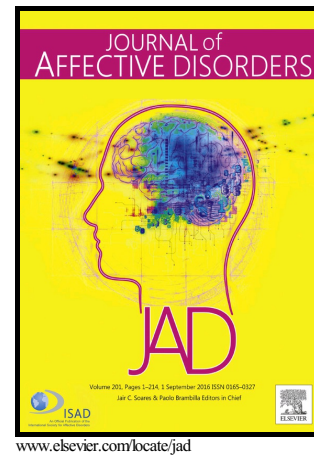


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Saffron in the treatment of depression, anxiety and other mental disorders: current evidence and potential mechanisms of action

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Abstract

Background:

Depression and anxiety are two common mental health problems with high economic and social costs. Currently, a number of treatments are available for patients with depression and anxiety disorders such as psychotherapy, electroconvulsive therapy and antidepressant drugs. Due to safety concerns, adverse effects, limited efficacy and low tolerability associated with many antidepressant and anti-anxiety medications, identification of novel agents with less toxicity and more favorable outcome is warranted.

Methods:

The current article provides a non-systematic review of the available *in vitro*, *in vivo* and clinical evidence on the efficacy, safety and mechanisms of action of saffron and its active ingredients in the treatment of anxiety, depression and other mental disorders.

Results:

Several interesting data have been reported about the antidepressant and anti-anxiety properties of saffron, the dried stigmas of *Crocus sativus* L., in several preclinical and clinical studies. In particular, a number of clinical trials demonstrated that saffron and its active constituents possess antidepressant properties similar to those of current antidepressant medications such as fluoxetine, imipramine and citalopram, but with fewer reported side effects.

Conclusion:

Saffron may exert antidepressant effects and represents an efficacious and safe treatment.

Keywords: Saffron; Crocin; Psychological disorders; Depression; Anxiety

1. Introduction

Depression is a common mental disorder which has a high burden of disease (Alonso et al., 2004; Ferrari et al., 2013) as well as a high economic burden (Greenberg et al., 2015; Gustavsson et al., 2011). It is mainly characterized by a cluster of psychological, physical, and behavioral symptoms including depressed mood, loss of interest in daily activities, fatigue, feelings of worthlessness or guilt, diminished ability to think or concentrate, recurrent thoughts of death and weight loss or weight gain as well as sleep and appetite disturbances (Association, 2013). About 8-12% of the world population experience depression at least once in their life (Andrade et al., 2003). A recent study showed that morbidity in both unipolar major depressive disorder (MDD) and bipolar disorder (BD) patients is remarkably high even in those treated by contemporary community standards (Baldessarini et al., 2017). In most cases, depression may co-occur with anxiety (Tyrer, 2001), another common mental health problem which is associated with poor quality of life (Griebel and Holmes, 2013). Patients with anxiety disorders often experience feeling tense, worried, frightened, unable to relax and/or panic (Association, 2013).

A number of treatments are currently available for patients with depression including antidepressant drugs, electroconvulsive therapy, psychotherapy, and other somatic treatments. After the discovery of antidepressants in the 1950s, a revolution occurred in the treatment of depression

with a considerable reduction in suicide risk among depressives (Hall et al., 2003; Isacson et al., 1996). However, the antidepressants used to treat depression possess several limitations such as low probabilities of remission (despite multiple treatment attempts, more than 30% of patients fail to achieve remission) (Rush, 2007) and low tolerability (28% of depressed patients stop taking their medication in the first month of treatment and 44% discontinue within 3 months) (Cassano and Fava, 2004; Lin et al., 1995). In the past, different classes of antidepressants were available such as tricyclic antidepressants (TCA) and MAO inhibitors (MAOI), known as “first generation” antidepressants, which act by increasing the extracellular availability of monoamines (Schatzberg and Nemeroff, 2009). However, nowadays these drugs are rarely used due to negative health effects associated with their consumption (Brown et al., 1989; PREDICTABLE, 2006). Although the side effects of newer antidepressants are not as significant as earlier ones, they are still present in second and third generation antidepressants such as sexual dysfunction, gastrointestinal effects, discontinuation syndrome, and etc. (PREDICTABLE, 2006). Concerning anxiety, there is evidence of the efficacy of certain drugs such as selective serotonin reuptake inhibitors (SSRI); however, current anti-anxiety medications have insufficient overall efficacy in short-term and long-term treatments and possess some adverse effects when prescribed for long periods (Baldwin et al., 2011). Thus, considering the limitations associated with currently available antidepressants and anti-anxiety drugs, there is a need looking for a less toxic therapy with more favorable outcomes in depressed patients.

