Thieme

Crocus sativus L. versus Citalopram in the Treatment of Major Depressive Disorder with Anxious Distress: A Double-Blind, Controlled Clinical Trial

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ABSTRACT

Introduction Saffron (Crocus sativus L.) has demonstrated antidepressant effects in clinical studies and extensive anxiolytic effects in experimental animal models.

Methods 66 patients with major depressive disorder accompanied by anxious distress were randomly assigned to receive either saffron (30 mg/day) or citalopram (40 mg/day) for 6 weeks. Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) were used to assess treatment effect during the trial.

Results 60 participants finished the study. Patients who received either saffron or citalopram showed significant improvement in scores of the Hamilton Rating Scale for Depression (P-value < 0.001 in both groups) and Hamilton Rating Scale for Anxiety (P-value < 0.001 in both groups). Comparison of score changes between the 2 trial arms showed no significant difference (P-value = 0.984). Frequency of side effects was not significantly different between the 2 groups.

Discussion The present study indicates saffron as a potential efficacious and tolerable treatment for major depressive disorder with anxious distress.

Introduction

Lifetime prevalence of major depression and anxiety disorders among adults in the United States (US) has been reported to be 16.6 and 28.8 percent, respectively [1]. In a large-scale study, 75 % of those with depression met the criteria for an anxiety disorder and 79 % of those with an anxiety disorder met the criteria for major depression during their lifetime [2]. The terminology mixed anxiety-depressive disorder (MADD) in DSM-IV-TR did not reappear in the appendix of DSM-5. Major depression, with anxious distress as a specifier, is the term currently being used as an evidence-based terminology [3].

Patients with depression and concomitant anxiety appear to have increased functional disability, significantly lower response and remission rates, longer illness duration, greater likelihood of treatment nonresponse, greater disruption of social, work and family life and a higher suicide risk compared to patients with non-anxious depression [4–9]. As a result, it is clinically beneficial to specify the precise presence and severity levels of anxious distress for treatment design and monitoring of the response to treatment in patients with concomitant major depressive disorder (MDD) and anxious distress [9].

* The first three authors contributed equally in this study.

Neurobiological evidence involving abnormalities of the serotonergic, noradrenergic, glutamatergic, and γ-aminobutyric acidergic (GABAergic) transmission are indicated to be involved in the pathophysiology of anxiety [10]. Hyperactivity within the amygdala is described to be one of the most consistent abnormalities in the presence of anxiety and depression in one person, which is shown to be in response to hyperactivity in the locus coeruleus [11, 12]. It cannot be concluded that the amygdala causes anxious depression, because depression and anxiety with neurotransmitter changes might cause alterations in the amygdala.

The ideal treatment for depression and anxiety should take the form of a single drug that is efficacious in the treatment of both disorders [13]. Treatment of depression and anxiety is not easily achieved with a single medication [14] because anxiety symptoms might occur during the anti-depressant treatment, although this side effect usually occurs only in the initial days of treatment and is commonly treated with benzodiazepine administration. In some cases where benzodiazepines are not indicated, quetiapine, olanzapine, an olanzapine-fluoxetine combination, pregabalin, and silexan could be assumed to have positive effects [15]. Safety in overdose is also important as there is a higher risk of suicide in patients with MDD with associated anxiety than in those with depression alone [16]. Selective serotonin reuptake inhibitors (SSRIs) are accepted as first-line treatment for this group of patients [17]. During SSRI therapy, the most troubling adverse effects are sexual dysfunction, gastrointestinal disturbances, weight gain, anxiety, agitation, and sleep disturbances [18–20]. Overall, citalopram appears to be the best-tolerated SSRI [21]. Agomelatine is also indicated to be efficacious in treating anxiety in major depression with few side effects, although more long-term studies seem to be needed to justify this medication [22]. Anticipated side effects of synthetic antidepressants decrease treatment compliance in many patients, resulting in inadequate response to the treatment course [18]. For this group of patients, switching medications, a combination therapy with benzodiazepines, psychological therapy or trying alternative herbal medicinal approaches seem to be reasonable steps [23]. Many effective herbal drugs, presented as "over-the-counter" psychotropics, offer advantages in terms of safety and present fewer side effects with better tolerability in comparison to conventional pharmacotherapies. A combination of imipramine and lavandula tincture has shown to be more effective than imipramine alone; saffron is indicated to have the same antidepressant efficacy compared to fluoxetine in patients with a prior history of PCI; short-term therapy with saffron capsules may safely and effectively improve some of the fluoxetine-induced sexual problems including arousal, lubrication, and pain [24–26]. Silexan (lavender) is another herbal medicine indicated to be efficacious and safe in the treatment of MADD [27]. Collected data of patients suffering from anxiety and depression shows that large numbers of patients, in some cases more than 50 %, reported using herbal, complementary and alternative medicine to treat their symptoms during the previous 12 months [28, 29]. Because not all frequently used phytomedicines are safe, targeting the safe and optimal dose of the employed herbal medicines should be considered carefully.

