Research report

Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial

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Abstract

Objective: Herbal remedies play an important role in treatment of psychiatric disorders. The aim of this study was to assess the efficacy of crocin, the main active constituent of saffron, as an adjunctive treatment in major depressive disorder (MDD).

Method: This study was a randomized, double-blind, placebo-controlled, pilot clinical trial. It was carried out during 4 weeks in two groups (placebo and treatment) on 40 MDD patients between 24 and 50 years old in Ibn-e-Sina psychiatric hospital, Mashhad, Iran, from March 2013 to December 2013. The crocin group (n = 20) was given one selective serotonin reuptake inhibitor (SSRI) drug (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus crocin tablets (30 mg/day; 15 mg BID) and placebo group (n = 20) was administered one SSRI (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus placebo (two placebo tablets per day) for 4 weeks. Both groups filled beck depression inventory (BDI), beck anxiety inventory (BAI), general health questionnaire (GHQ), the mood disorder questionnaire (MDQ), side effect evaluation questionnaire, and demographic questionnaire before and after one month intervention.

Results: The crocin group showed significantly improved scores on BDI, BAI and GHQ compared to placebo group (P value < 0.0001). The averages of decrease in BDI, BAI and GHQ scores in placebo group were 6.15, 2.6 and 10.3 respectively, whereas the values in crocin group were 17.6, 12.7 and 17.2 after 4 weeks trial.

Limitations: Poor patient compliance with medications and short trial period, small sample size and self-report assessments were the major limitations of this study.

Conclusion: These results demonstrated the effect of crocin in depression and could be administered in treatment of MDD patients.

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1. Introduction

Depression is one of the top five most prevalent diseases worldwide (Bauer et al., 2013). It is a common, chronic, and potentially debilitating illness that has tempered the human condition (Blanco et al., 2014). Depression typically presents as depressed mood, insomnia or sleeping too much, agitation, fatigue or loss of energy and lowered libido (Guo et al., 2010; Kircanski et al., 2012; Loprinzi et al., 2013). Recent studies indicated that the incidence of depression during lifetime has been increased (Heun et al., 2013). Previous investigations concluded that the annual incidence of mood disorders is approximately 10% in the adult population and also 6.7% of adults suffer from an episode of major depression in a period of 12 months (Judd, 1995; Kessler et al., 2005). Although there are several possible precipitating factors, it is currently believed that depression is primarily the result of biochemical variations in the brain (Hermann et al., 1999). Pharmacological treatments, including selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOI), cause changes in brain chemistry through neurotransmitter augmentation and regulation and they have been shown to be effective in the treatment of depression.
Long-time or life-time treatment is sometimes offered to prevent major depressive disorder (MDD) relapse (Corruble et al., 2013). Many adverse reactions such as anticholinergic effects, nausea, constipation, sedation, orthostatic hypotension, arrhythmias and cardiac toxicity, weight gain or weight loss and sexual dysfunction and many drug interactions may occur with antidepressant medicines (Cascade et al., 2009; Ferguson, 2001; Sarkar et al., 2013). Nowadays, herbal remedies play an important role in treatment of psychiatric disorders such as anxiety and depression (Hosseinzadeh et al., 2012). Although, herbs are medicines with lower potency, they have showed less side effects and drug interactions compared to the chemical drugs (Cheung et al., 2012; Sarris et al., 2011). Addition of herbal remedies to the conventional antidepressants reduces some side effects e.g. tremor and agitation and improves the mental condition which could be helpful in treatment of depression as the main problem (Saku, 1991; Sarris et al., 2011). There are many natural products and medicinal plants that are the sources of new chemical substances with potential therapeutic efficacy against mental disorders (Hosseinzadeh and Younesi, 2002). *Crocus sativus* L., commonly known as saffron, belongs to the family Iridaceae (Ayatollahi et al., 2014). It has four purple flowers with red stigmas and yellow stamens and grows to 20–30 cm. Each flower consists of three trumpet shape stigmas. The dried stigmas are applied mainly in various foods as a seasoning and coloring agent (Assimopoulou et al., 2005). Saffron contains several compounds such as safranal (responsible for saffron odor and aroma), picrocrocin (responsible for saffron bitter taste) and crocin (the main saffron antioxidant as a dye material) (Ríos et al., 1996). Saffron can influence the chemical neurotransmitters level in the brain such as dopamine, norepinephrine and serotonin. As a fact, these neurotransmitters are strongly affected in depression. Also saffron and its active constituents e.g. crocin are effective agents as antidepressant, anticonvulsant, memory enhancer and sedative in treatment of central nervous system disorders (Hosseinzadeh and Younesi, 2002; Abdullaev, 2002; Hosseinzadeh and Khosravan, 2002; Hosseinzadeh et al., 2004; Zhang et al., 1994). Some well-designed clinical trials have indicated the efficacy of saffron in mild and moderate depression. In these studies saffron was more effective or at least equivalent to therapeutic doses of imipramine and fluoxetine in depression using Hamilton Depression Rating Scale (Berger et al., 2011; Kashani et al., 2013; Sarris et al., 2011). Crocin, as the main antioxidant saffron constituent, is a water-soluble carotenoid with a deep red color (Papandreou et al., 2006). Previous studies indicated the antidepressant effects of crocin in animal’s models (Hosseinzadeh et al., 2007) but there is not a published clinical trial supporting this claim. All above mentioned clinical trials have focused on saffron extract (not its main components) and its effect on mental disorders. The aim of the present work was to assess the efficacy of crocin in treatment of MDD in a 4-week double-blind, placebo-controlled and randomized pilot clinical trial. The results of this study were promising and introduced crocin as an antidepressant agent in treatment of MDD patients.

