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# Hydro-alcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial

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**Abstract**

Depressive disorders are very common in clinical practice, with approximately 11.3 of all adults afflicted during any a year. Saffron is the world's most expensive spice and apart from its traditional value as a food additive, recent studies indicate several therapeutic effects for saffron. It is used for depression in Persian traditional medicine. Our objective was to compare the efficacy of hydro-alcoholic extract of *Crocus sativus* (stigma) with fluoxetine in the treatment of mild to moderate depression in a 6-week double-blind, randomized trial. Forty adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition for major depression based on the structured clinical interview for DSM-IV and with mild to moderate depression participated in the trial. In this double-blind, single-center trial and randomized trial, patients were randomly assigned to receive capsules of saffron 30 mg/day (BD) (Group 1) and capsule of fluoxetine 20 mg/day (BD) (Group 2) for a 6-week study. Saffron at this dose was found to be effective similar to fluoxetine in the treatment of mild to moderate depression ($F = 0.13$, d.f. = 1, $P = 0.71$). There were no significant differences in the two groups in terms of observed side effects. The results of this study indicate the efficacy of *Crocus sativus* in the treatment of mild to moderate depression. A large-scale trial is justified.


*Keywords:* *Crocus sativus*; Depression; Fluoxetine; Herbal medicine; Saffron; Stigma

## 1. Introduction

Depression, which is thought to result from biochemical changes in the brain, is a common disease of adulthood. This affective disorder afflicts about 5% of the adult population in the USA at any specific time (Judd, 1995). As defined by the American Psychiatric Association, depression is a heterogeneous disorder often manifested with symptoms at the psychological, behavioral and physiological levels (American Psychiatric Association, 1994). The advent of the first antidepressants—the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) in the 1950s and 1960s represented a dramatic leap forward in the clinical management of depression. The subsequent development of the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine in the past decade and a half has greatly enhanced the treatment of depression by offering patients medications that are as effective as the older agents, but are generally more tolerable and safer in an overdose. The introduction of atypical antidepressants, such as bupropion, nefazadone, and mirtazapine, has added substantially to the available pharmacopoeia for depression (Donoghue and Tylee, 1996; Mac Donald, 1997). Concurrent with research into the neurobiology of depression comes the necessity to seek improved clinical outcomes for our patients. Nearly one-third of patients receive no benefit, and one-third does not experience com-

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plete remission following an initial monotherapy trial with an antidepressant. Treatment resistance therefore remains a considerable problem, and the goal of treatment must be full remission, and not just symptom improvement (Richelson, 1994; Demyttenaere, 1997). Plant extracts are some of the most attractive sources of new drugs and have been shown to produce promising results for the treatment of depression (Ernst, 1995; De Smet and Nolen, 1996). As a therapeutically plant, saffron (*Crocus sativus* L. that belongs to the Iridaceae family) is considered an excellent stomach ailment and an antispasmodic, helps digestion and increases appetite. It also relieves renal colic, reduces stomachaches and relieves tension. In Persian tradition medicine is used for depression. Recent studies indicate its potential as an anti cancer agent and memory enhancer (Rios et al., 1996; Abe and Saito, 2000; Karimi et al., 2001; Abdullaev, 2002; Hosseinzadeh and Younesi, 2002). Many Persian medicinal plants textbooks refer to its antidepressant effect whereas there is no evidence-based document. Our objective was to compare the efficacy of saffron with fluoxetine in the treatment of mild to moderate depression in a 6-week double-blind and randomized trial.

## 2. Methods

This was a 6-week randomized and double-blind clinical trial. The investigation was conducted in the outpatient clinic of Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran, between January 2002 and March 2004.

### 2.1. Patients

Forty adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994) for major depression based on the structured clinical interview for DSM-IV participated in the trial. Patients have a baseline Hamilton Rating Scale for Depression (HAM-D 17-item) (Hamilton, 1960) score of at least 18. Prospective participants with the following DSM IV diagnosis were excluded: current cognitive disorder in the last year; or current or past history of bipolar disorder, schizophrenia and schizotypal personality disorder. Patients were required to be free of all psychotropic medications for at least 4 weeks before study entry. Patients were selected to range in age from 18 to 55 years of age. As depression is a serious and potentially life threatening condition and the participants were outpatients so extensive safeguards were needed. Patients were excluded if they posed a significant risk of suicide at any time during participation. Persons who scored greater than two on the suicide item of the HAM-D, or who were judged to have significant suicidal ideation or potential in the view of an investigator were excluded. Further, any clinically significant deterioration in the condition of the subject from baseline would result in exclusion. Those who left the study before completion were offered alternative and standard care immediately. Pregnant women or women not using medically accepted means of birth control were excluded. The trial was performed in accordance with the declaration of Helsinki and subsequent revisions and approved by ethics committee at Tehran University of Medical Sciences and Psychiatric Research Center. Written informed consents were obtained before entering into the study.

