**Crocus sativus** L. in the Treatment of Mild to Moderate Depression: A Double-blind, Randomized and Placebo-controlled Trial

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Depression is a serious disorder in today’s society, with estimates of lifetime prevalence as high as 21% of the general population in some developed countries. As a therapeutic plant, saffron is considered excellent for stomach ailments and as an antispasmodic, to help digestion and to increase appetite. It is also used for depression in Persian traditional medicine. Our objective was to assess the efficacy of the stigmas of *Crocus sativus* (saffron) in the treatment of mild to moderate depression in a 6-week double-blind, placebo-controlled and randomized trial.

Forty adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition for major depression based on the structured clinical interview for DSM IV participated in the trial. Patients had a baseline Hamilton rating scale for depression score of at least 18. In this double-blind, placebo-controlled, single-centre and randomized trial, patients were randomly assigned to receive a capsule of saffron 30 mg/day (BD) (Group 1) or a capsule of placebo (BD) (Group 2) for a 6-week study. At 6 weeks, *Crocus sativus* produced a significantly better outcome on the Hamilton depression rating scale than the placebo (d.f. = 1, F = 18.89, p << 0.001). There were no significant differences in the two groups in terms of the 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. Copyright © 2005 John Wiley & Sons, Ltd.

**Keywords:** Crocus sativus; depression; herbal medicine; saffron.

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**INTRODUCTION**

Depression is a serious disorder in today’s society. With estimates of lifetime prevalence as high as 21% of the general population in some developed countries (Judd, 1995). As defined by the American Psychiatric Association, depression is a heterogeneous disorder often manifested with symptoms at the psychological, behavioural and physiological levels (American Psychiatric Association, 1994). Such patients are often reluctant to take synthetic antidepressants in their appropriate doses due to their anticipated side effects including the inability to drive a car, dry mouth, constipation and sexual dysfunction. As a therapeutic alternative, effective herbal drugs may offer advantages in terms of safety and tolerability, possibly also improving patient compliance (Richelson, 1994; Demyttenaere, 1997). 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, nefazodone and mirtazapine, has added substantially to the available pharmacopoeia for depression (Donohue and Tylee, 1996; MacDonald, 1997). Nonetheless, rates of remission tend to be low and the risk of relapse and recurrence remains high. Thus, there is a need for more effective and less toxic agents (Richelson, 1994). 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).

Saffron is the world’s most expensive spice and apart from its traditional value as a food additive recent studies indicate its potential as an anticancer agent and memory enhancer (Rios et al., 1996; Abe and Saito, 2000; Abdullaev, 2002). The value of saffron (dried stigmas of *Crocus sativus* L.) is determined by the existence of three main secondary metabolites: crocin and its derivatives which are responsible for colour; picrocrocin, responsible for taste; and safranal responsible for odour. This plant belongs to the Iridaceae family and as a therapeutic plant, saffron it is considered as...
excellent for stomach ailments and an antispasmodic, helps digestion and increases appetite. It is also relieves renal colic, reduces stomachaches and relieves tension (Rios et al., 1996; Hosseinzadeh and Younesi, 2002). Saffron is used for depression in Persian traditional medicine. Many medicinal plant textbooks refer to its antidepressant effect, whereas there is no evidence-based literature (Karimi et al., 2001). Our objective was to assess the efficacy of *Crocus sativus* in the treatment of mild to moderate depression in a 6-week double-blind, placebo-controlled and randomized trial.

**METHODS**

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

**Patients.** Forty adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) (American Psychiatric Association, 1994) for major depression based on the structured clinical interview for DSM IV participated in the trial. Patients had 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 past 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, 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 2 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. All participants provided written informed consent, and the protocol satisfied the Tehran University of Medical Sciences Ethics Committee requirements.