Targeting multiple neuroendocrine systems in comparison to a single neurotransmitter might be a more successful approach due to the complexity of the psychiatric disorders. In addition, various research suggests that the presence of different psychoactive compounds in a plant might have a synergistic effect, and that the biological effects of plants might rely on synergistic and polyvalent interactions between their components [30]. The mechanism of action of medicinal plants involves both central nervous system (CNS) activity and endocrine system functionality [31, 32], which may potentially impact the treatment of comorbid psychiatric disorders (e. g., if depression is treated, then anxiety may also resolve) [33].

Crocus sativus L., commonly known as saffron, is an herb cultivated in various parts of the world such as Iran, China, Spain, India and Greece. In traditional folk medicine, saffron is recommended as an aphrodisiac, antispasmodic, eupeptic, digestive, anticatarrhal, expectorant, antiseptic, antidepressant, anticancer and anticonvulsant [34, 35]. Crocus sativus has been approved for use in major depression by the Canadian Network for Mood and Anxiety Treatments [36]. Suggested saffron mechanisms of action are as follows: increase in re-uptake inhibition of monoamines (dopamine, norepinephrine, and serotonin), N-methyl-D-aspartic acid (NMDA) receptor antagonism, and GABA-α agonism [32]. Saffron and its active constituents that act on different CNS processes have been widely studied and various benefits have been scientifically proven, including antidepressant [37], anti-anxiety [38], neuroprotective in a rat model of Parkinson's disease [39], antagonizing memory impairments in rodents [40, 41], and enhancing spatial cognitive abilities after chronic cerebral hypoperfusion [42, 43]. Spice supplementation with saffron is revealed to be effective for improving depressive symptoms in non-clinically depressed populations [44]. In clinical studies, saffron not only had significantly greater antidepressant properties compared with placebo [45, 46], but it also was shown to be as efficient as conventional antidepressants such as imipramine and fluoxetine [47–49]. In addition, saffron has demonstrated extensive anxiolytic effects in experimental models [42, 50, 51].

We hypothesized that saffron would show satisfactory outcomes in treatment of MDD with concomitant anxiety distress. Thus, our main objective was to compare the tolerability, safety and efficacy of Crocus sativus to citalopram in the treatment of MDD with anxious distress using a double-blind, randomized controlled trial design.

Methods

Trial design and setting

The study was conducted as a multicenter, prospective, 6-week, parallel-group, double-blind, randomized clinical trial at the outpatient clinic of Baharloo hospital (Tehran University of Medical Sciences, Tehran, Iran) and Farshchian Hospital (Hamadan University of Medical Sciences, Hamadan, Iran) from January 2015 to April 2016. The trial protocol was registered at the Iranian registry of clinical trials (www.irct.ir; trial identifier with the IRCT database: IRCT201501041556N71) and was approved by the institutional review board (IRB) of the Tehran University of Medical Sciences protocol (Grant No. 27225).

Participants

Eligible patients were men and women aged 18–65 years with a diagnosis of mild to moderate major depression with anxious distress according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5), with a score < 19 on the 17-item Hamilton Rating Scale for Depression (HAM-D) for mild to moderate depression and a score < 24 in the 14-item Hamilton Rating Scale for Anxiety (HAM-A) to be of mild to moderate severity. Participants were recruited during routine visits of psychiatric clinics. Based on the inclusion criteria, patients were fully informed about the project. Assessment of patients was on a routine 2-week-interval visit based on a questionnaire derivative of the HAM-D and HAM-A rating scales. 2 experienced and senior psychiatrists rated the patients in psychiatric outpatient clinics.

