Prev. Nutr. Food Sci. 2019;24(4):363-372
https://doi.org/10.3746/pnf.2019.24.4.363
pISSN 2287-1098 · eISSN 2287-8602

Review

A Review of Potential Efficacy of Saffron (*Crocus sativus* L.) in Cognitive Dysfunction and Seizures

Arezoo Rajabian[1], Azar Hosseini[1], Mahmoud Hosseini[2], and Hamid Reza Sadeghnia[2]

[1]Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad 9177944553, Iran
[2]Division of Neurocognitive Sciences, Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad 9177944553, Iran

ABSTRACT: *Crocus sativus* (saffron) is traditionally used to relieve several ailments. Experimental researches have also investigated applications of saffron and its active constituents for the treatment of a wide spectrum of disorders. This review discusses pharmacological/therapeutic properties of saffron and its main components on memory function, learning ability and seizures, to highlight their merit for alleviating these disorders. An extensive literature review was carried out using various databases including ISI Web of Knowledge, Medline/PubMed, Science Direct, Scopus, Google Scholar, Embase, Biological Abstracts, and Chemical Abstracts. The growing body of evidence showed the value of saffron and its' components, alone, or in combination with the other pharmaceuticals, for improving learning and memory abilities and controlling seizures. These findings may provide pharmacological basis for the use of saffron in cognitive disturbance and epilepsy. However, further preclinical and clinical studies are necessary.

Keywords: cognitive, *Crocus sativus*, learning, saffron, seizures

INTRODUCTION

Considering the link between diet and health, use of natural ingredients as food supplements has recently stimulated a new wave of interest in ethno-pharmacology (Newman et al., 2003; Pandit et al., 2011).

The stigma of *Crocus sativus* (Iridaceae), commonly named as saffron, is cultivated in several countries including Iran, India, and Greece (Hosseini et al., 2018). Although saffron has been traditionally used as a food spice and herbal medicine for several decades in many countries, previous studies show saffron may be beneficial for the treatment of human diseases including cancers, inflammatory diseases, diabetes, and atherosclerosis (Christodoulou et al., 2015).

Saffron has been used in traditional Persian and Indian medicine against central nervous system disorders including dementia, cognitive dysfunction, and mental diseases (Finley and Gao, 2017; Hatami, 2004; Akhondzadeh, 2007; Purushothuman, 2015), and as an anticonvulsant remedy (Hosseinzadeh and Khosravan, 2002; Khazdair et al., 2015). Therefore, much has explored its role in neuro-protection.

Phytochemical analysis has revealed that saffron stigma mainly contains carotenoid pigments, crocin (crocetin digentiobiose ester) and crocetin as well as safranal and picrocrocin. Crocin and crocetin are the terpenes responsible for saffron's odor whereas picrocrocin is responsible for its flavor (Gohari et al., 2013).

Crocin is converted to crocetin by gastrointestinal cells (Hosseini et al., 2018), and is then absorbed and distributed to body tissues including the central nervous system (CNS) (Kanakis et al., 2007).

In vitro experiments with porcine blood barrier brain (BBB) models have demonstrated that crocetin can penetrate the BBB to reach the CNS. To investigate permeation characteristics of trans-crocetin through the barrier system, porcine brain capillary endothelial cells (BCEC) and blood cerebrospinal fluid barrier (BCSFB) were used. Crocetin was shown to be transported through the barrier systems with a slow but constant velocity (Lautenschläger et al., 2015).

An overview of the preclinical and clinical literature exploring the potential neuroprotective and anticonvulsant properties of *C. sativus* and its effectiveness for learning and memory processes are explored in this review.

Received 18 February 2019; Accepted 5 July 2019; Published online 31 December 2019

Correspondence to Hamid Reza Sadeghnia, Tel: +98-513-882-8566, E-mail: sadeghniahr@mums.ac.ir
Author information: Arezoo Rajabian (Researcher), Azar Hosseini (Professor), Mahmoud Hosseini (Professor), Hamid Reza Sadeghnia (Professor)

PRECLINICAL STUDIES

Saffron efficacy on learning and memory ability

Learning refers to the process of acquiring knowledge, whereas memory, one of the most crucial mental capabilities, is retention and retrieval of acquired knowledge (Brem et al., 2013). Hippocampal long-term potentiation (LTP) is a form of activity-dependent synaptic plasticity thought to be the mechanism underling learning and memory via storing information in the central nervous system (Stuchlik, 2014). In this section, the evidence describing the efficacy of *C. sativus* and its constituents on cognitive skills such as memory, attention, and learning were detailed.

