	Under diploma=2(14%), diploma=5(33%), over diploma=8(53%)
Weight, kg (mean±SD)	71.4±9.7	69.3±9.1
Height, cm (mean±SD)	172.1±9.3	172.4±8.9
Baseline HDRS score, mean±SD	9.0±1.2	9.3±0.9
Baseline IIEF, total, (mean±SD)	49.3±11.4	43.2±12.9
Baseline IIEF, erectile function (mean±SD)	20.7±4.3	21.2±3.1
Baseline IIEF, satisfaction with intercourse (mean±SD)	8.3±2.8	7.3±3.4
Baseline IIEF, orgasmic function (mean±SD)	7.2±1.9	6.5±2.5
Baseline IIEF, sexual desire (mean±SD)	6.7±1.8	5.9±2.1
Baseline IIEF, overall satisfaction (mean±SD)	6.5±2.1	5.3±1.8

HDRS Hamilton depression rating scale, *IIEF* International Index of Erectile Function scale

[a]Diploma means high school diploma

F(1.444, 40.434)=6.154, P=0.009], indicating that the effect of two treatment groups was significantly different across time. Effect of treatment was also significant [F(1,28)=6.641, P=0.016]. Unpaired t test showed significantly greater improvement of total score in the saffron group than the placebo group at weeks 2 and 4 (Table 2).

Erectile function

There was no significant difference in baseline erectile function domain scores between the two groups (mean difference (95% CI)=−0.5(−3.3 to 2.3), t(28)=−0.389, P=0.700). Two-factor repeated-measure ANOVA showed significant effect for time×treatment interaction [F(2, 56)=19.613, P<0.001], indicating that the behavior of the two groups was significantly different across time. Results of unpaired t test showed significantly greater improvement of erectile function in the saffron group than the placebo group (Table 2). Three patients in the saffron group and one patient in the placebo group had moderate erectile dysfunction at baseline. All the other patients had mild erectile dysfunction at baseline. The proportion of subjects who were defined as having MCID at the end

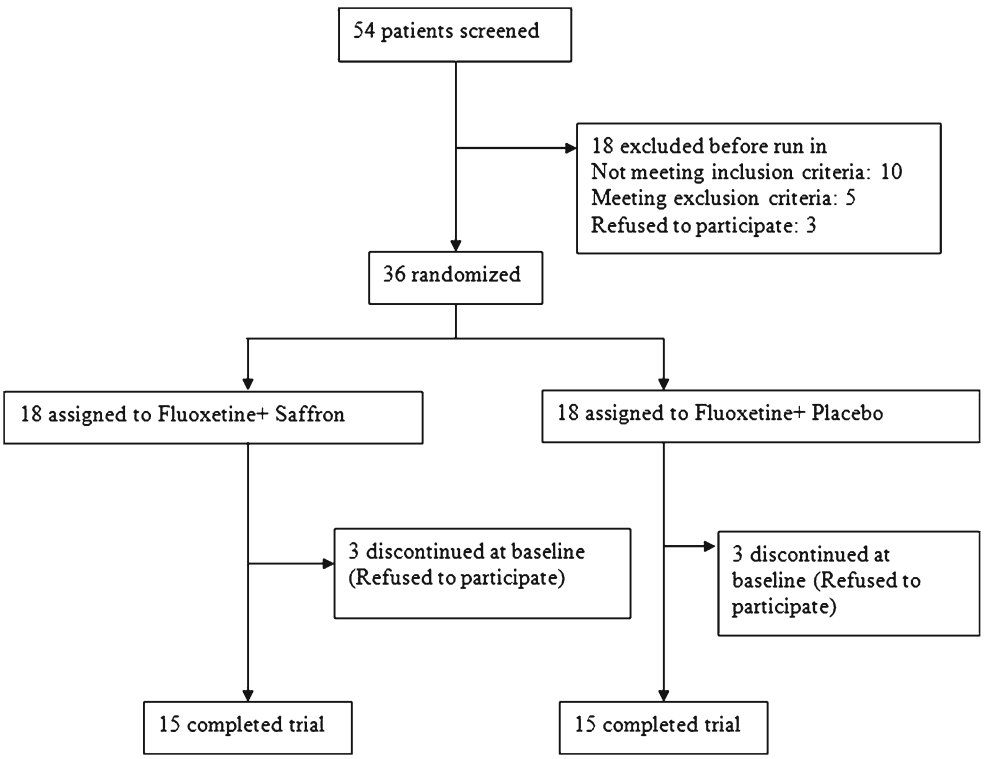

Fig. 1 Flow diagram of the trial

Table 2 Comparison of changes in IIEF total and domains scores from baseline between the two groups