Exclusion criteria

Receipt of any antidepressant medication during the previous month; receipt of electroconvulsive therapy (ECT) during the last 2 months; diagnosis of other mental disorders on the DSM-IV Axis I; alcohol or substance (with the exception of nicotine) dependence; severe depression or suicidal ideation (those who were judged to have substantial risk for suicide by the physician or scored > 2 on the suicide item of the HDRS); receipt of aspirin, anticoagulants or NSAIDs (Persian traditional medicine asserts that saffron at high dosages can induce abnormal bleeding); and any uncontrolled medical problem such as hypertension, hypothyroidism, or renal failure. Women who were nursing, pregnant, lactating, receiving OCP, or wanted to become pregnant in the near future were also excluded. In addition, any clinically significant deterioration in the condition of the subject from baseline would result in exclusion from the trial. The study was conducted in accordance with the established tenets of the Declaration of Helsinki and its subsequent revisions. After a complete description of the study details, the patients and their legally authorized representative provided informed consent in accordance with the procedures. The participants were informed that withdrawal from the study, at any time, was allowed without compromising their relationship with their health care provider.

Interventions

Eligible patients randomly received either citalopram (citalopram, Sobhan Darou, 20 mg capsules) or saffron (SaffroMood, IMPIRAN, containing 15 mg of saffron extract) in the same manner for 6 weeks. Following the selection phase, a capsule of saffron (15 mg) or a capsule of citalopram (20 mg) was given for the first week, after which the dose was increased to 2 capsules of saffron or citalopram per day for the rest of the trial. Therefore, the prominent dose of citalopram and saffron was 40 mg/day and 30 mg/day, respectively. Participants were not allowed to use any other psychotropic medication or undergo behavioral intervention therapy during the trial course. Medication adherence was measured using weekly capsule counts justified against participant reports of medication intake to calculate the proportion of dispensed medication doses that were actually ingested. Preparation of Crocus sativus stigma extract is described in detail in the Modabbernia et al. study [52]. The stigma extract was standardized based on crocin by means of spectrophotometry. The crocin value is expressed as a direct reading of the absorbance at about 440 nm. Each capsule had 1.65–1.75 mg crocin.

Primary and secondary outcome measures

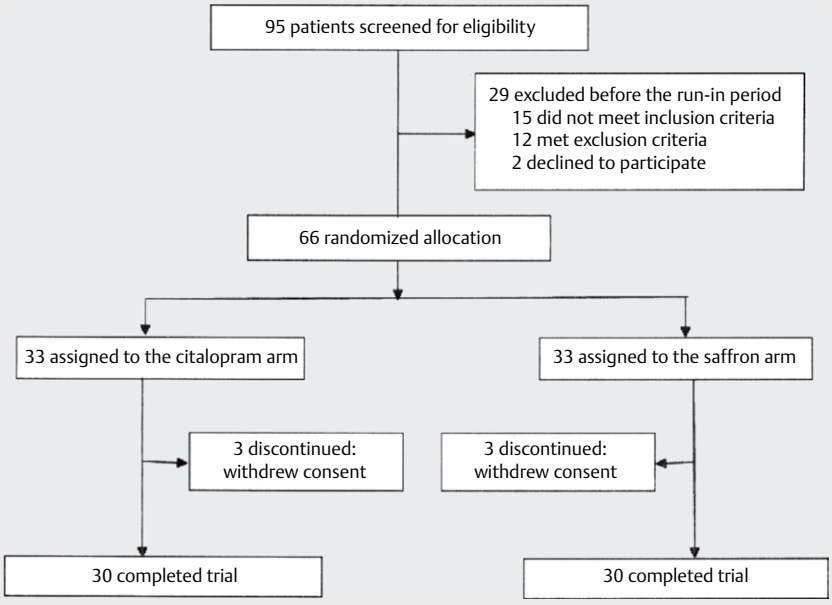
Participants were evaluated using HAM-D and HAM-A at baseline and at weeks 2, 4 and 6 post-intervention. HAM-D is a validated 17-item rating scale that has been widely applied in psychiatric studies to measure the severity of depressive symptoms and also has been used to evaluate treatment efficacy and severity of depressive symptoms in several clinical trials in Iran [53–57]. HAM-A is a 14-parameter rating scale to assess the patient's response to a course of treatment, and by administering the scale serially, results of drug treatment or psychotherapy could be documented. The primary outcome measure was to evaluate the efficacy of saffron in improving depressive and anxiety symptoms compared with citalopram during the trial course using a general, linear, repeated-measures model. The secondary outcome measures of this trial were comparison of changes in the HAM-D and the HAM-A score from baseline to each time point, response to treatment (defined as ≥ 50 % reduction in the HAM-D score) and remission (defined as HAM-D score ≤ 7) rates between the treatment groups, and evaluation of the antidepressant effects of saffron specifically. Treatment failure was defined as persistence of clinical signs and symptoms. Adverse events were systematically evaluated at each time point using a checklist. Furthermore, patients were first asked an open-ended question about any adverse event that was not mentioned on the checklist. Patients were also asked to immediately inform the research team of any unexpected symptom during the trial course. Electrocardiography was performed if patients complained of any typical or atypical cardiac syndromes. 2 experienced and senior psychiatrists rated the patients. We used the kappa correlation method to calculate inter-rater reliability. Interviews of raters with 6 random patients diagnosed with MDD and anxious distress resulted in > 90 % inter-rater reliability.