**Saffron capsule preparation.** The saffron was used in this study was donated by Novin Zaferan Co ( Mashhad, Iran) and was identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The stigma’s extract was prepared as follows: 120 g of dried and milled stigmas was extracted with 1800 mL ethanol (80%) by percolation procedure in three steps then the ethanol extract was dried by evaporation at a temperature of 35°C–40°C. Each capsule contained dried extract of saffron (15 mg), lactose (filler), magnesium stearate (lubricant) and sodium starch glycolate (disintegrant).

**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 a capsule of saffron or a capsule of placebo 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-centre trial, patients were randomly assigned to receive a capsule saffron 30 mg/day (BD) (Group A) or a capsule of placebo (BD) for a 6-week study. All patients completed the trial. 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 administered the medications, rater and patients were blind to assignments.

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

**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. The results are presented as mean ± SEM. Differences were considered significant with p < 0.05. To compare the demographic data and the frequency of side effects between the protocols, Fisher’s exact test (two sided) was performed. To consider, α = 0.05, β = 0.2, the final difference between the two groups, a score of at least 5 on the HAM-D total scores that is clinically detectable, S = 5 and power = 80%, the sample size was calculated to be at least 15 in each group. The intention to treat (ITT) analysis with the last observation carried forward (LOCF) procedure was performed.

**RESULTS**

No significant differences were identified between patients randomly assigned to the group 1 or 2 conditions with regard to basic demographic data including age and gender (Table 1). Thirty-five patients completed the trial. In the saffron and placebo group the number of dropouts were 1 and 4, respectively. Although the number of dropouts in the placebo group was higher than in the saffron group, no significant difference was
observed in the two groups in terms of dropout \((p = 0.34)\).

**Efficacy: saffron versus placebo**

The mean ± SEM scores of the two groups of patients are shown in Fig. 1. There were no significant differences between the two groups at week 0 (baseline) on the Hamilton depression rating scale \((t = 0.34, \text{d.f.} = 38, p = 0.73)\). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor \((\text{Greenhouse-Geisser correction; d.f.} = 1, F = 18.89, p < 0.001)\). The behaviour of the two treatments was not homogeneous across the time \((\text{groups-by-time interaction, Greenhouse-Geisser correction; } F = 21.04, \text{d.f.} = 1.85, p < 0.001)\). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on Hamilton depression rating scale scores \((p < 0.0001)\). The behaviour of the two protocols was significant at the endpoint \((t = 6.81, \text{d.f.} = 38, p < 0.0001)\). The changes at the endpoint compared with baseline were: \(-12.20 \pm 4.67\) (mean ± SD) and \(-5.10 \pm 4.71\) for saffron and placebo, respectively. A significant difference was observed in the change of scores of the Hamilton depression rating scale at week 6 compared with baseline in the two groups \((t = 4.78, \text{d.f.} = 38, p < 0.0001)\).

**Clinical complications and side effects**

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

**DISCUSSION**

Mental illness imposes a tremendous burden on the Western world. Mental disorders can strike early in life, and they are increasing in incidence in an aging population experiencing neurodegenerative diseases \((\text{Judd, 1995})\). The search for new and more effective therapeutic agents includes the study of plants used in traditional medicine systems to treat mental disorders \((\text{Richelson, 1994})\). After decades of predominant reliance on synthetic antidepressants, the treatment of mild and moderate severe forms of major depression with herbal medicine and in particular St John’s Wort is becoming popular \((\text{Ernst, 1995; De Smet and Nolen, 1996})\).

This study showed that patients with mild to moderate depression receiving saffron experienced statistically significant benefits in their mood after 6 weeks treatment. The clinical relevance of these findings was emphasized 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 other 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 the 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 an antidepressant effect \((\text{Hosseinzadeh and Younesi, 2002})\). In general, patients and their families may view alternative medicine as being complementary or even superior to conventional medicine. Therefore, it is of interest to document traditional medicine. The limitations of the present study, including using only a fixed dose of saffron, the small number of participants and the short period of follow up should be considered so that further research in this area is needed.
Indeed, 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.

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**REFERENCES**