Week	Saffron group (mean±SD)	Placebo group (mean±SD)	Mean difference(95% confidence interval)	$t(28)$, P value	Cohen's d (95% confidence interval)
Week 2, total	5.5±5.5	−1.1±9.5	6.6 (0.8 to 12.4)	2.325, 0.028	0.8(0.1 to 1.6)
Week 4, total	8.2±3.9	0.9±4.5	7.3 (41. To 10.4)	4.666, <0.001	1.7 (0.8 to 2.5)
Week 2, erectile function	2.2±1.1	−1.9±3.4	4.1 (2.2 to 6.0)	4.391, <0.001	1.6 (0.8 to 2.4)
Week 4, erectile function	4.5±2.5	−2.5±4.6	7.0 (4.2 to 9.7)	5.221, <0.001	1.9 (1.0 to 2.8)
Week 2, satisfaction with intercourse	1.4±1.8	−0.8±3.2	2.2 (0.3 to 4.1)	2.338, 0.027	0.8 (0.1 to 1.6)
Week 4, satisfaction with intercourse	2.1±1.6	−0.2±1.6	2.3 (1.1 to 3.5)	3.889, 0.001	1.4 (0.6 to 2.2)
Week 2, orgasmic function	0.7±1.4	0.1±1.3	0.7 (−0.3 to 1.7)	1.341, 0.191	0.5 (−0.2 to 1.2)
Week 4, orgasmic function	1.1±1.5	0.3±1.0	0.8 (−0.1 to 1.7)	1.727, 0.095	0.6 (−0.1 to 1.3)
Week 2, sexual desire	0.2±1.1	0.3±1.1	−0.1 (−0.9 to 0.7)	−0.167, 0.868	−0.1 (−0.8 to 0.7)
Week 4, sexual desire	0.5±1.7	0.2±1.0	0.3 (−0.7 to 1.4)	0.657, 0.517	0.2 (−0.5 to 0.9)
Week 2, overall satisfaction	0.7±1.5	0.7±1.0	0.1 (−0.9 to 1.0)	0.142, 0.888	0.05 (−0.7 to 0.8)
Week 4, overall satisfaction	1.2±1.7	0.7±1.2	0.5 (−0.6 to 1.6)	0.984, 0.334	0.3 (−0.4 to 1.1)

IIEF International Index of Erectile Function scale

of the study was significantly higher in the saffron (8 of 15, 53%) than in the placebo (2 of 15, 13%) group ($\chi^2(1)=5.400$, $P=0.020$). Nine patients (60%) in the saffron group and one patient (7%) in the placebo group achieved normal erectile function (score>25 on erectile function domain) at the end of the study (P value of Fisher's exact test=0.005).

Satisfaction with intercourse

There was no significant difference in baseline satisfaction with intercourse domain scores between the two groups (mean difference (95% CI)=0.9(−1.4 to 3.3), $t(28)=0.820$, $P=0.419$). Two-factor repeated-measure ANOVA showed significant effect for time×treatment interaction [Greenhouse–Geisser-corrected, F(1.448, 40.531)=3.443, $P=0.038$], indicating that the effect of two groups was significantly different across time. Results of t test showed significantly greater improvement of the satisfaction with intercourse domain scores in the saffron group than the placebo group at weeks 2 and 4 (Table 2).

Orgasmic function

There was no significant difference in baseline orgasmic function domain scores between the two groups (mean difference(95% CI)=0.7(−1.0 to 2.3), $t(28)=0.822$, $P=0.418$). Two-factor repeated-measure ANOVA did not show significant effect for time×treatment interaction [F(2, 56)=1.906, $P=0.158$], indicating that the effect of two groups was not significantly different across time. Results of t test showed nearly significant improvement of the orgasmic function domain scores in the saffron group compared with the placebo group at the end of the study (Table 2).

Sexual desire

There was no significant difference in baseline sexual desire domain scores between the two groups (mean difference (95% CI)=0. 7(−0.7 to 2.2), $t(28)=1.031$, $P=0.311$). Two-factor repeated-measure ANOVA did not show significant effect of time×treatment interaction [F(2, 56)=0.460, $P=0.634$], 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 sexual desire domain scores between the two groups (Table 2).

Overall sexual satisfaction

There was no significant difference in baseline overall sexual satisfaction domain scores between the two groups (mean difference (95% CI)=1.2(−0.2 to 2.6), $t(28)=1.697$, $P=0.101$). Two-factor repeated-measure ANOVA did not show significant effect of time×treatment interaction [Greenhouse–Geisser-corrected, F(1.550, 43.408)=0.820, $P=0.419$], 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 overall sexual satisfaction domain scores between the two groups at weeks 2 and 4 (Table 2).

Adverse events

Nine side effects were recorded during the study. Frequency of side effects did not differ between the two treatment groups (Table 3). All adverse events were mild and did not result in leaving the study.

