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The effects of saffron (*Crocus sativus* L.) and its components on depression: from basic to clinical studies

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Abstract

Depression is the most prevalent neuropsychiatric disorder that has emerged as a global health concern. Antidepressant drugs, such as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic are the first line used in treating depression. Although these drugs lack efficacy and have a delayed response time and numerous side effects, their widespread abuse and market continue to grow. Over time, traditional practices using natural and phytochemicals have emerged to treat many pathological conditions, including depression. These alternative therapies to chemical drugs show efficacy in depression with few or no side effects. Saffron is one of these alternatives that showed interesting pharmacological effects, such as antioxidant, anti-inflammatory, antihypertensive, anti-convulsant, antitussive, anxiolytic aphrodisiac, and antidepressant activity. This review will provide evidence of the use of saffron and its bioactive constituents in depression. Several preclinical and clinical studies have demonstrated that saffron and its phytochemical compounds, particularly crocin, crocetin, and safranal showed antidepressive proprieties. These effects are associated with the antioxidant, anti-inflammatory and neuroprotective actions of saffron or its ability to modulate the levels of neurotransmitters in the brain, particularly serotonin, dopamine, glutamate, and GABA.

Keywords: Saffron, Depression, Crocin, Crocetin, Picrocrocin, Safranal.

Introduction

Depression, as defined by the World Health Organisation (WHO), is a mood disorder characterised by specific symptoms including grief, loss of interest, lack of tension (lack of pleasure), lack of appetite, guilt, low self-esteem or self-disturbance, Focus, self-harm and suicide attempt or thought (WHO, 2021). Patients suffering from depression describe varying degrees of disability, despair, inability to concentrate, insomnia, loss of appetite, loss of interest in what they usually find fun, extreme feelings, sadness and guilt, often accompanied by thoughts of suicide. Globally, more than 322 million people suffer from depression, over 18% between 2005 and 2015 (WHO, 2017).

In Morocco, the National Epidemiological Survey on the Spread of Mental Disorders and Addictions, carried out by the Ministry of Health in collaboration with the WHO in 2005, marked a milestone as the first epidemiological study on mental health among the Moroccan population. The study included 5498 individuals aged 15 and above (56.2% women and 43.8% men). The study found that about 50% of the population surveyed suffered at least one psychiatric disorder, and 26.5% had depression (34.3% for women and 20.4% for men) (Asouab *et al.*, 2005).

Although these statistics are frightening, the covid-19 pandemic worsened the statistics in the last two years, adding significant cases of major depressive disorder estimated, for the year 2020, to over 53 million (COVID-19 Mental Disorders Collaborators, 2021).

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Depression is not only a simple condition with a simple cause, but it is the result of a combination of biological, social and environmental factors. In addition, depression is frequently comorbid whit several other mental disorders, including anxiety, drug abuse, behaviour, personality disorders, and other medical conditions (Goodwin, 2006).

The first line of treatment for depression is antidepressant drugs, which are among the most widely consumed, although they have proven to be less effective. The antidepressant market reached $ 14,538 million in 2020 and is expected to reach $ 17,233 million in 2026 (Antidepressant Market Report, 2021). (Table 1 summarises different antidepressant drugs, their mechanisms of action and their side effects).

Since antidepressant drugs lack effectiveness and have a delayed response time showed many adverse effects, researchers and clinicians have tried other alternatives, with little or no side effects for depression, and saffron was one of them.

Although the alternative, glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine is proposed as a fast and powerful antidepressant (Berman *et al*. 2000), unfortunately, it represents an addictive risk; see Liu *et al*. for review (Liu *et al*. 2016).

The pharmacology of saffron is wide-ranging and constantly expanding, particularly its effects on CNS disorders (recently reviewed by Xing *et al*., 2021; Khazdair *et al*., 2015; Saeedi & Rashidy-Pour; 2021; Singh, 2015) and a large number of which concern depression (Tóth *et al*., 2019; Shafiee *et al*. 2018; Lopresti & Drummond, 2014; Musazadeh *et al*., 2022).

This review will provide evidence of the use of saffron and its bioactive constituents in depression. Considerable data from fundamental and clinical studies have demonstrated that saffron and its phytochemical compounds, namely crocin, crocetin, and safranal showed antidepressive proprieties. These effects are associated with the antioxidant, anti-inflammatory and neuroprotective actions of saffron or its ability to modulate the levels of neurotransmitters in the brain, particularly serotonin, glutamate, and GABA.

Materials and Methods

The present review carried out a comprehensive search on saffron with antidepressant activity in PubMed, MEDLINE, Science Direct, and Web of Science electronic databases. The search terms for this study include a combination of the following keywords: saffron, crocin, crocetin, Safranal, antidepressant, depression, antioxidant, anti-inflammatory effects, animal models and clinical studies. The selection of the scientific publications is based on their overall quality of methodology. We only considered the publications written and published in English and not suspected be predator journals or publishers.

Saffron: *Crocus sativus* L. (Figure 1)

Saffron is a spice obtained from *C. sativus* L. (Stigma and styles are collected and dried). It is a monocotyledonous plant belonging to the Iridaceae family, native to the Mediterranean basin and Western Asia. The origin of this cultivated plant is unknown. However, it could be derived from *Crocus cartwrightianus* (Brandizzi & Grilli Caiola 1996; Harpke *et al.*, 2013; Nemati et al. 2019) and then selected for higher productivity in spice.

Since *C. sativus* is a sterile triploid (Ghaffari, 1986; Saxena, 2010), the propagation of this plant is insured, by the vegetative reproduction, by bulbs or corms (geophyte plant) (Mathew, 1982). During autumn, the germination of the corms (mother) produces flowers that contain three red stigmas for each, and leaves grow until spring. During this period, the mother corms, before degeneration, give birth to daughter corms, which enter into senescence (Tammaro, 1999).

