

## Petal and Stigma of *Crocus sativus* L. in the Treatment of Depression: A Pilot Double - blind Randomized Trial

Akhondzadeh Basti A (Ph.D.)<sup>1</sup>, Ghoreishi SA (M.D.)<sup>2</sup>, Noorbala AA (M.D.)<sup>3</sup>,  
Akhondzadeh SH (Ph.D.)<sup>3\*</sup>, Rezazadeh Sh (Ph.D.)<sup>4</sup>

1- Department of Food Hygiene, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

2- Department of Psychiatry, Zanjan University of Medical Sciences, Zanjan, Iran

3- Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

4- Institute of Medicinal Plants, ACECR, Karaj, Iran

\*Corresponding author: Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran 13337, Iran

Tel: +98-21-88281866, Fax: +98-21-55419113

E-mail: s.akhond@neda.net

Receive: 21 Jan. 2008

Acceptance: 17 Feb. 2008

### Abstract

Stigma of *Crocus sativus* L. (Iridaceae), commonly known as saffron, is the world's most expensive spice and apart from its traditional value as food additive recent studies indicate its potential as antidepressant. Because saffron is expensive, using it daily to address depression may not be practical. Moreover, recent study indicated antidepressant effect of petal of *Crocus sativus*. As petal of *Crocus sativus* is not expensive compared to stigma, there will be economical interests for further investigations by pharmaceutical industries. Our objective was to compare the efficacy of petal of *Crocus sativus* with stigma of *Crocus sativus* in the treatment of depressed outpatients in a 6-week pilot double-blind randomized trial. Forty four 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 *Crocus sativus* 15 mg bid (morning and evening) (Group 1) and capsule of stigma of *Crocus sativus* 15 mg bid (morning and evening) (Group 2) for a 6-week study. At the end of trial, petal of *Crocus sativus* was found to be effective similar to stigma of *Crocus sativus* in the treatment of mild to moderate depression (d.f.=1, F= 0.05, P=0.81). In addition, in the both treatments, the remission rate was 18%. 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 petal and stigma of *Crocus sativus*.

**Keywords:** *Crocus sativus*, Depression, Herbal Medicine, Petal, Stigma

## Introduction

Depression is the second most common medical condition seen in general medical practice. Only hypertension is more common. In the US, about 16% of adults experience major depression during their lifetime. Less than 25% of depressed patients get adequate treatment widespread [1, 2]. Depression is one of the 10 most frequent indications for using Complementary and Alternative Medicine (CAM). Depression is a significant cause of morbidity and mortality world-wide, imposing a range of costs on individuals, families and communities and accounting for a sizeable proportion of the global burden of disease and disability. A major problem is that much of depression is under-diagnosed and under-treated, and compliance with antidepressants is often low, a fact that assumes significance given the prevalence of CAM use by those who are depressed. The most widely used CAM approaches in depression are herbal medicine [3, 4]. There is increasing interest in use of herbal medicine among people with major depression, which appears to be driven by patients and general public [5, 6, 7, 8, 9]. Saffron (stigma of *Crocus sativus*) is a culinary spice used in many Middle Eastern dishes [10]. It has also been used in traditional Persian medicine to relieve stomachaches, ease the pain of kidney stones, and treat depression [11, 12]. Some studies suggest that saffron may also have anticancer and memory-enhancing properties [13, 14, 15]. Iran, the world's largest producer of saffron has been investing in research into saffron's potential medicinal uses. Much of the work surrounds its traditional application for alleviating depression [16, 17, 18, 19, 20]. The clinical findings suggest that saffron is a safe and effective antidepressant [16, 17, 18, 19, 20]. For example, in a randomized, double-

blind study, 30 mg of saffron extract (in capsules) given for 6 weeks resulted in significant alleviation of depression compared to those on placebo, and did so without evident side effects [17]. This study was a follow-up to a preliminary trial in which the same saffron preparation performed as well as imipramine for treating depression in a double-blind trial [16]. In further preliminary work, saffron was compared to the drug fluoxetine; it was found that saffron performed as well as the drug in the treatment of depression [18]. Because saffron is expensive, using it daily to address depression may not be practical. In addition, our recent study indicated antidepressant effect of petal of *Crocus sativus* compared to placebo and fluoxetine [19, 20]. As Petal of *Crocus sativus* is not expensive compared to its stigma (saffron) that is one of the most expensive spices in the world, there will be economical interests for further investigations by pharmaceutical industries. In this trial, we investigated the antidepressant effect of petal of *Crocus sativus* compared to stigma of *Crocus sativus* (saffron) in a 6-week double blind randomized trial.

