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A double-blind, randomized and placebo-controlled trial of Saffron (*Crocus sativus* L.) in the treatment of anxiety and depression

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Abstract

Background: Depression and anxiety are prevalent serious psychiatric disorders. Several drugs are used to treat these conditions but these are often associated with serious side effects. For this reason alternative therapies, including herbal medication such as saffron, have been proposed. We aimed to assess the effects of saffron extract for the treatment of anxiety and depression using a 12-week double-blind, placebo-controlled trial design.

Methods: Sixty adult patients with anxiety and depression were randomized to receive a 50 mg saffron capsule (*Crocus sativus L. stigma*) or a placebo capsule twice daily for 12 weeks. Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) questionnaires were used at baseline, 6 and 12 weeks after initiating medication. 54 subjects completed the trial.

Results: Saffron supplements had a significant effect on the BDI and BAI scores of subjects in comparison to placebo at the 12 week time-point ($p<0.001$).

Conclusions: Saffron appears to have a significant impact in the treatment of anxiety and depression disorder. Side effects were rare.

Keywords: anxiety, Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), depression, saffron

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Introduction

Depression is one of the most common mental health complaints, with a lifetime prevalence approaching 17%. It likely to be the second largest disease burden worldwide by 2020 [1]. Depression is a heterogeneous disorder with behavioral, psychological, and physiological symptoms [2]. Less than 25% of depressed individuals get adequate treatment and compliance with antidepressants is often low [1, 3]. Other patients receive no benefit, and do not experience complete remission following an initial monotherapy with an antidepressant. Resistance to this type of drug therapy remains an issue of concern emphasizing that the goal of treatment should be full remission, and not just symptom improvement [3, 4]. The management of depression may therefore benefit from adjuvant complementary and alternative medicine [5].

Generalized anxiety disorder is diagnosed in patients with excessive worry and anxiety, accompanied by symptoms for example tension and irritability which occurs more days for at least 6 months [6]. Generalized anxiety disorder is often diagnosed in primary care [7]. Some patients cannot tolerate the side effects of conventional drug therapy, or their response to these drugs may become attenuated. Natural herbs with psychotropic effects may have fewer side effects and may compliment the effects of conventional antidepressants [1, 8]. Saffron,

the dried stigmata of *Crocus sativus L.*, is a bulbous perennial of Iridaceae that are in foods [9]. In traditional medicine, it is used for the treatment of conditions including: cramps, depression, and asthma [9]. It also has an anti-inflammatory, anticancer, antioxidant and anti-platelet properties [9, 10].

The use of saffron for depressive mood has been reported previously. Saffron contains three major active components: crocin which is responsible for its color; safranal, giving saffron its characteristic aroma; and picrocrocin which is responsible for taste [11, 12]. It appears that crocin and safranal inhibit reuptake of dopamine, norepinephrine, and serotonin [1]. Recent studies have revealed that saffron has effective antidepressant property; the stigma and even the petals of *L. sativus* have been shown effective in the management depression both in human and for anxiety mostly in animal studies [4, 8, 12–16]. The aim of this study was to assess the efficacy of *L. sativus* in the treatment of mild-to-moderate depression and anxiety in a 12-week placebo-controlled, double-blind trial.

Materials and methods

The study was conducted from September 2010 to March 2011 in the Psychiatry clinic of Qaem Teaching Hospital, Mashhad, Iran. The study was compliant with the Declaration of Helsinki and all patients provided written informed consent. The study was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Population

Sixty patients with mild-to-moderate mixed anxiety and depression were diagnosed on the basis of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) [2] criteria. They initially participated in a semi-structured interview that was given by a single psychiatrist. Depression and anxiety were quantified on the basis of Beck Depression Inventory (BDI) questionnaire and Beck Anxiety Inventory (BAI) questionnaire.

The BDI and BAI consisted of 21 multiple choice questions. Each question has a set of four possible answer choices, ranging in intensity. A score of 0–3 is designated for each answer and then the total score summed for the severity of depression and anxiety. The standard cut-off values are used to define four degree of severity for depression and anxiety respectively [17]:

- 0–9: minimal depression
- 10–18: mild depression
- 19–29: moderate depression
- 30–63: severe depression.
- 0–7: minimal level of anxiety
- 8–15: mild anxiety
- 16–25: moderate anxiety
- 26–63: severe anxiety

Subjects were 18–70 years old. They had a baseline score for depression of 10–30 and anxiety 8–26, respectively. Patients were asked to be free of all medications for at least one-month prior to starting the study. Patient with, family or relationship problems and subjects with significant deterioration in their general condition from baseline were excluded from the study. The inclusion/exclusion criteria included: no sign of any other psychiatric disorder, confirmed by both the patient and his family; normal studies for organic disease, including thyroid function test and complete blood count testing; no sign of substance misuse disorder, mental retardation, suicidal thoughts or attempt; no pregnancy (confirmed by urine βHCG testing) and no grief reaction in the past 6 months.

