International Journal of Enhanced Research in Medicines & Dental Care (IJERMDC),
ISSN: 2349-1590, Vol. 9 Issue 11, November 2022, Impact Factor: 7.125

Saffron's Neuroprotective Potency Against Narcissistic personality, Neurogenic Maladies and Other Cognitive Disorders

Sonu Sharma[1], Shilpa Mamgain[1]*, Jyoti Gupta[2]

[1]Galgotias College of Pharmacy, Greater Noida, U.P
[1]*Galgotias College of Pharmacy, Greater Noida, U.P
[2]Galgotia College of Pharmacy, Greater Noida, U.P

ABSTRACT

In recent years, a serious issue has arisen due to the rising morbidity rates of brain disorders and diseases like anxiety, depression, Alzheimer's disease, and Parkinson's disease. Though many promising results have been reported from the extensive research done on these disorders, there are still just a few medications that can be used to treat them. Due to its antioxidant, anti-inflammatory, and antidepressant characteristics, saffron was frequently used in traditional Chinese medicine (TCM) to treat depression and various other inflammatory disorders in ancient China. Saffron and its components have been used to treat neuropsychiatric and neurodegenerative illnesses in modern times, both on their own and in TCM recipes. We discuss the neuroprotective characteristics of saffron and its constituents from chemical, pharmacokinetic, and pharmacological perspectives in this review, focusing primarily on recent clinical and preclinical trials of brain disorders in which saffron was utilised. We talk about the characteristics of saffron and its components, as well as how they might be used to treat brain illnesses. We hope that this review will be a thorough resource for research on the development of therapeutic saffron-based medications.

Keywords: saffron, saffron constituents, anti-depressant effect, anxiolytic effect, neuroprotective effects, traditional Chinese medicine

INTRODUCTION

In recent years, brain problems, such as neuropsychiatric and neurodegenerative diseases, have become a significant issue. Neuropsychiatric illnesses including anxiety and depression are mostly brought on by tense interpersonal interactions, particular drugs, and significant stressful life events (divorce or death of a loved one, etc.). A decrease or increase in appetite, hypersomnia or sleeplessness, psychomotor agitation or retardation, and persistent exhaustion are common symptoms in people with mental problems (Breen et al., 2011). Anxiety and sadness are both influenced by genetic factors. More than 800 families with recurrent depression have been discovered to have chromosome 3p25-26 (Pitsikas, 2015). In addition, anxiety and sadness are among the more prevalent co-morbidities (Bui and Fava, 2017). There is growing evidence that the pathogenesis of anxiety and depression shares many common mechanisms, including the regulation of hormone secretion, functional disturbances of the GABAergic system (gamma-aminobutyric acid, GABA), dysfunction of the glutamate-related nervous system (Howells and Russell, 2008; Jia et al., 2020), and functional disturbances of the GABAergic system. The pathogenesis of anxiety and depression is also influenced by a number of signalling pathways that control oxidative stress, neuroinflammation, dysfunctional neurotransmitters, and neurotrophic factors (such as brain derived neurotrophic factor, or BDNF) (Kalueff et al., 2006; Ehsanifar et al., 2019). Treatments that focus on these common mechanisms may therefore have a greater therapeutic impact. However, patients with anxiety and depression occasionally experience different symptoms. Patients who have been diagnosed with major depression, for example, are more likely to exhibit a depressed or sad mood, whereas patients who have been diagnosed with major anxiety primarily exhibit an anxious or panic mood The choice of an appropriate therapeutic approach becomes more difficult and challenging in these situations.

Parkinson's disease (PD) and Alzheimer's disease are two of the most common senile diseases in the elderly population (particularly those over 70 years old) (AD). The common signs of these two diseases include cognitive decline, slow, uncoordinated movements, gradual dementia, and personality changes; nonetheless, it's important to remember that both PD and AD are accompanied with psychiatric disorders. In addition to other brain problems,

neurodegenerative diseases are known to cause secondary alterations such as anxiety and depression. This demonstrates how complicated the overlap between brain illnesses is. Since there are no viable treatments for AD and PD's multifactorial illnesses, almost all of the medications currently available are primarily intended to treat their symptoms (Finley and Gao, 2017).

Natural products have a variety of chemical components that, by acting on a variety of targets, are more potent than single compounds at addressing the pathophysiology of multifactorial illnesses. This is why medications made from natural ingredients that have preventive effects against brain problems are so desired. For instance, in November 2019, China provisionally licenced sodium oligomannate (GV-971®), an oral oligosaccharide produced from marine algae, for the treatment of mild-to-moderate AD (to enhance cognitive performance). In contrast to the majority of other anti-PD and anti-AD medications now available, GV-971 is a novel medicine that therapeutically modifies gut microbiota and inhibits gut bacterial amino acids-shaped neuroinflammation to halt the progression of AD (Wang et al., 2019).

One of the most costly herbs on the market right now is saffron, which is the dry, crimson stigma of the Crocus sativus L plant. In order to improve flavour, colour, and scent in food, the bloom of the Crocus sativus L. has been frequently utilised as a natural addition in cooking. The cultivation of saffron has been practised all over the world, but particularly in Mediterranean Europe, India, and south-western Asia since the Crocus sativus was first domesticated in Crete during the Late Bronze Age. Saffron must be grown in fertile clay soil with direct sunlight in either a natural environment (which can increase yield) or a greenhouse (Galigani & Garbati, 1999; Gresta et al., 2008; Cavusoglu et al., 2009). Due to the high market price associated with hand harvesting and low production levels, saffron is often referred to as "red gold." Saffron is one of the most often contaminated goods, according to a review of food component fraud based on 677 references (Moore et al., 2012). As a result, saffron quality control is crucial for authentication. The components of saffron have been established and optimised using a variety of chromatographic and spectrometric approaches, including UV, HPLC, GC, NIR combined with MS, and PTR-TOF-MS (Tarantilis et al., 1995; Masi et al., 2016; Grinan-Ferre et al., 2018).

Carotenoids (crocin, crocetin), monoterpene aldehydes (picrocrocin, safranal), monoterpenoids (crocusatines), isophorones, and flavonoids are among the active components found in saffron (Rameshrad et al., 2018). Area to region differs in the amount of these active chemicals. Due to its hypolipidemic, anti-cancer, antioxidant, anti-inflammatory, and antidepressant effects, saffron has been utilised in traditional medicine (Rios et al., 1996). Saffron has been used in clinical trials for depression, anxiety, Alzheimer's disease, and other brain illnesses because of its pharmacological effects on the neurological system (Moshiri et al., 2015; Hosseini et al., 2018; Samarghandian and Farkhondeh, 2020). The use of saffron and its components for treating neuropsychiatric illnesses, neurodegenerative illnesses, and other brain disorders has been the subject of preclinical and clinical studies, which we have reviewed in this study (Figure 1).

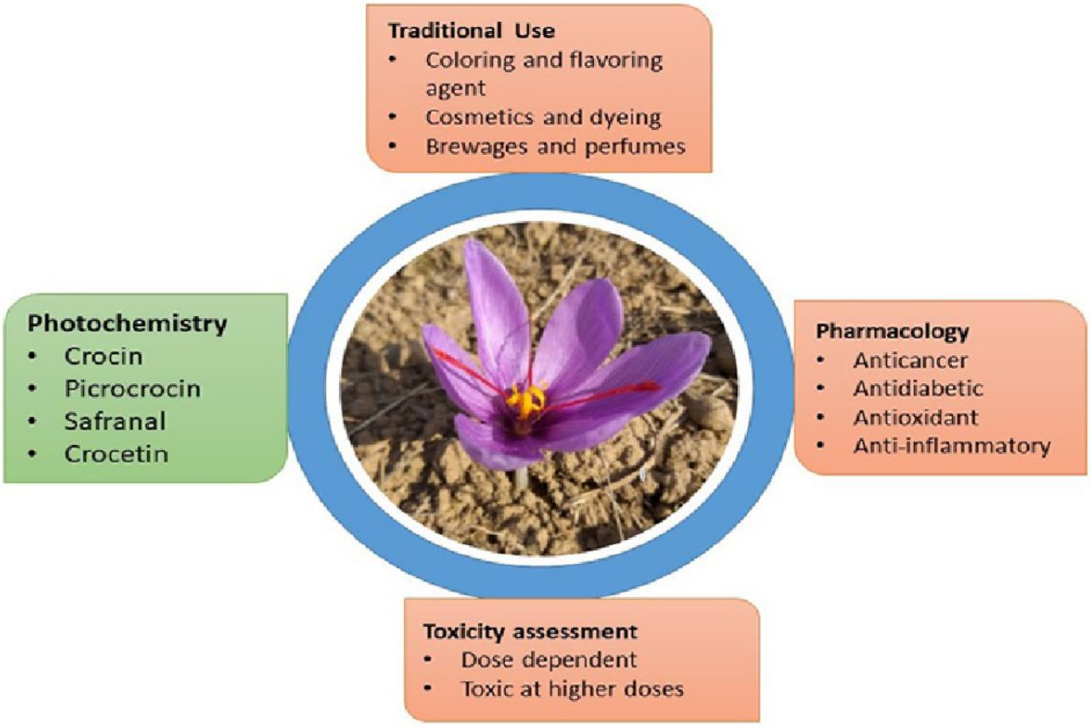


Figure 1. The therapeutic effects of saffron

Constituents of Saffron

Water, nitrogenous matter, carbohydrates, soluble extract, volatile oil, and fibres, in variable proportions, make up saffron. The biggest percentage of all the components is found in soluble extract (41-44%), which is followed by water (14-16%), sugar (12-15%), and nitrogenous materials (11-13%). (Christodoulou et al., 2015). Riboflavin (vitamin B2) and thiamine, two vitamins that are crucial for human health, are found in saffron (vitamin B1). The highest amount of riboflavin found in any food is found in saffron, which has a level that ranges from 56 to 138 g/g (Bhat and Broker, 1953). In addition to these two vital vitamins, saffron also contains trace amounts of beta-carotene, linoleic and linolenic acids, and important fatty acids. There have been discoveries of sterols like campesterol, stigmasterol, and -sitosterol as well as oleanolic, ursolic, palmitoleic, palmitic, and oleic acids.

In different proportions, saffron is made up of water, nitrogenous material, carbohydrates, soluble extract, volatile oil, and fibres. Soluble extract makes up the majority of the components (41-44%), followed by water (14-16%), sugar (12-15%), and nitrogenous materials (11-13%). (Christodoulou et al., 2015). Riboflavin (vitamin B2) and thiamine are two vitamins found in saffron that are crucial to human health (vitamin B1). Saffron has the greatest riboflavin level of any food, with a range of 56 to 138 g/g (Bhat and Broker, 1953). Saffron also contains trace amounts of carotene, important fatty acids, linoleic and linolenic acids, as well as these two vital vitamins. Along with oleanolic, ursolic, palmitoleic, palmitic, and oleic acids, sterols such campesterol, stigmasterol, and sitosterol have been found.

Chemical Structure and characteristic properties of Nonvolatile metabolites of Saffron.