Saffron, the dried stigmas of *Crocus sativus* L., is a highly valued agricultural product that is used exclusively for cooking purposes to give flavor, color and aroma to food (Sampathu et al., 1984). This member of the Iridaceae family is comprised mainly of carbohydrates including starch, reducing sugars, gums, pectin, pentosans, and dextrins (Rios et al., 1996). However, the value of saffron is determined by the existence of three main secondary metabolites, including crocin (responsible for the color), picrocrocin (responsible for the bitter taste) and safranal (responsible for the odor and aroma) (Liakopoulou-Kyriakides and Kyriakidis, 2002; Pfander and Wittwer, 1975). Saffron also contains crocetin, which is the hydrolysis product of crocin. As a component of traditional medicine, saffron has been utilized as a medicinal herb for treating various ailments (Javadi et al., 2013; Schmidt et al., 2007). Recent studies also confirmed the medicinal properties of saffron as an antioxidant

(Hosseinzadeh et al., 2009; Ochiai et al., 2004), anti-carcinogenic (Ashrafi et al., 2015; Samarghandian et al., 2010), memory enhancer (Abe and Saito, 2000; Ghadrdoost et al., 2011a; Hosseinzadeh and Ziaei, 2006), neuroprotective (Mehri et al., 2012), and cardioprotective (Goyal et al., 2010; Zhang et al., 2009).

Saffron and its constituents have been extensively investigated for its antidepressant effects and it has been suggested as a potential efficacious and tolerable treatment for depression and anxiety (Basiri-Moghadam et al., 2016; Mazidi et al., 2016; Noorbala et al., 2005; Talaei et al., 2015). This review summarizes the antidepressant and anti-anxiety effects of saffron and its components in preclinical and clinical studies.

2. Effects of Saffron and Its Constituents on Depression

2.1. Preclinical Studies

There are several studies investigating the antidepressant effects of crocin and ethanolic extracts of saffron *in vivo* (Amin et al., 2015; Hosseinzadeh et al., 2003; Hosseinzadeh et al., 2007; KARIMI et al., 2001; Wang et al., 2010). In a study by Hosseinzadeh et al., the antidepressant activity of *Crocus sativus* L. stigma extracts and their constituents, safranal and crocin were investigated using forced swimming test in mice. At the end of the experiment, *C. sativus* extracts and their constituents showed antidepressant activities. The authors suggested the activation of serotonergic, noradrenergic and dopaminergic system as the potential mechanism underlying this antidepressant activity (Hosseinzadeh et al., 2003). In a similar study, the antidepressant activity of kaempferol, another *C. sativus* petal constituent, was confirmed using forced swimming test in mice and rat (Hosseinzadeh et al., 2007). Wang et al., in a study assessing the antidepressant properties of stigmas and corms of *C. sativus* in an animal model of depression, introduced the low polarity parts of *C. sativus* corms as a new plant material for curing depression (Wang et al., 2010). Moreover, in a study conducted by Amin et al. the antidepressant effects of crocin and crocetin were evaluated using mice in two different regimens of acute and sub-acute administration. The researchers found crocetin more effective than crocin in treatment of depression since higher doses of crocin were required to show antidepressant effects (Amin et al., 2015).

2.2. Clinical Trials

The efficacy of saffron in the treatment of depression has been widely investigated in clinical trials with different intervention (Saffron or Crocin) and control (Placebo or Antidepressant) groups. The characteristics and main results of these clinical trials are summarized in Table 1.