### 2. Materials and methods

#### 2.1. Preparation of crocin tablets

Saffron stigmas were purchased from Novin Saffron Co. (Mashhad, Iran). Extraction and crystallization of crocin from saffron stigmas were done according to our previous study (Hadizadeh et al., 2010). Crocin and placebo were formulated into film coated tablet by Department of Pharmaceutics, School of Pharmacy, Mashhad University of Medical Science. Each tablet contained 15 mg crocin.

#### 2.2. Clinical trial design

The study was a double-blind, prospective, placebo-controlled, 4-weeks clinical trial. Two parallel groups of MDD outpatient in Ibn-e-Sina Psychiatric Hospital, Mashhad University of Medical Sciences, participated in our study from March 2013 to December 2013. All potential subjects were examined by psychiatrist according to the Structured Clinical Interview of the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Gadermann et al., 2012; Shemmassian and Lee, 2014). To improve the quality of our results, we applied inclusion and exclusion criteria for patients in this study. Inclusion criteria included: (1) diagnosis of MDD based on DSM-IV; (2) Patients in the range of 18–50 years old; (3) patient satisfaction for participation in clinical trial. Exclusion criteria included: (1) significant organic or neurological disorder, (2) patients taken psychotropic medications

![Flowchart of the trial](image-url)
in recent month, (3) current or past mood disorder, (4) personal disorder, (5) cognitive disorder, (6) psychotic disorder or (7) depression with psychotic features, (8) a history of substance abuse or substance dependence, and (9) patient with a significant risk of suicide. Consent form was obtained from each patient before entering the study. The patients were informed of their right to withdraw from the study without any negative effect on their relationship with health care providers. This trial was carried out in accordance with Ethical Committee Acts in Mashhad University of Medical Sciences. This clinical trial was registered at the Iranian Clinical Trials Registry (IRCT2013041813058N1; www.irct.ir). Forty six participants were included into this study (Fig. 1). The patients were randomly divided into the crocin (23 patients) and the placebo (23 patients) groups (Table 1) and a randomization code number was given to each pillbox (crocin or placebo) by Excel software. Six patients were excluded and finally 40 patients successfully completed the trial.

2.3. Interventions

The patients in crocin group were given one SSRI (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus crocin tablet (30 mg/day; 15 mg BID) for 4 weeks, whereas the patients in placebo group were given one SSRI (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus placebo (two placebo tablets per day, one tablet BID) for 4 weeks. The crocin and the placebo tablets had the same shape and color and each tablet container had a random code number to perform a double-blind clinical trial. Participants were not allowed to receive any other antidepressant drugs or behavior therapy during the study. The medication adherence and patient compliance were assessed through checking with the patient and his/her caregiver along with a pill count at each visit.