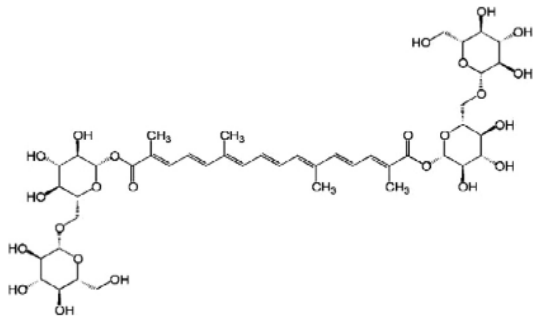
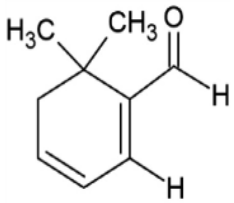
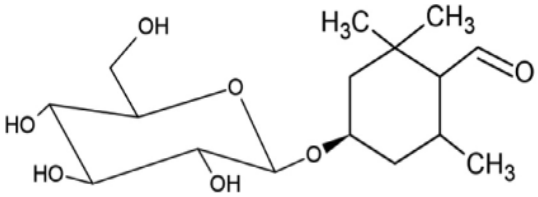
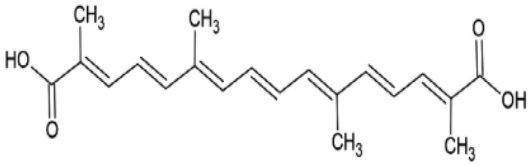
Metabolite	Chemical Structure	Characteristic Property
Crocin		Crocin ($C_{44}H_{64}O_{24}$) is a carotenoid chemical compound primarily responsible for the characteristic color of saffron
Safranal		Safranal ($C_{10}H_{14}O$) is a chemical compound isolated from saffron responsible for the saffron aroma
Picrocrocin		Picrocrocin ($C_{16}H_{26}O_7$) is responsible for the characteristic bitter taste of saffron. it is a monoterpene glycoside precursor of safranal
Crocetin		Crocetin ($C_{20}H_{24}O_4$) is a natural apocarotenoid dicarboxylic acid present in the flower of *Crocus sativus* and *Gardenia jasminoides*.

Figure 2: The structural formula of saffron.

Crocin

With a molecular weight of 976.96, crocin (8,8'-diapo-8,8'-carotenedioic acid with various glycosides) is a hydrophilic carotenoid that gives saffron its red hue. Different glycosyl esters, such as glucose, gentiobiose, and triglucose, can be substituted into the R1 and/or R2 positions on the side chain to create a range of crocin analogues (Figure 2). Crocin 1 (or -crocin), the most prevalent crocin in saffron, is made up of the dicarboxylic acid crocetin and the disaccharide gentiobiose (Samarghandian and Borji, 2014). The identification, quality assurance, standardisation, and process traceability of saffron products can be aided by qualitative and quantitative analysis of various glycosyl moieties and cis-/trans-isomeric forms of crocins (Rocchi et al., 2018).

Picrocrocin

The de-glycosylated precursor of the aromatic components in saffron, picrocrocin (C16H26O7), a crystalline terpene-glucoside with a molecular weight of 330.37, adds to its bitter flavour (Lage and Cantrell, 2009). By dehydrating by heating and enzymatic reactions occuring in storage, picrocin releases hydroxy-safranal (aglycone4-hydroxy-2, 6, 6-trimethyl-1-cyclohexene-1-carboxaldehyde). These processes are aided by -glucosidase. Safranal is produced naturally by dehydration during drying (Figure 3). (Samarghandian and Borji, 2014).

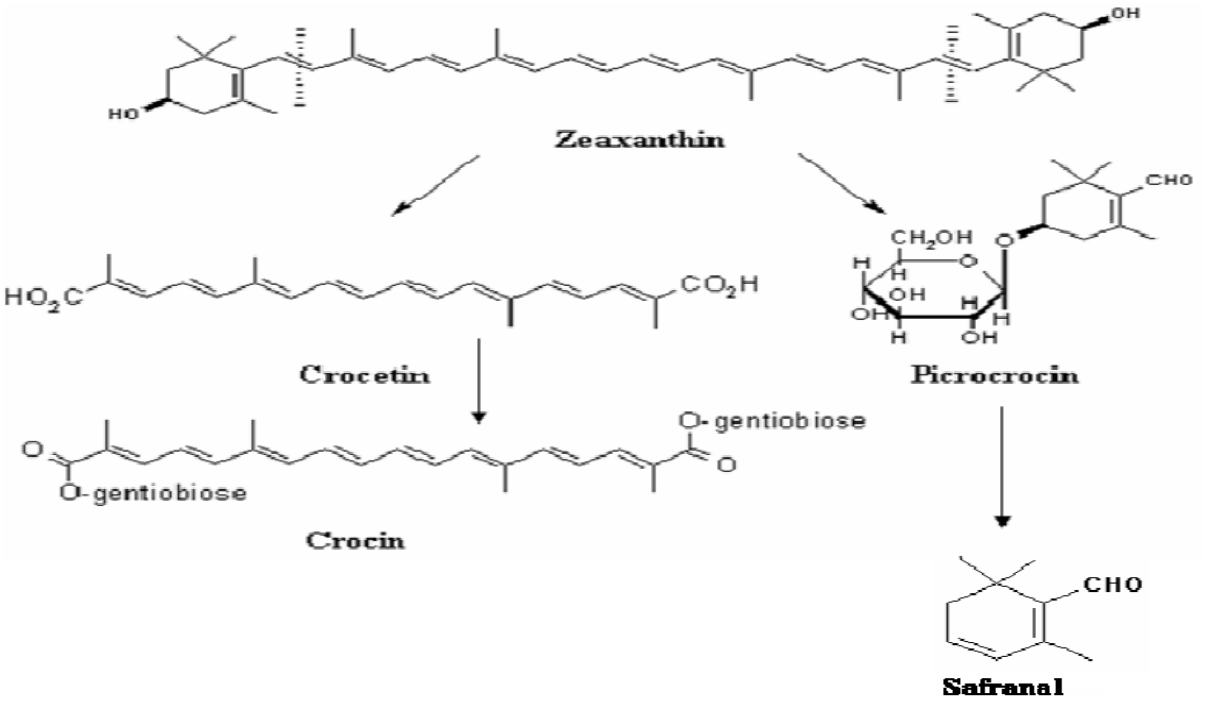


Figure 3: Biosynthesis pathway of important compounds in saffron stigmas.

Safranal

The primary ingredient in essential volatile oil, safranal (2,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde), is what gives saffron its distinctive aroma. Picrocrocin, which is de-glycosylated during post-harvest processing, can create safranal. As a result, storage duration and conditions affect the amount of safranal in saffron. Only one year after harvest can an essential volatile oil with a high safranal concentration be maintained (Maggi et al., 2010).

EVALUATION OF PHARMACOKINETICS AND SAFETY

Crocetin's pharmacokinetic profile differs significantly from that of crocetin. Before (in the gastrointestinal lumen) or during (in the intestinal mucosa) intestinal absorption, crocin can be degraded to crocetin (Asai et al., 2005). Despite the fact that crocetin is the bioactive ingredient in rat plasma, oral administration of crocin is preferred over that of crocetin since the latter chemical does not dissolve well in intestinal fluid (Zhang et al., 2017). Crocetin is hydrolyzed and then partially metabolised in the liver, intestinal mucosa, or both into mono- and diglucuronide conjugates (Asai et al., 2005; Zhang et al., 2017). Crocetin had a half-life of between 6.1 and 7.5 hours when it was removed from the body following a single oral dosage, according to a clinical pharmacokinetic study of healthy adult human volunteers. Additionally, the outcomes demonstrated that crocetin showed no significant deleterious effects at doses as high as 22.5 mg. Because of its tiny molecules and hydrophilic makeup, crocetin enters the bloodstream more quickly through the portal vein than through the lymphatics (Umigai et al., 2011).

Crocetin is produced in the digestive system from crocin following intravenous administration. Due to the weak crocetin-albumin interaction, crocetin has a diffuse distribution in tissue and a low plasma concentration. Additionally, due to its capacity to cross the blood-brain barrier (BBB), crocetin has therapeutic benefits on neurodegenerative disorders (Hosseini et al., 2017). Lautenschlager et al. developed models based on Caco-2 monolayer cells, porcine brain capillary endothelial cells (BCEC), and blood cerebrospinal fluid barrier to examine the underlying penetration mechanisms (BCSFB). Even at a high concentration of 1,000 M, Crocin-1 was unable to cross the Caco-2 monolayer, demonstrating how poorly it penetrates the intestinal barrier. Trans-crocetin, in contrast, can gradually pass the BBB in addition to the intestinal barrier in a dose-dependent way. Trans-crocetin is primarily absorbed via passive transcellular diffusion as opposed to the paracellular route (Lautenschlager et al., 2015).

Saffron exhibits negligible toxicity at therapeutic dosages in experimental and clinical studies. No obvious alterations have been observed in biochemical parameters, haematological parameters, or bodily organs, among other things, in acute, subacute, subchronic, and chronic toxicity studies. Safranal's LD50, the primary indicator of acute toxicity, is lower than those of saffron and crocin, indicating more toxicity (Bostan et al., 2017). In a sub-acute toxicity investigation, safranal increased serum urea nitrogen and lactic acid dehydrogenase (LDH) levels while decreasing total cholesterol, triglyceride, and alkaline phosphatase (ALP) levels (BUN). Additionally, histological findings show that safranal is harmful to the kidney and lung (Hosseinzadeh et al., 2013). Saffron tablets were given orally to patients in a short-term, double-blind, placebo-controlled clinical experiment at doses of 200 or 400 mg for 7 days, and the trial's results demonstrated outstanding safety (Modaghegh et al., 2008). At a dose of 20 mg per day for one month, crocin tablets were likewise generally safe in healthy volunteers (Mohamadpour et al., 2013). Studies comparing the effectiveness of saffron with a placebo in treating patients with neuropsychiatric illnesses found no significant negative effects (Mousavi et al., 2015; Mazidi et al., 2016; Lopresti and Drummond, 2017). Drugs with the same function may increase the risk of having low pharmacological efficiency when administered in combination with saffron because saffron's bioactive components might interact with CYP enzymes (Dovrtlová et al., 2015).

Saffron's Pharmacological Effects and Potential Therapeutic Applications

Saffron's pharmacological effects on psychological disorders and the central nervous system

Depression

The most common psychiatric condition in the world, depression has a significant social and financial burden. By the end of 2020, it is anticipated that up to 21% of people worldwide would experience depression (Murray and Lopez, 1997). The three types of antidepressants that are most frequently prescribed are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and selective serotonin noradrenaline reuptake inhibitors (SSNRIs). Serotonin and other neurotransmitters are made more readily available by antidepressants, which reduces depression symptoms (Nelson et al., 2008). Unfortunately, it is not unexpected that the results of practically all medications on the market are subpar given the lack of accuracy in addressing symptoms. As a result, to achieve a synergistic effect or to increase tolerability, combination therapy (including serotonergic, noradrenergic, and serotonergic and noradrenergic [and dopaminergic] medications) are used. In order to increase the effectiveness of medication therapy, psychotherapy and electroconvulsive therapy are also used (Moret, 2005). Insomnia, somnolence, dry mouth, constipation, and tachycardia are typical adverse effects. The main issues with currently available antidepressants include low rates of full remission, protracted delays in symptom resolution, significant post-treatment symptom persistence, and high relapse rates (Si and Yu, 2016). Some natural compounds, including saffron, resveratrol, green tea catechins, chocolate, omega-2, anthocyanins, and B vitamins, exhibit promisingly antidepressant properties. New medications made from natural product extracts are therefore becoming more and more sought-after, especially those that have been demonstrated to have minimal adverse effects when used to treat depression (Siddiqui et al., 2018).