2.2.1. Saffron vs Placebo

In a randomized controlled trial by Mazidi et al., 60 adult patients with anxiety and depression were randomized to receive a 50 mg saffron capsule (*Crocus sativus* L. stigma) or a placebo twice daily for 12 weeks. The authors observed a significant reduction of Beck Depression and Anxiety Inventory scores in subjects with saffron supplementation in comparison to placebo at the 12-week time-point (Mazidi et al., 2016). In another study assessing the efficacy of petal of *Crocus sativus* L. in the treatment of mild to moderate depression, forty adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) for major depression were randomly assigned to receive capsule of petal of *C. sativus* 30 mg/day (bid) and capsule of placebo (bid) for a 6-week study. At the end of this randomized controlled trial, petal of *C. sativus* produced a significantly better outcome on Hamilton Depression Rating Scale than placebo and there were no differences in the case of side effects (Moshiri et al., 2006). In a similar study by Akhondzadeh et al., the same results were obtained (Akhondzadeh et al., 2005). Sahraian and colleagues also designed a double blind placebo controlled clinical trial where 40 patients 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 results showed a significant improvement in depression severity in both groups at the end of the study; however, there was no significant difference between treatment and placebo groups which can be attributable to short duration of the study, given that antidepressant properties of saffron can be observed with longer duration of treatment (Sahraian et al., 2016).

In another randomized, double-blind, placebo-controlled study investigating the antidepressant effects of combined curcumin and saffron, 123 individuals with major depressive disorder were allocated to one of four treatment conditions, comprising placebo, low-dose curcumin extract (250 mg bid) (morning and evening), high-dose curcumin extract (500 mg bid), or combined low-dose curcumin extract plus saffron (15 mg bid) for 12 weeks. Lopresti and colleagues concluded

that different doses of curcumin and combined curcumin/saffron treatments were effective in reducing depressive and anxiolytic symptoms in people with major depressive disorder (Lopresti and Drummond, 2017).

2.2.2. Saffron vs Antidepressants

There are several studies comparing the antidepressant effects of saffron with usual antidepressant drugs (Akhondzadeh Basti et al., 2007; Akhondzadeh et al., 2004; Ghajar et al., 2016; Kashani et al., 2016; Noorbala et al., 2005; Shahmansouri et al., 2014). In a randomized, double-blind, clinical trial, 40 patients with a diagnosis of mild to moderate depression who had undergone percutaneous coronary intervention in the last six months were randomized to receive either saffron (30mg/day) capsule or fluoxetine (40mg/day) for six weeks. The authors observed no significant differences between two groups in reduction of depression scores and reported a same antidepressant efficacy for saffron capsules when compared with fluoxetine in short-term therapy (Shahmansouri et al., 2014). Noorbala et al. also compared the efficacy of hydro-alcoholic extract of *Crocus sativus* (stigma) with fluoxetine in the treatment of mild to moderate depression. Forty depressed subjects were randomly assigned to receive capsules of saffron (30 mg/day, bid) and capsule of fluoxetine (20 mg/day, bid) for a 6-week study. Saffron also at this dose had antidepressant effects similar to fluoxetine in the treatment of mild to moderate depression (Noorbala et al., 2005). In a pilot double-blind randomized trial with the aim of comparing the efficacy of petal of *C. sativus* with fluoxetine, forty depressed adult outpatients were randomly assigned to receive capsule of petal of *C. sativus* 15 mg bid and fluoxetine 10 mg bid for a duration of 8-week. The authors found no significant differences between the two treatments in the case of efficacy and observed side effects (Akhondzadeh Basti et al., 2007). Kashani et al. also conducted a double-blind, randomized clinical trial in which 68 women aged 18–45 years with mild to moderate postpartum depression were randomized to receive either a capsule of saffron (15 mg capsule) or fluoxetine (20 mg capsule) twice daily for 6 weeks. The authors observed that 40.6% of patients in the saffron group and 50% in the fluoxetine group experienced complete response ($\geq 50\%$ reduction in depression score), where there were no significant differences between two groups in this regard (Kashani et al., 2016).

Short-term administration of saffron (30 mg/day) for six weeks was also shown to be as effective as imipramine (100 mg/day) in treating mild to moderate depression, but with fewer reported adverse effects (Akhondzadeh et al., 2004). Moreover, in a recent double-blind, controlled clinical trial by Ghajar and colleagues, 66 patients with major depressive disorder accompanied by anxious distress were randomly assigned to receive either citalopram (40 mg/day) or saffron (30 mg/day) for 6 weeks. The researchers reported a significant improvement in scores of depression and anxiety in patients receiving either saffron or citalopram and there were no significant differences between two treatments in the case of efficacy and frequency of side effects (Ghajar et al., 2016). However, the sample size of these trials is relatively small, therefore necessitating further large-scale trials.