2.4. Blinding

Crocin and placebo tablets were prepared in the same way. They had identical shape, color, size, texture and odor. The tablets were packed in the same container with a code number. The tablets were prepared by a pharmacist. Thus, patients, physician and other investigators were all blind to the treatment group assignments.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crocin group</th>
<th>Placebo group</th>
<th>P value</th>
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<tr>
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<td>36.5 (7.67)</td>
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<tr>
<td>Gender</td>
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</tr>
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</tr>
<tr>
<td>Male</td>
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<td>4</td>
<td>0.66</td>
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<tr>
<td>Marital status (n)</td>
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<td></td>
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<td>16</td>
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</tr>
<tr>
<td>Single</td>
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<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>Divorced</td>
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<td>1.00</td>
</tr>
<tr>
<td>Widow</td>
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<td>0.48</td>
</tr>
<tr>
<td>Level of education (n)</td>
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<td></td>
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<td>0</td>
<td>−</td>
</tr>
<tr>
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<td>1.00</td>
</tr>
<tr>
<td>Previous treatment with psychiatric drugs</td>
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<td>0</td>
<td>−</td>
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</tr>
<tr>
<td>Current</td>
<td>0</td>
<td>0</td>
<td>−</td>
</tr>
</tbody>
</table>

2.5. Safety

The patients were requested to inform investigators about any adverse events or complaint during the trial. The symptoms were checked and recorded at the beginning and at each base-line visit. Also, possible side effects were checked and recorded via telephone call every week and the physician was responsible for continuing or discontinuing the drugs. The adverse effects check list was completed by independent raters.

2.6. Instruments

All the patients answered some questions about their socio-demographic information including age, sex, marital status, educational level, Beck depression inventory (BDI), general health questionnaire (GHQ), Beck anxiety inventory (BAI) and mood disorder questionnaire (MDQ). BDI is the most widely used self-rating scale and previous studies indicated its reliability and validity in patients with depression (Jolly et al., 1993). It is appropriate to all social levels and is neither age nor culture based (Kashani et al., 1990). It consists of 21 items of emotional, behavioral, and somatic symptoms. The scores between 0–9, 10–19 and 20–29 indicate normal, mild and moderate depression respectively. The score of 30 and more shows major depressive disorder (MDD) (Lindsay and Skene, 2007). GHQ is a screening device for detecting minor psychiatric disorder in patients (Masunaga et al., 2013). It is suitable for all ages (but not children) from adolescent upwards; it recognizes the patient’s current state and asks if that differs from his or her usual state. It has 28 items that diagnoses somatic symptoms, anxiety and insomnia, social dysfunction and severe depression. For each item four answer possibilities are available; 1: not at all, 2: no more than usual, 3: rather more than usual, and 4: much more than usual and the total scale score ranges from 28 to 112. The higher score shows the poorer psychological condition of patients (Martínez and Custódio, 2014). BAI is a brief measure of anxiety with a focus on somatic symptoms of anxiety (Adams et al., 2013). It has 21 items that measure the severity of an anxiety in adults and adolescents. The items of this inventory describe the emotional, physiological, and cognitive symptoms of anxiety. It can discriminate anxiety from depression. The total score ranges from 0 to 63. The score of 0–21: mild anxiety; 22–35: moderate anxiety and 35–63: severe anxiety (Ak et al., 2012). MDQ is a device for recognizing the signs and symptoms of manic or bipolar disorder, including mania and/or depression (Caddell and Clare, 2012).

2.7. Statistical analysis

The normality test was carried out for all data. The results before and after treatment and the difference values between scores passed the normality test. Thus, independent t-test was applied to evaluate the scores in two independent groups (crocin and placebo) after 4 weeks trial, whereas paired t-test was used to evaluate the scores within each group before and after treatment. Categorical data were compared using Fisher’s exact test. The variables were presented as means ± standard error of the mean (SEM) and the P value less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic characters and psychological conditions of the participants

Firstly, 46 patients were randomized in two groups, six patients could not complete the study and 40 patients successfully finished the trial. A total of 40 patients (34 female and 6 male, mean age
A comparison between groups and a 4 weeks trial between two groups. Independent t-test was applied to evaluate the differences between groups (crocin and placebo), whereas paired t-test was used to evaluate the scores within each group before and after treatment. **P < 0.0001** comparison between groups and ***P < 0.0001*** comparison within each group.

![Graph of BDI scores](image)

**Fig. 2.** Mean ± SEM scores of two groups of patients on the BDI. Statistical analysis showed a significant difference in reduction of BDI scores from the baseline after 4 weeks trial between two groups. Independent t-test was applied to evaluate the differences between groups (crocin and placebo), whereas paired t-test was used to evaluate the scores within each group before and after treatment. **P < 0.0001** comparison between groups and ***P < 0.0001*** comparison within each group.