Ethanolic extract of *C. sativus* (125 and 250 mg/kg) and crocin (50～200 mg/kg, orally), but not crocetin, were found to counteract ethanol (30%, 2 and 10 mL/kg, orally)-induced performance deficits, impaired learning and memory, and LTP suppression *in vitro* and *in vivo* in a dose-dependent manner (Sugiura et al., 1995a; Sugiura et al., 1995b; Sugiura et al., 1995c).

As indicated in a study conducted by Zhang et al. (1994), single doses of *C. sativus* extracted with ethanolic extract (125, 250, and 500 mg/kg) ameliorated ethanol-induced impairments of learning and memory acquisition and retrieval in step through and step down tests in animals. Inhibition of ethanol-induced hippocampal synaptic plasticity impairment was suggested to be related to the antagonistic effect of crocin on synaptic potentials mediated by *N*-methyl-D-aspartate (NMDA) receptors in the dentate gyrus of rat hippocampal slices (Zhang et al., 1994; Sugiura et al., 1995a; Sugiura et al., 1995b; Abe et al., 1998; Kumar et al., 2011).

Crocetin gentiobiose glucose ester and crocetin di-glucose ester, are analogs of crocin but show lower activity on ameliorating the LTP blocking effect of ethanol than crocin. The activity was proportional to the amount of glucose. Beneficial effects on learning and memory may be attributed to crocin, the active component in saffron that possesses four glucoses in each molecule (Zhang et al., 1994).

Another study confirmed the protective effect of *C. sativus* aqueous extract (0.0025～0.56 g/kg), crocin (50 and 200 mL/kg), and safranal (0.2 mL/kg) against scopolamine-induced learning impairment in rats using a Morris water maze (MWM) task (Hosseinzadeh and Ziaei, 2006).

Investigation of the effects of *C. sativus* extract (30 and 60 g/kg) and its active constituent crocin (15～30 mg/kg) on recognition and spatial memory revealed an antagonistic effect against loss of recognition memory. These extracts also attenuated scopolamine-induced spatial memory performance deficits indicated using a novel object recognition test (NORT) and the radial water maze task in rats. Crocin (30 mg/kg) antagonized scopolamine-induced reference and working memory deficits (Pitsikas and Sakellaridis, 2006; Pitsikas et al., 2007; Kumar et al., 2011).

An *in vivo* study demonstrated the effectiveness of crocin [30 mg/kg, intraperitoneally (i.p.), 3 weeks] for antagonizing performance deficits induced by intra-cerebroventricular (ICV) streptozocin (STZ) in passive avoidance and spatial Y-maze memory procedures (Khalili and Hamzeh, 2010). Also, using the same procedure, Naghizadeh et al. demonstrated that oral administration of crocin (100 mg/kg) effectively attenuated spatial memory deficits and oxidative stress induced by STZ (3 mg/kg, ICV) in rats (Naghizadeh et al., 2013; Naghizadeh et al., 2014).

The synergistic effects of the combination of *Nardostachys jatamansi* extract (200 mg/kg), crocetin (25 mg/kg), and selenium (0.05 mg/kg) was investigated in a model of experimental dementia (Khan et al., 2012). ICV infusion of STZ resulted in induction of oxidative stress, depletion of endogenous antioxidants, and cognitive loss due to failure of cellular energetics (Javed et al., 2015). In the combination-pretreated rats, cognitive performance was restored through attenuation of oxidative stress (Khan et al., 2012).