Preclinical Research

In a mouse depression model, saffron extracts (both aqueous and ethanolic) were shown to have antidepressant effects. Saffron's antidepressant properties were verified by Hosseinzadeh et al. using mice in a forced swimming test. According to the findings, crocin (50–600 mg/kg), safranal (0.15–0.5 mg/kg), and saffron stigma extracts (0.2–0.8 g/kg) all shorten immobility times when compared to the saline group. Both the extracts and safranal lengthened swimming time in a way akin to fluoxetine. This suggested that the dopaminergic, noradrenergic, and serotonergic systems may be activated as the underlying mechanism (Hosseinzadeh et al., 2004). In a related study, also carried out by Hosseinzadeh, kaempferol, another component of saffron, showed beneficial effects in depression models in mice and rats. Wang et al. verified the therapeutic effects of saffron on depression in a different preclinical investigation. Based on the polarity at which the petroleum ether fraction and dichloromethane fraction demonstrated dose-dependent antidepressant effects in a behavioural model of depression, the aqueous ethanol extract of saffron was separated in this work (Wang et al., 2010). Since a higher dose of crocin was required in acute and subacute delivery regimens, Amin et al. concluded that crocetin has a stronger antidepressant effect than crocin (Amin et al., 2015). Aqueous saffron extracts were found to have antidepressant effects in several different experimental depression models, which involved modifying the BDNF, CREB, and VGF pathways. Crocin has also demonstrated anti-inflammatory effects by inhibiting NF-kB and NLRP3 signalling pathway activity in a mouse model of inflammation brought on by LPS; neuroinflammation has been proposed as a potential mechanism.

Clinical Studies

Numerous clinical trials on saffron have been conducted over the past few decades as a result of the effectiveness of saffron in the treatment of depression that has been shown in numerous preclinical investigations. The similar conclusion was reached by Moshiri et al. and Akhondzadeh et al., namely that patients who took saffron 30 mg/day (b.i.d.) for 6 weeks had better outcomes than those who got a placebo (b.i.d.). The DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria for depression were met by 40 outpatients in both studies, who

either received saffron treatment or a placebo. Saffron has been shown to lessen the severity of depression in another clinical trial. 40 participants in the 4-week study, who met the DSM-IV criteria for serious depression, were randomly assigned to receive fluoxetine and saffron or fluoxetine and a placebo. Even though the intensity of the depression was lessened in both groups, there were no significant group differences at the end of the research, showing that taking saffron together with fluoxetine had no further benefits. It is important to look into treatment outcomes over a longer period of time (Sahraian et al., 2016). Lopresti and associates observed 123 patients for 12 weeks in a different randomised double-blind study. They came to the conclusion that curcumin at different doses and combined with saffron can lessen anxiolytic and depressive symptoms in people with major depressive disorder. Similar findings were made by Mazidi et al. who discovered that individuals taking 50 mg of saffron (b.i.d.) for 12 weeks improved their anxiolytic and depressive symptoms in comparison to the placebo group. After giving birth, new mothers may experience postpartum depression, a subtype of depression. On 60 women experiencing postpartum depression, a randomized, double-blind, placebo-controlled trial was conducted. At the final evaluation, 43% of patients in the placebo group were in remission compared to 96% of patients in the saffron group. In comparison to the placebo group, the saffron group's complete response rate was 60%, which was higher. Additionally, a number of clinical studies have been conducted to assess the antidepressant properties of crocin, the primary active component of saffron. Crocin combined with one SSRI (fluoxetine, sertraline, or citalopram) had a stronger antidepressant effect than SSRI combined with placebo, according to Talaei et al (Talaei et al., 2015).

Several research compared saffron with prescription antidepressants in addition to clinical studies evaluating the antidepressant effects of saffron versus placebo. In a 6-week trial, Shahmansouri et al. and Noorbala et al. investigated the therapeutic effects of saffron and fluoxetine on depression. In all investigations, saffron's therapeutic impact on mild-to-moderate depression was comparable to that of fluoxetine. Akhondzadeh et al. reported a comparable outcome to the two trials listed above in a pilot double-blind randomised study with no side effects (Noorbala et al., 2005; Akhondzadeh Basti et al., 2007; Shahmansouri et al., 2014). In a double-blind, randomised clinical trial, it was discovered that after receiving either fluoxetine (20 mg capsule, b.i.d.) or saffron (15 mg capsule, b.i.d.), nearly 50% of the patients in each group saw improvements in their depressive symptoms and scores dropped.

There were no notable variations between the groups (Kashani et al., 2017). Two further investigations contrasted saffron's antidepressant properties with either imipramine or citalopram. Although the results were comparable to those previously reported, saffron had fewer negative effects than imipramine (Akhondzadeh et al., 2004; Ghajar et al., 2017). Therefore, strong clinical data suggests that saffron is a useful alternative to antidepressant medications for the treatment of depression.

Anxiety

More than 6% of the world's population suffers from anxiety, a significant mental problem that can take the form of social anxiety disorder, agoraphobia, panic disorder, or other phobias. In accordance with current worldwide recommendations, SSRIs, SNRIs, and pregabalin are the first-line treatments. However, it might be challenging to acquire the best therapeutic result and continuing treatment is often not recommended due to side effects, delayed action, and aggravation of anxious symptoms at the beginning of treatment. Natural remedies have also shown anti-anxiety properties, including bacopa monniera, centella asiatica, galphimia glauca, and matricaria recutita, among others (Sarris, 2018). Natural product-derived new drugs may have a promising future due to their quick onset and reduced side effects.

Preclinical Research

Using an elevated plus maze test in a mouse model of anxiety, Hosseinzadeh et al. examined the anxiolytic and hypnotic effects of saffron extract, crocin, and safranal. The findings demonstrated that crocins lacked the hypnotic and anxiolytic properties of saffron aqueous extract and safranal (Hosseinzadeh and Noraei, 2009). Using a light/dark test, a different study found comparable results in an animal model of anxiety. In contrast to Hosseinzadeh et altrials, .'s crocin and diazepam both increased the "darkness entering latency of rats" in a light/dark test, indicating that crocin had effects akin to those of an anti-anxiety drug (Pitsikas et al., 2008). Rats were subjected to stress during adolescence by Ghalandari-Shamami et al. in order to assess the anxiolytic properties of crocin and exercise (voluntary wheel running exercise). Adolescent stress-related behavioural and morphological impairments were reduced by crocin, exercise, and the combined intervention (Ghalandari-Shamami et al., 2019). Other research looked at how crocin treated anorexia brought on by stress and obsessive-compulsive disorder. The outcomes demonstrated the ability of crocin and aqueous saffron extracts to lessen symptoms, albeit to varying degrees.

Clinical Research

Saffron or saffron extracts have undergone several randomised double-blind clinical trials to determine its effectiveness in reducing anxiety. Another 6-week trial examined the anxiolytic effects of saffron (30 mg/day) with citalopram (40 mg/day) in 66 patients with significant depression and anxiety. There was a clear improvement in

the symptoms of anxiousness, and neither group experienced any serious adverse effects (Ghajar et al., 2017). Afron®, an unique saffron extract, was tested in two clinical trials for its ability to reduce anxiety in both adults and children. Afron® (28 mg/day for 4 weeks) significantly reduced anxiety-like symptoms in healthy people, according to the results of the first trial by Kell et al (Kell et al., 2017). The second experiment concentrated on young people (ages 12 to 16) who had mild-to-moderate symptoms of anxiety or sadness. The findings demonstrated that giving young people affron® (14 mg, b.i.d.) for eight weeks reduced their anxiety and depressed symptoms (Lopresti et al., 2018).

Milajerdi et al. also looked at whether saffron can treat patients with type 2 diabetes mellitus (DM) who experience mild to moderate depression and anxiety. After 8 weeks of saffron therapy, anxiety and sleep disturbances in DM patients were alleviated. Different outcomes, however, were obtained from a 12-week, double-blind, randomized, placebo-controlled clinical trial. The trial included both men and women who had undergone on-pump coronary artery bypass grafting (CABG) and gave them either saffron capsules (15 mg/twice daily) or a placebo. The findings contradicted the theory that saffron could treat sadness and anxiety symptoms in post-CABG patients. The study had several drawbacks, including a small sample size, a brief study period, and an incomplete study design.

Alzheimer's Disease and Parkinson's Disease

Alzheimer's Disease

Alzheimer's disease (AD) is a slowly advancing neurological condition that causes progressive loss of learning and memory function. A variety of molecular dysfunctions in the brain, including the development of neurofibrillary tangles (NFT) and amyloid plaques, can result in pathological changes that eventually impair memory and learning. One of the most typical causes of dementia, particularly in older populations, is AD. By 2040, there will be about 50 million persons with AD-related dementia (Finley and Gao, 2017). Therefore, the need for novel medications to treat AD is critical. Current "hot topics" in neurodegenerative illnesses centre on natural remedies. Saffron has been shown to have therapeutic effects on brain illnesses, including its ability to lessen AD symptoms.

Anxiety and depression are two common and difficult comorbidities of AD. Depression and anxiety are frequently overlooked and have a detrimental effect on quality of life when they are accompanied by personality changes. According to studies, depressed patients were more likely to have severe AD. Additionally, melancholy and anxiety may hasten the progression of AD patients' disease and raise their mortality. Saffron is likely to be beneficial to patients due to its antidepressant and anti-anxiety properties (Van der Mussele et al., 2013; Chi et al., 2015; Gracia-Garcia et al., 2015).

Preclinical Studies

In experimental animal models, saffron and its components show neuroprotective properties against chemically induced cognitive deterioration (Dashti et al., 2012; Naghibi et al., 2012; Naghizadeh et al., 2013; Asadi et al., 2015; Ghaffari et al., 2015). Additionally, phosphorylated tau proteins, the amyloid-(A) peptide, and their related signalling pathways are possible key therapeutic targets for AD intervention. Numerous in vitro investigations have proven that crocin and crocetin have neuroprotective properties. The findings demonstrated that by lowering A aggregation, phosphorylated tau production, and synaptic loss, both crocin and crocetin could offer neuroprotection. AD is a neurodegenerative condition that cannot be cured and is controlled by intricate systems. Saffron and its components, particularly crocin and crocetin, have been shown to have a neuroprotective effect by reducing oxidative stress, endoplasmic reticulum stress, neuroinflammation, BBB damage, and apoptosis in neuronal cells (Papandreou et al., 2006; Ahn et al., 2011; Deslauriers et al., 2011; Ghahghaei et al., 2012; Ghahghaei et al., 2013; Kong et al., 2014; Karakani et al., 2015; Rashedinia et al., 2015). The MAPK and PI3K pathways may play a role in the neuroprotective properties of saffron, according to a new study (Rafieipour et al., 2019).

Clinical Studies

The development of therapies is placing a strong emphasis on natural goods because there are no effective medications for AD. There aren't many clinical trials that have contrasted saffron's benefits with those of standard treatments or a placebo. Saffron may be a wise choice for treating moderate cognitive impairment, according to Tsolaki et al., who found that it helped patients' Mini-Mental State Examination results (Tsolaki et al., 2016). Akhondzadeh et al. carried out a clinical trial to contrast the effects of saffron with the first-line medications taken by AD patients.

According to the findings, donepezil (10 mg/day) and saffron (30 mg/day) were equally effective treatments for mild-to-moderate AD patients.Another double-blind, random trial examined the efficacy of memantine and saffron in reducing cognitive impartment. In that study, saffron's ability to slow down cognitive deterioration in AD patients was on par with memantine. According to studies (Akhondzadeh et al., 2010a; Akhondzadeh et al., 2010b; Farokhnia et al., 2014; Cicero et al., 2017), saffron has synergistic effects with other nutraceuticals (Bacopa monnieri, l-theanine, copper, folate, and vitamins of B) to affect cognitive performance. mg/day) for mild.

Parkinson's Disease

The loss of dopaminergic neurons in the substantia nigra pars compacta is a frequent neurodegenerative illness characteristic of Parkinson's disease (PD). Tremor, bradykinesia, stiff muscles, poor balance, and the lack of automatic motions are some of the signs of Parkinson's disease. Saffron may be an interesting target for treatments for Parkinson's disease, according to preclinical findings (Pan et al., 2016).

