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# Therapeutic effects of saffron (*Crocus sativus*) versus fluoxetine on Irritable Bowel Syndrome: A double-blind randomized clinical trial

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ABSTRACT

*Background:* Irritable Bowel Syndrome (IBS) is an expensive and prevalent functional bowel disorder that can reduce work productivity and quality of life especially among youth. IBS is characterized by recurrent abdominal pain associated with defecation or a change in bowel habits and commonly accompanied by depression and anxiety as comorbid situations. On the other hand, saffron (*Crocus sativus*) is an herbal medicine with anti-depressive properties. This study aimed to compare efficacy of saffron and fluoxetine in increasing IBS patients' quality of life.
*Methods:* Sixty-six patients with IBS, according to Rome III criteria, participated in a double-blinded parallel group randomized trial. Patients were equally divided into two groups and either received saffron or fluoxetine for 6 weeks. Every 2 weeks, each patient was requested to complete IBS quality of life and hospital anxiety and depression scale questionnaires and asked to report side effects of treatment.
*Results:* Baseline characteristics of groups were insignificantly different. General linear model repeated measures revealed no significant within subject effect for time × treatment interaction difference among two groups for quality of life score (p-value = 0.755), depression (p-value = 0.643) and anxiety (p-value = 0.150) scores among groups.
*Conclusions:* Our findings demonstrated that saffron could be as effective as fluoxetine in increasing IBS patients' quality of life with similar anti-depressive and anxiolytic effect among these patients. What might make saffron a proper medical treatment alternative for IBS is its rare side effects, wide range of use and greater patient compliance. However, further investigation and research in the area is recommended.



## 1. Introduction

Functional bowel disorders (FBDs) are a spectrum of chronic gastrointestinal (GI) disorders characterized by predominant symptoms or signs of abdominal pain, bloating, distention, and/or bowel habit abnormalities. Irritable Bowel Syndrome (IBS) is a FBD in which recurrent abdominal pain is associated with defecation or a change in bowel habits [1]. According to a 2012 meta-analysis on 80 studies, global prevalence of IBS is 11.2% (95% confidence interval (CI): 9.8%–12.8%), while it is more prevalent in the younger population (younger than 50 years old) and has a modestly higher odds ratio among women (OR = 1.67; 95% CI: 1.53–1.82) [2]. There are 4 main subtypes of IBS including: IBS-D (diarrhea predominant), IBS-C (constipation predominant), IBS-M (with mixed bowel habits), and IBS-U (unclassified). Multiple factors are believed to play a role in IBS pathogenesis such as early life psychological stressors, food intolerance, abnormal pain perception, abnormal brain-gut interaction, dysbiosis, small intestine bacterial overgrowth, visceral hypersensitivity, and increased gut mucosal immune activation [3–6]. Some of the common comorbid conditions accompanying IBS are psychological disorders such as anxiety and depression [7]. According to the Rome IV criteria, diagnosis of IBS is based on presence of recurrent abdominal pain for at least 1 day per week, on average, for the last 3 months associated with at least two of the following three: (1) defecation, (2) change in frequency of stool, (3) change in form of stool. Also, symptom onset must be more than 6 months prior to diagnosis [1].

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Saffron is dried stigma of the *Crocus sativus* L. flower, which has been long used as a spice because of its flavor, color, and aroma [8]. Main components of saffron include crocin, crocetin ester, picrocrocin and safranal [8,9]. Saffron has been traditionally used as anti-spasmodic, eupeptic, sedative, carminative, diaphoretic, expectorant, stomachic, stimulant, aphrodisiac, and abortifacient [10]. Saffron therapeutic effects on different diseases such as depression, anxiety, obsessive compulsive disorder, macular degeneration, and cancer have been recently investigated [11–17]. This phytomedicine has been shown to have therapeutic effects, especially on depression, among different populations and different associated conditions [18–28].