Sample size determination

A minimal sample size of 58 (29 patients in each group) was calculated assuming a clinically significant difference of 3 on the HAM-D score, an SD of 4 (based on our pilot study), a two-sided significance level of 0.05, and a power of 80 %. A final sample size of 65 was planned, assuming an attrition rate of 10 %. To achieve a perfect score ratio of 1.0 for the saffron and citalopram allocation groups, the required sample size was calculated at 66 patients (33 patients in each group).

Protocol of randomization and drug allocation

An independent group that was not involved elsewhere in the study was in charge of generation of randomization codes, using a computerized random number generator (blocks of 4, allocation ratio 1:1). Concealment of allocation was performed through sequentially numbered and sealed opaque and stapled packages. Separate people were responsible for random allocation and rating of patients. Citalopram and saffron capsules were visually identical in terms of shape, odor, and color. The participants, the physician who referred the patients, the physician who prescribed the medications, the investigators who rated the participants and the statistician were all blinded to the treatment group assignment.



▶ **Fig. 1** Flow diagram representing case selection for the trial program.

Statistical methods

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS Version 20.0 IBM Corporation, Armonk, NY, USA). All analyses were performed based on the intention-to-treat principles with 3 post-baseline measurements. Categorical variables and continuous variables were reported as frequency (percentage) and mean ± SD, respectively. Baseline continuous variables were compared using the independent t-test. The mean difference (MD) between the saffron and the citalopram group was reported as MD (95 % CI). A two-factor repeated-measures analysis of variance (ANOVA) was used to evaluate time × treatment interaction. Results of Greenhouse-Geisser adjustment were reported if Mauchly's test of sphericity was significant. The independent t-test and Cohen's d effect size were used to compare score changes from baseline to each time interval between the 2 study groups. To compare HAM-D and HAM-A scores at baseline with each time point in each group, the paired t-test was used. Categorical variables were compared using the χ^2 test or Fisher's exact test. The Kaplan-Meier estimation with log-rank test was used for comparison of the time needed to partially respond to treatment between groups. P-values < 0.05 were considered the bare minimum to flag statistically significant correlations.

Results

A total of 94 patients were screened for eligibility: 66 patients were randomly assigned to receive either saffron (n = 33) or citalopram (n = 33), but only 60 patients (divided into 2 equal groups of 30 for each arm) completed the trial program and remained compliant with their treatment during the running study period. Those 60 had 2 post-baseline measurements at weeks 2, 4 and 6 of the follow-up period (▶ **Fig. 1**). The 6 patients who discontinued the study withdrew consent for personal reasons before the first evaluation in week 2. As summarized in ▶ **Table 1**, baseline recorded data were comparable between the saffron and the citalopram treatment arms.

HAM-A score

Baseline HAM-A scores were not significantly different between the citalopram and the saffron intervention groups: mean citalopram-saffron difference (MD) (95 %CI) = − 0.57 (− 2.45 to 1.31); t (58) = − 0.607; P-value = 0.547 (▶ **Table 1**). Two-factor repeated-measures ANOVA demonstrated that the effect of time × intervention interaction term on reducing the HAM-D scores was not statistically significant during the follow-up period: F (2.49, 144.41) = 0.005; p = 0.999 (▶ **Fig. 2**). In line with this observation, improvements made in the HAM-A score were not significantly different at week 2, 4 or 6 post-intervention between the treatment groups (▶ **Fig. 2** and ▶ **Table 2**). However, there were significant improvements in the HAM-A score at weeks 2, 4 and 6 for both the citalopram and the saffron treatment groups (▶ **Table 3**).