Table 1. Antidepressants drugs, their mechanism of action, and their side effects based on the label notices for these medications. **Abbreviations: MAOIs**, Monoamine Oxidase Inhibitors; **SNRIs**, Serotonin and norepinephrine reuptake inhibitors; **SSRIs**, Selective Serotonin Reuptake Inhibitors; **TCAs**, Tricyclic antidepressants.

Antidepressants	Mechanism of action	Side effects
TCAs	TCAs increased the concentrations of norepinephrine and serotonin in the synapse by blocking the reuptake of these neurotransmitters.	They cause sweating (especially at night), often significant weight gain, risk of arrhythmias (palpitations or tachycardia), dry mouth, slight blurring of vision, constipation, problems passing urine, drowsiness and dizziness.
MAOIs	MAOIs increase the synaptic availability of monoamine neurotransmitters (dopamine, serotonin, melatonin, epinephrine, and norepinephrine) by inhibiting the activity of monoamine oxidase.	MAOIs can cause dangerously high levels of serotonin, known as serotonin syndrome, insomnia, nausea, weight gain, sexual dysfunction and addiction because of their stimulating effects.
SSRIs	SSRIs increase serotonin levels in the synapse by blocking selectively the reuptake of this neurotransmitter into neurons.	SSRI can cause agitation, anxiety, insomnia, loss of appetite, nausea and sexual dysfunction.
SNRIs	SNRIs increase serotonin and norepinephrine by blocking their reuptake into the presynaptic level.	SNRIs can cause indigestion and stomachaches, diarrhoea or constipation, loss of appetite, dizziness, headaches, and sexual dysfunction (erectile dysfunction and loss of libido).

Figure 1. The aerial parts of saffron plant *C. sativus* L. with Arabic names of each of its part (Personal picture). Stigma and styles from *C. sativus* L. flowers are collec-ted and dried constitute the saffron used as a spice used in cooking.

Worldwide, saffron production is dominated by Iran, with 430 tons in 2019 (more than 90 % of Saffron production worldwide) (Statista, 2021). Referring to the ministry of agriculture, Morocco produced 6.5 tons in 2019, and more than 90% of the Moroccan production is in the Talouin area in the province of Taroudant (Souss-Massa region) and Taznakht, province of Ouarzazat (Daraa Tafilalet region) (Moroccan Ministry of Agriculture).

Chemical compositionof saffron (Figure 2)

Crocin and its metabolite, crocetin, are the principal active constituents of saffron stigmas (Crocin = trans-crocetin bis (b-D-gentiobiosyl) ester). They are derivatives of carotenoids responsible for the

colour of saffron (Carmona *et al.*, 2006). There are many crocin molecules in saffron, depending on the molecules attached on either side of the crocetin molecule. If crocetin binds gentiobiose disaccharide on both sides, it gives crocin-I (Figure 2). Li *et al.* identified four crocins in saffron (Li *et al.*, 1999). Suchareau et al. identified ten crocins in a commercial saffron extract (Saffr'activ®) (Suchareau *et al.*, 2021). In a recent review, Song et al. reported 25 different forms of crocins (Song *et al.*, 2021). Cronin-I is more studied and has antide-pressive effects (Table 2). The second important compound is picrocrocin, a monoterpene glycol-side responsible for the bitter taste. Picrocrocin generated a third volatile essential oil compound, safranal, which is responsible for the aroma of saffron (Pfander & Schurter-beger, 1982; Amanpour *et al.*, 2019).

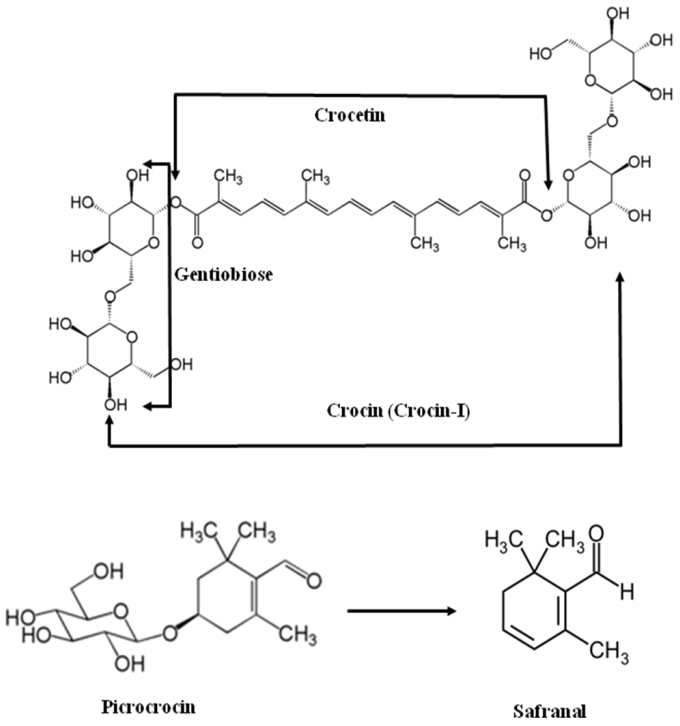

Figure 2. The main biochemical compounds of saffron. The main biochemical compounds of saffron are crocin (crocin-I) (crocetin binds gentiobiose disaccharide on both sides) and its metabolite, crocetin, which are derived from carotenoids responsible for the colour of saffron. Picrocrocin is a monoterpene glycoside, responsible for the bitter taste, and gives by transformation a third volatile essential oil compound, safranal, which is responsible for the aroma of saffron.

Basic and clinical studies

Basic or fundamental studies

In fundamental studies (Table 2), the effects of saffron on depression are based on the model of the Forced Swimming Test (FST) and Tail Suspension Test (TST), which are the most models in studying depression in small animals such as rats and mice.

Forced Swimming Test (FST)

The behavioural despair test is the most anti-depressive test that attempts to reproduce conditions similar to human depression in animals (For example, reaction to an unpleasant environment) and was, firstly, used to select potentially antidepressant molecules (Porsolt *et al.*, 1977). In the FST model, a rat or a mouse is placed in a water-filled chamber, from which it cannot escape. It swims for a while and then stops trying to escape, stands still and floats (immobile). This renunciation of swimming reflected a desperate behaviour. After administration of antidepressants, the animal swims longer (reduction in immobility time and extension of the hope for a favourable outcome).