Treatment of IBS remains a challenge since sufficient data in some areas are not in hand. Moreover, unclear and unique pathophysiological interactions in individuals with IBS can cause different responses to treatment. Considering the association of psychological stressors and depression with IBS, alongside anti-depressive and anti-spasmodic properties of saffron, we hypothesized saffron can be beneficial in treatment of IBS. Since no gold standard medical treatment for IBS exists, the choice of comparison group (as the non-inferiority nature of study dictates) is a challenge, but fluoxetine was chosen for a number of reasons. Data for use of SSRIs in IBS symptoms are sometimes conflicting but mostly favorable. Fluoxetine, among other SSRIs, will not need a titration to achieve effective dose is IBS symptoms [29]. Similar anti-depressive and anxiolytic effects between fluoxetine and saffron exist [12]. The current study mainly aims to compare saffron and fluoxetine effects on IBS patient quality of life with regards to depression and anxiety and to investigate relative side effects.

## 2. Materials and methods

### 2.1. Study design

The current study was a randomized, double-blind and parallel group clinical trial. Trial was conducted at the Imam Hospital Complex (Tehran, Iran) outpatient clinic between June 2016 and June 2017. Participants were followed throughout a 6-week course and visited every 2 weeks. The Study protocol was approved by the institutional review board (IRB) of Tehran University of Medical Science (IR.TUMS.REC.1394.670) and conducted consistent with Declaration of Helsinki and subsequent revisions. The trial was registered at the Iranian registry of clinical trials (www.irct.ir; registration number: IRCT201509201556N81) prior to the study. Participant rights were fully explained and informed consent was obtained individually.

### 2.2. Participants

Patients aged between 18–55 years, who had a diagnosis of IBS according to ROME III criteria [30] were recruited. Patients were included if none of the following was present: any organic intestinal disease, intestinal infection, history of chronic colorectal diseases, history of major abdominal surgery, current pregnancy or lactation, being professional athletes or on bed rest, history of breast cancer (neither in the patient, nor in a family member), and severe psychosis. Moreover, patients who lately (during last three months prior to evaluation) used either antibiotics, anti-constipation or anti-diarrhea drugs, immune suppressors, metoclopramide, cisapride, diphenoxylate, opium, or non-steroidal-anti-inflammatory drugs (NSAIDs) were not included. The exclusion criteria of our study consisted of: dieting during the study, no desire to complete the study, and presenting severe adverse effects of the supplement. Assuming a mean difference of 5 on the IBS-Qol score between two groups, with a standard deviation (SD) of 6.5 on the same score, a power of 80%, a two tailed significance level of 0.05, and 20% dropout rate, 35 patients were recruited in each group.

### 2.3. Interventions

Patients underwent clinical and laboratory assessment prior to initiation of drug administration to evaluate Rome III criteria and to rule out any other possible causes of symptoms and to ascertain meeting the inclusion criteria. Evaluations include thorough medical, drug, and psychological history, physical examination, and indicated laboratory tests. Eligible participants were then randomized to two groups (namely saffron and fluoxetine groups). The saffron group received a capsule of saffron (each capsule containing 15 mg of saffron extract; the preparation protocol was according to Modabbernia et al. study [31] twice daily and the fluoxetine group received a fluoxetine capsule (Abidi, Iran, each capsule containing 20 mg fluoxetine) twice daily in the same manner as saffron. Treatments continued for 6 weeks. During the study course, participants were asked not to use neither psychotropic nor any behavioral intervention therapy.

### 2.4. Outcome

The primary outcome of our study was any changes in the IBS Quality of Life (IBS-Qol) questionnaire score during study course [32]. The secondary outcomes were changes in Hospital Anxiety and Depression Scale (HADS) questionnaire in each anxiety and depression domains. IBS-Qol questionnaire is a 34 item self-administered questionnaire with 1–5 scale answers designed and validated to assess overall IBS patient quality of life considering different domains (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, relationship) [32]. The HADS questionnaire is also a self-assessment scale developed and found to be a reliable instrument for detecting states of depression and anxiety in the setting of a hospital medical outpatient clinic. HADS questionnaire is a 14-item questionnaire assessing two domains of anxiety and depression, each of which are validated scales of attributed conditions [33]. Each participant filled the above mentioned questionnaires prior to commencement and at 2, 4, and 6 weeks of treatment. At each post-baseline visit, participants were requested to fill a 25 item adverse effect checklist form and were asked about any adverse effects not listed in the form [34]. They were also encouraged to contact our research team any time during course of the trial to report adverse effects.