## Methods

This was a 6-week randomized and double blind clinical trial. The trial was conducted in the outpatient clinic of Roozbeh Psychiatric between December 2005 and January 2007.

## Participants

Forty four adult outpatients who met the DSM-IV criteria for major depression based on the structured clinical interview for DSM IV participated in the trial [21]. Patients have a baseline HAM-D (17-item) score of at least 18 and  $\leq 25$  [22]. 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.

### Preparation of *Crocus sativus*

The petal and stigma of *Crocus sativus* in this study was identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The petal and stigma extract was prepared as follow: 120 g of dried and milled petal or stigma 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 or stigma of *Crocus*

*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.

### 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 *Crocus sativus* or capsule of stigma of *Crocus sativus* 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 trial, patients were randomly assigned to receive capsules of petal or stigma of *Crocus sativus* 15 mg bid (Group A or B) for a 6-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, and 6 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  $\leq 7$ . 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.

### 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).

### 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  $\pm$  SD.

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,  $\alpha = 0.05$ ,  $\beta = 0.2$ , 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 calculated at least 15 in each group. ITT analysis with 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). Forty two patients completed the trial.

**Table 1. Baseline data**

	Petal of <i>Crocus sativus</i> Group	Stigma of <i>Crocus sativus</i> Group
Women	10	12
Man	9	13
Age (Mean $\pm$ SD)	34.31 $\pm$ 8.40 (year)	35.13 $\pm$ 5.85 (year)
Weight (Mean $\pm$ SD)	71.04 $\pm$ 10.04	69.18 $\pm$ 9.00
Height (cm)	173.95 $\pm$ 7.66 (cm)	175.27 $\pm$ 9.28 (cm)
Duration of recent episode (Mean $\pm$ SD)	2.45 $\pm$ 1.81 (month)	2.52 $\pm$ 1.89 (month)
Medications history	Fluoxetine: 16; Nortriptyline: 2; Sertraline: 2; Citalopram: 2	Fluoxetine: 15; Nortriptyline: 4; Sertraline: 2; Citalopram: 1

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

Side Effects	Petal of <i>Crocus sativus</i>	Stigma of <i>Crocus sativus</i>	P
Anxiety	5	6	1.00
Decreased Appetite	4	3	1.00
Increased Appetite	4	6	0.72
Sexual Dysfunction	3	3	1.00
Tremor	2	1	1.00
Nausea	3	4	1.00
Headache	4	3	0.69
Sweating	2	3	1.00
Heart Pounding	3	5	0.69
Insomnia	3	3	1.00

### Efficacy: Petal of *Crocus sativus* versus fluoxetine

The mean  $\pm$  SD scores of two groups of patients are shown in Figure 1. There were no significant differences between the two groups in week 0 (baseline) on the Hamilton Depression Rating Scale ( $t=0.41$ , d.f. = 42,  $P=0.68$ ). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse-Geisser correction; d.f. = 1,  $F=0.05$ ,  $P=0.81$ ). The behavior of two treatments was homogeneous across the time (groups-by-time interaction, Greenhouse-Geisser correction;  $F=0.63$ , d.f. = 1.92,  $P=0.52$ ). 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 petal and stigma 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 6) ( $t=1.01$ , d.f. = 42,  $P=0.31$ ). The changes at the endpoint compared to baseline were:  $-13.45 \pm 4.84$  (mean $\pm$ SD) and  $-12.18 \pm 3.72$  for stigma and petal of *Crocus sativus* 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 ( $t=0.97$ , d.f. = 42,  $P = 0.33$ ). 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) (stigma of *Crocus sativus*: 77.27%, 17 of 22 and petal of *Crocus sativus*: 68.18%, 15 of 22). In addition, in the both treatments, the remission rate was 18%.