HAM-D score

A two-factor generalized linear model repeated measures on the HAM-D score (effect: time × treatment interaction term) did not demonstrate a significant reducing effect on the severity of depressive symptoms ($F_{2.42,\ 140.66}$ = 0.393, P-value = 0.715, ▶ **Fig. 3**). Similar to the HAM-A score, there were no statistically significant differences in baseline HAM-D scores between the citalopram and the saffron arms [17.50 ± 0.63 vs. 17.20 ± 1.40; respectively, MD for citalopram-saffron (95 % CI) = 0.30 (− 0.26 to 0.86), t (58) = 1.07, P-value = 0.289]. Reductions in HAM-D scores were comparable across the citalopram and saffron intervention arms by week 2 (2.17 ± 2.63 vs. 1.83 ± 3.70, p = 0.689), week 4 (5.97 ± 3.42 vs. 5.07 ± 5.11, p = 0.689) and week 6 (11.27 ± 3.67 vs. 10.13 ± 5.96, p = 0.380) of the follow-up period (▶ **Table 2**). Moreover, score re-

▶ **Table 1** Baseline characteristics of study population.

Item	Citalopram Arm (n = 30)	Saffron Arm (n = 30)	*P*-value
Age (y)	34.17 ± 10.41	37.90 ± 11.56	0.194
Sex, Male (%)	15 (50)	11 (36.7)	0.297
Marital Status, n (%)			0.312α
Married	23 (76.7)	19 (63.3)	
Single	6 (20)	10 (33.3)	
Widow/Widower	0	1 (3.3)	
Divorcee	1 (3.3)	0	
Educational Status, n (%)			0.376α
Illiterate	1 (3.3)	4 (13.3)	
Primary School	8 (26.7)	7 (23.3)	
Secondary School	5 (16.7)	9 (30)	
Diploma	9 (30)	6 (20)	
University Degree	7 (23.3)	4 (13.3)	
Occupation			0.210α
Unemployed	0	3 (10)	
Worker	3 (10)	6 (20)	
Clerk	5 (16.7)	2 (6.7)	
Student	6 (20)	2 (6.7)	
Housewife	13 (43.3)	14 (46.7)	
Other	3 (10)	3 (10)	
Duration of Illness, months, mean ± SD	3.33 ± 1.35	3.93 ± 1.64	0.127
Addiction, n (%)			0.353α
Yes	1 (3.3)	4 (13.3)	
No	29 (96.7)	26 (86.7)	
Baseline HAM-A Score	19.10 ± 2.60	19.67 ± 4.40	0.547
Baseline HAM-D Score	17.50 ± 0.63	17.20 ± 1.40	0.289

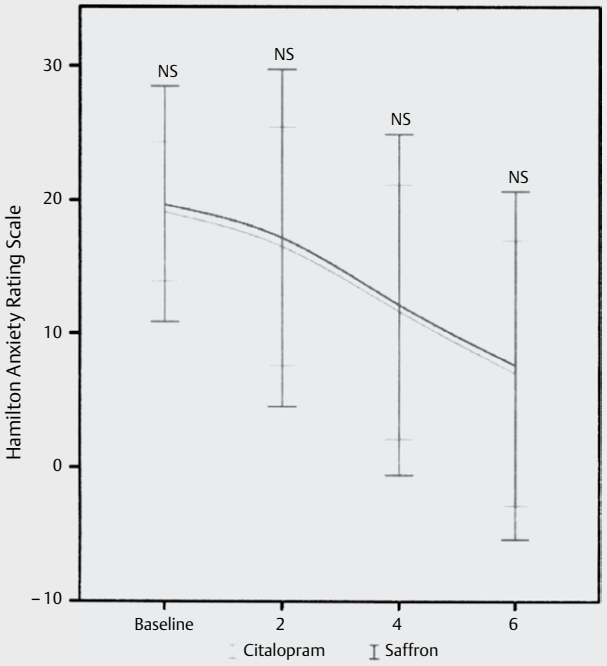
HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression

α *P*-value reported by Fisher's exact test

ductions for the HAM-D score were significant for both groups of individuals receiving citalopram and saffron at each post-baseline checkpoint at week 2, 4 and 6 (▶ **Table 3**).