Early-stage PD patients may have non-motor symptoms as insomnia, sadness, and anxiety. Non-motor symptoms may even show up first in some circumstances. Studies have indicated that, due to variations in diagnostic criteria and study groups, the morbidity of depression in individuals with PD ranges from 2.7% to 90%. Nearly 97% of people with Parkinson's disease (PD) have two or more non-motor symptoms, including anxiety, according to epidemiological research. It is evident that the onset of non-motor symptoms is positively connected with the severity of PD. Given its depressive and anxiolytic properties, saffron needs additional consideration as a potential treatment for Parkinson's disease (Arabia et al., 2007; Pontone et al., 2009; Schrag and Taddei, 2017; Ryan et al., 2019).

Preclinical Studies

Multiple neuroprotective benefits of saffron have been demonstrated in a variety of disease types. Crocetin, one of the components of saffron, was discovered by Abdullah et al. to have neuroprotective benefits in a 6-OHDA-induced rat PD model via reducing oxidative stress (Ahmad et al., 2005). In a different investigation, saffron protected the nigral and retinal dopaminergic cells in mice treated with MPTP (Purushothuman et al., 2013). Crocin, a different saffron component, was demonstrated by Guo-Feng Zhang et al. to protect pheochromocytoma (PC-12) cells from MPP+-induced damage by preventing mitochondrial malfunction and ER stress (Zhang et al., 2015). In a malathion-induced rat model, crocin was demonstrated to ameliorate motor impairments and decrease inflammatory cytokines (Mohammadzadeh et al., 2018). In an in vitro model of rotenone-induced Parkinson's disease (PD), the antioxidative and antiapoptotic properties of safranal were examined. Through the Keap1/Nrf2 signalling pathway, safranal shielded primary dopaminergic cells against oxidative stress and death (Pan et al., 2016). Inhibiting the aggregation and buildup of -synuclein has also been found to have neuroprotective benefits for saffron and its components crocin and crocetin (Inoue et al., 2018). Saffron restored lead-induced damage to the dopaminergic and noradrenergic systems in a study by Tamegart et al (Tamegart et al., 2019). Rao et al. further validated the neuroprotective properties of saffron and crocin in a drosophila model of parkinsonism in addition to in animal and cell models (Rao et al., 2016).

Other Brain Disorders

Post-Traumatic Stress Disorder (PTSD)

A catastrophic event, such as a natural disaster, war, serious accident, assault, rape, or abuse, can result in post-traumatic stress disorder (PTSD), a mental disorder. The most typical symptoms experienced by PTSD patients include nightmares, flashbacks to the incident, avoiding particular places, feeling tense, and these symptoms (Auxemery, 2018). Psychological illnesses, including various forms of anxiety and depression, are widely believed to be caused by hormonal changes, including an increase in adrenaline, vasopressin, and corticotropin-releasing hormone (CHR) (Newport and Nemeroff, 2000; Asalgoo et al., 2015). Psychological therapies, such as cognitive behavioural therapy and talk therapy, pharmaceuticals, such as antidepressants and cannabis, or a combination of other treatments are the recommended standard treatments for PTSD patients (Watson, 2019).

Preclinical research on the effects of saffron and its components on PTSD mice has shown some positive findings. Iranian researchers discovered that crocin and saffron extract may both drastically lower the plasma corticosterone level and the anorexia period in a PTSD rat model (Sahraei et al., 2012). According to Asalgoo et al. and his colleague, saffron extract and crocin can improve spatial learning capacity and lessen freezing behaviour in PTSD rat models (Asalgoo et al., 2018). Another study regarding the treatment of anxiety-related behaviour revealed that deep brain stimulation (DBS) therapy in combination with oral saffron intake was more effective than DBS therapy alone (Hashtjini et al., 2018).

Schizophrenia

Schizophrenia is a serious mental illness characterised by odd behaviour, weird speech, a diminished capacity for reality understanding, and dysfunction in social, professional, and personal spheres. Schizophrenia's genesis and pathophysiology are yet unknown. The variety of chronic and persistent psychotic symptoms reflects the complexity of schizophrenia (positive symptoms, negative symptoms, and cognitive disturbances). Because schizophrenia is so complicated, current antipsychotic medications have only proven effective for positive symptoms including hallucinations, delusions, and catatonic conduct. Negative symptoms (social withdrawal, anhedonia, avolition), as well as cognitive abnormalities (deficits in concentration and memory), are not treatable with medicines (Pitsikas, 2016).

The effects of saffron in schizophrenia-like models have not been extensively studied. According to Georgia Georgiadou et al., crocin (50 mg/kg, i.p.) can lessen the stereotypies, ataxia, and hypermotility brought on by ketamine. Additionally, in the social interaction test, crocin (50 mg/kg, i.p.) prevented ketamine-induced social isolation (Georgiadou et al., 2014). Another study demonstrated that crocin (15 and 30 mg/kg) restored recognition memory deficiencies brought on by apomorphine in rat schizophrenia-like models by using the new object recognition task (NORT) (Pitsikas and Tarantilis, 2017).

Saffron was used in two clinical investigations with schizophrenia patients, although they only looked at how it affected non-schizophrenia symptoms. Saffron extract has been shown to help with metabolic syndrome, according to Fadai et al., while Mousavi et al. discovered that saffron aqueous extract and crocin (15 mg bi-daily) showed no negative side effects in individuals with schizophrenia (Fadai et al., 2014; Mousavi et al., 2015).

Epilepsy

Due to an imbalance between the excitatory neurotransmission mediated by the glutamatergic signalling system and the GABAergic signalling pathway, epilepsy is characterised by aberrant hypersynchrony of neuronal activity. A extremely serious health issue and economical burden, epilepsy affects between 50 and 65 million people globally. Recurrent seizures are epilepsy's primary symptom (Eyo et al., 2017).

Safranal has been found to shorten the duration of seizures and postpone the beginning of tonic-clonic seizures (Hosseinzadeh and Talebzadeh, 2005; Hosseinzadeh and Sadeghnia, 2007). Additionally, a study discovered that safranal may interact with opioid receptors and showed anticonvulsant efficacy via the GABAA-benzodiazepine receptor complex (Hosseinzadeh and Sadeghnia, 2007). In a rat model of epilepsy brought on by penicillin, Iranian researchers discovered that administering crocin (100 g) produced an anticonvulsant effect equivalent to that of diazepam (10 g), demonstrating the involvement of the GABAA-benzodiazepine receptor (Tamaddonfard et al., 2012). In a different study, crocin (5, 10, and 20 mg/kg p.o.) reduced ROS production and NF-B pathway signalling to alleviate cognitive impairment in male Swiss albino mice (Mazumder et al., 2017). Additionally, evoked postsynaptic potentials (PSPs) were suppressed and glutamate-induced membrane depolarization was decreased by hydroethanolic saffron extract (CSE) (10-200 g/ml) (Berger et al., 2011). Other studies have demonstrated that stigma from Crocus sativus L. may be beneficial for both absence and tonic-clonic seizures (Hosseinzadeh and Khosravan, 2002). By inhibiting ROS production and NF-B pathway signalling, crocin (5, 10, and 20 mg/kg p.o.) alleviated cognitive impairment in male Swiss albino mice (Mazumder et al., 2017).

Stroke

Stroke Both in industrialised and developing nations,is one of the leading causes of illness and mortality. There is growing evidence that the pathologic course of stroke is caused by oxidative stress, inflammation, mitochondrial dysfunction, and excitotoxicity in ischemic areas (Luo et al., 2019). Particularly connected to stroke, oxidative stress is one of the factors that contributes to brain cell malfunction and death (Barnham et al., 2004). As a result, medications that combat oxidative stress may be effective in the management of stroke.

Crocin, a strong antioxidant, can stop the death of PC-12 cells by reducing the production of ROS (Ochiai et al., 2004; Ochiai et al., 2007). By reducing excessive oxidation and boosting antioxidant activities in rat and mouse models, saffron extract (Saleem et al., 2006), crocin (Ochiai et al., 2007; Zheng et al., 2007; Vakili et al., 2014), crocetin (Higashino et al., 2014), and safranal (Hosseinzadeh and Sadeg Crocin's neuroprotective effects on the ischemic cortex were linked to its modulation of MDA, SOD, GPx, and the JNK pathway (Ochiai et al., 2007; Vakili et al., 2014).

In a recent clinical experiment, patients with acute ischemic stroke were randomly assigned to one of two treatment groups and given either standard stroke care or standard stroke care along with saffron capsule therapy (200 mg/day) for a 3-month follow-up observation. According to the Institute of Health Stoke Scale (NIHSS), the first four days of saffron treatment dramatically reduced stroke severity. Additionally, the saffron-treated group showed decreased serum neuron specific enolase, s100, and elevated BDNF. brain (Ochiai et al., 2007; Vakili et al., 2014). (Ochiai et al., 2007; Vakili et al., 2014). At the end of this trial, patients in saffron-treated group showed a higher mean Barthel index, which measures functional independence and mobility in patients with chronic and disabling conditions, than patients in control group (Asadollahi et al., 2019).

CONCLUSION

Saffron is one of the most expensive spices available, and its components, including crocin, crocetin, and safranal, have demonstrated a variety of biochemical and pharmacological activities. We sought to outline the chemical profiles, pharmacological actions, and therapeutic uses of saffron and its constituents in disorders of the central nervous system in this in-depth review. Preclinical studies and clinical trials both indicated that saffron was efficient and risk-free with no negative side effects. Current scientific research shows that saffron and its bioactive

chemicals are effective in treating a wide range of ailments, including cancer, diabetes, cardiovascular disease, and neurological diseases. Preclinical research established that saffron primarily inhibits oxidative stress, inhibits neuroinflammation, inhibits apoptosis, and acts on other associated pathways to achieve its neuroprotective effects. Saffron's ability to reduce depressive and anxiety-like symptoms in those with anxiety and depression was also supported by clinical research. In clinical investigations employing saffron for treating neurodegenerative illnesses including AD and PD, improvement of cognition impairment was noted. Together, the results offer a distinct viewpoint that may help in the creation of novel neuroprotective medications derived from saffron and its bioactive components. Regarding saffron's potential to treat neuropsychiatric illnesses, more research is required, including preclinical and clinical investigations.