Tail Suspension Test (TST)

The tail suspension test (TST) is a behaviour test described by Steru *et al.* (1985) as an alternative to Porsolt's forced swimming test, based on a similar concept (a measure of the response to the stress conditions). In this model, the tail of a mouse or a rat is attached to a horizontal bar for 5-6 min. Following a failure to escape, the animal adapts to a state of hopelessness that results in resting immo-

bile. Antidepressant molecules significantly reduced this immobility time by comparison to controls. Since depression and anxiety are often comorbid, these despair tests are usually used in combination with other tests that measure anxiety-like behaviour as an endophenotype of depression, such as the open field test (OFT), elevated plus maze (EPM), and Dark/Light box test.

Table 2 summarises the results of fundamental studies on the antidepressive effects of saffron and its bioactive compounds.

Clinical studies

In clinical studies, Doctors first diagnose and identify the level of depression by asking their patients to complete a depression-rating questionnaire. For example:

The Beck Depression Inventory (BDI) is widely used to screen for depression and measure behavioural manifestations and severity of depression. The BDI is suitable for ages 13 to 80. The inventory contains 21 self-report items, which individuals complete using multiple-choice response formats that measure characteristic attitudes and symptoms of depression (Beck *et al*., 1961).

The Hamilton Rating Scale for Depression, abbreviated HDRS, HRSD, or HAM-D, measures the severity of major depression in patients before, during, and after treatments. The scale contains 21 items but is scored based on the first 17 items measured either on 5-point or 3-point scales. It takes 15 to 20 minutes to complete (Hamilton, 1967). Table 3 summarises the results of clinical studies on the antidepressive effects of saffron and its bioactive compounds.

Discussion

It is clear from preclinical (Table 2) and clinical (Table 3) studies that saffron and its major chemical components exert anti-depressive effects, which could be the result of many mechanisms, including the involvement of different neurotransmitters, oxidative stress, neuroinflammation, hormones and neurotrophic factors.

Action on neurotransmitters

The monoaminergic hypothesis was one of the earliest advanced explanations of depression. This hypothesis suggested a hypofunction of the monoaminergic pathways (serotonin, 5-HT, noradrenaline, and dopamine, DA) in depression, which antidepressants would restore.

Some studies suggested the interaction of crocin (major active constituents of saffron stigmas) with the serotonergic system in alleviating Obsessive-compulsive in Wistar rats (Georgiadou *et al*., 2012). Either, the DAergic system is involved in relieving schizophrenia-like behavioural deficits induced by apomorphine in rats (Pitsikas & Tarantilis, 2017). In addition, crocin ameliorated depression-like behaviour in Parkinson's disease in mice by protecting the DA projection neurons in the ventral tegmental area (VTA) (Tang *et al*., 2020).

Moreover, crocin showed neuroprotective effects in the rotenone-induced group by increasing the enzyme tyrosine hydroxylase (T.H) (T.H plays an essential role in the metabolism of L-tyrosine and thus in the synthesis of catecholamines) and dopamine (DA) in rats (Salama *et al*. 2020), and improved 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson disease (Haeri *et al*., 2019), by preventing the MPTP-induced the damage of T.H. neurons and protecting dopaminergic in the substantia nigra (source of dopamine). In a recent preclinical study in mice, Moghadam et al. showed that chronic oral administration of a saffron extract, Safr'InsideTM, (6.25 mg/Kg/day for four weeks) ameliorated depressive-like behaviour by reducing hippocampal expression of the serotonin transporter SERT (an increase of 5-HT neurotransmission), and by increases DA levels in the striatum and, decreases DA

Table 2. Basic studies of the effects of saffron (*C. sativus*) or its derivative compounds in the treatment of depression using animal model of depression.

Animal model	Treatment and part of Crocus used	Results and proposed mechanism	References
FST and TST in mice	Acute and sub-acute administration of crocin (40 mg/kg) and crocetin(20 and 40 mg/kg)	Acute crocin (40 mg/kg) and crocetin (20 and 40 mg/kg) produced antidepressant-like effect in FST. Sub-acute oral administration of crocin decreased immobility time only at dose (100 mg/kg). Crocetin (12.5, 25 and 50 mg/kg) was able to decrease immobility time in FST and TST.	Amin *et al.,* 2015
FST and EPM in male Sprague Dawley rats using rat models for anxiety and behavioral despair	5 group of rats (n = 11 per group) received crocin (50 mg/kg), flumazenil (3 mg/kg), midazolam (1.5 mg/kg), or saline i.p.	Crocin attenuated the anxiolytic effects of midazolam as showed by EPM. FST showed a significant increase in mean time mobile in the midazolam plus crocin group.	Ceremuga *et al.,* 2018
FST in male Wistar rats using malathion (50 mg/kg/day, i.p.) induced depressive- like behaviour	Crocin (10, 20 and 40 mg/kg/day, i.p.), imipramine (20 mg/kg/day, i.p.) and vitamin E (200 mg/kg, three times a week, i.p.) respectively for 14 days.	Crocin and vitamin Ereversed Malathion-induced depression and-increased the MDA and decreased GSH byprevented the decreasing effect of malathion on BDNF.	Dorri *et al.,* 2015
FST in rats using CRS chronic restraint stress	Crocetin (20, 40, 60 mg/kg) or vehicle daily for 21 days	Crocetin ameliorated the depressivelike behaviour induced by CRS by decreasing oxidative damage in the brain.	Farkhondeh *et al.,* 2018
FST in rats	The aqueous extract of saffron (40, 80 and 160 mg/kg/day) and imipramine 10 mg/kg/day were injected i.p. for 21 days to rats.	Saffron reduced the immobility time by increasing the protein levels of BDNF, CREB and p-CREB as well as the transcript levels of BDNF.	Ghasemi *et al.,* 2015
FST in in mice	corm, leaf, petal, and stigma of saffron ethanolic extracts	Petal and stigma extracts showed antidepressant effects by reducing immobility, while corm and leaf extract indicated moderate to mild antidepressant efficacy.	Khan *et al.,* 2020
FST and OFT in ICR mice using CRS-induced depressive-like behaviours	Orally administered of crocetin (20, 40, 80 mg/kg), fluoxetine (20 mg/kg) or distilled water	Crocetin was neuroprotective and ameliorated depressive-like behaviours caused by chronic restraint stress-induced depressive mice by regulating the MKP-1-ERK1/2-CREB signalling and intestinal ecosystem.	Lin *et al.,* 2021
OFT, FST, TST and PST in mice using CUMS model	Crocin (30 mg/kg) in vivo and (12.5 μmol/L) in vitro CORT (and 200 μmol/L) model of PC12 was set up to explore the antidepressant mechanism of crocin.	Crocin alleviated CUMS induced depression-like behaviours, reversed the decrease of body weight and elevation of serum CORT in mice, and protected PC12 cells against CORT-induced injury by increasing PACAP and its downstream ERK and CREB signalling pathways.	Lu *et al.,* 2020
FST in mice using Parkinson's disease depression model induced	Crocin (15, 30, 40 mg/kl)50 mg/kg/day) by the i.g. route for another 7 days after induction of depression by PPTM (30 mg/kg daily for 7 days).	Crocin treatment alleviated the depressive-like behaviour induced by MPTP. This effect associated protection of the DA projection neurons in the VTA through activating mTOR, and improving the neural synaptic plasticity of mPFC	Tang *et al.,* 2020