2.2.3. Crocin vs Placebo

Talaei et al. designed a randomized, double-blind, placebo-controlled, pilot clinical trial in which 40 MDD patients aged 24 to 50 years were divided into two groups (placebo and treatment). The crocin group (n=20) was given crocin tablets (30 mg/day; 15 mg bid) plus one selective serotonin reuptake inhibitor (SSRI) drug (fluoxetine 20 mg/day or sertraline 50mg/day or citalopram 20mg/day) and the placebo group (n=20) was administered the same amount of SSRI plus placebo (two placebo tablets per day) for 4 weeks. The crocin group showed significantly improved scores on beck depression inventory (BDI), beck anxiety inventory (BAI), and general health questionnaire (GHQ) compared to placebo group. The authors suggested that the antidepressant effects of saffron might be attributed to crocin as the main antioxidant constituent in saffron stigmas (Talaei et al., 2015).

2.3. Adverse events

Adverse events reported in placebo-controlled trials and antidepressant-controlled trials (fluoxetine, imipramine and citalopram) are presented in Table 2 and Table 3, respectively. The total number of side effects experienced in individuals receiving either saffron or antidepressant was 245, which included 86 in the saffron group and 159 in the antidepressant group (Table 3). The most common adverse effects of saffron reported in both placebo-controlled and antidepressant-controlled trials were nausea, decreased appetite, anxiety and headache. However, headache, nausea, dry mouth and anxiety were the most common side effects reported by patients taking antidepressants. Menometrorrhagia,

Dyspnea and Agitation were the only adverse events observed in subjects receiving crocin (Talaei et al., 2015).

3. Effects of Saffron and Its Constituents on Anxiety

3.1. Preclinical Studies

Hosseinzadeh and Noraei used elevated plus maze test to investigate the anxiolytic and hypnotic effects of saffron aqueous extract and its constituents, crocin and safranal in mice and found that the aqueous extracts of saffron (56 and 80 mg/kg) and safranal (0.15 and 0.35 mL/kg), but not crocin, have hypnotic and antianxiety properties (Hosseinzadeh and Noraei, 2009). Pitsikas and colleagues used light/dark test to investigate whether crocins possess anxiolytic effects in an animal model of anxiety. In disagreement with Hosseinzadeh et al., the authors reported that either crocins (50mg/kg) or the reference drug, diazepam (1.5mg/kg) significantly increased the latency of rats to enter the dark compartment which support the anxiolytic-like effects of crocin (Pitsikas et al., 2008). Moreover, Georgiadou et al. showed that crocins are able to attenuate obsessive-compulsive disorder (OCD)-like behavior in rats which cannot be attributed to changes in locomotor activity (Georgiadou et al., 2012). Finally, Halataei et al. showed that administration of aqueous extracts of saffron (1–10 mg/kg) as well as crocin (1–10 mg/kg) reduced stress-induced anorexia in mice and did not influence plasma corticosterone levels (Halataei et al., 2011b).

3.2. Clinical Trials

Up to now, only one randomized clinical trial has been performed to assess the efficacy of saffron extracts in treatment of anxiety. Basiri-Moghadam et al. conducted a double-blind randomized study to compare the anxiolytic effects of dried extract of saffron and diazepam on 102 patients who are candidate for herniorrhaphy operation. The participants in the intervention group received 25 mg/day dried extract of saffron and individuals in the control group received 5 mg/day oral diazepam for a duration of 8 months. The authors reported that saffron was more effective than diazepam in exerting anti-anxiety effects (Basiri-Moghadam et al., 2016). Considering the high comorbidity rates of anxiety disorder and bipolar disorder (Simon et al., 2003), saffron may also be beneficial for the treatment of bipolar disorder.

4. Effects of Saffron and Its Constituents on other Mental Disorders

4.1. Schizophrenia

Georgiadou et al. investigated the ability of crocins to counteract the schizophrenia-like behavioral deficits produced by noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine in rats. The authors observed that acute administration of crocins in doses of 15–30 mg/kg and 50 mg/kg could reverse ketamine (3 mg/kg)-induced performance deficits and ketamine (8 mg/kg)-induced social isolation, respectively (Georgiadou et al., 2014).