REFERENCES

[1]. Ahmad A. S., Ansari M. A., Ahmad M., Saleem S., Yousuf S., Hoda M. N., et al. (2005). Neuroprotection by crocetin in a hemi-parkinsonian rat model. Pharmacol. Biochem. Behav. 81 (4), 805–813. 10.1016/j.pbb.2005.06.007 [PubMed] [CrossRef] [Google Scholar]

[2]. Ahn J. H., Hu Y., Hernandez M., Kim J. R. (2011). Crocetin inhibits beta-amyloid fibrillization and stabilizes beta-amyloid oligomers. *Biochem. Biophys. Res. Commun.* 414 (1), 79–83. 10.1016/j.bbrc.2011.09.025 [PubMed] [CrossRef] [Google Scholar]

[3]. Akhondzadeh Basti A., Moshiri E., Noorbala A. A., Jamshidi A. H., Abbasi S. H., Akhondzadeh S. (2007). Comparison of petal of Crocus sativus L. and fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized trial. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31 (2), 439–442. 10.1016/j.pnpbp.2006.11.010 [PubMed] [CrossRef] [Google Scholar]

[4]. Akhondzadeh S., Fallah-Pour H., Afkham K., Jamshidi A. H., Khalighi-Cigaroudi F. (2004). Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. *BMC Complement. Altern. Med.* 4, 12. 10.1186/1472-6882-4-12 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[5]. Akhondzadeh S., Tahmacebi-Pour N., Noorbala A. A., Amini H., Fallah-Pour H., Jamshidi A. H., et al. (2005). Crocus sativus L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytother. Res.* 19 (2), 148–151. 10.1002/ptr.1647 [PubMed] [CrossRef] [Google Scholar]

[6]. Akhondzadeh S., Sabet M. S., Harirchian M. H., Togha M., Cheraghmakani H., Razeghi S., et al. (2010. a). A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. *Psychopharmacology* 207 (4), 637–643. 10.1007/s00213-009-1706-1 [PubMed] [CrossRef] [Google Scholar]

[7]. Akhondzadeh S., Shafiee-Sabet M., Harirchian M. H., Togha M., Cheraghmakani H., Razeghi S., et al. (2010. b). Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. *J. Clin. Pharm. Ther.* 35 (5), 581–588. 10.1111/j.1365-2710.2009.01133.x [PubMed] [CrossRef] [Google Scholar]

[8]. Amin B., Nakhsaz A., Hosseinzadeh H. (2015). Evaluation of the antidepressant-like effects of acute and sub-acute administration of crocin and crocetin in mice. *Avicenna J. Phytomed.* 5 (5), 458–468. [PMC free article] [PubMed] [Google Scholar]

[9]. Arabia G., Grossardt B. R., Geda Y. E., Carlin J. M., Bower J. H., Ahlskog J. E., et al. (2007). Increased risk of depressive and anxiety disorders in relatives of patients with Parkinson disease. *Arch. Gen. Psychiatry* 64 (12), 1385–1392. 10.1001/archpsyc.64.12.1385 [PubMed] [CrossRef] [Google Scholar]

[10]. Asadi F., Jamshidi A. H., Khodagholi F., Yans A., Azimi L., Faizi M., et al. (2015). Reversal effects of crocin on amyloid beta-induced memory deficit: Modification of autophagy or apoptosis markers. *Pharmacol. Biochem. Behav.* 139, 47–58. 10.1016/j.pbb.2015.10.011 [PubMed] [CrossRef] [Google Scholar]

[11]. Asadollahi M., Nikdokht P., Hatef B., Sadr S. S., Sahraei H., Assarzadegan F., et al. (2019). Protective properties of the aqueous extract of saffron (Crocus sativus L.) in ischemic stroke, randomized clinical trial. *J. Ethnopharmacol.* 238:111833. 10.1016/j.jep.2019.111833 [PubMed] [CrossRef] [Google Scholar]

[12]. Asai A., Nakano T., Takahashi M., Nagao A. (2005). Orally Administered Crocetin and Crocins Are Absorbed into Blood Plasma as Crocetin and Its Glucuronide Conjugates in Mice. *J. Agric. Food Chem.* 53, 7302–7306. 10.1021/jf0509355 [PubMed] [CrossRef] [Google Scholar]

[13]. Asalgoo S., Jahromi G. P., Meftahi G. H., Sahraei H. (2015). Posttraumatic Stress Disorder (PTSD): Mechanisms and Possible Treatments. *Neurophysiology* 47 (6), 482–489. 10.1007/s11062-016-9559-9 [CrossRef] [Google Scholar]

[14]. Asalgoo S., Jahromi G. P., Hatef B., Sahraei H. (2018). The Effect of Saffron Aqueous Extract and Crocin on PTSD Rat Models: The Focus on Learning and Spatial Memory. *J. Adv. Med. BioMed. Res.* 26 (119), 34–42. [Google Scholar]

[15]. Asrari N., Yazdian-Robati R., Abnous K., Razavi B. M., Rashednia M., Hasani F. V., et al. (2018). Antidepressant effects of aqueous extract of saffron and its effects on CREB, P-CREB, BDNF, and

VGF proteins in rat cerebellum. *J. Pharmacopuncture* 21 (1), 35–40. 10.3831/KPI.2018.21.005 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[16]. Auxemery Y. (2018). Post-traumatic psychiatric disorders: PTSD is not the only diagnosis. *Presse. Med.* 47 (5), 423–430. 10.1016/j.lpm.2017.12.006 [PubMed] [CrossRef] [Google Scholar]

[17]. Barnham K. J., Masters C. L., Bush A. I. (2004). Neurodegenerative diseases and oxidative stress. *Nat. Rev. Drug Discov.* 3 (3), 205–214. 10.1038/nrd1330 [PubMed] [CrossRef] [Google Scholar]

[18]. Berger F., Hensel A., Nieber K. (2011). Saffron extract and trans-crocetin inhibit glutamatergic synaptic transmission in rat cortical brain slices. *Neuroscience* 180, 238–247. 10.1016/j.neuroscience.2011.02.037 [PubMed] [CrossRef] [Google Scholar]

[19]. Bhat J. V., Broker R. (1953). Riboflavine and thiamine contents of saffron, Crocus sativus linn. *Nature* 172 (4377), 544. 10.1038/172544a0 [PubMed] [CrossRef] [Google Scholar]

[20]. Boskabady M. H., Farkhondeh T. (2016). Antiinflammatory, Antioxidant, and Immunomodulatory Effects of Crocus sativus L. and its Main Constituents. *Phytother. Res.* 30 (7), 1072–1094. 10.1002/ptr.5622 [PubMed] [CrossRef] [Google Scholar]

[21]. Bostan H. B., Mehri S., Hosseinzadeh H. (2017). Toxicology effects of saffron and its constituents: a review. *Iran J. Basic Med. Sci.* 20 (2), 110–121. 10.22038/ijbms.2017.8230 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[22]. Breen G., Webb B. T., Butler A. W., van den Oord E. J., Tozzi F., Craddock N., et al. (2011). A genome-wide significant linkage for severe depression on chromosome 3: the depression network study. *Am. J. Psychiatry* 168 (8), 840–847. 10.1176/appi.ajp.2011.10091342 [PubMed] [CrossRef] [Google Scholar]

[23]. Bui E., Fava M. (2017). From depression to anxiety, and back. *Acta Psychiatr. Scand.* 136 (4), 341–342. 10.1111/acps.12801 [PubMed] [CrossRef] [Google Scholar]

[24]. Cavusoglu A., Erkel E. I., Sulusoglu M. (2009). Saffron (Crocus sativus L.) studies with two mother corm dimensions on yield and harvest period under greenhouse condition. *Am.-Eurasian J. Sustain. Agric.* 3 (2), 126–129. [Google Scholar]

[25]. Chi S., Wang C., Jiang T., Zhu X. C., Yu J. T., Tan L. (2015). The prevalence of depression in Alzheimer's disease: a systematic review and meta-analysis. *Curr. Alzheimer Res.* 12 (2), 189–198. 10.2174/1567205012666150204124310 [PubMed] [CrossRef] [Google Scholar]

[26]. Christodoulou E., Kadoglou N. P., Kostomitsopoulos N., Valsami G. (2015). Saffron: a natural product with potential pharmaceutical applications. *J. Pharm. Pharmacol.* 67 (12), 1634–1649. 10.1111/jphp.12456 [PubMed] [CrossRef] [Google Scholar]

[27]. Cicero A. F., Bove M., Colletti A., Rizzo M., Fogacci F., Giovannini M., et al. (2017). Short-Term Impact of a Combined Nutraceutical on Cognitive Function, Perceived Stress and Depression in Young Elderly with Cognitive Impairment: A Pilot, Double-Blind, Randomized Clinical Trial. *Jpad-J. Prev. Alzheimers Dis.* 4 (1), 12–15. 10.14283/jpad.2016.110 [PubMed] [CrossRef] [Google Scholar]

[28]. Clark D. A., Beck A. T., Beck J. S. (1994). Symptom differences in major depression, dysthymia, panic disorder, and generalized anxiety disorder. *Am. J. Psychiatry* 151 (2), 205–209. 10.1176/ajp.151.2.205 [PubMed] [CrossRef] [Google Scholar]

[29]. Dashti R. M., Zeinali F., Anvari M., Hosseini S. M. (2012). Saffron (Crocus sativus L.) extract prevents and improves D-galactose and NaNO2 induced memory impairment in mice. *EXCLI J.* 11, 328–337. [PMC free article] [PubMed] [Google Scholar]

[30]. Deslauriers A. M., Afkhami-Goli A., Paul A. M., Bhat R. K., Acharjee S., Ellestad K. K., et al. (2011). Neuroinflammation and endoplasmic reticulum stress are coregulated by crocin to prevent demyelination and neurodegeneration. *J. Immunol.* 187 (9), 4788–4799. 10.4049/jimmunol.1004111 [PubMed] [CrossRef] [Google Scholar]

[31]. Dorri S. A., Hosseinzadeh H., Abnous K., Hasani F. V., Robati R. Y., Razavi B. M. (2015). Involvement of brain-derived neurotrophic factor (BDNF) on malathion induced depressive-like behavior in subacute exposure and protective effects of crocin. *Iran J. Basic Med. Sci.* 18 (10), 958–966. [PMC free article] [PubMed] [Google Scholar]

[32]. Dovrtělová G., Nosková K., Juřica J., Turjap M., Zendulka O. (2015). Can bioactive compounds of Crocus sativus L. influence the metabolic activity of selected CYP enzymes in the rat? *Physiol. Res.* 64 4), S453–S458. 10.33549/physiolres.933203 [PubMed] [CrossRef] [Google Scholar]

[33]. Ehsanifar M., Tameh A. A., Farzadkia M., Kalantari R. R., Zavareh M. S., Nikzaad H., et al. (2019). Exposure to nanoscale diesel exhaust particles: Oxidative stress, neuroinflammation, anxiety and depression on adult male mice. *Ecotoxicol. Environ. Saf.* 168, 338–347. 10.1016/j.ecoenv.2018.10.090 [PubMed] [CrossRef] [Google Scholar]

[34]. Eyo U. B., Murugan M., Wu L. J. (2017). Microglia-Neuron Communication in Epilepsy. *Glia* 65 (1), 5–18. 10.1002/glia.23006 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[35]. Fadai F., Mousavi B., Ashtari Z., Ali beigi N., Farhang S., Hashempour S., et al. (2014). Saffron aqueous extract prevents metabolic syndrome in patients with schizophrenia on olanzapine treatment: a randomized triple blind placebo controlled study. *Pharmacopsychiatry* 47 (4-5), 156–161. 10.1055/s-0034-1382001 [PubMed] [CrossRef] [Google Scholar]

[36]. Farokhnia M., Sabet M. S., Iranpour N., Gougol A., Yekehtaz H., Alimardani R., et al. (2014). Comparing the efficacy and safety of Crocus sativus L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial. *Hum. Psychopharmacol.-Clin. Exp.* 29 (4), 351–359. 10.1002/hup.2412 [PubMed] [CrossRef] [Google Scholar]

[37]. Finley J. W., Gao S. (2017). A Perspective on Crocus sativus L. (Saffron) Constituent Crocin: A Potent Water-Soluble Antioxidant and Potential Therapy for Alzheimer's Disease. *J. Agric. Food Chem.* 65 (5), 1005–1020. 10.1021/acs.jafc.6b04398 [PubMed] [CrossRef] [Google Scholar]

[38]. Galigani P. F., Garbati P. F. (1999). "Mechanized saffron cultivation including harvesting," in *Saffron*. Ed. Negbi M. (Australia: Crocus sativus L. Harwood Academic Publishers;), 115–126. [Google Scholar]

[39]. Gallagher-Michaels J. (2013). Treatment Plans and Interventions for Depression and Anxiety Disorders, 2nd edition. *Behav. Cogn. Psychother.* 41 (1), 123–124. 10.1017/S1352465812000938 [CrossRef] [Google Scholar]

[40]. Georgiadou G., Tarantilis P. A., Pitsikas N. (2012). Effects of the active constituents of Crocus Sativus L., crocins, in an animal model of obsessive-compulsive disorder. *Neurosci. Lett.* 528 (1), 27–30. 10.1016/j.neulet.2012.08.081 [PubMed] [CrossRef] [Google Scholar]