by MPTP	The behavioural tests were carried out on the 15th day and biochemical on the 16 day.		
OFT, FST and TST in male ICR mice	Aqueous stigmas and corms of *C. sativus*extract 150, 300, and 600 mg/kg	Administration of *C. sativus*corms extract produces antidepressant-like effects. Aqueous stigmas extract also exerted antidepressive effects in the behavioural models. Antidepressant-like properties of aqueous stigma extracts may be due to crocin 1.	Wang *et al.,* 2010
FST and TST in Mice	Saffron was given at the doses of 200, 400 and 800mg/kg i.p/ imipramine (15mg/kg).	Saffron stigmas showed significant antidepressant like activity and added to the action of submaximal dose of imipramine.	Reddy *et al.,* 2013
FST and TST in mice	The aqueous extract of *C. sativus*linn.(15 & 30 mg/kg)/Fluoxotine (20 mg/kg) respectively by oral feeding.	Saffron with 15 mg/kg and 30 mg/kg significantly decrease the immobility period by comparison to control group.	Sunanda *et al.,* 2014
FST in male Wistar rats.	Crocin (12.5, 25, and 50 mg/kg), imipramine (10 mg/kg; positive control) and saline (1 mL/kg; neutral control) were administered i.p. to male Wistar rats for 21 days.	Crocin significantly reduced the immobility time in the FST by increasing the levels of CREB and BDNF (25 and 50 mg/kg) and the VGF as well as the transcript levels of BDNF (12.5 mg/kg).	VahdatiHassani *et al.,* 2014
OFT, FST and TST in male C57BL/6 J mice using a model of chronic CORT-induced depression	Mice were treated with crocin-I of 20 mg/kg and 40 mg/kg for 2 weeks, 4 weeks after induction of depression with 20 mg/kg corticosterone by subcutaneous injection in mice	Crocin-I showed a significant antidepressant effects probably by the suppression of hippocampal neuroinflammation (IL-1β) and oxidative stress in the mouse.	Xiao *et al.,* 2019
SPT and FST in male C57BL/6 J mice exposed to four-week CRS	Mice were treated for six-week by oral administration of crocin-Iat a dose of 40 mg/kgin CRS- induced depressionfor four-week	Crocin-I at a dose of 40 mg/kg for six weeks alleviated depression-like in CRS-induced depression in mice. This effect of Crocin-I was accompanied by reduction of LPS, IL-6 and TNF-α in serum and TNF-α expression in the hippocampus, and the increase in the hippocampal BDNF in addition crocin-I mitigated the gut microbiotadysbiosis in depressed mice.	Xiao *et al.,* 2020
FST and TST in male C57BL/6 mice using COPD-induced depression induced by cigarette smoke for 7 weeks	Crocin (50 mg/kg), was injected to mice once a day.	Crocin reversed markers of depression and inflammation probably by the regulation of PI3K/Akt-mediated inflammatory pathways.	Xie *et al.,* 2019
FST in male C57BL/6J mice	Oral administrationof saffron extract (Safr'Inside^{TM}) (6.25 mg/Kg)	Acute Safr'Inside administration (6.25 mg/Kg) reduces immobility time in the FST (antidepressive effect). Chronic oral Safr'Inside administration (6.25 mg/Kg for 4 weeks) decreased mRNA expression of DRD1 and DRD2 in the FC and decreases SERT expression in the HPC.	Monchaux De Oliveira *et al.,* 2021

Abbreviations: BDNF, Brain derived neurotrophic factor; **COPD**, Chronic obstructive pulmonary disease; **CORT**, Corticosterone; **CREB**, Response element-binding; **CRS**, Chronic restraint stress; **CUMS**, Chronic unpredictable mild stress; **DA**, Dopamine; **DMSO**, Dimethyl sulfoxide (Vehicle); **DRD1**, Dopamine receptor D1 gene; **DRD2**, Dopamine receptor D2 gene; **EPM**, Elevated plus maze; **ERK1/2**, Extracellular signal-regulated kinase 1/2; **FC**, Frontal cortex; **FST**, Forced swimming test; **GSH**, Glutathione; **HPC**, Hippocampus; **i.p.**, Intraperitoneal; **IL-1β**, Interleukine-1 beta; **MDA**, Malondealdehyde; **MKP**-1, Mitogen-activated protein kinase phosphatase-1; **mPFC**, Medial prefrontal cortex; **MPTP**, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **mTOR**, Mammalian target of rapamycin; **OFT**, Open field test; **PACAP**, Pituitary adenylatecyclase-activating polypeptide; **PDD**, Parkinson's disease depression; **SERT**, Serotonin transporters; **SPT**, Sucrose preference test; **TST**, Tail suspension test; **VTA**, Ventral tegmental area.