Mousavi et al. conducted the only clinical trial regarding the safety and tolerability of both saffron and crocin in adult patients with schizophrenia. This double-blind, placebo-controlled study was performed on 62 schizophrenic males, who received a 12-week treatment with saffron aqueous extract (15 mg twice daily), crocin (15 mg twice daily) or placebo in addition to their normal treatment. The results of this study showed that saffron extracts and crocin were safe and well tolerated in schizophrenic patients (Mousavi et al., 2015).

4.2. Alzheimer's disease

The protective effects of saffron and its constituents on chemically induced memory impairment in experimental animal models have been widely investigated in the literature (Asadi et al., 2015; Dashti-r et al., 2012; Ghaffari et al., 2015; Naghibi et al., 2012; Naghizadeh et al., 2013). Asadi and colleagues introduced crocin as a potential pharmaceutical agent for management of Alzheimer's disease (AD), due to its inhibitory effect on beta amyloid induced apoptosis in neuronal cells (Asadi et al., 2015). Naghizadeh et al. also reported improved cognitive performance in streptozotocin-lesioned rats following crocin administration, which suggest the beneficial effects of this active constituent in the treatment of neurodegenerative disorders such as AD (Naghizadeh et al., 2013).

In a study investigating the efficacy of saffron in patients with amnesic and multi domain mild cognitive impairment (MCI), Tsolaki et al. found improved Mini-Mental State Examination scores in patients treated with saffron and introduced this spice as a good choice for management of MCI (Tsolaki et al., 2016). In a study by Akhondzadeh et al., forty-six patients with probable AD were randomly assigned to receive capsule of saffron (15 mg twice per day) or capsule of placebo

(two capsules per day) for a duration of 16 weeks. The results revealed that saffron is both safe and effective in mild to moderate AD (Akhondzadeh et al., 2010a). Akhondzadeh et al. also conducted a 22-week double-blind study in which fifty-four adults 55 years of age or older were randomly assigned to receive either a capsule of saffron (30 mg/day) or donepezil (10 mg/day). At the end of the trial, saffron was as effective as donepezil in the treatment of mild-to-moderate AD; however, vomiting occurred significantly more frequently in the donepezil group (Akhondzadeh et al., 2010b). In another study comparing the efficacy and safety of saffron with memantine, 68 patients with moderate to severe AD received memantine (20 mg/day) or saffron extract (30mg/day) capsules for 12 months. The authors found saffron extract capsules comparable to memantine in reducing cognitive decline in these patients (Farokhnia et al., 2014). It has also been shown that saffron exerts synergistic effects with other nutraceuticals on cognitive functions (Cicero et al., 2016). Cicero et al. reported that 2 months of combined therapy of nutraceuticals including saffron, *Bacopa monnieri*, L-theanine, copper, folate and vitamins of B and D group significantly improved the cognitive functions tested with the Mini-Mental State Examination (MMSE), Perceived Stress Questionnaire (PSQ)-Index and Self-Rating Depression Scale (SRDS) score (Cicero et al., 2016). Therefore, saffron exerts protective effects on AD, alone or in combination with other nutraceuticals.

The potential antidepressant mechanisms of saffron

Several mechanisms have been suggested to be involved in the antidepressant-like effects of saffron and its constituents (Figure 1). In the following section, we have discussed these potential mechanisms in details.

Anti-inflammatory effects

In recent years, a large body of research has provided evidence supporting the role of inflammation and immune dysfunction in the etiology of depression and anxiety disorders (Danner et al., 2003; Duivis et al., 2013; Gimeno et al., 2009; Shafiee et al., 2017). To further support the role of inflammation, we previously showed that depression and anxiety are associated not only with serum

level of hs-CRP, but also with inflammation-linked conditions such as obesity and current smoking habit (Tayefi et al., 2017).

