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Comparison of petal of *Crocus sativus* L. and fluoxetine in the treatment of depressed outpatients: A pilot double-blind randomized trial

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Abstract

Depression is one of the most common neuropsychiatric conditions, with a lifetime prevalence approaching 17%. Although a variety of pharmaceutical agents is available for the treatment of depression, psychiatrists find that many patients cannot tolerate the side effects, do not respond adequately, or finally lose their response. On the other hand, many herbs with psychotropic effects have far fewer side effects. They can provide an alternative treatment or be used to enhance the effect of conventional antidepressants. A number of recent preclinical and clinical studies indicate that stigma and petal of *Crocus sativus* have antidepressant effect. Our objective was to compare the efficacy of petal of *C. sativus* with fluoxetine in the treatment of depressed outpatients in an 8-week pilot double-blind randomized trial. Forty adult outpatients who met the DSM- IV criteria 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 score of at least 18. In this double-blind and randomized trial, patients were randomly assigned to receive capsule of petal of *C. sativus* 15 mg bid (morning and evening) (Group 1) and fluoxetine 10 mg bid (morning and evening) (Group 2) for a 8-week study. At the end of trial, petal of *C. sativus* was found to be effective similar to fluoxetine in the treatment of mild to moderate depression ($F=0.03$, $d.f.=1$, $P=0.84$). In addition, in the both treatments, the remission rate was 25%. There were no significant differences in the two groups in terms of observed side effects. The present study is supportive of other studies which show antidepressant effect of *C. sativus*.

Keywords: *Crocus sativus*; Depression; Fluoxetine; Herbal medicine; Petal

1. Introduction

Depression is a major worldwide health problem. Indeed, by 2020, depressive disorders are estimated to represent the second largest disease burden worldwide (Judd, 1995; Donoghue and Tylee, 1996; De Smet and Nolen, 1996; Demyttenaere, 1997). Although a variety of pharmaceutical agents is available for the treatment of depression, psychiatrists find that many patients cannot tolerate the side effects, do not respond adequately, or finally lose their response (Richelson, 1994; Demyttenaere, 1997; MacDonald, 1997). On the other hand, many herbs with psychotropic effects have far fewer side effects. They can provide an alternative treatment or be used to enhance the effect of conventional antidepressants (Ernst, 1995; De Smet and Nolen, 1996). A number of studies showed that herbal medicine may be as effective as conventional antidepressant treatment among patients with mild and moderate depression (Ernst, 1995; Linde et al., 2005). Saffron (stigma of *Crocus sativus*) is the world's most expensive spice and apart from its traditional value as a food additive recent studies indicate its potential as an anti-cancer agent

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; DSM, Diagnostic and Statistical Manual of Mental Disorders; ITT, Intention to Treat; LOCF, Last Observation Carried Forward.

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and memory enhancer (Rios et al., 1996). Recent preclinical studies and clinical trials found that stigma and petal of *C. sativus* are effective for treatment of mild to moderate major depression (Karimi et al., 2001, Hosseinzadeh and Younesi, 2002; Akhondzadeh et al., 2004, 2005; Noorbala et al., 2005; Moshiri et al., 2006). Our previous reports showed antidepressant effects of stigma of *C. sativus* compared to imipramine, placebo and fluoxetine (Akhondzadeh et al., 2004, 2005; Noorbala et al., 2005). In addition, our recent study indicated antidepressant effect of petal of *C. sativus* compared to placebo. In this trial, we investigated the antidepressant effect of petal of *C. sativus* compared to fluoxetine in an 8-week double-blind randomized trial.

2. Methods

This was an 8-week randomized and double-blind clinical trial. The trial was conducted in the outpatient clinic of Roozbeh Psychiatric between September 2004 and April 2006.

2.1. Participants

Forty adult outpatients who met the DSM-IV criteria for major depression based on the structured clinical interview for DSM IV participated in the trial (American Psychiatric Association, 1994). Patients have a baseline HAM-D (17-item) score of at least 18 and ≤25 (Hamilton, 1960). 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, schizotypal personality disorder and border line 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 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. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and all participants provided written informed consent, and the protocol satisfied the Tehran University of Medical Sciences Ethics Committee requirements.