Table 3. Effects of saffron (*C. sativus*) or its derivative compounds in the treatment of depression: clinical trials.

Author	Sample size	Intervention	Control	Duration	Results
Salek *et al.,* 2021	72 patient with breast cancer	30 mg/day of crocin	Placebo	during chemotherapy	The degree of anxiety and depression decreased in the crocin group and increased in the placebo-group
Akhondzadeh *et al.,* 2020	73 women with comorbid with mild-to-moderate depression	30 mg/day of saffron capsules	Placebo	12-week	Mean depression scores in the saffron group significantly decreased compared to placebo
Ahmadpanah *et al.,* 2019	50 older patients	Saffron (60 mg/day)	Sertraline (100 mg/day)	6-week	Symptoms (HAM-D) of depression decreased over time (Timepoints: 0, 2, 4, 6), with no advantages or disadvantages for the saffron or sertraline condition.
Tabeshpour *et al.,* 2017	60 new mothers	Saffron (15 mg/Bid)	Placebo	8-week	Saffron had a more significant impact on the BDI-II than the placebo, when administered to treat minor PPD in breastfeeding mothers.
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.,* 2006	40 patients	Saffron (60 mg/day)	Placebo	6-week	C. sativus produced a significantly better outcome on Hamilton depression rating Scale than placebo
Akhondzadeh *et al.,* 2005	40 patients	Saffron (60 mg/day)	Placebo	6-week	C. sativus produced a significantly better outcome on the Hamilton depression rating scale than placebo
Sahraian et *et al.,*	40 patients	Saffron (30 mg/day) +	Placebo + Fluoxetine (20	4-week	The two groups improved significantly in depression severity at the end of the study without

2016		Fluoxetine (20 mg/day)	mg/day)		significant difference.
Lopresti and Drummond, 2017	123 patients	low-dose curcumin (250 mg bid), high-dose curcumin (500 mg bid), combined low-dose curcumin + saffron (15 mg bid)	Placebo	12-week	Different doses of curcumin and combined curcumin/saffron treatments were effective in reducing depressive and anxiolytic symptoms in patients with major depressive disorder.
Shahmansouri *et al.,* 2014	40 patients	Saffron (30 mg/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.
Noorbala *et al.,* 2005	40 patients	Saffron (30 mg/day)	Fluoxetine (20 mg/day)	8-week	Petal of C. sativus was found to be effective similar to fluoxetine in the treatment of mild to moderate depression.
AkhondzadehBasti *et al.,* 2007	40 patients	Saffron (30 mg/day)	Fluoxetine (20 mg/day)	8-week	Petal of C. sativus was found to be effective similar to fluoxetine in the treatment of mild to moderate depression.
Kashani *et al.,* 2017	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.,* 2004	30 patients	Saffron (30 mg/day)	Imipramine (100 mg/day)	6-week	Saffron at this dose was found to be effective similar to imipramine in the treatment of mild to moderate depression.
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 HAM-D and HAM-A.
Talaei *et al.,* 2015	40 patients	Crocin (30 mg/day) + SSRI	Placebo + SSRI	4-week	The crocin group showed significantly improved scores on BDI, BAI, and GHQ compared to placebo group.

Abbreviations: BAI, Beck Anxiety Inventory; **BDI**, Beck Depression Inventory; **GHQ**, General Health Questionnaire; **HAM-A**, Hamilton Rating Scale for anxiety; **HAM-D**, Hamilton Rating Scale for depression; **PCI**, percutaneous coronary intervention; **SSRI**, selective serotonin reuptake inhibitor.

metabolites levels (DOPAC and HVA) in the frontal cortex (Monchaux De Oliveira *et al.*, 2021). A biochemical study revealed that Saffron water extract increased brain dopamine concentration in a dose-dependent manner in rats (Shams *et al*., 2010). In a randomized controlled trial study, supplementation with saffron (150 mg, for six weeks) to participants in resistance training improved the levels of dopamine and serotonin concentrations (Moghadam *et al*., 2021). These suggest that saffron or its ingredients could modulate serotonergic and dopaminergic systems to exert their antidepressive effects.

In addition to the action on DA and 5-HT, saffron and its bioactive compounds could mediate their antidepressive effects via interacting with glutamate and γ-aminobutyric acid (GABA). There is increasing evidence that altered levels of excitatory, glutamate, and inhibitory amino acid GABA neurotransmitters were associated with mood disorders, including depression (Choudary et al., 2005; Hasler *et al*., 2007; Lener *et al*., 2017; Duman *et al*., 2019; Draganov *et al.*, 2020). Treatment with antidepressants corrected these deficits in GABA (Bhagwagar *et al*., 2004; Sanacora *et al*., 2006; Dubin *et al*., 2016) and glutamate in rodents (Fu *et al.*, 2012; Chowdhury *et al.,* 2017) and humans (Taylor *et al*., 2008; Abdellah *et al*., 2018) (Duman, 2014 Review). In this context, several studies demonstrated that saffron and or its active compounds exert their antidepressive effects by involving glutamate and GABA via their receptors, particularly NMDA and GABAA receptors.

A biochemical study revealed that Saffron water extract (250 mg/kg i.p.) increased brain glutamate concentration in rats (Shams *et al.,* 2010). Berger et al. showed that hydro-ethanolic saffron extract inhibited glutamate synaptic transmission at the NMDA receptors, and trans-crocetin was involved in this effect (Berger *et al*., 2011). Crocin (20 mg/kg) significantly elevated the expression of the AMPA receptor (Vahdati Hassani *et al*., 2020). Receptor binding studies showed that saffron extracts and crocetin, but not crocin or picrocrocin, bind at the phencyclidine binding site of the NMDA receptor at the sigma-1 receptor (Lechtenberg *et al*., 2008). Safranal (291 mg/kg, i.p.) reduces the glutamate and aspartate extracellular concentrations in the rat hippocampus following kainic acid administration (Hosseinzadeh *et al*., 2008).

