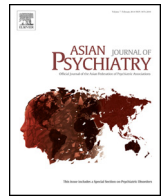




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Study the effects of saffron on depression and lipid profiles: A double blind comparative study

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ABSTRACT

Depression is a one of the most prevalent psychiatric disorder. Despite several pharmacological treatments, still treating depression is a challenge. Herbal medicine that is better culturally accepted may play an important role in treatment of depression. In this double blind placebo controlled clinical trial, 40 patients that were suffering from major depression according to DSM-IV criteria were randomly allocated to take either fluoxetine and saffron (20 patients) or fluoxetine and placebo (20 patients). The patients of the two groups were evaluated with Beck depression scale at the beginning of the study and after four weeks. Lipid profile (total Triglyceride (TG) level, total cholesterol level, low density lipoprotein (LDL) level and high density lipoprotein (HDL) level) of the patients also was measured at the beginning and end of the trial. 30 patients (19 in saffron group and 11 in placebo group) completed the study. The two groups improved significantly in depression severity at the end of the study without significant difference ($P: 0.560$). The lipid profile of the two groups did not change significantly. Our study did not demonstrate antidepressive effects for saffron. We did not observe any lipid lowering effect in saffron group too. Of note is that our study is preliminary and larger studies with more patients and longer duration are needed to prove our results.

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1. Introduction

Major depressive disorder (MDD) is a severe and deteriorating illness that would cause a great decrease in human health and overall functioning (Hasin et al., 2006; Mathers and Loncar, 2006; Ustün et al., 2000). Despite the availability of several antidepressants in recent decades, more than one third of patients will not respond to the first antidepressant prescribed, and 15 to 33% will get resistant to more than two antidepressant trials (Berlim et al., 2008; Cain, 2007). Many MDD patients suffer from a chronic course without sufficient improvement that would lead to disability (Little, 2009). Therefore more studies are needed to find new lines of treatment.

Herbal medicine with better culturally acceptance are good lines for research for their efficacy in depression in future researches (Sarris et al., 2011; Velehorsch et al., 2014). More than 20 herbal remedies have been identified that may potentially be applied in medicine as antidepressive, anxiety relieving or

sleep-inducing agents (Szafranski, 2014). St John's wort is an example of herbal medicine which people use to manage their depression with better preference than generic medicines (Pirodda et al., 2014).

Saffron, a spice derived from the flower of *Crocus sativus* L., has shown antidepressant effects in several surveys (Schmidt et al., 2007; Abdullaev and Espinosa-Aguirre, 2004). Hausenblas et al. in their review of clinical trials examining the effects of saffron on psychological symptoms found that saffron improves the clinical symptoms of patients with major depression (Hausenblas et al., 2013, 2015). In a systemic review of six clinical trials of the effects of saffron on depression, the improving effect of saffron for mild to moderate depression was observed (Lopresti and Drummond, 2014). The exact mechanism of effect of saffron on depression is not well known. *C. sativus* L. was found to have medical effects for Persian physicians from long time ago. *C. sativus* L. is widely cultivated in Khorasan province in north east of Iran. In our study, we used saffron as add-on treatment along with standard antidepressants to survey its effects as a potentiating agent for standard antidepressant in treating depressive symptoms. We also aimed to study the side effects that emerged following adding saffron to fluoxetine.

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Changes in serum lipid levels are associated with psychological problems like depression, suicidal behavior and impulsivity (Ainiyet and Rybakowski, 2014; Steegmans et al., 2000). Recent studies have demonstrated an association between depression and metabolic alterations (Tedders et al., 2011; Sjögren et al., 2006; Patra et al., 2014). Saffron has demonstrated beneficial effects on lipid profile in one recent survey (Azimi et al., 2014). In another study, it was shown that saffron could prevent the metabolic syndrome associated with olanzapine treatment in schizophrenia patients (Fadai et al., 2014). Further studies need to be done regarding the metabolic effects of saffron.

In this study the antidepressant effect of saffron will be surveyed in a double blind placebo control trial. The effects of saffron on lipid profile of the patients also will be probed.

2. Method

2.1. Patients

Forty adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994) criteria for major depressive disorder based on structured clinical interview entered the trial. The inclusion criteria were: diagnosis of MDD according to DSM-IV-TR criteria, age range 18–65 years and giving informed consent. Exclusion criteria's were history of suicide; presence of any medical or psychiatry disease; use of any antidepressant or lipid lowering drug in the past six months and pregnancy.

The trial was performed in accordance with the declaration of Helsinki and subsequent revisions and approved by ethic committee of Shiraz University of Medical Sciences. Written informed consents were obtained from patients before entering into the study.

2.2. Saffron capsule preparation

The saffron which was used in this study was obtained from the first grade saffron fields in Khorasan province, Iran. The part of *C. sativus* L. that are being used as herbal medicine is packed into capsules. Each capsule contained 30 mg of the powder.

2.3. Study design

This was a 4-week randomized, double-blind clinical trial. This survey was done in Hafez psychiatry clinic affiliated by Shiraz University of Medical Sciences, Shiraz, Iran.