![Graph of BAI scores](image)

**Fig. 3.** Mean ± SEM scores of two groups of patients on the BAI. Statistical analysis showed a significant difference in reduction of BAI scores from the baseline after 4 weeks trial between two groups. Independent t-test was applied to evaluate the differences between groups (crocin and placebo), whereas paired t-test was used to evaluate the scores within each group before and after treatment. **P < 0.0001** comparison between groups and ***P < 0.0001*** comparison within each group.

![Graph of GHQ scores](image)

**Fig. 4.** Mean ± SEM scores of two groups of patients on the GHQ. Statistical analysis showed a significant difference in reduction of GHQ scores from the baseline after 4 weeks trial between two groups. Independent t-test was applied to evaluate the differences between groups (crocin and placebo), whereas paired t-test was used to evaluate the scores within each group before and after treatment. **P < 0.0001** comparison between groups and ***P < 0.0001*** comparison within each group.

36.2 years) could finish the study. There were no significant differences (P-value > 0.05) between demographic characters of the patients in two groups (Table 1). The BDI and GHQ scores were not significantly different between groups (P-value > 0.05), whereas the mean difference in BAI score was 3.1 (the score in crocin group was slightly more than placebo group, P-value = 0.028) at the baseline visit (Figs. 2–4).

### 3.2. Efficacy measures

According to our results, administration of crocin tablets (30 mg/day; 15 mg BID) in crocin group, gradually improved scores in all inventories during the trial. Fig. 2 indicated a 17.6 reduction (42.2%) in BDI score in crocin group, whereas the decrease in placebo group was 6.1 BDI score (15.9%). Also, the reductions in BAI and GHQ scores were 12.7 (33%) and 17.2 (21.5%) in crocin group, whereas the values in placebo group were 2.6 (7.5%) and 10.3 (12.3%) (Figs. 3 and 4). The statistical analysis demonstrated that the differences between two groups were significant (P-value < 0.0001) in all inventories (Table 2). The maximum and minimum reductions in BDI scores in crocin group were 51.3% and 31.0% respectively, whereas the maximum and minimum reduction values in placebo groups were 38.2% and 0%. These results showed a significant improve in depressive symptoms in crocin group compared to the placebo group.

### 3.3. Clinical complications and adverse effect

Although 46 patients were included firstly into two groups in the study, finally 40 patients finished the experiment and six patients were excluded. No serious adverse effect was reported in this trial. In placebo group one person did not continue the study without any side effect, whereas one patient reported the urinary incontinency. Also, one case of dyspnea was reported in placebo group. In crocin group dyspnea, agitation and menometrorrhagia were reported in 3 different patients. Thus, they did not continue to finish the study. Therefore 40 patients between 24 and 50 years old enrolled in the study; 20 patients assigned to the crocin group and 20 patients assigned to the placebo group. The two groups were well matched, and no statistically significant difference was observed between groups in the frequency of side effects (Table 3).