Table 3 Frequency of adverse events in the two groups

Adverse events	Saffron(n=15)	Placebo(n=15)
Abdominal pain (%)	0	1 (7%)
Daytime drowsiness (%)	1 (7%)	1 (7%)
Nausea (%)	1 (7%)	3 (20%)
Decreased appetite (%)	3 (20%)	1 (7%)
Dry mouth (%)	3 (20%)	2 (13%)
Nervousness (%)	1 (7%)	0
Restlessness (%)	1 (7%)	0
Morning drowsiness (%)	1 (7%)	0
Increased appetite (%)	1 (7%)	1 (7%)

Discussion

The present study provided evidence for beneficial effects of saffron on fluoxetine-induced sexual dysfunction. This was particularly evident in the erectile and intercourse satisfaction domains of IIEF. There was also a trend toward significant improvement in orgasmic function. Baseline characteristics of the patients in the two study groups did not differ significantly from each other, suggesting that the observed difference between the two groups can be attributed to the aphrodisiac effect of saffron. Of note, depressive symptoms did not differ between the two groups at the end of the trial, suggesting that improvement in sexual function cannot be attributed to depression improvement. Although antidepressant effects of saffron have been established in several previous studies (Akhondzadeh et al. 2004, 2005; Noorbala et al. 2005), absence of such effect in the present study was due to absence of significant depressive symptoms in the patients. In other words, because of depressive symptom stabilization with fluoxetine, antidepressant effect of saffron could not be evaluated.

The findings of the present study are in line with some previous studies (Hosseinzadeh et al. 2008; Shamsa et al. 2009). Hosseinzadeh et al. (2008) showed aphrodisiac effect of saffron in rats. Shamsa et al.(2009) studied the effect of 300 mg/day saffron on 20 male patients with erectile dysfunction for 10 days. There was improvement in all domains of IIEF in the patients. Total score was improved by about 14 in their study compared with 5.5 (by week 2) in our study, suggesting that the effect of saffron might be dose-related. Lack of a placebo group, absence of a factor which exacerbated sexual function (SSRI), and high dose of saffron used in their study might explain the differences observed in improvement of domains between studies.

In line with previous studies, side effect profile of saffron was comparable to placebo in the present study (Noorbala et al. 2005; Agha-Hosseini et al. 2008; Akhondzadeh et al. 2010a, b). This finding is important because most pharmacotherapies for SSRI-induced sexual impairment are associated with significant side effects, and some may even reverse the beneficial effect of SSRIs on mood (DeBattista et al. 2005; Taylor et al. 2005). On the other hand, antidepressant effect of saffron is an additional advantage to its aphrodisiac effect, which makes it a potentially useful adjunct to SSRIs in treatment of moderate to severe MDD.

The fact that saffron did not show beneficial effects on some domains of IIEF may reflect its selective effect on sexuality. Mechanism of action of saffron on sexual function remains to be elucidated. Overall, excessive serotonin is thought to be related to SSRI-induced sexual dysfunction (Andersson 2011; Keltner et al. 2002), although each serotonin receptor might have a distinct effect on sexual dysfunction (Hull et al. 2004). Besides its central inhibitory effects on sexual reflexes (Andersson 2011), serotonin induces contraction in corpus cavernosa in rabbits (Furukawa et al. 2003). Saffron appears to interact with several neurotransmitter systems (Berger et al. 2011; Nemati et al. 2008; Boskabady et al. 2010), although its direct interaction with serotonin has not been studied yet. Furthermore, both nitric oxide and opioid system play important roles in erectile function (Andersson 2011), and saffron seems to interact with both (Khori et al. 2011; Hosseinzadeh and Jahanian 2010). In addition, saffron has shown anti-inflammatory, radical scavenging, and neuroprotective properties in several studies (Hosseinzadeh and Younesi 2002; Hosseinzadeh and Sadeghnia 2005; Hosseinzadeh et al. 2012). Whether the underlying mechanisms of these effects are related to the beneficial sexual effects of saffron certainly requires additional studies.

Effect of saffron on erectile function was relatively large in the present study as shown by improvement of more than half of the patients in the saffron group compared with only 13% of the patients in the placebo group. An average mean difference of 4.1 at week 2 and 7 at week 4 on the erectile function domain was observed between the two groups. This difference conforms to the definition of minimal clinically important difference defined as an average score of 4 on the erectile function domain (Rosen et al. 2011). Although the effect of saffron on erectile function was comparable to that of phosphodiesterase inhibitors in other studies (Nurnberg et al. 2003), effect of saffron on other domains were less satisfactory than that of phosphodiestrase inhibitors. Selective effect of saffron on some domains in its daily dose of 30 mg might explain the cause of this difference. However, as shown by Shamsa et al.(2009), higher dose of saffron might exert more beneficial effect on sexual function and can probably improve other IIEF domains as well.

Although the present study showed beneficial effects of saffron on sexual dysfunction, it also had some limitations. Inability to detect significant difference in some domains (for example, orgasmic function) which showed near-significant

results might be due to relatively small sample size. Moreover, because our study was of short duration, we cannot generalize the findings to long-term outcomes. The present study also had relatively high drop-out rates which might be because of cultural factors in seeking and adhering to the treatment of sexual dysfunction in this country. Nevertheless, the high drop-out rate is unlikely to affect our findings because the frequency and cause of drop-outs were similar between the two study groups.

Conclusion

In summary, our study provided evidence for tolerability and efficacy of saffron in treatment of fluoxetine-related erectile dysfunction.

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.

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Conflict of interest The authors declare no conflict of interests.

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