The anti-inflammatory effects of saffron and its constituents have been confirmed in various inflammatory diseases such as arthritis (Ding et al., 2013; Hemshekhar et al., 2012; Rathore et al., 2015; Zamani Taghizadeh Rabe et al., 2015), asthma (Mahmoudabady et al., 2013; Vosooghi et al., 2013; Xiong et al., 2015), and colitis (Kawabata et al., 2012). Hemshekhar et al. investigated the antiarthritic and anti-inflammatory potentiality of crocin on Freund's adjuvant-induced arthritic rats. Crocin effectively neutralized the augmented serum levels of enzymatic and non-enzymatic inflammatory mediators, probably due to its antioxidant nature (Hemshekhar et al., 2012). In another study, crocin exerted anti-inflammatory activity in a rabbit osteoarthritic model by inhibiting interleukin (IL)-1 β -induced activation of the nuclear factor kappa B (NF- κ B) pathway (Ding et al., 2013). Rathore et al. also introduced *Crocus sativus* extract as an effective agent in modulating pro-inflammatory molecules and scavenging free radicals in an animal model of arthritis (Rathore et al., 2015). In a study investigating the potential of crocin as an anti-asthma agent in a murine model, this active constituent of saffron suppressed airway inflammation and hyper-reactivity and reduced bronchoalveolar lavage fluid IL-4, IL-5, IL-13 and tryptase (Xiong et al., 2015). Mahmoudabady and colleagues reported that treatment of ovalbumin-sensitized rats with different doses of *C. sativus* extract significantly reduce WBC count and the percentage of neutrophil and eosinophil in lung lavage fluid (Mahmoudabady et al., 2013). Moreover, crocin decreased the mRNA expression of tumor necrosis factor α (TNF- α), IL-1 β , IL-6, interferon- γ (IFN- γ), NF- κ B, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), in chemically induced colitis in mice (Kawabata et al., 2012).

Antioxidant effects

Depression and anxiety disorders are associated with elevated levels of oxidative stress and reduced antioxidant defenses (Bouayed et al., 2009; Palta et al., 2014; Rawdin et al., 2013; Sarandol et al., 2007). A meta-analysis on the association between depression and oxidative stress markers showed that both 8-Hydroxy-2'-deoxyguanosine (8-OHdG) and F₂-isoprostanes are increased in depression (Black et al., 2015). Another meta-analysis of 115 articles showed that total antioxidant capacity,

paraoxonase and antioxidant levels are lower, and serum free radical and oxidative damage products, including RBC malondialdehyde (MDA), serum MDA and F₂-isoprostanes are higher in depressed patients when compared with healthy controls (Liu et al., 2015). Depression is associated with not only increased markers of oxidative stress, but also with lower antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Lopresti et al., 2014).

Many studies have confirmed the antioxidant nature of saffron and its constituents, crocin, crocetin and safranal (Asdaq and Inamdar, 2010; Hemshekhar et al., 2012; Mashmoul et al., 2013; Ochiai et al., 2004). In a study on hyperlipidemic rats, both saffron and crocin decreased the elevated levels of MDA, glutathione peroxidase enzyme activity (GSHPx), total glutathione (GSH), and oxidized glutathione (GSSG) in serum and increased SOD, CAT, ferric reducing/antioxidant power (FRAP), and total sulfhydryl (SH) values in liver tissue with reduction in thiobarbituric acid reactive species (TBARS) (Asdaq and Inamdar, 2010). Interestingly, treating neuronally differentiated pheochromocytoma (PC-12) cells with 10 μ M crocin exhibited more effective antioxidant effects than those of α -tocopherol at the same concentration (Ochiai et al., 2004).

Neuroprotective effects

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin superfamily, which includes growth factors that promote cell survival, differentiation and death of specific neuronal populations (Russo-Neustadt, 2003). Several studies suggest that low BDNF levels play a pivotal role in the pathogenesis of depression and anxiety disorders (Hashimoto, 2007; Karege et al., 2002; Shimizu et al., 2003; Shirayama et al., 2002; Siuciak et al., 1997). For instance, Shimizu et al. reported a significant negative correlation between serum BDNF and Hamilton rating scale for depression (HAM-D) scores (Shimizu et al., 2003). Karege et al. also found significantly lower levels of BDNF in depressed patients when compared with healthy controls (Karege et al., 2002). Moreover, BDNF was shown to exert antidepressant-like effects in animal models of depression (Shirayama et al., 2002; Siuciak et al., 1997). Interestingly, BDNF levels were elevated following a course of antidepressant treatment (Sen et al., 2008), suggesting that increased BDNF levels is a potential mechanism of antidepressants in reducing depressive symptoms.