Saffron capsule

L. sativus stigma was obtained from Novin Saffron Co. (Mashhad, Iran). It was formulated as a capsule containing 50 mg of dried saffron stigma. Placebo capsules were matched for size, shape, and volume of content and manufactured by the same company.

Study design

Patients underwent a standard clinical assessment, consisting of a full medical history, a psychiatric examination, and a structured diagnostic interview. In this double-blind, single-center trial, patients were randomly assigned to receive a 50 mg capsule of saffron twice daily as the study group or the same dosage of a placebo capsule as the control group for 12 weeks. Randomization was carried out using a computer-generated code. Patients were examined by a single psychiatrist at baseline, 3, 6, and 12 weeks of study initiation. If any major changes occurred in the patient's condition, mainly exacerbation of the depressive disorder, having suicidal thoughts or plans or any other psychotic symptoms, the essential interventions were promptly taken. The BDI and BAI questionnaires were completed for each participant at baseline, 6 and 12 weeks of survey initiation. Mean changes in BDI and BAI scores were assessed as the main outcome for calculating of depression and anxiety responses to treatment. Also side effects were noted during the survey. Throughout the study the person in charge of administering the drugs, the psychiatrist and the patient were blind to the treatment.

Statistical analyses

A repeated measures analysis of variance and unpaired Student's t-test was used for data analysis. The values are presented as mean ± SEM. A p-value <0.05 was considered significant. Fisher's exact test was used for comparison between the two groups.

Results

60 patients entered the study, met the inclusion criteria and provided an informed consent. During the treatment

course and in the 8th and 9th weeks of receiving the prescribed medication 6 participants were excluded from case group; 1 due to symptoms of saffron-induced allergy, 1 due to an operative procedure for an unrelated reason, and 4 others due to non-cooperation.

No significant difference was observed between patients and control groups regarding the demographic data including age, gender, marital status, educational level, and occupation status (Table 1). 54 participants completed the trial.

Table 1: Demographic data at the baseline.

	Study group	Control group
Women, n	22	20
Men, n	8	10
Age, years (mean ± SD)	42.8 ± 10.65	43.6 ± 8.83
Marital status		
Married n (%)	25 (83.3)	26 (80.8)
Single, n (%)	5 (16.7)	5 (19.2)
Educational level		
Basic, n (%)	5 (16.7)	5(16.7)
Diploma, n (%)	13 (43.3)	11 (36.7)
Graduate and higher, n (%)	12 (40)	14 (46.6)
Occupation status		
Employed, n (%)	20 (66.7)	17 (56.7)
Unemployed, n (%)	10 (33.3)	13 (43.3)

Efficacy: saffron versus placebo Anxiety

Statistical analysis showed no significant differences between the two groups at baseline on the BAI score for anxiety ($t = 0.164$, d. f. = 52, $p = 0.074$). A significant difference was observed between the two treatment groups at 12 weeks (Greenhouse-Geisser correction; d. f. = 1.909, $F = 211.028$, $p < 0.001$). There was no homogeneity in the effect of the two treatments across the time (groups-by-time interaction, Greenhouse-Geisser correction; $F = 1.909$, d. f. = 11.118, $p < 0.001$). A statistically significant effect of treatment for the BAI scores between saffron group compared to the place group ($p < 0.001$) was detected. Similar effects were observed for the two protocols at the endpoint (week 12) ($t = -1.636$, d. f. = 52, $p < 0.05$). This difference at the endpoint compared to baseline was: −8.65 ± 2.59 for the saffron group and −5.46 ± 2.82 for the placebo group.

Depression

No significant differences were found between the two groups at baseline for the BDI score for depression ($t = 0.190$, d. f. = 52, $p = 0.105$). Moreover, there was a significant difference between the two protocols as indicated by the group effect, the between-subject factor (Greenhouse-Geisser correction; d. f. = 1.663, $F = 72.517$, $p < 0.001$). There was no homogeneity of behavior of the two protocol across the time (groups-by-time interaction, Greenhouse-Geisser correction; $F = 1.663$, d. f. = 3.328, $p < 0.05$). Also, a significant effect of saffron treatment was noticed on BDI scores in the saffron group when compared to the control group ($p<0.001$). Significant changes on the BDI scores were detected in the saffron compared to the placebo group. Also significant difference between the two protocols at the endpoint was initiate (week 12) ($t = -1.516$, d. f. = 52, $p < 0.05$). These values were: −6.69 ± 2.73 and −4.35 ± 4.60 in the saffron and placebo groups, respectively.