### 4. Discussion

As mentioned before, all patients received one SSRI per day such as sertraline, fluoxetine or citalopram. Some of the above mentioned side effects such as difficulty with breathing, urinary incontinency and agitation have been reported previously in administration of SSRI antidepressant drugs (Ferguson, 2001; Murphy et al., 2008; Rief et al., 2009; Zullino and Khazaal, 2005). Also, menstrual irregularities have been observed with sertraline (Uguz et al., 2012). Thus, the reported side effects in our study can be attributed to administration of SSRIs. Mohamadpour et al. evaluated the safety of crocin in healthy volunteers. They investigated the effects of crocin tablets (20 mg per day for one month) on biochemical, hormonal, hematological and urinary parameters in pre and post-treatment periods (Mohamadpour et al., 2013). Crocin tablets did not show major side effects or change the above mentioned factors except decreased mixed white blood cells, amylases and PTT during trial. According to our data and previous studies crocin does not have a serious adverse effect in therapeutic doses. However, more investigations are recommended. The experimental results showed that orally administration of crocin as an adjunct to SSRIs leads to significantly greater decrease in depressive symptoms in comparison with SSRI alone treatment. Reduction in the BDI, BAI and GHQ scores was the clinical
depression (Noorbala et al., 2005). A research group reported that saffron has a similar performance in treatment of depression symptoms (Akhondzadeh et al., 2005). Another work biologically, administration of saffron extract resulted in significant decrease in depression symptoms (Akhoundzadeh et al., 2005). Another work reported that saffron extract may alleviate the symptoms of premenstrual syndrome including depression (Agha-Hosseini et al., 2013). Nowadays herbal medicine holds a valorous place in treatment of psychiatric diseases like MDD (Gautam et al., 2012). As we said before antidepressant effect of crocin in animal models (Hosseinzadeh and Khosravan, 2002; Hosseinzadeh et al., 2004). Furthermore, another research indicated that oxidative stress, due to an accumulation of free radicals, especially superoxide anions and thereby protect cells from oxidative stress and antidepressant treatment (Chung et al., 2013; Michel et al., 2012; Zhou et al., 2006). The carotenoids clean free radicals, especially superoxide anions and thereby protect cells from oxidative stress (Bors et al., 1982). Due to these effects, crocin can be an effective adjuvant for the treatment of mild to moderate depression and anxiety in patients. Furthermore, our findings supported previous works and were in conformance with antidepressant effect of crocin in animal models (Hosseinzadeh and Khosravan, 2002; Hosseinzadeh et al., 2004). Nowadays herbal medicine holds a valorous place in treatment of psychiatric disorder such as depression, anxiety and the other mental problems. According to some research works, saffron can be used as a valuable agent in the treatment of depression. Proverbially, administration of saffron extract resulted in significant decrease in depression symptoms (Akhoundzadeh et al., 2005). Another work reported that saffron has a similar performance in treatment of depression (Noorbala et al., 2005). A research group reported that petal of saffron in addition to stigma has antidepressant effect in rat and mice (Hosseinzadeh et al., 2007). Furthermore, another research reported that saffron extract may alleviate the symptoms of premenstrual syndrome including depression (Agha-Hosseini et al., 2008). But all these studies were about saffron extract and there was not any data about antidepressant effects of crocin in human. All of these effects may be attributed to a synergistic action of many constituents in saffron such as crocin, picrocrocin, safranal and flavonoids. In this study, we assessed the effect of crocin compared to placebo. However the role of crocin in treatment of mild to moderate depression is not well understood, a group of evidence indicated that oxidative stress, due to an accumulation of free radicals, may play an important role in the pathogenesis of neurological and psychiatric diseases like MDD (Gautam et al., 2012). As we said before crocin is the main antioxidant constituent in saffron stigmas (Rt os et al., 1996). Some studies showed that oxidative stress was increased in depressed patients and reported the correlations between reduced oxidative stress and antidepressant treatment (Chung et al., 2013; Michel et al., 2012; Zhou et al., 2006). The carotenoids clean free radicals, especially superoxide anions and thereby protect cells from oxidative stress (Bors et al., 1982). Due to these effects, adjunctive therapy with crocin may provide further protection as it is powerful antioxidant and plays an important role in preventing free radical-induced damage in the brain (Behr et al., 2012). Also, our experimental findings showed that the decrease in depressive symptoms in patients may be attributed to the synergistic antidepressant effect of crocin and psychiatric drugs (SSRIs). Finally, in this study, for a short period of time, contributors were only treated and assessed. But, we suggest that the long term studies for better investigation of the crocin effects as an adjunct to SSRIs are needed.

4.1. Limitations

Although the results of this study showed the efficacy of crocin as an effective therapeutic adjuvant, it also had some limitations. Six patients could not finish the treatment period and were excluded from the study. In placebo group one person did not continue the study without any side effects, whereas one patient reported the urinary incontinency. Also, one case of dyspnea was reported in placebo group. In crocin group dyspnea, agitation and menometrorrhagia were reported in 3 different patients. Thus, they did not continue to finish the study. Therefore, the small sample size was one of our study limitations. Also, the trial was carried out in a short time. It could be done in a longer trial period. Self-report assessments and poor patient compliance with prescribed medications were other limitations of this study.

5. Conclusion

In this work, addition of crocin tablets (30 mg/day, 15 mg BID) amplified the effects of SSRIs in treatment of patients with mild to moderate depression. Also, due to absence of substantial side effects, crocin was shown to be a particularly effective therapeutic adjuvant. Improvements in psychiatric tests (mentioned above) were the clinical relevance of the antidepressant effect of crocin. These findings suggested that the antidepressant effects of saffron extract could be attributed to crocin as the main antioxidant constituents in saffron stigmas. However, further research works are required to clarify the mechanism of this effect.

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Conflict of interest

The authors have declared there is no conflict of interest.

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References