Saffron and its active compounds could achieve its effects by activating GABAA receptors. For example, Safranal is an effective anticonvulsant shown to act as an agonist at GABAA receptors (Hosseinzadeh & Sadeghnia, 2007). Autoradiography studies showed that Safranal reduced [3H] flunitrazepam binding in the cortex, hippocampus, and thalamus of the mouse brain (Sadeghnia *et al*., 2008).

Oxidative stress and neuroinflammation (Figure 3)

Clinical studies have shown that depressed patients have increased levels of some markers of inflammation and oxidative stress (Lindqvist *et al*., 2018). In addition, pro-inflammatory lipopolysaccharide (LPS) induced depression-like behaviour (Shen *et al*., 2021; Géa *et al*., 2019), and exposition to chronic ozone inhalation results in high levels of oxidative stress and depression (Mokoena *et al*., 2015) in rodents. Xie et al. showed that chronic obstructive pulmonary disease (COPD)-induced depression by exposition to cigarette smoke for seven weeks. Crocin administration (50 mg/kg. once a day) reversed COPD-induced depression in FST and TST models in mice. These anti-depressive effects of crocin coincided with the anti-inflammatory effects in the

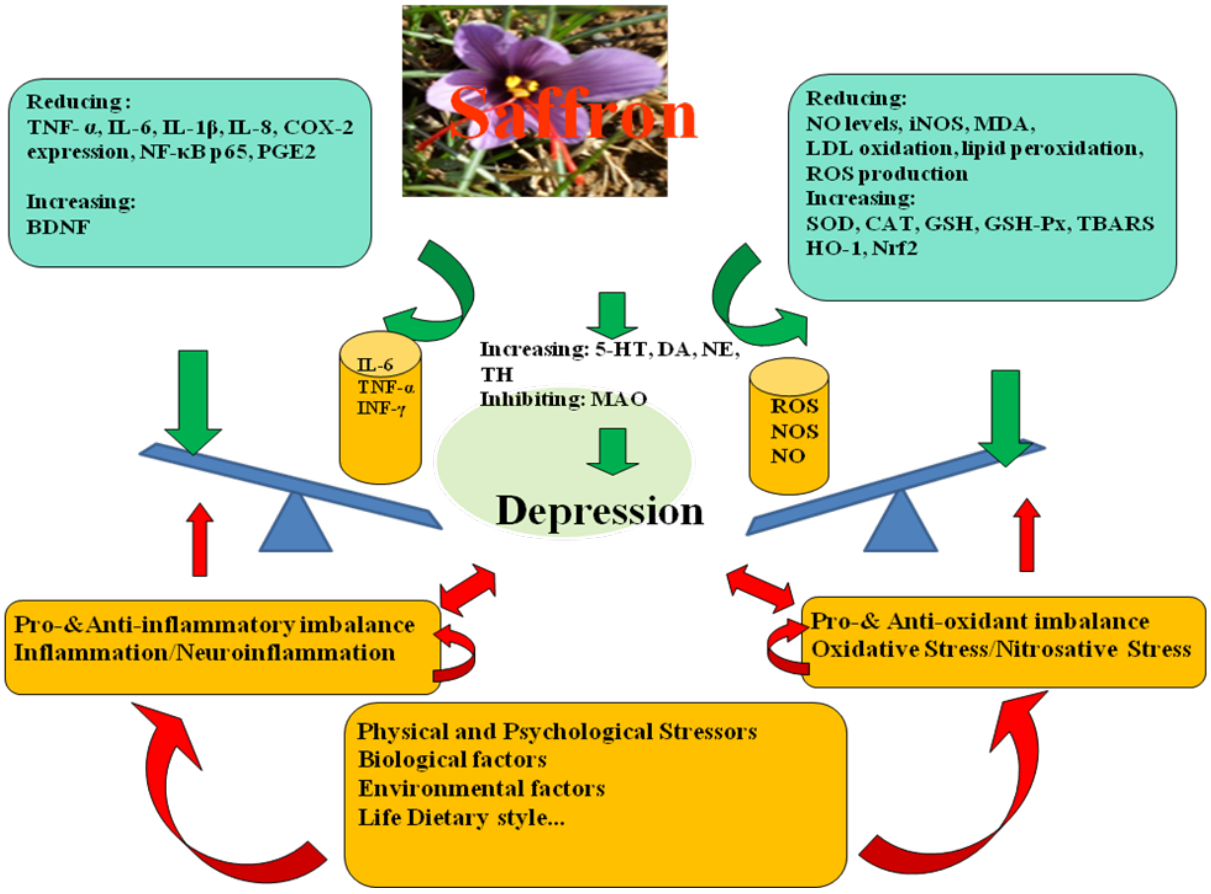

Figure 3. Antidepressive effects of saffron is related to its antioxidant and anti-inflammatory effects. Considerable studies have shown that oxidative stress with inflammation are involved in degenerative diseases, including depression. In turn, antidepressive drugs have shown their anti-inflammatory and antioxidant effects. Evidence from clinical and basic studies demonstrate that saffron and its biochemical compounds possess antioxidant and anti-inflammatory effects. Thus, saffron could exert its antidepressive effects by relieving oxidative and inflammatory damage.Red arrows indicate a depressive effect; green arrows indicate an antidepressant effect.