### 2.5. Randomization and blinding

A random sequence was generated by an independent party who was not involved elsewhere in the study, with blocks of 6 and allocation ratio of one. The allocation was performed by receiving the group number according to the sequence in a sealed opaque envelope. Outcome assessors, participants and research coordinators were all blind to allocation. Both saffron and fluoxetine capsules were similar in hue, shape, texture, and smell.

### 2.6. Statistical analysis

Categorical variables and continuous variables were reported as frequency and mean ± S.D., respectively. Baseline variables of two groups were compared using either independent *t*-test (for continues variables), or chi-square test (or fisher exact test when appropriate, for categorical variables). To compare IBS-Qol and HADS score changes between and within groups, general linear model repeated measures were used. In case sphericity could not

be assumed (using Mauchly's test), Greenhouse-Geisser adjustment was used for degrees of freedom. At each post-baseline measurement, paired sample *t*-test was used to compare each questionnaire and each domain score to their baseline amount. Statistical analysis was undertaken using the Statistical Package of Social Science Software (SPSS version 20, IBM Company, USA).

## 3. Results

Eighty-eight patients were screened for the eligibility criteria and seventy patients among them met the criteria. Participants were randomized to saffron and fluoxetine groups and 35 patients in each group. Sixty-six participants completed the trial (Fig. 1). Comparison of groups, baseline characteristics wise, yielded no significant difference. Baseline characteristics of therapeutic groups are presented in Table 1.

### 3.1. Primary outcome

Baseline IBS-Qol mean scores among groups were not significantly different for saffron and fluoxetine (60.00 ± 9.15 vs. 59.18 ± 7.28 respectively [MD (95%CI) =−0.82(−3.25 to 4.89), p-value = 0.689]). According to the general linear model repeated measures, within subjects effect for time × treatment interaction on the IBS-Qol score was insignificant [F (1.33, 2.89) = 0.167, Greenhouse-Geisser p-value = 0.755]. However, the same model showed significant time effect for both saffron and fluoxetine groups in improving IBS-Qol scores [F (1.25, 1069) = 49.73, Greenhouse-Geisser p-value<0.001 and F (1.43, 1026) = 76.71, Greenhouse-Geisser p-value<0.001 respectively]. Means plot for treatment groups can be reviewed in Fig. 2. IBS-Qol score mean ± SD for each measurement can be reviewed in Table 2. Analysis of variances (ANOVA) for IBS subtypes in saffron group in terms of mean score increase revealed no significant difference among groups (F (2, 30) = 0.55, p-value = 0.580). Comparison of mean IBS-Qol score increase for each subtype among two groups is presented in Table 3.

### 3.2. Secondary outcomes

As Table 1 demonstrates, baseline scores in domains of HADS scale are insignificantly different between groups (HADS depression domain: 7.48 ± 1.80 vs 7.88 ± 1.85 [MD (95%CI) =−3.94(−1.29 to 0.50), p-value = 0.385]; HADS anxiety domain: 7.27 ± 1.72 vs 7.45 ± 1.60 [MD (95%CI) =−0.18(−1.00 to 0.64), p-value = 0.658]; for saffron and fluoxetine respectively). General linear model repeated measures demonstrated that in HADS score domains for saffron (F (1.92, 27.90) = 26.69, Greenhouse-Geisser p-value<0.001; F (2.06, 4.70) = 12.26, Greenhouse-Geisser p-value<0.001 for depression and anxiety domains respectively) and fluoxetine groups (F (1.39, 38.83) = 21.31, Greenhouse-Geisser p-value<0.001; F (1.95, 4.17) = 6.89, Greenhouse-Geisser p-value<0.001 for depression and anxiety domains respectively) improved significantly over course of treatment. But, the same model once again showed no significant effect for time × treatment interaction between groups for HADS depression and anxiety domains score (F(1.67, 0.53) = 0.39,Greenhouse-Geisser p-value = 0.643; and F (2.04, 0.93) = 1.92, Greenhouse-Geisser p-value = 0.150 respectively) (Figs. 3 and 4). Mean ± SD for each domain of HADS questionnaire during course of trial is presented in Table 2.

### 3.3. Adverse events

The frequency of adverse events did not differ significantly between treatment groups (Table 4). No serious adverse event occurred.