Crocin reversed latency paradigm transfer in the elevated plus-maze, an index of learning and memory, in STZ-induced diabetic rats (Tamaddonfard et al., 2013). Considering the presence of insulin and insulin receptors in the hippocampus that are involved in learning and memory (Zhao et al., 2004), and the fact that hyperglycemia induces neuronal degeneration through oxidative stress following diabetes (Li and Sima, 2004), the authors suggested that crocin improved cognitive deficits via inducing anti-hypoinsulinemic, anti-hyperglycemic, antioxidant, and neuroprotective properties (Tamaddonfard et al., 2013). As in previous study, treatment of diabetic rats with crocin (15, 30, and 60 mg/kg, i.p., 6 weeks) significantly improved spatial memory impairment and cerebral oxidative damage in MWM paradigm (Ahmadi et al., 2017). Aqueous *C. sativus* extracts (60 mg/kg, i.p.) also attenuated cognitive deficits caused by STZ, as identified using passive avoidance and Y-maze tasks. Therefore, this extract and its constituents crocin and crocetin, may have therapeutic potential for aging and age-related neurodegenerative disorders where cognitive impairment is involved (Khalili et al., 2009).

Using MWM tasks, safranal was found to improve spatial learning and memory impairments in STZ-induced diabetic rats. Safranal (0.1 and 0.4 mg/kg) recovered behavioral, histopathological, and biochemical changes. These effects have been linked to antioxidant, anti-inflammatory, and antiapoptotic effects of safranal (Delkhosh-Kasmaie et al., 2018).

A study was also performed to evaluate the effect of *C. sativus* hydro-alcoholic extract on *D*-galactose and sodium nitrite ($NaNO_2$)-induced amnestic mice. Prolonged systemic administration of the extract (30 mg/kg/d, i.p., 15 days) and induction of amnesia induced preventive and ameliorative effects against learning and memory impairments, examined by one way passive and active avoidance tests (Dashti-R et al., 2012).

Crocin was also found to improve spatial learning, memory disturbance and synaptic dysfunction in D-galactose aging model. Crocin suppressed formation of advanced glycation products and brain inflammatory mediators [interleukin (IL)-1, tumor necrosis factor (TNF)-α, and nuclear factor (NF)-κB]. The neuroprotective effects against oxidative stress was suggested to be related to increases in phosphoinositide 3-kinase/Akt and mitogen-activated protein kinases/extracellular signal-regulated kinases pathway activity (Heidari et al., 2017).

A single post-training injection of crocin (15 and 30 mg/kg) in rats prevented recognition memory deficits produced by the NMDA glutamate receptor antagonist, ketamine in the NORT (Georgiadou et al., 2014). On other hand, safranal reduced extracellular concentrations of the excitatory amino acids glutamate and aspartate in the rat hippocampus following kainate exposure (Hosseinzadeh et al., 2008).

Crocin (2 mg/kg, i.p.) inhibited ketamine-induced retrograde amnesia and restored the passive avoidance response in rats (Yousefvand et al., 2016). *C. sativus* and its constituents reduced extracellular glutamate levels, which may be involved in the beneficial effects of crocin on ketamine-induced behavioral deficits. *C. sativus* hydro-ethanolic extracts also prevent glutamatergic synaptic transmission through interacting with NMDA receptors in a concentration-dependent manner (Berger et al., 2011).

Treatment of the mice with 150 or 450 mg/kg aqueous saffron extract increases the time latency for entering the dark compartments of morphine-induced memory impairment at 24 and 48 h after training and retention trials in passive avoidance tasks (Naghibi et al., 2012). Haghighizad et al. (2008) also showed that saffron has beneficial effects at lower doses (10, 30, and 50 mg/kg, i.p.) on spatial learning and memory parameters in animals receiving morphine indicated in MWM tasks.

Considering neurotoxicity and learning and memory disturbances following tramadol administration (Abdel-Zaher et al., 2011; Baghishani et al., 2018), an *in vivo* study was designed to evaluate the ability of crocin to attenuate cognitive deficits in tramadol-treated rats. Crocin prevented rats from the deleterious effects on learning and memory abilities as measured by MWM and passive avoidance tests. The memory-enhancing effects were associated with neuroprotective effects: decreased numbers of dark neurons and apoptotic cells in the hippocampus (Baghishani et al., 2018).

Beneficial roles of saffron and its constituents on several neurotransmitter systems, including glutamatergic, cholinergic, gamma-aminobutyric acid (GABA)ergic, and dopaminergic systems, on the beneficial effects for learning and memory have been proposed. As mentioned above, NMDA receptors may be involved in the beneficial effect of saffron and its constituents on memory (Abe et al., 1998; Abe et al., 1999). Saffron also restores cognitive dysfunction caused by cholinergic blockade (Pitsikas and Sakellaridis, 2006; Pitsikas et al., 2007).