Discussion

Depression and anxiety are serious and potentially life-threatening mental disorders [14, 18]. Various drugs have been used to treat these mental disorders, but these are associated with several side effects. Previous work has investigated the benefits of herbal remedies, including saffron, in the treatment of depression, and clinical trials suggest that saffron has antidepressant possessions [4, 13, 14, 19].

Saffron may exert its antidepressant effect by moderating the levels of certain neurotransmitters, comprising serotonin (a mood-elevating neurotransmitter). Though it has been suggested that saffron upsurges serotonin levels in the brain [20, 21], the precise mechanism of action for this is unidentified. More specifically, saffron extract may inhibit serotonin reuptake in synapses. Inhibiting synaptic serotonin reuptake maintains serotonin levels in the brain. This suggested mechanism is supported by animal studies, which support the antidepressant properties in extracts sourced from multiple parts of the saffron plant [20, 21]. These medicinal properties of saffron may be recognized to a number of its composites such as crocetin, crocins, and safranal, which have strong antioxidant and radical scavenger properties to defend against a diversity of reactive radical oxygen species and pro-inflammatory cytokines. Though, the exact mechanisms of saffron that affect mood states and improve symptoms of depression have not been recognized.

This study showed that saffron initiated enhanced mood in patients with mild-to-moderate depression and anxiety associated to the placebo group after 12 weeks of treatment. This finding showed improvements in the

scores of the BDI and BAI questionnaires comparing between two groups.

The results of the current trial are in line with four recent randomized controlled trials that have reported antidepressant effects for saffron. Use of 30 mg of saffron was associated with improvement of depression over placebo based on the Hamilton Depression Rating Scale (HAM-D) [8, 14]. Two randomized clinical trials were described an equivalent therapeutic response the synthetic agents, imipramine and fluoxetine comparing saffron [4, 14]. For instance, Akhondzadeh et al. reported that 30 mg/day saffron stigma ethanolic extract is effective similar to the antidepressant drug imipramine in the treatment of mild-to-moderate depression [19]. In 2005, another study was conducted comparing saffron to placebo. It drew a similar conclusion stating that 30 mg/day saffron for six weeks statistically improves the patients moods compared to placebo. A recent study revealed that the effectiveness 30 mg/day intake of saffron extracts for six weeks is similar to fluoxetine (the antidepressant, Prozac) in patient with mild-to-moderate depression [4]. The study detects no significant differences between treatment with fluoxetine or saffron and this data therefore support the antidepressant properties of saffron [4]. In the present study a higher dosage of the prescribed herbal medication was used for a longer duration than previous similar trials.

Hosseinzadeh and Noraei studied the effects of anti-anxiety and anti-hyptoniceffects of an aqueous extract of saffron aqueous extract and its constituents, crocin and safranal in an animal model [16]. Hosseinzadeh et al. determined that safranal, at doses of 0.15 and 0.35 mL/kg displayed anxiolytic effects and increased the total sleep time. It decreased some locomotion activity parameters in 0.05 and 0.15 mL/kg doses of crocin. Safranal had no effects on motor coordination. They concluded that saffron aqueous extract and safranal has anxiolytic and hypnotic properties [16]. These outcomes displayed a different effect resulting from consumption of whole saffron compared to its individual components [16]. Again the synergistic effects of different phytochemicals may contribute to saffron's more powerful treatment of insomnia and anxiety. Though, the mechanisms of this function are still unknown [16]. It has been described that crocin and safranal as two recognized components of saffron inhibit reuptake of dopamine, norepinephrine and serotonin [13].

It is worth noting that each complementary and alternative medicine treatment must be examined separately in adequately controlled clinical trials [9]. At this time, several complementary and substitute medicine managements appear promising and deserve further study [22]. Moreover, the greatest risk of pursuing a complementary and substitute medicine therapy is the possible delay of other well-established treatments [22].

Limitations of the present study were a single dose of saffron, the minor sample size and the temporary follow up should be considered in further survey.

Conclusions

The consequences of this study confirm the efficacy of saffron (*L. sativus*) for mild-to-moderate mixed anxiety and depression. Further studies should be undertaken in order to investigate the exact constituent of saffron as effective agent, and the dosage required for optimum effect on anxiety and depression. A large-scale trial is yet warranted, perhaps followed by some clinical end-point studies.

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