## 4. Discussion

IBS is a prevalent and expensive condition that significantly impairs health-related quality of life and reduces work productivity [34]. Different treatment options have been proposed for this syndrome, however, none can alleviate symptoms totally in every patient. Treatments suggested to be efficacious in the literature include: dietary interventions, life style modifications, probiotics,

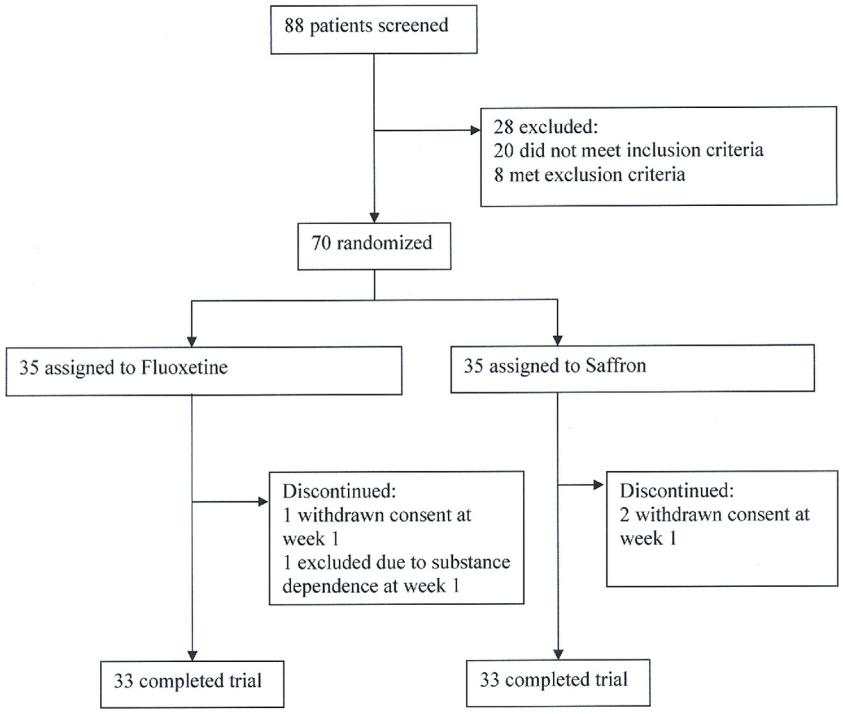


**Fig. 1.** Flow diagram of the trial.

**Table 1**
Participant baseline characteristics.

| Variable | | Treatment group | | | | |
|---|---|---|---|---|---|---|
| | | Saffron (n = 33) | | Fluoxetine (n = 33) | | |
| | | Count | Mean ± SD | Count | Mean ± SD | *p-value* |
| Gender | Male | 14 | | 13 | | 0.80 |
| | Female | 19 | | 20 | | |
| Age | | | 30.88 ± 5.33 | | 31.24 ± 5.27 | 0.78 |
| Body Mass Index | | | 27.48 ± 3.73 | | 28.48 ± 3.30 | 0.25 |
| Duration of IBS (years) | | | 3.73 ± 1.91 | | 4.97 ± 7.58 | 0.36 |
| Type of IBS | Constipation predominant | 13 | | 10 | | 0.73 |
| | Diarrhea predominant | 11 | | 12 | | |
| | Mixed | 9 | | 11 | | |
| Smoking | Yes | 15 | | 15 | | 1.0 |
| | No | 18 | | 18 | | |
| Education | Illiterate | 3 | | 3 | | 0.77 |
| | Primary school | 10 | | 10 | | |
| | High school diploma | 16 | | 13 | | |
| | Higher | 4 | | 7 | | |
| IBS-QoL baseline score | | | 60.00 ± 9.15 | | 59.18 ± 7.28 | 0.689 |
| HADS depression domain baseline score | | | 7.48 ± 1.80 | | 7.88 ± 1.85 | 0.385 |
| HADS anxiety domain baseline score | | | 7.27 ± 1.72 | | 7.45 ± 1.60 | 0.658 |

n = number; SD = standard deviation; IBS = irritable bowel syndrome; Qol = quality of life; HADS = hospital anxiety and depression scale.