Treatment response and remission rates

As ▶ **Table 4** demonstrates, the number of responses (≥ 50 % reduction in the HAM-D score) and remissions (HAM-D ≤ 7) at weeks 2, 4 and 6 post-intervention were not statistically different among individuals receiving either citalopram or saffron (▶ **Table 4**). However, the remission rate was not far from being significant after 6 weeks (P-value = 0.072). Average (± SD) time to response and time to remission intervals in the entire study population were 5.23 ± 0.17 and 5.57 ± 0.13, respectively. Using Kaplan-Meier estimate curves, we observed participants in the saffron arm display comparable time-to-response periods compared with those consuming citalopram (mean ± SD time to response: 5.07 ± 0.25 vs. 5.40 ± 0.22 weeks, respectively; log-rank p = 0.706). Moreover, patients who were on saffron or citalopram also achieved similar average times to remission (5.40 ± 0.22 vs. 5.73 ± 0.13; log-rank p = 0.306).



▶ **Fig. 2** Comparison of mean ± SD of Hamilton Rating Scale for Anxiety scores at baseline and post-intervention with citalopram or saffron over time. (NS denotes the nonsignificant difference in the Hamilton Rating Scale for Anxiety scores between the trial arms at each measurement).

Adverse events

Aside from vertigo that seemed to occur more frequently in the citalopram arm (although was not statistically significant), frequencies of other observed adverse outcomes were comparable across the intervention groups (▶ **Table 5**). No symptoms of adverse cardiovascular events occurred in the study population, which was confirmed by physical examination and normal ECG recordings. No serious adverse events or deaths were observed. Vertigo and anger/rage were the most commonly observed adverse symptoms in the citalopram arm. By comparison, headache and nausea/vomiting were the only adverse outcomes affecting the individuals receiving saffron, each affecting 2 of the patients. No treatment discontinuation was observed as a result of drug adverse events. Symptoms had begun to decrease by the third week and were sustained until study completion (▶ **Table 5**).

Discussion

The present study provides evidence for satisfactory outcomes with saffron in the treatment of mild to moderate MDD with anxious distress (15 mg, 2 capsules per day). In this double-blind and randomized clinical study of Crocus sativus stigma vs. citalopram in the treatment of mild to moderate depression with concomitant anxiety, Crocus sativus was demonstrated to be as safe and effective as citalopram for up to 6 weeks after treatment initiation. The clinical relevance of this finding was emphasized by the improvements seen in HAM-D and HAM-A measures in both groups. The response rate (≥ 50 % reduction in the HAM-D score) and remission rate

▶ **Table 2** Comparison of score changes between the 2 trial arms using the Independent *t*-test.