bronchoalveolar lavage fluid, the lung tissue, and the hippocampus is probably due to inhibiting cigarette smoke-induced IκB phosphorylation (inhibition of NF-κB transcription factor activation), degradation, and nuclear factor-kappa B (NF-κB)p65 translocation (Xie *et al*., 2019). COPD increased the mRNA levels of IL-6 and tumour necrosis factor-α (TNF-α) in rats. However, the co-administration of crocin to the cigarette smoke rats decreased cytokine gene expression and levels of IL-6 and TNF-α (Dianat *et al*., 2018). Considering that nuclear erythroid-related factor 2 (Nrf2) is a transcriptional factor that regulates the expression of antioxidant enzymes, including glutamate-cysteine ligase catalytic subunit (GCLc), heme oxygenase-1 (HO-1), and quinone oxidoreductase (NQO-1), saffron and its major chemical components could induce their effects through regulating Nrf2, which activates anti-inflammatory response and antioxidant defences. Indeed, exposition to cigarette smoke for 2-month induced COPD in rats and increased oxidative stress via the production of high levels of lipid peroxidation marker malondialdehyde (MDA), which was associated with decreased levels of Nrf2, glutamate-cysteine ligase catalytic subunit (GCLc) gene expression, GSH amount and other antioxidant enzymes activity in the lung tissue (Dianat *et al*., 2018). Conversely, the mRNA expression of Nrf2 and GCLc increased in the crocin's co-treatment cigarette smoke rats compared with cigarette smoke groups, and these

were in parallel with an increase in mRNA of Nrf2 regulator enzymes such as protein kinase C (PKC), phosphoinositide-3-kinase (PI3K) and mitogen-activated protein kinases (MAPK).

Xiao et al. showed that crocin-I exerts antidepressant effects in chronic corticosterone (CORT)-induced depression as evidenced by OFT, FST and TST in mice, and these are in conjunction with the suppression of neuroinflammation interleukin-1β (IL-1β) and oxidative stress in the mouse hippocampus (Xiao *et al*., 2019). The same team showed that crocin-I reduced the LPS, IL-6, and TNF-α levels in serum and TNF-α expression in the hippocampus (Xiao *et al*., 2020). In addition, oral administration of saffron (100 mg/kg of body weight) 7 days before the induction of acute cerebral ischemia in rats eliminated MDA, reinforced antioxidant defence enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (G.R.), glutathione-S-transferase (GST), and reduced glutathione (R.GSH) activities (Saleem et al. 2006). Krishnaswamy *et al*. confirmed these effects of crocin (50 mg/kg/day and 150 mg/kg/day) by reversing age-associated oxidative stress and neuroinflammatory markers in old rats (Krishnaswamy *et al*., 2020). In addition to its antioxidant role, Nrf2 exerts an anti-inflammatory effect by suppressing the activation of NF-κB (Bao *et al*., 2018). Thus, the anti-inflammatory effects of saffron and its active compounds could be exerted indirectly by activating Nrf2. Indeed, several studies using a different model of diseases in rodents showed that saffron or its ingredients crocin or crocetin (a metabolite of crocin) exerted their antioxidant and anti-inflammatory effects through activating the transcriptional Nrf2 factor (Godugu *et al*., 2020; Khodir *et al*., 2019; Liu et al., 2020; Singh et al., 2021; Shaheen *et al*. 2021). Given its antioxidant and anti-inflammatory effects, it is not surprising that Nrf2 knockout mice exhibited chronic inflammation and depressive-like behaviour and expressed a low level of brain-derived neurotrophic factor (BDNF) (Martín-de-Saavedra *et al*., 2013; Mendez-David *et al*., 2015; Yao *et al*., 2016). Interestingly, Nrf2 knockout mice also exhibited a reduction of DA and 5-HT synthesis in the mice's prefrontal cortex (PFC) (Martín-de-Saavedra *et al*., 2013). These would suggest that not only is Nrf2 necessary for BDNF activation, but it also can increase the synthesis of the neurotransmitters DA and 5-HT, which are deficient in depression. However, the observation that chronic fluoxetine increased cortical and hippocampal BDNF in wild-type and Nrf2 knockout mice would suggest that Nrf2 could also act via inhibiting SERT than direct activating BDNF (Mendez-David *et al*., 2015). In summary, these studies show that saffron exerts anti-inflammatory and antioxidant activities via transcription factors such as BDNF and Nrf2 leading to the normalization of synaptic transmission.

Hormonal effects

The possible involvement of the hypothalamic-pituitary-adrenal axis (HPA) in depression has the basis on the clinical observation that patients suffering from depression had higher cortisone levels than controls (Lok *et al*., 2012; Wisniewski *et al*., 2006). Antidepressants remediate this HPA activation by restoring the excessive glucocorticoids via feedback control on adrenocorticotropic hormone (ACTH) and then reducing cortisone and ACTH (Inder *et al*., 2001). In addition, preclinical studies used chronic CORT treatment to induce depression, as evidenced by OFT, FST and TST, in rodents (Xiao *et al*., 2019; Xie *et al*., 2018).

An intracerebroventricular infusion of crocin can reduce HPA axis activity in post-traumatic stress disorder by reducing hypothalamic corticotrophin-releasing hormone (CRH) and pituitary glucocorticoid receptors (G.Rs.) expression (Asalgoo *et al*., 2017). A study on (CORT)-induced

injury in PC12 cells showed that ethanol extract of saffron protected PC12 cells by changes in RNA expression of MAPK pathway and other genes (Chen *et al*., 2022). In the same way, Lu et al. showed that crocin at the dose of 30 mg/kg reversed the increased serum CORT in CUMS induced depression-like behaviours in mice and 12.5 μmol/L of crocin protected PC12 cells against CORT-induced injury. These effects probably involved the upregulation of the protein expression of pituitary adenylate cyclase-activating polypeptide (PACAP), phosphorylation of extracellular regulated protein kinases (ERK) and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) (Lu *et al*., 2020). In other studies, saffron extract or crocin prevents the impairment of learning and memory and the oxidative stress damage to the hippocampus induced by chronic stress, and these in parallel with decreased plasma levels of CORT in chronic restraint stressed rats (Ghadrdoost *et al.,* 2011). Similarly, the administration of crocin (30 mg/kg) decreased CORT levels in the hippocampus and frontal cortex in rats exposed to stress (Dastgerdi *et al.,* 2017). Crocin (25 and 50 mg/kg) reduced corticosterone levels induced in adolescent stressed rats (Ghalandari-Shamami *et al*., 2021). These studies demonstrated that saffron or its active ingredients as an antidepressant do deactivate HPA probably by activating the negative feedback loop on G.Rs. sensitivity.