2.2. Preparation of C. sativus

The petal of *C. sativus* in this study was identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The petal's extract was prepared as follow: 120 g of dried and milled petal was extracted with 1800 ml ethanol (80%) by percolation procedure in three steps then the ethanolic extract was dried by evaporation in temperature between 35–40 °C. Each capsule had dried extract of petal of *C. sativus* (15 mg), lactose (filler), magnesium stearate (lubricant), and sodium starch glycolate (disintegrant). The extract was standardized by safranal. Each capsule had 0.30–0.35 mg safranal and dried hydoalcholic extract in capsules did not have any different taste compared to capsules of fluoxetine.

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 petal of *C. sativus* or fluoxetine in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until the point of analysis of data. The randomization and allocation process was done by the pharmacist of the Roozbeh hospital. In this double-blind, patients were randomly assigned to receive capsule petal of *C. sativus* 15 mg bid (Group A) or fluoxetine 10 mg bid (Group B) for an 8-week study. Two patients dropped out over the trial due to consent withdraw (one from the each group). Patients were assessed by a psychiatrist at baseline and after 1, 2, 4, 6 and 8 weeks after the medication started. The principal measure of the outcome was the 17-item HAM-D. Remission was defined as an endpoint HAM-D total score of ≤7. The rater (psychiatrist) 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.

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, 42 and 56 (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 six 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 was 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 5 on the HAM-D total scores that is clinically detectable, $S=5$ and power = 80%, the sample size was

Table 1
Baseline data

	Petal of *Crocus sativus* group	Fluoxetine group
Women	10	11
Man	10	9
Age (mean±SD)	35.55±8.05 (year)	34.09±5.50 (year)
Age of onset	31.75±7.16 (year)	32.85±5.24 (year)
Weight (mean±SD)	72.45±10.44	70.35 ±10.33
Height (cm)	175.45±8.21 (cm)	177.65±7.61 (cm)
Duration of recent episode (mean±SD)	2.30±1.70 (month)	2.40±1.80 (month)
Number of previous episodes	3.42±0.76	3.63±0.89
Medications history	Fluoxetine: 15; Nortriptyline: 3; Sertraline: 2	Fluoxetine: 13; Nortriptyline: 4; Sertraline: 3

calculated at least 15 in each group. ITT analysis with LOCF procedure was performed.

3. 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-eight patients completed the trial.

3.1. Efficacy: Petal of C. sativus versus fluoxetine

The mean±SEM 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=0.86, $d.f.$=38, P=0.39). The difference between the two treatments was not significant as indicated by the effect of

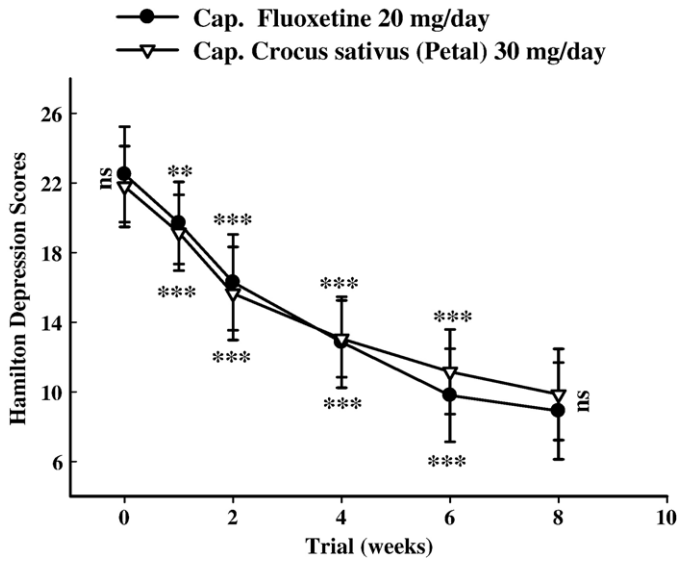

Fig. 1. Mean±S.E.M. scores of two groups of patients on the Hamilton Depression Rating Scale. ns = non-significant, ** = P<0.01 and *** = P<0.001. The horizontal symbols (** and ***) were used to express statistical significance versus their respective baseline value and vertical symbols (ns) were used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