[41]. Georgiadou G., Grivas V., Tarantilis P. A., Pitsikas N. (2014). Crocins, the active constituents of Crocus Sativus L., counteracted ketamine-induced behavioural deficits in rats. *Psychopharmacology* 231 (4), 717–726. 10.1007/s00213-013-3293-4 [PubMed] [CrossRef] [Google Scholar]

[42]. Ghaffari S., Hatami H., Dehghan G. (2015). Saffron ethanolic extract attenuates oxidative stress, spatial learning, and memory impairments induced by local injection of ethidium bromide. *Res. Pharm. Sci.* 10 (3), 222–232. [PMC free article] [PubMed] [Google Scholar]

[43]. Ghahghaei A., Bathaie S. Z., Bahraminejad E. (2012). Mechanisms of the Effects of Crocin on Aggregation and Deposition of A beta 1-40 Fibrils in Alzheimer's Disease. *Int. J. Pept. Res. Ther.* 18 (4), 347–351. 10.1007/s10989-012-9308-x [CrossRef] [Google Scholar]

[44]. Ghahghaei A., Bathaie S. Z., Kheirkhah H., Bahraminejad E. (2013). The protective effect of crocin on the amyloid fibril formation of a beta 42 peptide in vitro. *Cell. Mol. Biol. Lett.* 18 (3), 328–339. 10.2478/s11658-013-0092-1 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[45]. Ghajar A., Neishabouri S. M., Velayati N., Jahangard L., Matinnia N., Haghighi M., et al. (2017). Crocus sativus L. versus Citalopram in the Treatment of Major Depressive Disorder with Anxious Distress: A Double-Blind, Controlled Clinical Trial. *Pharmacopsychiatry* 50 (4), 152–160. 10.1055/s-0042-116159 [PubMed] [CrossRef] [Google Scholar]

[46]. Ghalandari-Shamami M., Nourizade S., Yousefi B., Vafaei A. A., Pakdel R., Rashidy-Pour A. (2019). Beneficial Effects of Physical Activity and Crocin Against Adolescent Stress Induced Anxiety or Depressive-Like Symptoms and Dendritic Morphology Remodeling in Prefrontal Cortex in Adult Male Rats. *Neurochem. Res.* 44 (4), 917–929. 10.1007/s11064-019-02727-2 [PubMed] [CrossRef] [Google Scholar]

[47]. Ghasemi T., Abnous K., Vahdati F., Mehri S., Razavi B. M., Hosseinzadeh H. (2015). Antidepressant Effect of Crocus sativus Aqueous Extract and its Effect on CREB, BDNF, and VGF Transcript and Protein Levels in Rat Hippocampus. *Drug Res. (Stuttg)* 65 (7), 337–343. 10.1055/s-0034-1371876 [PubMed] [CrossRef] [Google Scholar]

[48]. Gracia-Garcia P., de-la-Camara C., Santabarbara J., Lopez-Anton R., Quintanilla M. A., Ventura T., et al. (2015). Depression and incident Alzheimer disease: the impact of disease severity. *Am. J. Geriatr. Psychiatry* 23 (2), 119–129. 10.1016/j.jagp.2013.02.011 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[49]. Gresta F., Lombardo G. M., Siracusa L., Ruberto G. (2008). Saffron, an alternative crop for sustainable agricultural systems. A review. *Agron. Sustain. Dev.* 28 (1), 95–112. 10.1051/agro:2007030 [CrossRef] [Google Scholar]

[50]. Grinan-Ferre C., Corpas R., Puigoriol-Illamola D., Palomera-Avalos V., Sanfeliu C., Pallas M. (2018). Understanding Epigenetics in the Neurodegeneration of Alzheimer's Disease: SAMP8 Mouse Model. *J. Alzheimers Dis.* 62 (3), 943–963. 10.3233/JAD-170664 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[51]. Halataei B. A. S., Khosravi M., Arbabian S., Sahraei H., Golmanesh L., Zardooz H., et al. (2011). Saffron (Crocus sativus) Aqueous Extract and its Constituent Crocin Reduces Stress-induced Anorexia in Mice. *Phytother. Res.* 25 (12), 1833–1838. 10.1002/ptr.3495 [PubMed] [CrossRef] [Google Scholar]

[52]. Hashtjini M. M., Jahromi G. P., Meftahi G. H., Esmaeili D., Javidnazar D. (2018). Aqueous extract of saffron administration along with amygdala deep brain stimulation promoted alleviation of symptoms in post-traumatic stress disorder (PTSD) in rats. *Avicenna J. Phytomed.* 8 (4), 358–369. [PMC free article] [PubMed] [Google Scholar]

[53]. Higashino S., Sasaki Y., Giddings J. C., Hyodo K., Sakata S. F., Matsuda K., et al. (2014). Crocetin, a carotenoid from Gardenia jasminoides Ellis, protects against hypertension and cerebral thrombogenesis in stroke-prone spontaneously hypertensive rats. *Phytother. Res.* 28 (9), 1315–1319. 10.1002/ptr.5130 [PubMed] [CrossRef] [Google Scholar]

[54]. Hosseini A., Razavi B. M., Hosseinzadeh H. (2017). Pharmacokinetic Properties of Saffron and its Active Components. *Eur. J. Drug Metab. Pharmacokinet.* 43 (4), 383–390. 10.1007/s13318-017-0449-3 [PubMed] [CrossRef] [Google Scholar]

[55]. Hosseini A., Razavi B. M., Hosseinzadeh H. (2018). Pharmacokinetic Properties of Saffron and its Active Components. *Eur. J. Drug Metab. Pharmacokinet.* 43 (4), 383–390. 10.1007/s13318-017-0449-3 [PubMed] [CrossRef] [Google Scholar]

[56]. Hosseinzadeh H., Khosravan V. (2002). Anticonvulsant effects of aqueous and ethanolic extracts of Crocus sativus L. stigmas in mice. *Arch. Irn. Med.* 5 (1), 44–47. [Google Scholar]

[57]. Hosseinzadeh H., Noraei N. B. (2009). Anxiolytic and hypnotic effect of Crocus sativus aqueous extract and its constituents, crocin and safranal, in mice. *Phytother. Res.* 23 (6), 768–774. 10.1002/ptr.2597 [PubMed] [CrossRef] [Google Scholar]

[58]. Hosseinzadeh H., Sadeghnia H. R. (2005). Safranal, a constituent of Crocus sativus (saffron), attenuated cerebral ischemia induced oxidative damage in rat hippocampus. *J. Pharm. Pharm. Sci.* 8, 394–399. [PubMed] [Google Scholar]

[59]. Hosseinzadeh H., Sadeghnia H. R. (2007). Protective effect of safranal on pentylenetetrazol-induced seizures in the rat: involvement of GABAergic and opioids systems. *Phytomedicine* 14 (4), 256–262. 10.1016/j.phymed.2006.03.007 [PubMed] [CrossRef] [Google Scholar]

[60]. Hosseinzadeh H., Talebzadeh F. (2005). Anticonvulsant evaluation of safranal and crocin from Crocus sativus in mice. *Fitoterapia* 76 (7-8), 722–724. 10.1016/j.fitote.2005.07.008 [PubMed] [CrossRef] [Google Scholar]

[61]. Hosseinzadeh H., Karimi G., Niapoor M. (2004). Antidepressant effect of Crocus sativus L. stigma extracts and their constituents, crocin and safranal, in mice. *Proc. 1st Int. Symp. Saffron Biol. Biotechnol.* 650), 435–445. 10.17660/ActaHortic.2004.650.54 [CrossRef] [Google Scholar]

[62]. Hosseinzadeh H., Shakib S. S., Sameni A. K., Taghiabadi E. (2013). Acute and Subacute Toxicity of Safranal, a Constituent of Saffron, in Mice and Rats. *Iran J. Pharm. Res.* 12 (1), 93–99. [PMC free article] [PubMed] [Google Scholar]

[63]. Howells F. M., Russell V. A. (2008). Glutamate-stimulated release of norepinephrine in hippocampal slices of animal models of attention-deficit/hyperactivity disorder (spontaneously hypertensive rat) and depression/anxiety-like behaviours (Wistar-Kyoto rat). *Brain Res.* 1200, 107–115. 10.1016/j.brainres.2008.01.033 [PubMed] [CrossRef] [Google Scholar]

[64]. Inoue E., Shimizu Y., Masui R., Hayakawa T., Tsubonoya T., Hori S., et al. (2018). Effects of saffron and its constituents, crocin-1, crocin-2, and crocetin on alpha-synuclein fibrils. *J. Nat. Med.* 72 (1), 274–279. 10.1007/s11418-017-1150-1 [PubMed] [CrossRef] [Google Scholar]

[65]. Jia Y. F., Wininger K., Ho A. M., Peyton L., Baker M., Choi D. S. (2020). Astrocytic Glutamate Transporter 1 (GLT1) Deficiency Reduces Anxiety- and Depression-Like Behaviors in Mice. *Front. Behav. Neurosci.* 14, 57. 10.3389/fnbeh.2020.00057 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[66]. Kalueff A. V., Nutt D. J. (2007). Role of GABA in anxiety and depression. *Depress Anxiety* 24 (7), 495–517. 10.1002/da.20262 [PubMed] [CrossRef] [Google Scholar]

[67]. Kalueff A. V., Avgustinovich D. F., Kudryavtseva N. N., Murphy D. L. (2006). BDNF in anxiety and depression. *Science* 312 (5780), 1598–1598. 10.1126/science.312.5780.1598 [PubMed] [CrossRef] [Google Scholar]

[68]. Karakani A. M., Riazi G., Mahmood Ghaffari S., Ahmadian S., Mokhtari F., Jalili Firuzi M., et al. (2015). Inhibitory effect of corcin on aggregation of 1N/4R human tau protein in vitro. *Iran J. Basic Med. Sci.* 18 (5), 485–492. [PMC free article] [PubMed] [Google Scholar]

[69]. Kashani L., Eslatmanesh S., Saedi N., Niroomand N., Ebrahimi M., Hosseinian M., et al. (2017). Comparison of Saffron versus Fluoxetine in Treatment of Mild to Moderate Postpartum Depression: A Double-Blind, Randomized Clinical Trial. *Pharmacopsychiatry* 50 (2), 64–68. 10.1055/s-0042-115306 [PubMed] [CrossRef] [Google Scholar]

[70]. Kell G., Rao A., Beccaria G., Clayton P., Inarejos-Garcia A. M., Prodanov M. (2017). affron (R) a novel saffron extract (Crocus sativus L.) improves mood in healthy adults over 4 weeks in a double-blind, parallel, randomized, placebo controlled clinical trial. *Complement. Ther. Med.* 33, 58–64. 10.1016/j.ctim.2017.06.001 [PubMed] [CrossRef] [Google Scholar]

[71]. Kong Y., Kong L. P., Luo T., Li G. W., Jiang W., Li S., et al. (2014). The Protective Effects of Crocetin on A beta(1-42)-Induced Toxicity in Ht22 Cells. *CNS Neuro. Disord.-Drug Targets* 13 (9), 1627–1632. 10.2174/1871527313666140806125410 [PubMed] [CrossRef] [Google Scholar]

[72]. Lage M., Cantrell C. L. (2009). Quantification of saffron (Crocus sativus L.) metabolites crocins, picrocrocin and safranal for quality determination of the spice grown under different environmental Moroccan conditions. *Sci. Hortic.* 121 (3), 366–373. 10.1016/j.scienta.2009.02.017 [CrossRef] [Google Scholar]

[73]. Lautenschlager M., Sendker J., Huwel S., Galla H. J., Brandt S., Dufer M., et al. (2015). Intestinal formation of trans-crocetin from saffron extract (Crocus sativus L.) and in vitro permeation through

intestinal and blood brain barrier. *Phytomedicine* 22 (1), 36–44. 10.1016/j.phymed.2014.10.009 [PubMed] [CrossRef] [Google Scholar]