There are several animal models that have confirmed the neuroprotective effects of saffron and its constituents against forced swimming test (Dorri et al., 2015; Ghasemi et al., 2015; Hassani et al., 2014). In a study investigating the antidepressant effects of crocin administration in rats, it was observed that crocin has antidepressant-like action by increasing cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), BDNF and VGF levels in hippocampus (Hassani et al., 2014). This finding is also supported by Ghasemi et al. who suggested that the antidepressant effects of *C. sativus* aqueous extract may be due to increasing the levels of VGF, BDNF, CREB and phospho-CREB (P-CREB) in rat hippocampus (Ghasemi et al., 2015). It has also been shown that crocin can attenuate some neurochemical and behavioral effects induced by malathion, at least in part by its neuroprotective effect on BDNF (Dorri et al., 2015). In an *in vitro* model, crocin also protected PC12 cells against potent neurotoxic effects of acrylamide via downregulation of Bcl-2 and the upregulation of Bax and decreasing apoptosis (Mehri et al., 2012).

Hypothalamus-pituitary-adrenal-modulating effects

Alterations in hypothalamic–pituitary–adrenocortical (HPA) system have long been observed in depression, which results in HPA hyperactivity and elevated cortisol levels (Pariante and Lightman, 2008). These alterations in HPA activity can often be reversed by antidepressant therapy with temporally associated changes in both mood and hormones (Holsboer and Barden, 1996).

Hooshmandi et al. investigated the effects of saffron water extract and safranal on the behavioral and metabolic signs induced by electroshock stress in rats. The authors reported that stress did not affect the corticosterone plasma concentration in rats receiving either extract or safranal (Hooshmandi et al., 2011). Similarly, the plasma corticosterone level did not increase in the aqueous extract and crocin treated mice, following stress induced anorexia (Halataei et al., 2011a). Moreover, the injection of crocin significantly decreased plasma levels of corticosterone in rats being exposed to chronic restraint stress (Ghadrdoost et al., 2011b). In a study conducted by Fukui and colleagues, thirty-five female participants were exposed to saffron odor for 20 minutes. This significantly decreased cortisol levels in both follicular and luteal phases, and was accompanied by reduction in symptoms of anxiety (Fukui et al., 2011).

Conclusion

In conclusion, saffron may exert antidepressant effects comparable to those of pharmaceutical antidepressants such as fluoxetine, citalopram, and imipramine, with possibly fewer observed side effects. Further studies are needed to clarify exact mechanisms responsible for antidepressant-like effects of this spice.

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Figure 1. Schematic representation of potential antidepressant mechanisms of saffron.

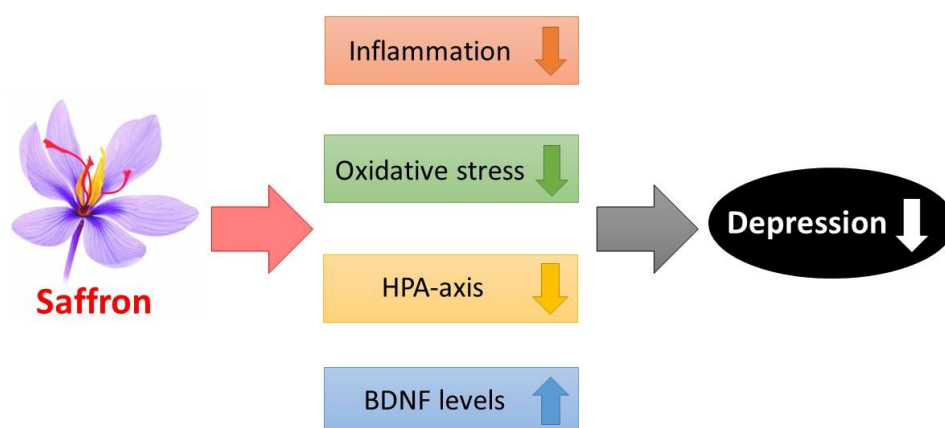


Table 1. Effects of saffron (*Crocus sativus*) in treatment of depression in clinical trials.