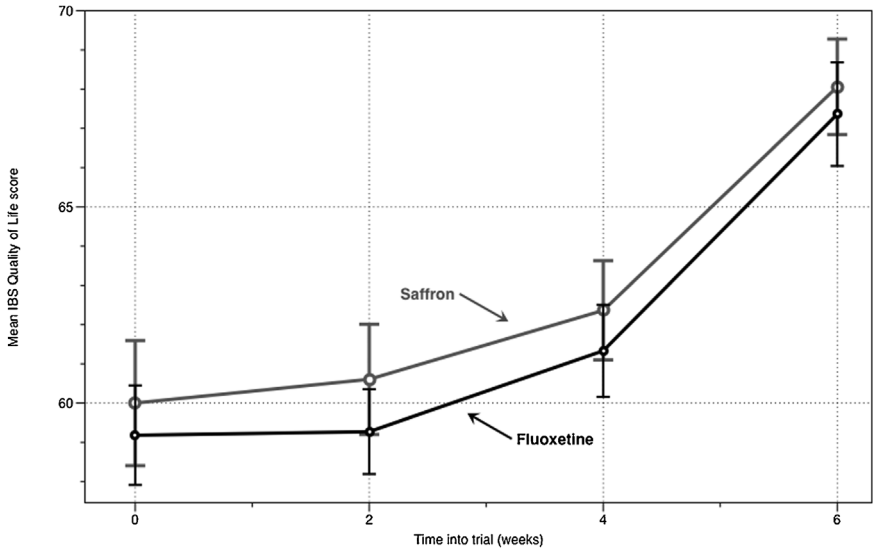


**Fig. 2.** Demonstrates means of IBS quality of life score for each group during trial course. Error bars represent Standard Error (SE).

chemically synthetized medications (such as laxatives, μ-opioid receptor agonist, antibiotics, selective 5-$HT_3$ antagonist, guanylate cyclase-c agonists, Tricyclic antidepressant agents (TCAs), selective serotonin reuptake inhibitors (SSRIs), and mast cell stabilizers), and psychological and behavioral treatments [1,29,35–39]. Although all of the above mentioned possible treatments are available, none have been established to be ideal because some can be solely used either in IBS-D or IBS-C, some only show efficacy in a portion of patients and some (especially chemical medications) have adverse effects [1]. The latter problem has initiated search for alternative treatments for IBS with a wider possible range of use and less side effects. Phytomedicine is a viable choice in this area as fewer side effects and more acceptability among patients exist.

Our study compared efficacy of saffron (*Crocus sativus*) extract and fluoxetine in improving IBS patients' quality of life. Results of the current study demonstrated no significant difference between saffron and fluoxetine in increasing quality of life while baseline characteristics among groups were similar. No significant difference was observed during the 6-week course of this study between groups in IBS-Qol score, however, both agents could significantly increase the score individually. On the other hand, secondary outcomes analysis revealed that saffron and fluoxetine reduce HADS depression and anxiety domain scores similarly while fluoxetine, as an SSRI. is treatment of choice for depression and anxiety situations. However, since anxiety and depression variables were not primary outcome of our study, many factors could be counted as possible cofounder of the latter finding such as 5HTT polymorphism [40]. To the best of our knowledge, this study is the first study to investigate effect of saffron on IBS, therefore, comparison with previous studies on the topic cannot take place. Importance of our findings is three folds. Firstly, according to the literature, no major side effect for saffron has been reported in the therapeutic dose [41,42] in spite of frequent SSRI side effects like

**Table 2**
Primary and secondary outcome measurements.

| Questionnaire | Weeks into treatment | Treatment Groups | | | | | |
|---|---|---|---|---|---|---|---|
| | | Saffron | | | Fluoxetine | | |
| | | Mean | SD | *p-value*[*] | Mean | SD | *p-value*[*] |
| IBS-Qol | Baseline | 60.00 | 9.15 | | 59.18 | 7.28 | |
| | 2 weeks | 60.61 | 8.07 | 0.033 | 59.27 | 6.21 | 0.753 |
| | 4 weeks | 62.36 | 7.27 | <0.001 | 61.33 | 6.74 | <0.001 |
| | 6 weeks | 68.06 | 7.00 | <0.001 | 67.36 | 7.58 | <0.001 |
| HADS-Depression domain | Baseline | 7.48 | 1.80 | | 7.88 | 1.85 | |
| | 2 weeks | 7.36 | 1.52 | 0.525 | 7.45 | 1.64 | <0.001 |
| | 4 weeks | 6.58 | 1.23 | <0.001 | 6.76 | 1.12 | <0.001 |
| | 6 weeks | 5.91 | 0.98 | <0.001 | 6.21 | 0.86 | <0.001 |
| HADS-Anxiety domain | Baseline | 7.27 | 1.72 | | 7.45 | 1.60 | |
| | 2 weeks | 7.03 | 1.76 | 0.058 | 7.61 | 1.34 | 0.201 |
| | 4 weeks | 6.79 | 1.62 | 0.001 | 7.39 | 1.30 | 0.690 |
| | 6 weeks | 6.55 | 1.50 | <0.001 | 6.94 | 0.90 | 0.019 |