Cognitive impairment may follow epilepsy and alterations in normal synaptic transmission and LTP processes (Sgobio et al., 2010). Protective effect of safranal, an active constituent of saffron, against pentylenetetrazole-induced seizures are thought to be mediated via modulation of the GABAergic system (Hosseinzadeh and Sadeghnia, 2007). Oral administration of crocin (5, 10, and 20 mg/kg) improves learning and memory impairments in pentylenetetrazol-kindled mice. These findings are supported by reduced neuronal damage in the hippocampal pyramidal layer (Mazumder et al., 2016).

A study was also performed to investigate whether crocin can counteract non-spatial and spatial recognition memory impairments induced by apomorphine, a dopamine receptor agonist, in rats (Pitsikas and Tarantilis, 2017). Administration of crocin (15 and 30 mg/kg) prevented apomorphine-induced performance deficits in the NORT but not spatial recognition memory deficits produced in the novel object location tasks. In this study, crocin was shown to antagonize spatial memory deficits produced by muscarinic receptor antagonist (scopolamine) in rats (Pitsikas et al., 2007). As shown above, crocin also improved recognition memory deficits caused by dysfunction of the glutamatergic system (Georgiadou et al., 2014). These results show saffron and its constituents are capable of antagonizing the deleterious effects of ethanol, scopolamine, ketamine, morphine, tramadol, and apomorphine on learning and memory acquisition.

Crocin effectively counteracts acute hypobaric hypoxia-induced cognitive deficits indicated as improvement of learning and memory in rats using a MWM test. Analysis of changes to the structures of nerve cells and mitochondria using transmission electron microscope revealed that crocin may repair the ultrastructure of hippocampal cells. Up-regulation of the sirtuin-1/peroxisome proliferator-activated receptor-γ co-activator1α (SIRT1/PGC-1α) pathway in the hippocampus may be involved in dose-dependent neuroprotective effects of crocin (25, 50, and 100 mg/kg) against acute hypobaric hypoxia (Zhang et al., 2018).

Low doses of crocin (30 mg/kg) show memory-enhancing effects in a 6-hydroxydopamine (6-OHDA) model of Parkinson's disease. Treatment of rats subjected to uni-

lateral injection of 6-OHDA (16 μg) with crocin (30 and 6 weeks) improved memory, decreased nitric oxide production, and inhibited nitrosative stress. Oxidative stress has been suggested to be an effective factor in 6-OHDA-induced cognitive impairment (Hritcu et al., 2008). Crocin may therefore improve aversive memory through its anti-inflammatory and antioxidant activities (Rajaei et al., 2016).

Chronic restraint stress can lead to impairment of brain functions and memory processing (Ranjbar et al., 2014; Dastgerdi et al., 2017). Crocin (30 mg/kg) prevents against harmful effects of chronic restraint stress on memory. The beneficial effects of crocin on cognitive deficit in this emotional stress model were measured by the passive avoidance test and accompanied by modulation of corticosterone levels in the hippocampus and the frontal cortex (Dastgerdi et al., 2017).

The influence of crocins on different memory processes (acquisition, storage, and retrieval of information) and of co-administration of crocins with memantine on recognition memory using NORT were evaluated. Crocins (15 and 30 mg/kg) and crocins (5 mg/kg) with memantine (3 mg/kg) counteracted delay-dependent recognition memory deficits in rats (Pitsikas and Tarantilis, 2018).

The potential ability of crocetin to protect against neuropathological alterations and special learning impairment in a rat model of chronic cerebral hypoperfusion was investigated. Crocetin (8 mg/kg) effectively ameliorated cerebrocortical and hippocampus neural injury caused by permanent occlusion of common carotids. Crocetin was shown to enhance memory, as evaluated by MWM (Tashakori-Sabzevar et al., 2013).