[74]. Lopresti A. L., Drummond P. D. (2017). Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: A randomised, double-blind, placebo-controlled study. *J. Affect. Disord.* 207, 188–196. 10.1016/j.jad.2016.09.047 [PubMed] [CrossRef] [Google Scholar]

[75]. Lopresti A. L., Drummond P. D., Inarejos-Garcia A. M., Prodanov M. (2018). affron (R), a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. *J. Affect. Disord.* 232, 349–357. 10.1016/j.jad.2018.02.070 [PubMed] [CrossRef] [Google Scholar]

[76]. Luo S., Li H., Mo Z., Lei J., Zhu L., Huang Y., et al. (2019). Connectivity map identifies luteolin as a treatment option of ischemic stroke by inhibiting MMP9 and activation of the PI3K/Akt signaling pathway. *Exp. Mol. Med.* 51 (3), 37. 10.1038/s12276-019-0229-z [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[77]. Maggi L., Carmona M., Zalacain A., Kanakis C. D., Anastasaki E., Tarantilis P. A., et al. (2010). Changes in saffron volatile profile according to its storage time. *Food Res. Int.* 43 (5), 1329–1334. 10.1016/j.foodres.2010.03.025 [CrossRef] [Google Scholar]

[78]. Maron E., Nutt D. (2017). Biological markers of generalized anxiety disorder. *Dialogues Clin. Neurosci.* 19 (2), 147–158. 10.1176/appi.focus.16205 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[79]. Masi E., Taiti C., Heimler D., Vignolini P., Romani A., Mancuso S. (2016). PTR-TOF-MS and HPLC analysis in the characterization of saffron (Crocus sativus L.) from Italy and Iran. *Food Chem.* 192, 75–81. 10.1016/j.foodchem.2015.06.090 [PubMed] [CrossRef] [Google Scholar]

[80]. Mazidi M., Shemshian M., Mousavi S. H., Norouzy A., Kermani T., Moghiman T., et al. (2016). A double-blind, randomized and placebo-controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression. *J. Complement. Integr. Med.* 13 (2), 195–199. 10.1515/jcim-2015-0043 [PubMed] [CrossRef] [Google Scholar]

[81]. Mazumder A. G., Sharma P., Patial V., Singh D. (2017). Crocin Attenuates Kindling Development and Associated Cognitive Impairments in Mice via Inhibiting Reactive Oxygen Species-Mediated NF-κB Activation. *Basic Clin. Pharmacol. Toxicol.* 120, 426–433. 10.1111/bcpt.12694 [PubMed] [CrossRef] [Google Scholar]

[82]. Milajerdi A., Jazayeri S., Shirzadi E., Hashemzadeh N., Azizgol A., Djazayery A., et al. (2018). The effects of alcoholic extract of saffron (Crocus satious L.) on mild to moderate comorbid depression-anxiety, sleep quality, and life satisfaction in type 2 diabetes mellitus: A double-blind, randomized and placebo-controlled clinical trial. *Complement. Ther. Med.* 41, 196–202. 10.1016/j.ctim.2018.09.023 [PubMed] [CrossRef] [Google Scholar]

[83]. Moazen-Zadeh E., Abbasi S. H., Safi-Aghdam H., Shahmansouri N., Arjmandi-Beglar A., Hajhosseinn Talasaz A., et al. (2018). Effects of Saffron on Cognition, Anxiety, and Depression in Patients Undergoing Coronary Artery Bypass Grafting: A Randomized Double-Blind Placebo-Controlled Trial. *J. Altern. Complement. Med.* 24 (4), 361–368. 10.1089/acm.2017.0173 [PubMed] [CrossRef] [Google Scholar]

[84]. Modaghegh M. H., Shahabian M., Esmaeili H. A., Rajbai O., Hosseinzadeh H. (2008). Safety evaluation of saffron (Crocus sativus) tablets in healthy volunteers. *Phytomedicine* 15 (12), 1032–1037. 10.1016/j.phymed.2008.06.003 [PubMed] [CrossRef] [Google Scholar]

[85]. Mohamadpour A. H., Ayati Z., Parizadeh M. R., Rajbai O., Hosseinzadeh H. (2013). Safety Evaluation of Crocin (a constituent of saffron) Tablets in Healthy Volunteers. *Iran J. Basic Med. Sci.* 16 (1), 39–46. [PMC free article] [PubMed] [Google Scholar]

[86]. Mohammadzadeh L., Hosseinzadeh H., Abnous K., Razavi B. M. (2018). Neuroprotective potential of crocin against malathion-induced motor deficit and neurochemical alterations in rats. *Environ. Sci. Pollut. Res. Int.* 25 (5), 4904–4914. 10.1007/s11356-017-0842-0 [PubMed] [CrossRef] [Google Scholar]

[87]. Moore J. C., Spink J., Lipp M. (2012). Development and application of a database of food ingredient fraud and economically motivated adulteration from 1980 to 2010. *J. Food Sci.* 77 (4), R118–R126. 10.1111/j.1750-3841.2012.02657.x [PubMed] [CrossRef] [Google Scholar]

[88]. Moret C. (2005). Combination/augmentation strategies for improving the treatment of depression. *Neuropsychiatr. Dis. Treat* 1 (4), 301–309. [PMC free article] [PubMed] [Google Scholar]

[89]. Moshiri E., Basti A. A., Noorbala A. A., Jamshidi A. H., Hesameddin Abbasi S., Akhondzadeh S. (2006). Crocus sativus L. (petal) in the treatment of mild-to-moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytomedicine* 13 (9-10), 607–611. 10.1016/j.phymed.2006.08.006 [PubMed] [CrossRef] [Google Scholar]

[90]. Moshiri M., Vahabzadeh M., Hosseinzadeh H. (2015). Clinical Applications of Saffron (Crocus sativus) and its Constituents: A Review. *Drug Res. (Stuttg)* 65 (6), 287–295. 10.1055/s-0034-1375681 [PubMed] [CrossRef] [Google Scholar]

[91]. Mousavi B., Bathaie S. Z., Fadai F., Ashtari Z., Ali Beigi N., Farhang S., et al. (2015). Safety evaluation of saffron stigma (Crocus sativus L.) aqueous extract and crocin in patients with schizophrenia. *Avicenna J. Phytomed.* 5 (5), 413–419. [PMC free article] [PubMed] [Google Scholar]

[92]. Murray C. J., Lopez A. D. (1997). Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 349 (9064), 1498–1504. 10.1016/S0140-6736(96)07492-2 [PubMed] [CrossRef] [Google Scholar]

[93]. Naghibi S. M., Hosseini M., Khani F., Rahimi M., Vafaee F., Rakhshandeh H., et al. (2012). Effect of Aqueous Extract of Crocus sativus L. @ on Morphine-Induced Memory Impairment. *Adv. Pharmacol. Sci.* 2012:494367. 10.1155/2012/494367 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[94]. Naghizadeh B., Mansouri M. T., Ghorbanzadeh B., Farbood Y., Sarkaki A. (2013). Protective effects of oral crocin against intracerebroventricular streptozotocin-induced spatial memory deficit and oxidative stress in rats. *Phytomedicine* 20 (6), 537–542. 10.1016/j.phymed.2012.12.019 [PubMed] [CrossRef] [Google Scholar]

[95]. Nelson J. C., Thase M. E., Khan A., Nelson J. C. (2008). Are antidepressants effective? What's a clinician to think? *J. Clin. Psychiatry* 69 (6), 1014–1015. 10.4088/jcp.v69n0619 [PubMed] [CrossRef] [Google Scholar]

[96]. Newport D. J., Nemeroff C. B. (2000). Neurobiology of posttraumatic stress disorder. *Curr. Opin. Neurobiol.* 10 (2), 211–218. 10.1016/S0959-4388(00)00080-5 [PubMed] [CrossRef] [Google Scholar]

[97]. Noorbala A. A., Akhondzadeh S., Tahmacebi-Pour N., Jamshidi A. H. (2005). Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. *J. Ethnopharmacol.* 97 (2), 281–284. 10.1016/j.jep.2004.11.004 [PubMed] [CrossRef] [Google Scholar]

[98]. Ochiai T., Ohno S., Soeda S., Tanaka H., Shoyama Y., Shimeno H. (2004). Crocin prevents the death of rat pheochromyctoma (PC-12) cells by its antioxidant effects stronger than those of alpha-tocopherol. *Neurosci. Lett.* 362 (1), 61–64. 10.1016/j.neulet.2004.02.067 [PubMed] [CrossRef] [Google Scholar]

[99]. Ochiai T., Shimeno H., Mishima K., Iwasaki K., Fujiwara M., Tanaka H., et al. (2007). Protective effects of carotenoids from saffron on neuronal injury in vitro and in vivo. *Biochim. Biophys. Acta* 1770 (4), 578–584. 10.1016/j.bbagen.2006.11.012 [PubMed] [CrossRef] [Google Scholar]

[100]. Pan P. K., Qiao L. Y., Wen X. N. (2016). Safranal prevents rotenone-induced oxidative stress and apoptosis in an in vitro model of Parkinson's disease through regulating Keap1/Nrf2 signaling pathway. *Cell. Mol. Biol.* 62 (14), 11–17. 10.14715/cmb/2016.62.14.2 [PubMed] [CrossRef] [Google Scholar]

[101]. Papandreou M. A., Kanakis C. D., Polissiou M. G., Efthimiopoulos S., Cordopatis P., Margarity M., et al. (2006). Inhibitory activity on amyloid-beta aggregation and antioxidant properties of Crocus sativus stigmas extract and its crocin constituents. *J. Agric. Food Chem.* 54 (23), 8762–8768. 10.1021/jf061932a [PubMed] [CrossRef] [Google Scholar]

[102]. Pitsikas N., Tarantilis P. A. (2017). Crocins, the active constituents of Crocus sativus L., counteracted apomorphine-induced performance deficits in the novel object recognition task, but not novel object location task, in rats. *Neurosci. Lett.* 644, 37–42. 10.1016/j.neulet.2017.02.042 [PubMed] [CrossRef] [Google Scholar]

[103]. Pitsikas N., Boultadakis A., Georgiadou G., Tarantilis P. A., Sakellaridis N. (2008). Effects of the active constituents of Crocus sativus L., crocins, in an animal model of anxiety. *Phytomedicine* 15 (12), 1135–1139. 10.1016/j.phymed.2008.06.005 [PubMed] [CrossRef] [Google Scholar]

[104]. Pitsikas N. (2015). The Effect of Crocus sativus L. and Its Constituents on Memory: Basic Studies and Clinical Applications. *Evid. Based Complement. Alternat. Med.* 2015:926284. 10.1155/2015/926284 [PMC free article] [PubMed] [CrossRef] [Google Scholar].