SD = standard deviation, IBS = irritable bowel syndrome, QoL = quality of life, HADS = hospital anxiety and depression scale.
[*] *p-values* are for paired sample t-tests comparing values to their baseline amount.

**Table 3**
Mean IBS-Qol score increase for each IBS subtype.

| IBS subtype | Treatment group | | | | |
|---|---|---|---|---|---|
| | Saffron (n = 33) | | Fluoxetine (n = 33) | | |
| | mean | SE | mean | SE | p-value |
| IBS-C | 8.00 | 2.17 | 6.90 | 1.31 | 0.69 |
| IBS-D | 6.72 | 1.26 | 6.16 | 1.37 | 0.77 |
| IBS-M | 9.78 | 2.16 | 11.54 | 1.41 | 0.49 |

SE = Standard Error, IBS-C = Constipation dominant IBS, IBS-D = Diarrhea dominant IBS, IBS-M = Mix IBS.

sexual dysfunction, anxiety attenuation and GI upset [43]. Secondly, saffron showed an increase in quality of life with regards to depression and anxiety in this study. Finally, as an herbal agent and old medical plant, saffron is widely accepted and cultivated in different parts of the world like Middle East and India. This can improve patient compliance culturally [9].

Since no clear and definite image of IBS pathophysiology is available, understanding underlying mechanisms of saffron on IBS is a challenge. Reviewing saffron studies suggest it can play different roles in IBS pathology. The anti-depressant effects of saffron are well known and believed to be in part due to saffron's serotonergic, dopaminergic and generally monoamine oxidation inhibitory nature [24,44,45]. Similarly, just like TCAs and SSRIs, saffron can be efficacious in IBS that is thought to be a disorder of the brain-gut axis. The other pathways in which saffron may alleviate IBS symptoms are smooth muscle relaxation and anti-microbial properties [1,10,46]. This mechanism could be similar to peppermint oil and other smooth muscle relaxants [47]. It is also noteworthy that saffron exerts antimicrobial effects on Escherichia coli, which is among predominant species cultured from the upper GI tract of IBS patients with small intestine bacterial overgrowth [6,10].

### 4.1. Limitations

The small number of participants and short follow-up time period were the two major shortcomings of our study. Absence of a placebo group may also lessen the strength of our results, though the antidepressant effect of saffron has already been investigated in comparison with placebo. Given that no other study on saffron has been conducted as an IBS treatment so far, other trials with larger sample sizes and longer follow-up periods can strengthen our knowledge.