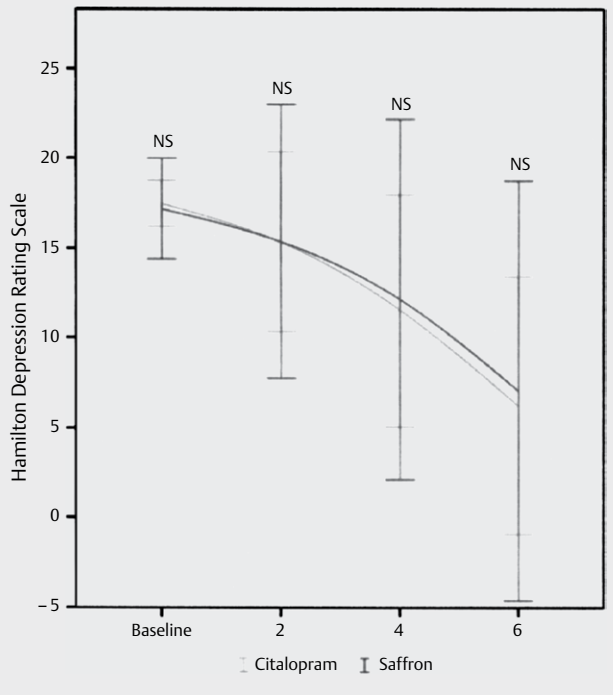
Outcome	Citalopram Arm (n = 30)	Saffron Arm (n = 30)	Mean Difference: Citalopram-Saffron (95 % CI)	Cohen's *d*	*P*-Value
HAM-A Score					
Change from baseline to week 2, mean ± SD	2.60 ± 4.98	2.50 ± 4.49	0.10 (−2.35 to 2.55)	0.02	0.935
Change from baseline to week 4, mean ± SD	7.47 ± 5.22	7.53 ± 5.56	−0.07 (−2.86 to 2.72)	−0.01	0.962
Change from baseline to week 6, mean ± SD	12.07 ± 6.03	12.03 ± 7.02	0.03 (−3.35 to 3.42)	0.01	0.984
HAM-D Score					
Change from baseline to week 2, mean ± SD	2.17 ± 2.63	1.83 ± 3.70	0.33 (−1.33 to 2.00)	0.11	0.689
Change from baseline to week 4, mean ± SD	5.97 ± 3.42	5.07 ± 5.11	0.90 (−1.35 to 3.15)	0.21	0.427
Change from baseline to week 6, mean ± SD	11.27 ± 3.67	10.13 ± 5.96	1.13 (−1.44 to 3.70)	0.23	0.380

Abbreviations are given at ▶ **Table 1**

▶ **Table 3** Comparison of the scores at each time point with the baseline values in each trial arm using the paired *t*-test.

Outcome	Score at Week 2, Mean ± SD	*P*-Value	Score at Week 4, Mean ± SD	*P*-Value	Score at Week 6, Mean ± SD	*P*-Value
HAM-A Score						
Citalopram Arm (n = 30)	16.50 ± 4.46	0.008	11.63 ± 4.75	< 0.001	7.03 ± 4.96	< 0.001
Saffron Arm (n = 30)	17.17 ± 6.30	0.005	12.13 ± 6.37	< 0.001	7.63 ± 6.52	< 0.001
HAM-D Score						
Citalopram Arm (n = 30)	15.33 ± 2.51	< 0.001	11.53 ± 3.22	< 0.001	6.23 ± 3.59	< 0.001
Saffron Arm (n = 30)	15.37 ± 3.81	0.011	12.13 ± 5.01	< 0.001	7.07 ± 5.84	< 0.001

Abbreviations are given at ▶ **Table 1**



▶ **Fig. 3** Comparison of mean ± SD of Hamilton Rating Scale for Depression scores at baseline and post-intervention with citalopram or saffron over time. (NS denotes the nonsignificant difference in the Hamilton Rating Scale for Depression scores between the trial arms at each measurement).

(HAM-D ≤ 7) were not significantly different between patients receiving either saffron or citalopram, and although the comparison of remission rates after 6 weeks (P-value = 0.072) might be of interest, it might never be significant. These findings are especially noteworthy because the baseline characteristics of patients were comparable across the 2 trial arms.

After decades of predominant reliance on synthetic antidepressants, complementary psychopharmacology research is becoming an area of interest due to safety concerns and side effects of conventional antidepressant treatments. Phytomedicines are becoming increasingly popular as alternatives to approved medications [33]. Better cultural acceptability and largely better profiles of side effects has made complementary medicine the backbone of therapy predominantly in primary health care of developing countries and for approximately 75–80 % of the world population. Recently, developed nations have also experienced a major growth in complementary medicine use [58].

To the best of our knowledge, the current study is the first clinical trial of saffron in treatment of MDD with anxious distress. Results of previous clinical trials showed that saffron is more effective than placebo therapy [45, 46] and can be compared with fluoxetine [48] and imipramine [49] in the treatment of major depression at the same dose used in the current study. Fluoxetine is as effective as either petal [47] or stigma [48] of saffron. At present, it is not possible to draw valid comparisons with results from other trials in the field of anxiety although animal studies have shown significant saffron effects as an anxiolytic agent [42].

Our results show the same efficacy in treatment with citalopram (40 mg/day) or saffron (30 mg/day). It can be conjectured that high-

▶ **Table 4** Comparison of response to treatment and remission rates at different study points between the 2 trial arms.