[105]. Pitsikas N. (2016). Constituents of Saffron (Crocus sativus L.) as Potential Candidates for the Treatment of Anxiety Disorders andSchizophrenia. *Molecules* 21 (3):303. 10.3390/molecules21030303 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[106]. Pontone G. M., Williams J. R., Anderson K. E., Chase G., Goldstein S. A., Grill S., et al. (2009). Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. *Mov. Disord.* 24 (9), 1333–1338. 10.1002/mds.22611 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[107]. Purushothuman S., Nandasena C., Peoples C. L., El Massri N., Johnstone D. M., Mitrofanis J., et al. (2013). Saffron pre-treatment offers neuroprotection to Nigral and retinal dopaminergic cells of MPTP-Treated mice. *J. Parkinsons Dis.* 3 (1), 77–83. 10.3233/JPD-130173 [PubMed] [CrossRef] [Google Scholar]

[108]. Rafieipour F., Hadipour E., Emami S. A., Asili J., Tayarani-Najaran Z. (2019). Safranal protects against beta-amyloid peptide-induced cell toxicity in PC12 cells via MAPK and PI3 K pathways. *Metab. Brain Dis.* 34 (1), 165–172. 10.1007/s11011-018-0329-9 [PubMed] [CrossRef] [Google Scholar]

[109]. Rameshrad M., Razavi B. M., Hosseinzadeh H. (2018). Saffron and its derivatives, crocin, crocetin and safranal: a patent review. *Expert Opin. Ther. Pat.* 28 (2), 147–165. 10.1080/13543776.2017.1355909 [PubMed] [CrossRef] [Google Scholar]

[110]. Rao S. V., Muralidhara, Yenisetti S. C., Rajini P. S. (2016). Evidence of neuroprotective effects of saffron and crocin in a Drosophila model of parkinsonism. *Neurotoxicology* 52, 230–242. 10.1016/j.neuro.2015.12.010 [PubMed] [CrossRef] [Google Scholar]

[111]. Rashedinia M., Lari P., Abnous K., Hosseinzadeh H. (2015). Protective effect of crocin on acrolein-induced tau phosphorylation in the rat brain. *Acta Neurobiol. Exp. (Wars)* 75 (2), 208–219. [PubMed] [Google Scholar]

[112]. Razavi B. M., Sadeghi M., Abnous K., Vahdati Hasani F., Hosseinzadeh H. (2017). Study of the Role of CREB, BDNF, and VGF Neuropeptide in Long Term Antidepressant Activity of Crocin in the Rat Cerebellum. *Iran J. Pharm. Res.* 16 (4), 1452–1462. [PMC free article] [PubMed] [Google Scholar]

[113]. Rios J. L., Recio M., Giner R., Manez S. (1996). An Update Review of Saffron and its Active Constituents. *Phytother. Res.* 10 (3), 189–193. 10.1002/(SICI)1099-1573(199605)10:3<189::AID-PTR754>3.0.CO;2-C [CrossRef] [Google Scholar]

[114]. Rocchi R., Mascini M., Sergi M., Compagnone D., Mastrocola D., Pittia P. (2018). Crocins pattern in saffron detected by UHPLC-MS/MS as marker of quality, process and traceability. *Food Chem.* 264, 241–249. 10.1016/j.foodchem.2018.04.111 [PubMed] [CrossRef] [Google Scholar]

[115]. Ryan M., Eatmon C. V., Slevin J. T. (2019). Drug treatment strategies for depression in Parkinson disease. *Expert Opin. Pharmacother.* 20 (11), 1351–1363. 10.1080/14656566.2019.1612877 [PubMed] [CrossRef] [Google Scholar]

[116]. Sadeghnia H. R., Shaterzadeh H., Forouzanfar F., Hosseinzadeh H. (2017). Neuroprotective effect of safranal, an active ingredient of Crocus sativus , in a rat model of transient cerebral ischemia. *Folia Neuropathol.* 55 (3), 206–213. 10.5114/fn.2017.70485 [PubMed] [CrossRef] [Google Scholar]

[117]. Sahraei H., Fatahi Z., Eidi A., Haeri-Rohani A., Hooshmandi Z., Shekarforoush S., et al. (2012). Inhibiting Post Traumatic Stress Disorder (PTSD) induced by electric shock using ethanol extract of saffron in rats. *J. Biol. Res.-Thessaloniki* 18, 320–327. [Google Scholar]

[118]. Sahraian A., Jelodar S., Javid Z., Mowla A., Ahmadzadeh L. (2016). Study the effects of saffron on depression and lipid profiles: A double blind comparative study. *Asian J. Psychiatr.* 22, 174–176. 10.1016/j.ajp.2015.10.012 [PubMed] [CrossRef] [Google Scholar]

[119]. Saleem S., Ahmad M., Ahmad A. S., Yousuf S., Ansari M. A., Khan M. B., et al. (2006). Effect of saffron (Crocus sativus) on neurobehavioral and neurochemical changes in cerebral ischemia in rats. *J. Med. Food* 9, 246–254. 10.1089/jmf.2006.9.246 [PubMed] [CrossRef] [Google Scholar]

[120]. Samarghandian S., Borji A. (2014). Anticarcinogenic effect of saffron (Crocus sativus L.) and its ingredients. *Pharmacogn. Res.* 6 (2), 99–107. 10.4103/0974-8490.128963 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[121]. Samarghandian S., Farkhondeh T. (2020). "Saffron and Neurological Disorders," in *Saffron* (Elsevier;), 103–116. [Google Scholar]

[122]. Sarris J. (2018). Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. *Phytother. Res.* 32 (7), 1147–1162. 10.1002/ptr.6055 [PubMed] [CrossRef] [Google Scholar]

[123]. Schrag A., Taddei R. N. (2017). Depression and Anxiety in Parkinson's Disease. *Int. Rev. Neurobiol.* 133, 623–655. 10.1016/bs.irn.2017.05.024 [PubMed] [CrossRef] [Google Scholar]

[124]. Shahmansouri N., Farokhnia M., Abbasi S. H., Kassaian S. E., Noorbala Tafti A. A., Gougol A., et al. (2014). A randomized, double-blind, clinical trial comparing the efficacy and safety of Crocus sativus L. with fluoxetine for improving mild to moderate depression in post percutaneous coronary intervention patients. *J. Affect. Disord.* 155, 216–222. 10.1016/j.jad.2013.11.003 [PubMed] [CrossRef] [Google Scholar]

[125]. Si T., Yu X. (2016). Current Problems in the Research and Development of more Effective Antidepressants. *Shanghai Arch. Psychiatry* 28 (3), 160–165. 10.11919/j.issn.1002-0829.216017 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[126]. Siddiqui M. J., Saleh M. S. M., Basharuddin S., Zamri S. H. B., Mohd Najib M. H. B., Che Ibrahim M. Z. B., et al. (2018). Saffron (Crocus sativus L.): As an Antidepressant. *J. Pharm. Bioallied Sci.* 10 (4), 173–180. 10.4103/JPBS.JPBS_83_18 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[127]. Tabeshpour J., Sobhani F., Sadjadi S. A., Hosseinzadeh H., Mohajeri S. A., Rajabi O., et al. (2017). A double-blind, randomized, placebo-controlled trial of saffron stigma (Crocus sativus L.) in mothers suffering from mild-to-moderate postpartum depression. *Phytomedicine* 36, 145–152. 10.1016/j.phymed.2017.10.005 [PubMed] [CrossRef] [Google Scholar]

[128]. Talaei A., Moghadam M. H., Tabassi S. A. S., Mohajeri S. A. (2015). Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial. *J. Affect. Disord.* 174, 51–56. 10.1016/j.jad.2014.11.035 [PubMed] [CrossRef] [Google Scholar]

[129]. Tamaddonfard E., Gooshchi N. H., Seiednejad-Yamchi S. (2012). Central effect of crocin on penicillin-induced epileptiform activity in rats. *Pharmacol. Rep.* 64 (1), 94–101. 10.1016/s1734-1140(12)70735-1 [PubMed] [CrossRef] [Google Scholar]

[130]. Tamegart L., Abbaoui A., Makbal R., Zroudi M., Bouizgarne B., Bouyatas M. M., et al. (2019). Crocus sativus restores dopaminergic and noradrenergic damages induced by lead in Meriones shawi: A possible link with Parkinson's disease. *Acta Histochem.* 121 (2), 171–181. 10.1016/j.acthis.2018.12.003 [PubMed] [CrossRef] [Google Scholar]

[131]. Tarantilis P. A., Tsoupras G., Polissiou M. (1995). Determination of saffron (Crocus sativus L.) components in crude plant extract using high-performance liquid chromatography-UV-visible photodiode-array detection-mass spectrometry. *J. Chromatogr. A.* 699 (1), 107–118. 10.1016/0021-9673(95)00044-N [PubMed] [CrossRef] [Google Scholar

[132]. Tsolaki M., Karathanasi E., Lazarou I., Dovas K., Verykouki E., Karacostas A., et al. (2016). Efficacy and Safety of Crocus sativus L. @ in Patients with Mild Cognitive Impairment: One Year Single-Blind Randomized, with Parallel Groups, Clinical Trial. *J. Alzheimers Dis.* 54 (1), 129–133. 10.3233/JAD-160304 [PubMed] [CrossRef] [Google Scholar]

[133]. Umigai N., Murakami K., Ulit M. V., Antonio L. S., Shirotori M., Morikawa H., et al. (2011). The pharmacokinetic profile of crocetin in healthy adult human volunteers after a single oral administration. *Phytomedicine* 18 (7), 575–578. 10.1016/j.phymed.2010.10.019 [PubMed] [CrossRef] [Google Scholar]

[134]. Vakili A., Einali M. R., Bandegi A. R. (2014). Protective effect of crocin against cerebral ischemia in a dose-dependent manner in a rat model of ischemic stroke. *J. Stroke Cerebrovasc. Dis.* 23 (1), 106–113. 10.1016/j.jstrokecerebrovasdis.2012.10.008 [PubMed] [CrossRef] [Google Scholar]

[135]. Van der Mussele S., Bekelaar K., Le Bastard N., Vermeiren Y., Saerens J., Somers N., et al. (2013). Prevalence and associated behavioral symptoms of depression in mild cognitive impairment and dementia due to Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 28 (9), 947–958. 10.1002/gps.3909 [PubMed] [CrossRef] [Google Scholar]

[136]. Wang Y., Han T., Zhu Y., Zheng C. J., Ming Q. L., Rahman K., et al. (2010). Antidepressant properties of bioactive fractions from the extract of Crocus sativus L. *J. Nat. Med.* 64 (1), 24–30. 10.1007/s11418-009-0360-6 [PubMed] [CrossRef] [Google Scholar]

[137]. Wang X., Sun G., Feng T., Zhang J., Huang X., Wang T., et al. (2019). Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res.* 29 (10), 787–803. 10.1038/s41422-019-0216-x [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[138]. Watson P. (2019). PTSD as a Public Mental Health Priority. *Curr. Psychiatry Rep.* 21 (7), 1–12. 10.1007/s11920-019-1032-1 [PubMed] [CrossRef] [Google Scholar]

[139]. Zhang G. F., Zhang Y., Zhao G. (2015). Crocin protects PC12 cells against MPP+-induced injury through inhibition of mitochondrial dysfunction and ER stress. *Neurochem. Int.* 89, 101–110. 10.1016/j.neuint.2015.07.011 [PubMed] [CrossRef] [Google Scholar]

[140]. Zhang Y., Fei F., Zhen L., Zhu X., Wang J., Li S., et al. (2017). Sensitive analysis and simultaneous assessment of pharmacokinetic properties of crocin and crocetin after oral administration in rats. *J. Chromatogr. B. Analyt. Technol. BioMed. Life Sci.* 1044–1045, 1–7. 10.1016/j.jchromb.2016.12.003 [PubMed] [CrossRef] [Google Scholar]

[141]. Zhang L., Previn R., Lu L., Liao R. F., Jin Y., Wang R. K. (2018). Crocin, a natural product attenuates lipopolysaccharide-induced anxiety and depressive-like behaviors through suppressing NF-kB and NLRP3 signaling pathway. *Brain Res. Bull.* 142, 352–359. 10.1016/j.brainresbull.2018.08.021 [PubMed] [CrossRef] [Google Scholar]

[142]. Zheng Y. Q., Liu J. X., Wang J. N., Xu L. (2007). Effects of crocin on reperfusion-induced oxidative/nitrative injury to cerebral microvessels after global cerebral ischemia. *Brain Res.* 1138, 86–94. 10.1016/j.brainres.2006.12.064 [PubMed] [CrossRef] [Google Scholar]