### 2.2. Saffron capsule preparation

The saffron was used in this study was dedicated by Novin Zaferan Co. (Mashhad, Iran) and was identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The part of *Crocus sativus* that are being used as additive and also herbal medicine is stigma. The stigma's extract was prepared as follow: 120 g of dried and milled stigmas were extracted with 1800 ml ethanol (80%) by percolation procedure in three steps then the ethanolic extract was dried by evaporation in temperature between 35 and 40 °C. Each capsule had dried extract of saffron (15 mg), lactose (filler), magnesium stearate (lubricant), and sodium starch glycolate (disintegrant). The dose of each capsule was calculated according to an animal study (Karimi et al., 2001). The extract was standardized by safranal. Each capsule had 0.30–0.35 mg safranal.

### 2.3. Study design

Patients underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview and a medical history. Patients were randomized to receive capsule of saffron or capsule of fluoxetine in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until the point of allocation. The randomization and allocation process was done by the pharmacist of the Roozbeh hospital. In this double-blind, single-center trial, patients were randomly assigned to receive capsule saffron 30 mg/day (BD)(Group 1) or capsule fluoxetine 20 mg/day (BD) (Group 2) for a 6-week study. Patients were assessed by a third year resident of psychiatry at baseline and after 1, 2, 4 and 6 weeks after the medication started. The principal measure of the outcome was the 17-item HAM-D. The rater used standardized instructions in the use of HAM-D. The mean decrease in HAM-D score from baseline was used as the main outcome measure of response of depression to treatment. Throughout the study the person who administrated the medications, rater and patients were blind to assignments. No significant differences were identified among patients randomly assigned to the Group 1 or 2 conditions with regard to basic demographic data including age and gender (Table 1). Thirty-eight patients completed the trial. In the saffron and fluoxetine group the number of dropouts was one patient. No significant difference was observed in the two groups in terms of dropout ($P = 1.51$).

Table 1
Baseline data of participants

| | Saffron group | Fluoxetine group |
|---|---|---|
| Women | 9 | 11 |
| Men | 11 | 9 |
| Age (Mean ± S.D.) (year) | 37.30 ± 8.56 | 36.5 ± 7.27 |

Table 2
Clinical complications and side effects were reported as number per group

| Side effects | Saffron | Fluoxetine | *P* |
|---|---|---|---|
| Anxiety | 3 | 6 | 0.45 |
| Decreased appetite | 2 | 5 | 0.40 |
| Increased appetite | 5 | 2 | 0.40 |
| Sedation | 1 | 0 | 1.00 |
| Nausea | 2 | 4 | 0.66 |
| Headache | 3 | 6 | 0.45 |
| Sexual dysfunction | 0 | 4 | 0.10 |
| Tremor | 0 | 4 | 0.10 |
| Sweating | 0 | 3 | 0.23 |

### 2.4. Side effects

Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on day 3, 7, 14, 21, 28 and 42 (Table 2).

### 2.5. Statistical analysis

A two-way repeated measures analysis of variance (time–treatment interaction) was used. The two groups as a between-subjects factor (group) and the five weekly measurements during treatment as the within-subjects factor (time) were considered. This was done for HAM-D total scores. In addition, a one-way repeated measures analysis of variance with a two-tailed post-hoc Tukey mean comparison test were performed in the change from baseline for HAM-D scores in each group. To compare the two groups at baseline and the outcome of two groups at the end of the trial, an unpaired Student's *t*-test with a two-sided *P*-value was used. Results are presented as mean ± S.E.M. Differences were considered significant with $P < 0.05$. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test (two-sided) was performed. To consider, $a = 0.05$, $\beta = 0.2$, the final difference between the two groups at least score of five on the HAM-D total scores that is clinically detectable, $S = 5$ and power = 80%, the sample size was calculated at least 15 in each group. Intention to treat (ITT) analysis with last observation carried forward (LOCF) procedure was performed.