Action as MAOIs

Monoamine oxidases (MAO) are a group of enzymes involved in the catabolism of neurotransmitters monoamines, particularly serotonin, dopamine, and norepinephrine (Youdim *et al*., 1988). Monoamine oxidase inhibitors (MAOIs) prevented the breakdown of monoamine neurotransmitters, thereby increasing their availability in the brain. These MAOIs were the first used as antidepressant drugs, but they are now less used because of their adverse effects (Table 1).

Derivatives of safranal inhibited both human MAO (MOA-A and MAO-B) enzymes (De Monte et al., 2014). Linardaki et al. showed that Aluminium intoxication increased the whole brain MAO activity, and co-administration of a saffron extract with aluminium reversed aluminium (Al)-induced changes in monoamine oxidase and inhibition of cerebellar MAO-B (Linardaki *et al*., 2013).

Neurotrophic factors

Brain-derived neurotrophic factor is one of the neurotrophic factors family responsible for the growth and survival of developing neurons and the maintenance of mature neurons and synaptic transmission. The importance of BDNF in the pathophysiology and treatment of depression comes from several clinical studies demonstrating that depressed patients had low BDNF serum levels and antidepressants restored this deficiency (Hellweg *et al*., 2008; Huang *et al*., 2008; Matrisciano *et al*., 2009; Wolkowitz *et al*., 2011). Furthermore, an animal model of depression exhibited low levels of BDNF (Gawali *et al*., 2017; Zhao *et al*., 2019; Li *et al*., 2020; Song *et al*., 2020), and chronic treatment with antidepressants increased BDNF levels in different brain areas (Musazzi *et al*., 2009; Balu *et al*., 2008; Sachs & Caron, 2014; Mendez-David *et al*., 2015). Many preclinical studies reported that the anti-depressive effects of saffron or its active molecule, crocin, were in parallel with an increase in the BDNF levels (Vahdati Hassani *et al*., 2014; Dorri *et al*., 2015; Ghasemi *et al*., 2015; Razavi *et al*., 2017; Xiao *et al*., 2020; Ghalandari-Shamami *et al*., 2021).

It is interesting to note, from the above studies, that the anti-depressive effects of saffron or its active compounds were associated with upregulation of both BDNF and Nrf2, which were down-regulated in depression-like conditions. Recent studies showed that BDNF

promotes neuronal antioxidant response by inducing Nrf2 nuclear translocation (Bouvier *et al*., 2017; Bruna et al., 2018), and in turn, Nrf2 activation induces the expression of BDNF (Yao *et al*., 2021).

BDNF modulates serotonin glutamate GABA

BDNF and 5-HT play an essential role in ensuring brain development and plasticity, and one regulates each other; for review, see (Martinowich & Lu, 2008; Popova *et al.,* 2016). BDNF and 5-HT with its transporter or 5-HT2R receptor were associated with depression (Kim *et al*., 2012). SERT knockout rats displayed low BDNF levels in the hippocampal and prefrontal cortex (Molteni *et al*., 2010; Calabrese *et al*., 2015), and chronic fluoxetine increased BDNF mRNA levels in PFC of adult wild-type rats but not in SERT knockout rats (Molteni *et al*., 2010). SERT regulates BDNF. Mice lacking brain 5-HT (tryptophan hydroxylase knockout mice) induced BDNF expression (Kronenberg *et al*., 2016). In another study, a combination of saffron (saffron extract 40 mg/kg) treatment with exercise increased BDNF and serotonin and its metabolite, 5-hydroxyindoleacetic acid 5-HIAA, in the hippocampus of rats (Akbari-Fakhrabadi *et al*., 2021). Considering that BDNF, through its receptor, tropomyosin-related kinase B (TrkB), controls 5-HT, saffron may mediate its antidepressive effects via modulating BDNF and 5-HT through the TrkB receptor.

BDNF affects GABA neurotransmission through regulation of α5-GABAA receptor levels in pyramidal neuron dendrites (Tomoda *et al*., 2022) and knocking down BDNF mRNA in aged mice resulted in further dysfunction of GABAergic neuroplasticity and higher anxiety phenotype (Zhu *et al*., 2019). BDNF interacts with glutamate to regulate neurotransmission (Martin *et al*., 2011). These indicate that BDNF is involved in depression through its effects on regulating serotonin, Glutamate and GABA neurotransmission.

CREB BDNF interrelation

Considering that the transcription factor cyclic AMP response element-binding protein (CREB) is a regulator of BDNF-induced gene expression (BDNF activates CREB by phosphorylation) (Finkbeiner *et al*., 1997), CREB activation could mediate many BDNF responses, including antidepressants responses. By using CREB-deficient mice, Conti et al. showed that not only is CREB an upstream activator of BDNF, but it is necessary for the chronic antidepressant treatment response of desipramine, but not fluoxetine (Conti *et al*., 2002). It is noteworthy that many studies demonstrated that saffron or its active ingredient, namely crocin and crocetin, exerted their anti-depressive effects, at least, by activating CREB (Vahdati Hassani *et al*., 2014; Ghasemi *et al*., 2015; Asrari *et al*., 2018; Lu *et al*., 2020; Lin *et al*., 2021).

Conclusions

This review has summarised the antidepressant effects of saffron and its active ingredients, including crocin, crocetin, and safranal. Many fundamental and clinical studies showed that saffron is effective in depression and proposed different mechanisms explaining its effects. The most important of them is the one involving the anti-inflammatory and antioxidant effects, followed by the action on neurotransmitters in favour of the hypothesis of their deficiency in depression. Neurotrophic factors, particularly BDNF, are also of interest since they are involved, even if indirectly, in the regulation of neurotransmitters such as 5-HT, DA, glutamate and GABA and in various types of signalling such as CREB.

Conflict of interest statement

The author reports no conflicts of interest.

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