All the patients were interviewed by a psychiatrist before the study. The patients were administered Beck depression rating scale at the beginning and end of the survey 0.5 cm³ of venous blood was obtained from patients before and after treatment. The blood was evaluated for complete lipid profile. We used a standard randomization procedure generated by a computer to obtain random sample sets. The placebo and saffron capsules had the same shape and color. The study group was named as “Group-A”

and control group as “Group-B”. Group A received saffron capsule and 20 mg of fluoxetine and Group B received placebo capsule and 20 mg of fluoxetine daily for 4 weeks. Throughout the study, the examiner and the patients were blind to assignments. After four weeks, the patients were evaluated for depression severity with Beck depression scale.

2.4. Statistical analysis

The data are shown with mean (SD). The demographic data and Depression severity of the groups were compared at the beginning of the study using χ^2 and Mann–Whitney *U* tests.

We used Mann–Whitney *U* test to compare the groups for significantly different effects, and the Wilcoxon signed ranks test was used to assess the changes within groups. *P* value of <0.05 was noted significant.

3. Results

Of 40 patients who were randomized to treatment, 30 patients completed the trial and there were 10 dropouts (1 dropout in Saffron and 9 in placebo group). The only dropout in saffron group was because of headache and nausea and the drop outs in placebo group were mainly because of headache, abdominal discomfort and nausea.

Treatment groups were comparable at baseline on the variables of sex, age, and education. Overall, in this study, the mean age was 43.4 years (range, 18–55 years), and 56.8% were women. The number of patients that completed the study in group A (saffron) was 19 and in group B (Placebo) was 11.

The Beck depression score and the lipid profile of patients' pre and post treatment are depicted in Table 1. The two groups did not differ significantly regarding depression scale and lipid profile at the beginning of the study.

In both groups, the patients demonstrated significant improvement in Beck depression scale after four weeks (Saffron group: *P* = 0.003; Placebo group = 0.000). But the improvement in depression scale did not differ significantly between the two groups (*P* = 0.560) (Table 1).

At the end of the study, the lipid profile (total TG level, total Cholesterol level, LDL level and HDL level) of the patients of both groups did not change significantly (Table 1).

4. Discussion

This double blind placebo controlled study revealed that saffron was not effective in potentiating the antidepressant effect of fluoxetine. The patients in both groups showed improvement in depression scales without significant difference. The lipid profile of the two groups also did not change significantly at the end of the study.

In several placebo-comparison trials, saffron had large treatment effects on depression and when compared with antidepressant medications, had similar antidepressant efficacy (Karimi et al.,

Table 1

Beck depression scale and lipid profile before and after treatment.

	Saffron and fluoxetine group			Placebo and fluoxetine group			Comparison of the groups
	Pretreatment	Post treatment	<i>P</i> value	Pretreatment	Post treatment	<i>P</i> value	
Beck depression scale	22.12	16.04	0.003	22.54	15.43	0.000	0.560
Total TG level	122.58	115.06	0.534	111.27	106.27	0.654	0.252
Total Chol level	168.37	170.28	0.919	164.72	166.18	0.785	0.736
LDL level	109.53	104.78	0.760	99.90	98.56	0.987	0.669
HDL level	45.26	44.50	0.893	49.10	50.55	0.867	0.804

TG: triglyceride, Chol: cholesterol, LDL: low density lipoprotein, HDL: high density lipoprotein.

2001; Lopresti and Drummond, 2014; Talaei et al., 2014; Hausenblas et al., 2013; Shahmansouri et al., 2014). Saffron's antidepressant effects have been shown to be due to its serotonergic, antioxidant, anti monoamine oxidases (MAO), anti-inflammatory, neuro-endocrine and neuroprotective effects (De Monte et al., 2014). In contrast to these studies, our study did not show antidepressant effect for saffron. This may be because our study was an add-on survey and also the short duration of the study. It is likely that with longer duration of treatment, more benefits with saffron may emerge.

Raeder et al. in a cross-sectional survey in Hordaland County in Norway demonstrated that patients taking SSRIs may be associated with some metabolic changes. This study reported that sertraline, fluoxetine, or fluvoxamine, in 131 patients, was associated with hypercholesterolemia. However, in 187 patients on paroxetine and 142 patients on citalopram, the use of the drug did not show association with hypercholesterolemia (Raeder et al., 2006). Shahsavand Ananloo et al. in their study showed that fluoxetine in contrast to imipramine can decrease total cholesterol and triglyceride level in short term (Shahsavand Ananloo et al., 2013). Our survey demonstrated that fluoxetine did not alter the lipid profile of the patients. This may be due to short duration of the study. The study period may not have been long enough to show the chronic effects of fluoxetine on lipid profile. Unlike to some previous studies (Azimi et al., 2014; Fadai et al., 2014), our study revealed that saffron has no effect on lipid profile of the depressed patient.

The pitfalls of our study were its short duration, the noncooperation of some patients and the fix dose of saffron during the study.

Of note is that our study is preliminary and larger studies with more patients and longer duration are needed to confirm the results.

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