## 3. Results

### 3.1. Efficacy: saffron versus fluoxetine

The mean ± S.E.M. scores of two groups of patients are shown in Fig. 1. There were no significant differences between the two groups in week 0 (baseline) on the Hamilton Depression Rating Scale ($t = 0.31$, d.f. = 38, $P = 0.75$). The difference between the two protocols was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser correction; d.f. = 1, $F = 0.13$, $P = 0.71$). The behavior of the two treatments was homogeneous across the time (groups–by–time interaction, Greenhouse–Geisser correction; $F = 1.82$, d.f. = 1.73, $P = 0.17$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on Hamilton Depression Rating Scale scores ($P < 0.0001$). In the saffron and fluoxetine group post-hoc comparisons showed a significant change from week on the Hamilton Depression Rating Scale scores. The difference between the two protocols was not significant at the endpoint (week 6) ($t = 1.68$, d.f. = 38, $P = 0.09$). The changes at the endpoint compared to baseline were: −12.20 ± 4.67 (mean ± S.D.) and −15.00 ± 5.88 for saffron and fluoxetine, respectively. No significant difference was observed on the change of scores of the Hamilton Depression Rating Scale at week 6 compared to baseline in the two groups ($t = 1.66$, d.f. = 38, $P = 0.10$).

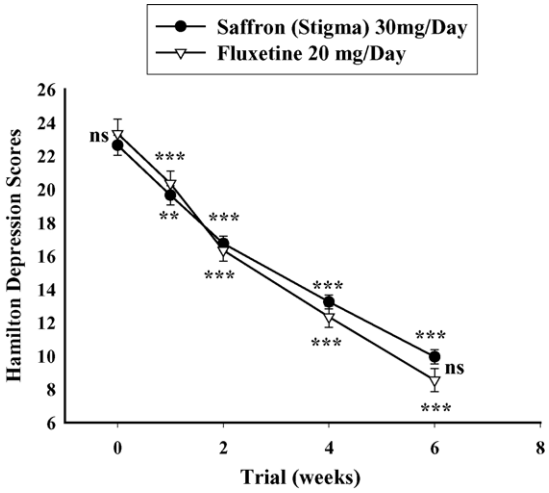


Fig. 1. Mean ± S.E.M. scores of two groups of patients on the Hamilton Depression Rating Scale. (ns) Non-significant; (**) $P < 0.01$ and (***) $P < 0.001$. The horizontal symbols (** and ***) were used to express statistical significance vs. their respective baseline value and ns were used for between group comparisons.

### 3.2. Clinical complications and side effects

Nine side effects were observed over the trial. The difference between the saffron and fluoxetine in the frequency of side effects was not significant (Table 2).

## 4. Discussion

The morbidity and mortality associated with depression are considerable and continue to increase. Depression currently ranks fourth among the major causes of disability

worldwide, after lower respiratory infections, prenatal conditions, and HIV/AIDS (Judd, 1995). The search for new and more effective therapeutic agents includes the study of plants used in traditional medicine systems to treat mental disorders (Richelson, 1994). After decades of predominant reliance on synthetic antidepressants, the treatment of mildly and moderately severe forms of major depression with herbal medicine and in particular St. John's Wort is becoming popular (Ernst, 1995; De Smet and Nolen, 1996).

In this small preliminary double-blind and randomized comparison of saffron and fluoxetine in the treatment of mild to moderate depression, saffron at this dose was found to be effective similar to fluoxetine. The clinical relevance of these findings was emphasised by the improvements seen in the Hamilton Depression Rating Scale measures in the saffron group. To best of our knowledge, this study is the first clinical trial of saffron in the treatment of mild to moderate depression so it is not possible to draw any comparisons with others trials. There were no significant differences in the two groups in terms of observed side effects. Moreover, saffron at this dose did not induce any abnormal bleeding that is one of reported side effects of *Crocus sativus*. In addition, our results are in the line with a recent published animal study that *Crocus sativus* extracts showed antidepressant effect (Karimi et al., 2001). It has been reported that saffron inhibits platelet adhesion so its use is contraindicated in pregnancy (Karimi et al., 2001). In addition, it has been suggested that crocin and safranal two major components of saffron inhibit reuptake of dopamine, norepinephrine and serotonin (Karimi et al., 2001). In general, patients and their families may view alternative medicine that is, those treatments that are not traditionally taught in medical schools or generally practiced by clinicians, as being complementary or even superior to conventional medicine. In majority of cases there are no evidence-based documents. Therefore, it is of interest to document traditional medicine. The limitations of the present study, including lack of a placebo group, using only a fixed dose of saffron, the small number of participants and short period of follow up should be considered so further research in this area is needed.

## 5. Conclusion

The results of this study indicate the efficacy of *Crocus sativus* L. in the treatment of mild to moderate depression. On the other hand, a tolerable side effects profile of saffron, may well confirm the application of saffron as an alternative treatment for depression in Persian traditional medicine and these results deserve further investigations.

## Competing interest

None declared.

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