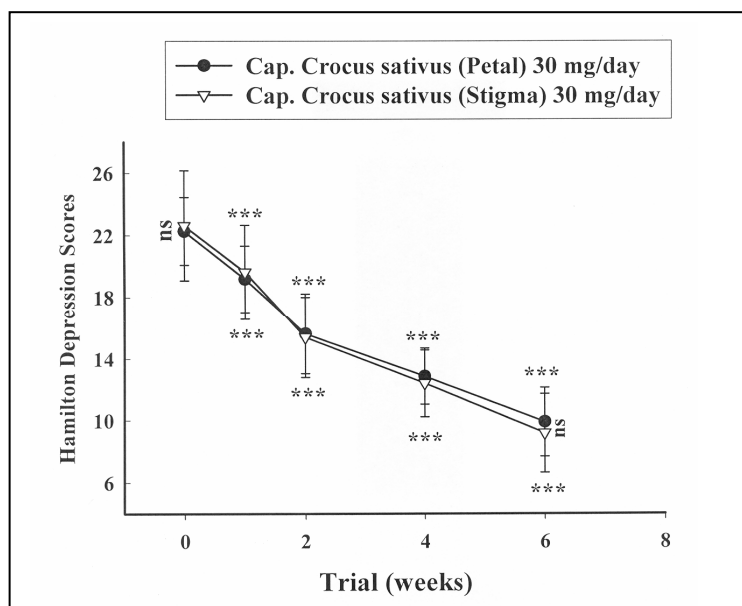
### Clinical complications and side-effects

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

### Discussion

Despite a long history of folk and anecdotal use, complementary medicine modalities have received relatively little attention in the conventional medical world until recently. Modalities such as botanical medicines, lifestyle, nutrition, and acupuncture have silently played a role in the treatment of depressive illness, as they are clearly sought by the public, and the perception has been that their utilization has increased [8].

The Persian herb saffron, long used in cooking, is made from the dried stigma (top of the female portion) of the *Crocus sativa* flower. As a spice it is used for coloring and flavor improving while giving a distinct aroma and a beautiful golden color [10]. As a therapeutically plant, saffron it is considered an excellent stomach ailment and an antispasmodic, helps digestion and increases appetite [10]. The best evidence for medicinal effects of saffron involves treatment of depression [16, 17, 18, 19, 20, 23]. Because saffron is the most expensive spice, this limitation makes it less interesting for pharmaceutical industry. The present study was carried out to compare antidepressant effect of petal and stigma of *Crocus sativus*. In this small preliminary double-blind and randomized comparison of petal and stigma of *Crocus sativus* in the treatment of mild to moderate depression, petal of *Crocus sativus* at this dose was found to be effective similar to stigma of *Crocus sativus*. The clinical relevance of this



**Figure 1.** Mean  $\pm$  SD scores of two groups of patients on the Hamilton Depression Rating Scale. Ns = non - significant and \*\*\* =  $P < 0.001$ . The horizontal symbols (\*\*\*) were used to express statistical significance versus their respective baseline value and vertical symbols (ns) were used for between group comparisons.

finding was emphasized by the improvements seen in the Hamilton Depression Rating Scale measures in the both group. Moreover, there were no significant differences in the two groups in terms of observed side effects. It has been reported that stigma of *Crocus sativus* has antidepressant effect by at least three clinical trials [16, 17, 18]. Moreover, this study is in line with our recent reports that suggest antidepressant effect for petal of *Crocus sativus* [19, 20]. The result of this study is in the line with a preclinical study that has reported an antidepressant effect for petal of *Crocus sativus* that was similar with its

stigma in an animal model for depression [10].

## Conclusion

The main overall finding from this study is that petal of *Crocus sativus* as well as stigma of *Crocus sativus* may be of therapeutic benefit in the treatment of mild to moderate depression. A large- scale trial is warranted.

## Acknowledgements

This study was supported by a grant from Tehran University of Medical Sciences to Dr. Shahin Akhondzadeh.

## References

- Judd L. Mood disorders in the general population represent an important and worldwide public health problem. *Int. J. Clin. Psychopharm.* 1995; 10: (suppl 4) 5 - 10.
- Donoghue JM, Tylee A. The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. *Br. J. Psych.* 1996; 168, 164 - 8.