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

Side effects	Petal of *Crocus sativus*	Fluoxetine	P
Anxiety	4	7	0.48
Decreased appetite	5	4	1.00
Increased appetite	1	3	0.60
Sexual dysfunction	3	5	0.69
Tremor	2	5	0.40
Nausea	3	4	1.00
Headache	2	5	0.40
Sweating	2	3	1.00
Heart Pounding	3	2	1.00
Insomnia	3	3	1.00

group, the between-subjects factor (Greenhouse–Geisser correction; $d.f.$=1, F=0.03, P=0.84). The behavior of two treatments was homogeneous across the time (groups-by-time interaction, Greenhouse–Geisser correction; F=1.70, $d.f.$=1.68, P=0.19). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on Hamilton Depression Rating Scale scores (P<0.0001). In the *C. sativus* and fluoxetine group post-hoc comparisons showed a significant change from week 1 on the Hamilton Depression Rating Scale scores. The difference between the two treatments was not significant at the endpoint (week 8) (t=1.11, $d.f.$=38, P=0.27). The changes at the endpoint compared to baseline were: −12.00±4.10 (mean±SD) and −13.50±4.91 for *C. sativus* and fluoxetine respectively. No significant difference was observed on the change of scores of the Hamilton Depression Rating Scale at week 8 compared to baseline in the two groups (t=1.04, $d.f.$=38, P=0.30). There were no significant differences between two treatments in terms of the percentage of responders (at least 50% drop in the Hamilton Depression Rating Scale score) (fluoxetine: 85%, 17 of 20 and petal of *C. sativus*: 75%, 15 of 20; P=0.69). In addition, in the both treatments, the remission rate was 25%.

3.2. Clinical complications and side-effects

Ten side effects were observed over the trial. The difference between the *C. sativus* and fluoxetine in the frequency of side effects was not significant (Table 2).

4. Discussion

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 (Demyttenaere, 1997; Linde et al., 2005). Saffron is an herb most people are unlikely to utilize, either for medicinal or culinary purposes, primarily because the material has a justified reputation for being extraordinarily expensive. Saffron is used for depression in Persian traditional medicine (Akhondzadeh et al., 2004). Indeed, it is a Persian herb with a history as long as the Persian Empire itself. 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).

Table 3
Summary of five studies of *Crocus sativus* in the treatment of depression

References	Number of patients	Medications	Principal measure of the outcome	Time of treatment	Results
Akhondzadeh et al. (2004)	30 (15 in each arm)	Imipramine vs stigma of *C. sativus*	17-item HAM-D	6	Stigma of *C. sativus* was found to be effective similar to imipramine in the treatment of mild to moderate depression
Akhondzadeh et al. (2004)	40 (20 in each arm)	Placebo vs stigma of *C. sativus*	17-item HAM-D	6	Stigma of *C. sativus* produced a significantly better outcome on the Hamilton depression rating scale than the placebo
Noorbala et al. (2005)	40 (20 in each arm)	Fluoxetine vs stigma of *C. sativus*	17-item HAM-D	6	Sigma of *C. sativus* was found to be effective similar to fluoxetine in the treatment of mild to moderate depression
Moshiri et al. (2006)	40 (20 in each arm)	Placebo vs petal of *C. sativus*	17-item HAM-D	6	Petal of *C. sativus* produced a significantly better outcome on Hamilton Depression Rating scale than placebo
Present study	40 (20 in each arm)	Fluoxetine vs petal of *C. sativus*	17-item HAM-D	8	Petal of *C. sativus* was found to be effective similar to fluoxetine in the treatment of mild to moderate depression

The present study was carried out to compare antidepressant effect of petal of *C. sativus* compared with fluoxetine. In this small preliminary double-blind and randomized comparison of petal of *C. sativus* and fluoxetine in the treatment of mild to moderate depression, petal of *C. sativus* at this dose was found to be effective similar to fluoxetine. The clinical relevance of this finding was emphasized by the improvements seen in the Hamilton Depression Rating Scale measures in both groups.

Moreover, there were no significant differences in the two groups in terms of observed side effects. Nevertheless, in the both groups, it could not be differentiated whether insomnia, anxiety and decreased appetite are side effects or symptoms of depression. It has been reported that stigma of *C. sativus* has antidepressant effect by at least three clinical trials (Akhondzadeh et al., 2004; 2005; Noorbala et al., 2005) (Table 3). Moreover, this study is in line with our recent report that suggests antidepressant effect for petal of *C. sativus* (Moshiri et al., 2006). The result of this study is in the line with a preclinical study that has reported an antidepressant effect for petal of *C. sativus* that was similar with its stigma in an animal model for depression (Hosseinzadeh and Younesi, 2002). As petal of *C. sativus* is too cheap compared to stigma (saffron) that is one of the most expensive spices in the world, there will be economical interests for further investigations by pharmaceutical industries. The limitations of the present study, including lack of a placebo group, using only a fixed dose of *C. sativus*, 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 main overall finding from this study is that petal of *C. sativus* may be of therapeutic benefit in the treatment of mild to moderate depression. A large-scale trial is warranted.

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