Author	Sample size	Intervention	Control	Duration	Results
Mazidi et al. (Mazidi et al., 2016)	60 patients	Saffron (100 mg/day)	Placebo	12-week	Saffron capsule found to be effective in reduction of depression and anxiety scores.
Moshiri et al. (Moshiri et al., 2006)	40 patients	Saffron (60 mg/day)	Placebo	6-week	<i>C. sativus</i> produced a significantly better outcome on Hamilton depression rating Scale than placebo.
Akhondzadeh et al. (Akhondzadeh et al., 2005)	40 patients	Saffron (60 mg/day)	Placebo	6-week	<i>C. sativus</i> produced a significantly better outcome on the Hamilton depression rating scale than placebo.
Sahraian et al. (Sahraian et al., 2016)	40 patients	Saffron (30 mg/day) + Fluoxetine (20 mg/day)	Placebo + Fluoxetine (20 mg/day)	4-week	The two groups improved significantly in depression severity at the end of the study without significant difference.
Lopresti et al. (Lopresti and Drummond, 2017)	123 patients	low-dose curcumin (250 mg bid), high-	Placebo	12-week	Different doses of curcumin and combined curcumin/saffron treatments were effective in reducing

		dose curcumin (500 mg bid), combined low-dose curcumin + saffron (15 mg bid)			depressive and anxiolytic symptoms in patients with major depressive disorder.
Shahmansouri et al. (Shahmansouri et al., 2014)	40 patients	Saffron (30mg/day)	Fluoxetine (40 mg/day)	6-week	Short-term therapy with saffron capsules showed the same antidepressant efficacy compared with fluoxetine in patients with a prior history of PCI.
Noorbalaa et al. (Noorbala et al., 2005)	40 patients	Saffron (60 mg/day)	Fluoxetine (40 mg/day)	6-week	Saffron at this dose was found to be effective similar to fluoxetine in the treatment of mild to moderate depression.
Akhondzadeh Basti et al. (Akhondzadeh Basti et al., 2007)	40 patients	Saffron (30 mg/day)	Fluoxetine (20 mg/day)	8-week	Petal of <i>C. sativus</i> was found to be effective similar to fluoxetine in the treatment of mild to moderate depression.
Kashani et al. (Kashani et al., 2016)	68 women	Saffron (30 mg/day)	Fluoxetine (40 mg/day)	6-week	40.6% of the patients in the saffron group experienced complete response compared with 50 % in the fluoxetine group and the difference between the 2 groups was not significant in this regard.
Akhondzadeh et al. (Akhondzadeh	30 patients	Saffron (30 mg/day)	Imipramine (100	6-week	Saffron at this dose was found to be effective similar to imipramine in the treatment of

et al., 2004)			mg/day)		mild to moderate depression.
Ghajar et al. (Ghajar et al., 2016)	66 patients	Saffron (30 mg/day)	Citalopram (40 mg/day)	6-week	Patients who received either saffron or citalopram showed significant improvement in scores of the Hamilton Rating Scale for depression and Hamilton Rating Scale for anxiety.
Talaei et al. (Talaei et al., 2015)	40 patients	Crocine (30mg/day) + SSRI	Placebo + SSRI	4-week	The crocin group showed significantly improved scores on BDI, BAI, and GHQ compared to placebo group.

Table 2. Number of reported adverse events in placebo-controlled trials

Adverse event	Placebo-controlled Trials (n=3)	
	Saffron	Placebo
Nausea	7	3
Anxiety	7	3
Decreased appetite	6	4
Headache	6	3
Increased appetite	5	1
Stomach pain	4	2
Heart pounding	4	2
Tremor	3	1
Sweating	2	1
Hypomania	2	1
Sedation	1	2
Total	47	23

Table 3. Number of reported adverse events in antidepressant-controlled trials

Adverse event	Antidepressant-controlled Trials (n=6)	
	Saffron	Antidepressant
Nausea	13	15
Decreased appetite	13	11
Anxiety	11	14
Headache	11	20
Increased appetite	7	10
Constipation	5	12
Dry mouth	4	15
Drowsiness	4	6
Sexual dysfunction	3	9

Heart Pounding	3	3
Sweating	3	9
Insomnia	3	3
Tremor	2	9
Hypomania	2	1
Sedation	1	6
Urinary Retention	1	5
Nervousness	0	1
Vertigo	0	5
Gastritis	0	2
Anger/Rage	0	3
Total	86	159

Highlights

- Depression and anxiety impose high economic and social costs.
- Clinical findings have shown that saffron and its active constituents possess antidepressant properties
- Antidepressant efficacy of saffron and crocin is comparable to those of standard drugs.
- This review provides updates on the antidepressant and antianxiety properties of saffron and its mechanisms of action.