Aflatoxin B1, which is produced by species of the mold *Aspergillus*, is a natural mycotoxin (Rushing and Selim, 2018). To investigate the protective effects of saffron tea in a model of aflatoxin B1-induced neurotoxicity, Balb-c mice received saffron infusion (90 mg styles/200 mL, *ad libitum* access, 2 weeks) and were exposed to aflatoxin B1 (0.6 mg/kg/d, i.p., 4 days). Saffron tea prevented cognitive defects indicated using step-through passive avoidance tasks. Improvements in memory retention were accompanied by restoring oxidative damage biomarkers including glutathion and lipid peroxidation as well as modulating the activities of acetylcholinesterase (AChE) and monoamine oxidase (MAO) isoforms in the whole brain and cerebellum (Linardaki et al., 2017).

Overall, in addition to the ability of saffron and its constituents to prevent cognitive disturbance caused by oxidative damage, they have been proposed to modulate multiple signal transduction pathways such as of AChE, MAO isoforms and to up-regulate the SIRT1/PGC-1α pathway. Moreover, they may exert some of their beneficial biological effects via interaction with NMDA, GABAergic, and dopaminergic systems.

Protective effects of saffron against oxidative damage

Oxidative damage to lipids, proteins, and nucleic acids contributes to the cytotoxicity and dysfunction of neurotransmitters/neurotrophin systems and is considered to be a critical pathogenic factor in several neurodegenerative disorders accompanied by progressive cognitive deficits (Muriach et al., 2010; Hampel et al., 2018). It has been well documented that the memory-enhancing effects of saffron and its constituents may be related to their antioxidant potential.

Some *in vitro* and *in vivo* preclinical experiments proposed a protective role for *C. sativus* extracts, crocin, and safranal, on cerebral ischemia (Table 1).

Neuroprotective properties of saffron in Alzheimer's disease and concomitant cognitive deficits

We also reviewed the potential effects of *C. sativus* and its components in dementia, including Alzheimer's disease (AD). AD is considered the most common cause of dementia that involves memory impairment (May et al., 2018).

AD is clinically characterized by cognitive and memory deterioration. Formation of neuritic amyloid plaques and neurofibrillary tangles of tau protein in neurons are the main molecular process underlying AD. Oxidative stress may be involved in promoting amyloid beta (Aβ) fibril formation and deposition (Ballard et al., 2011).

There is some evidence that saffron extracts may inhibit Aβ aggregation, a key step in the pathogenesis of AD, in animal experimental models (Papandreou et al., 2006). Measurement of thioflavine T-based fluorescence of $A\beta_{1\text{-}40}$ showed that the water : methanol (50:50, v/v) extracts of *C. sativus* prevents Aβ fibrillogenesis in both concentration- and time-dependent manners, suggesting a possible use of saffron and its constituents in preventing aggregation and deposition of Aβ in the human brain (Papandreou et al., 2006).

Loss of cholinergic neurons due to Aβ and tau formation correlates with cognitive deficits (Hampel et al., 2018). *In vitro* enzymatic and molecular docking studies revealed that the inhibitory action of saffron extract and its constituents (crocetin, dimethylcrocetin, and safranal) on acetylcholinesterase increases synaptic acetylcholine levels (Geromichalos et al., 2012).

The neuroprotective effects of trans-crocetin against $A\beta_{42}$-induced toxicity in hippocampal-derived cells has also been demonstrated (Kong et al., 2014). Consistent with this finding, another study suggests that low micromolar concentrations of trans-crocetin enhances $A\beta_{42}$ degradation in monocytes isolated from AD patients through upregulating the lysosomal protease cathepsin B (Tiribuzi et al., 2017).

Another study indicated the neuroprotective properties of crocetin against $A\beta_{1\text{-}42}$-induced cytotoxicity in mu-

Table 1. Protective effects of saffron and its components against oxidative damage