3. Richelson E. Pharmacology of antidepressants-characteristic of the ideal drug. *Mayo Clin. Proceed.* 1994; 69: 1069 - 81.
4. Demyttenaere K. Compliance during treatment with antidepressants. *J. Affec. Dis.* 1997; 43: 27 - 39.
5. Ernst E. St. John's wort, an antidepressant? A systematic, criteria based review. *Phytomed.* 1995; 2: 67 - 71.
6. De Smet PAGM, Nolen WA. St. John's wort as an antidepressant. *Br. Med. J.* 1996; 313: 241 - 2.
7. MacDonald TM. Treatment of depression: prescription for success? *Prim Care Psychiatry* 1997; 3: (suppl 1) 7 - 10.
8. Eisenberg DM, Davis RB, Ettner SL, Appel MS, Wilkey S, Van Rompay M. Trends in alternative medicine use in the United States, 1990 - 1997: results of a follow-up national survey. *JAMA* 1998; 280: 1569 - 75.
9. Linde K, Mulrow CD, Berner M, Egger M, St John's wort for depression. *Cochrane Database Syst. Rev.* CD000448. 2005.
10. Rios JL, Recio MC, Giner RM, Manez S, An update review of saffron and its active constituents. *Phytother. Res.* 1996; 10, 189-93.
11. Karimi G, Hosseinzadeh H, Khaleghpanah P. Study of antidepressant effect of aqueous and ethanolic of *Crocus sativus* in mice. *Iranian J. Basic Med. Sci.* 2001; 4: 11- 5.
12. Hosseinzadeh H, Younesi H. Petal and stigma extracts of *Crocus sativus* L. have antinociceptive and anti-inflammatory effects in mice. *BMC Pharmacol.* 2002; 2: 7.
13. Abdullaev FI, Espinosa - Aguirre JJ. Biomedical properties of saffron and its potential use in cancer therapy and chemoprevention trials. *Cancer Detect. Prev.* 2004; 28: 426 - 32.
14. Pitsikas N, Sakellaridis N, *Crocus sativus* L. extracts antagonize memory impairments in different behavioural tasks in the rat. *Behav. Brain Res.* 2006; 173: 112 - 5.
15. Papandreou MA, Kanakis CD, Polissiou MG, Efthimiopoulos S, Cordopatis P, Margarity M, Lamari FN. Inhibitory activity on amyloid-beta aggregation and antioxidant properties of *Crocus sativus* stigmas extract and its crocin constituents. *J. Agric. Food. Chem.* 2006; 15: 8762 - 8.
16. Akhondzadeh S, Fallah Pour H, Afkham K, Jamshidi AH, Khalighi-Cigarodi F. Comparison of *Crocus sativus* L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. *BMC Comp. Alt. Med.* 2004; 4: 12.
17. Akhondzadeh S, Tamacebi-pour N, Noorbala AA, Amini H, Fallah Pour H, Jamshidi AH, Khani M. *Crocus sativus* L. in the treatment of mild to moderate depression: A double-blind, randomized and placebo controlled trial. *Phytother. Res.* 2005; 19: 25 - 9.
18. Noorbala AA, Akhondzadeh S, Tamacebi-pour N, Jamshidi AH. Hydro-alcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression: A double-blind, randomized pilot trial. *Ethnopharmacol.* 2005; 97: 281 - 4.
19. Moshiri E, Basti AA, Noorbala AA, Jamshidi AH, Abbasi SH, Akhondzadeh S, *Crocus sativus* L. (petal) in the treatment of mild-to-moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytomed.* 2006; 13: 607 - 11.

- 20.** Akhondzadeh Basti A, Moshiri E, Noorbala AA, Jamshidi AH, Abbasi SH, Akhondzadeh S. Comparison of petal of *Crocus sativus* L. and fluoxetine in the treatment of depressed outpatients: A pilot double - blind randomized trial. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2007; 31: 439 - 42.
- 21.** American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). American Psychiatric Association, Washington, D. C.
- 22.** Hamilton M. A rating scale for depression. *J. Neuro. Neurosurg. Psychiat.* 1960; 3: 62 - 6.
- 23.** Akhondzadeh S. Herbal Medicine in the treatment of neurological and mental disorders: In: L'Abate, L., (Eds.), Low-cost approaches to promote physical and mental health. Springer Science + Business Media, New York, 2007, pp: 119 - 38.