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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.

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

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(Cascade et al., 2009; Hermann et al., 1999). 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 occurr 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, herbals 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

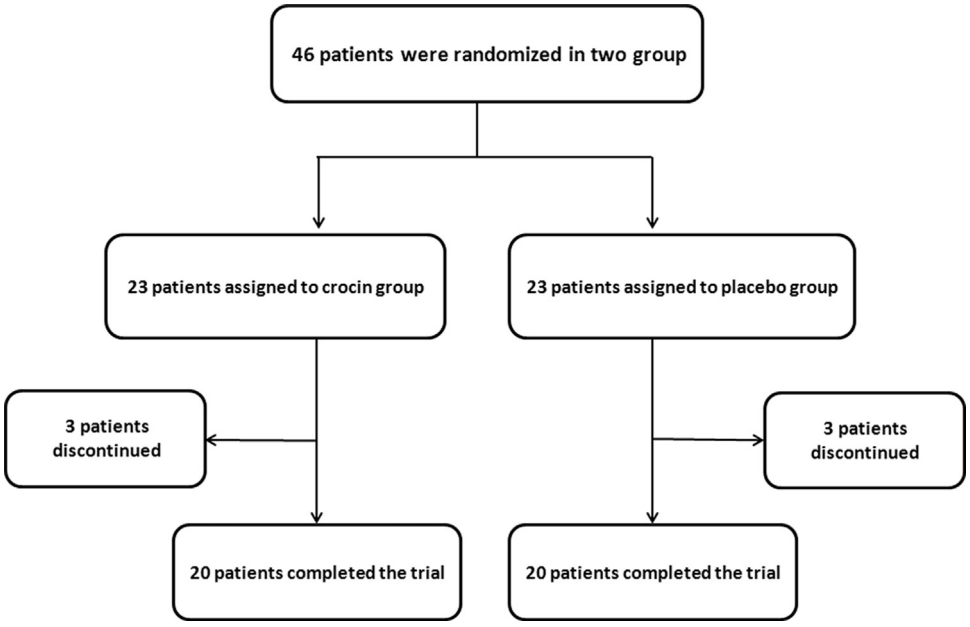

Fig. 1. Flowchart of the trial.