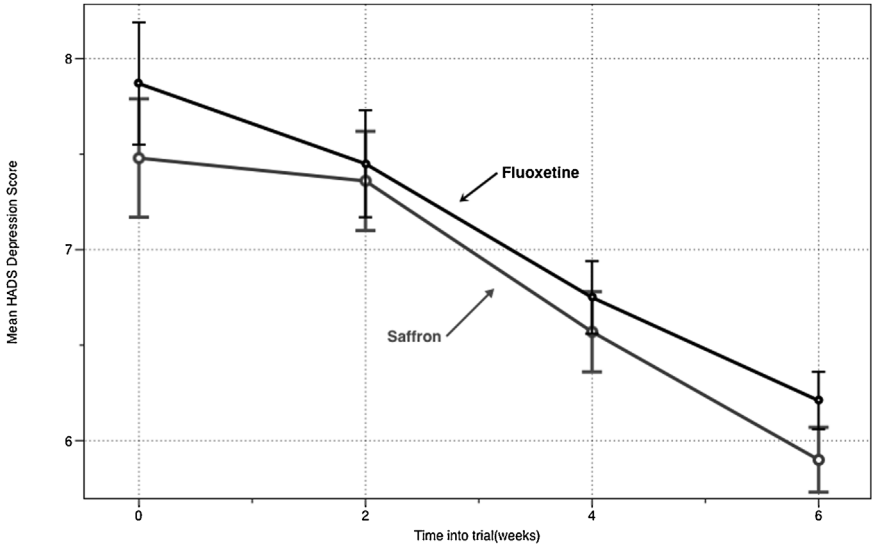


**Fig. 3.** Demonstrates means of Hamilton depression score for each group during trial course. Error bars represent Standard Error (SE).

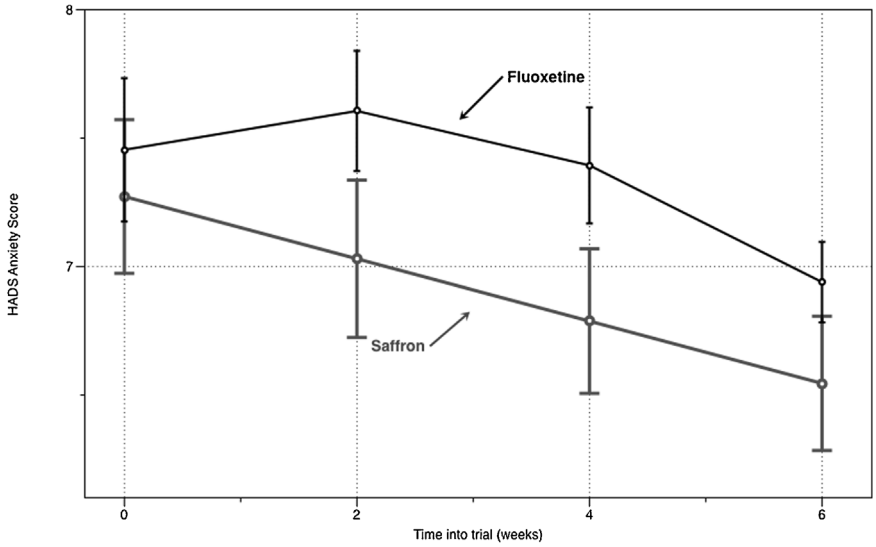


**Fig. 4.** Demonstrates means of Hamilton anxiety score for each group during trial course. Error bars represent Standard Error (SE).

**Table 4**
The frequency of different side effects in study population.

| Adverse event | Treatment groups | | | | |
|---|---|---|---|---|---|
| | Saffron (n = 33) | | Fluoxetine (n = 33) | | |
| | n | % | n | % | P-value* |
| Headache | 3 | 9 | 4 | 12.1 | 1.0 |
| Dry mouth | 3 | 9 | 4 | 12.1 | 1.0 |
| Nausea | 3 | 9 | 4 | 12.1 | 1.0 |
| Daytime drowsiness | 4 | 12.1 | 4 | 12.1 | 1.0 |
| Constipation | 3 | 9 | 3 | 9 | 1.0 |
| Sweating | 2 | 6 | 3 | 9 | 1.0 |
| Vomiting | 2 | 6 | 3 | 9 | 1.0 |

* Fisher's exact test.

### *4.2. Conclusion*

Our trial revealed that saffron may be an effective treatment for IBS with no significant difference with fluoxetine. However, further investigation and studies are recommended to fortify our conclusion. Saffron appears to be a promising treatment for IBS with few side effects, a wide range of potential mechanisms and high patient compliance.

## Author contributions

SA, principal investigator and data Management from October 2016-December 2017; BTN, KG, TRK and EV data collection and data analysis from October 2016-December 2017; AN and NED, writing the manuscript and data analysis from October 2016-December 2017.

## Disclosure of interests

None of the authors contributing to this article have any conflict of interest to report.

## Ethical statement

The Study protocol was approved by the institutional review board (IRB) of Tehran University of Medical Science (IR.TUMS.REC.1394.670) and conducted consistent with Declaration of Helsinki and subsequent revisions. The trial was registered at the Iranian registry of clinical trials (www.irct.ir; registration number: IRCT201509201556N81) prior to the study. Participant rights were fully explained and informed consent was obtained individually.

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