Outcome	Citalopram Arm (n = 20)	Saffron Arm (n = 20)	*P*-value[α]	Odds ratio
HAM-D				
Number (%) of responders, at week 2	1 (3.3)	3 (10)	0.612[α]	0.64
Number (%) of responders, at week 4	7 (23.3)	11 (36.7)	0.260	0.74
Number (%) of responders, at week 6	27 (90)	22 (73.3)	0.181[α]	1.62
Number (%) of remissions, at week 2	0	2 (6.7)	0.492	n/a
Number (%) of remissions, at week 4	4 (13.3)	7 (23.3)	0.506	0.738
Number (%) of remissions, at week 6	26 (86.7)	19 (63.3)	0.072[α]	1.737

α reported by Fisher's exact test. n/a: not applicable

▶ **Table 5** Frequency [n (%)] of unwanted side effects among the 2 trial arms.

Side effect	Citalopram Arm (n = 30)	Saffron Arm (n = 30)	*P*-Value[α]
Headache	2 (6.7)	2 (6.7)	1.000
Vertigo	5 (16.7)	0	0.052
Nausea/Vomiting	2 (6.7)	2 (6.7)	1.000
Drowsiness	2 (6.7)	0	0.492
Gastritis	2 (6.7)	0	0.492
Anger/Rage	3 (10.0)	0	0.237
Palpitation	1 (3.3)	0	1.000

α reported by Fisher's exact test

Abbreviations are given at ▶ **Table 1**

er doses of saffron might exert even greater beneficial effects, as higher doses of saffron showed greater results in 2 articles on sexual function [52, 59]. At this point, we recommend further clinical trials with higher doses of saffron and greater trial duration to evaluate the effect of higher doses in patients with MDD with anxious distress. The mechanism of action of saffron is not entirely known. According to previous studies, anti-inflammatory, antioxidant, HPA-modulating, neuroprotective effects, reuptake inhibition of monoamines, NMDA antagonism, improved brain-derived neurotrophic factor signaling, and serotonin reuptake inhibition in synapses may be among the main mechanistic factors [60–63].

In terms of safety, no significant difference was detected between the 2 trial arms in the frequency of adverse events. In a review of clinical trials on saffron, no severe adverse events were reported associated with the use of saffron supplementation. The Jadad score for all the trials included in the review was 5, indicating high-quality trials. Headache, nausea, anxiety, and decreased appetite were the most frequently reported adverse effects [61]. Compared with synthetic antidepressants, the long-term safety profile of saffron seems positive, although this requires further investigation. Long-term studies of saffron have indicated few adverse effects at 22 weeks and up to 1 year after initiation of the therapy [64, 65]. A small number of adverse effects have been reported after high dose administration of saffron in laboratory settings, but to the best of our knowledge, no serious adverse event has been observed to date in well-designed clinical trials investigating therapeutic doses of saffron in various disorders [51, 66, 67]. In an animal study, LD50 values of saffron stigma and petal extracts were 1.6 g/kg and 6 g/kg, respectively [66], which is much higher than routine daily or therapeutic doses, indicating no serious concern regarding overdose by saffron therapy. Regarding the cardiovascular system, saffron is not only safe but also has some valuable cardioprotective properties such as improving lipid profiles, decreasing blood pressure, and inhibiting atherosclerotic plaque formation [68]. Drawing a firm conclusion about using saffron as a first-line treatment in MDD with anxious distress is not possible yet largely due to a lack of precise data on the mechanism of action of saffron. Endurable side effects of saffron may well confirm the application of saffron as an alternative medication in Persian traditional medicine, which justifies its importance as a drug of the future.

Limitations

Even though the present study has several advantages such as the multicenter, double-blind, randomized design and the rigorous adjustment for baseline clinical variables, various limitations should be addressed to prevent over-generalization of the findings. Although the superiority of saffron in relation to placebo for treatment of depression has been well documented [45, 46], the lack of a placebo control trial arm and the use of only a fixed dose of saffron therapy are considered as being among the main limitations. The study population size was relatively small and the short follow-up period should also be considered.

Conclusion

The current study indicates that during a 6-week trial period, administration of saffron is as safe and as effective as citalopram in the treatment of MDD with anxious distress. It might be time to look more seriously at this valuable herbal medication. This observation suggests saffron as a possibly useful strategy for monotherapy or as part of alternative management in patients with MDD and concomitant anxious distress.

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Conflicts of Interest

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

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