Saffron preparation or its constituents/dose/administration route	*In vitro* or *in vivo* model	Outcome (reference)
Saffron stigma aqueous extract (100 mg/kg, orally)	Middle cerebral artery occlusion (MCAO) animal model	Restored glutathione and antioxidant enzymes, and inhibited lipid peroxidation (Saleem et al., 2006; Akbari et al., 2018)
Crocin (20 mg/kg, intraperitoneally)	Mice model of transient global cerebral ischemia	Counteracted oxidative/nitrative injury induced by reperfusion (Zheng et al., 2007)
Safranal (727.5, 363.75, and 145.5 mg/kg, intraperitoneally)	Global and focal cerebral ischemia-reperfusion injury in rat hippocampus	Improved oxidative/nitrative injury (Hosseinzadeh and Sadeghnia, 2005; Sadeghnia et al., 2017)
Saffron extract (1 mg/kg/d, intraperitoneally)	Rats exposed to the mitochondrial toxin, 3-nitropropionic acid	Impairment of energy metabolism and oxidative stress (Del-Angel et al., 2006)
Safranal (72.75, 145.5, and 291 mg/kg, intraperitoneally)	Neurodegenerative disorder induced by quinolinic acid in rat	Reduced lipid peroxidation and DNA injury and restored thiol redox and antioxidant status (Sadeghnia et al., 2013)
Crocin (10~50 μM)	Acrylamide-induced apoptotic cell death in PC12 cells	Inhibited intracellular reactive oxygen species production and apoptosis (Mehri et al., 2012)
Crocin (12.5, 25, and 50 mg/kg, intraperitoneally)	Damages in the rat cerebral cortex and cerebellum following exposure to acrylamide	Improved behavioral index and histopathological changes (Mehri et al., 2015)
Hydroalcoholic extract of saffron (100~250 mg/kg, intraperitoneally) and crocin (5~30 mg/kg, intraperitoneally)	spatial cognitive deficits following chronic cerebral hypo-perfusion in rats	Improve spatial cognitive abilities (Ghaeni et al., 2012; Hosseinzadeh et al., 2012)
Saffron (1~250 μg/mL), crocetin, and safranal (1~125 μM)	H_2O_2-induced toxicity in human neuroblastoma SH-SY5Y cells	Reduced lipid peroxidation and apoptosis (Papandreou et al., 2011)
C. sativus extracts (30 mg/kg, intraperitoneally) or crocin (15~30 mg/kg, intraperitoneally) 21 days	Oxidative stress and impairment of spatial learning and memory retention	Blocked oxidative stress and impairment of spatial learning and memory retention (Ghadrdoost et al., 2011)
Saffron extract (5 and 10 μg/rat)	Intra-hippocampal injection of ethidium bromide on spatial memory and learning	Alleviated detrimental effects via modulation of oxidative stress markers (Ghaffari et al., 2015)

rine HT-22 hippocampal neuronal cells through counteracting oxidative stress (Yoshino et al., 2014).

Modulation of microglial activity is considered to be effective in preventing neurodegeneration. Crocin and crocetin suppressed lipopolysaccharide-induced production of nitric oxide, intracellular reactive oxygen species, TNF-α, IL-1β, and NF-κB activation as well as nitric oxide release from microglial cells of cultured rat brains (Nam et al., 2010).

Batarseh conducted *in vitro* and *in vivo* studies to investigate the mechanisms by which *C. sativus* and crocin exert protective effects against AD. *C. sativus* ethanolic extracts and crocin ameliorated Aβ brain pathology by enhancing Aβ clearance pathways, including BBB clearance, enzymatic degradation, and apolipoprotein E clearance pathway. Neuroprotective effects were also liked to reduced neuroinflammation (Batarseh et al., 2017).

The environmental factor aluminum has also been suggested to induce neurotoxicity in the pathogenesis of neurodegenerative diseases (Domingo, 2006). Aqueous saffron extract (200 mg/kg) and honey syrup are protective against neurotoxicity following administration of aluminum chloride, possible due to antioxidant activity (Shati et al., 2011).

In a recent study, the potential of *C. sativus* extracts (60 mg/kg, i.p. 6 days) to counteract changes accompanying aluminum neurotoxicity has been investigated. Short-term co-administration of saffron failed to reverse aluminum-induced impairment of learning/memory ability in mice during a passive avoidance test but considerably inhibited the aluminium-induced neurotoxicity and oxidative stress, and restored monoamine oxidase and acetylcholinesterase activities in the whole brain and cerebellum (Linardaki et al., 2013).

Traditionally, herbal drugs are used to enhance cognitive functions and to alleviate other functions associate with AD (Rao et al., 2012; Shal et al., 2018). *C. sativus* and its constituents are thought to target pathways involved in AD and enhance cognitive functions, preventing Aβ fibrillogenesis whilst increasing $A\beta_{42}$ degradation and clearance. In addition to inhibition of neuroinflammation following modulation of microglia activity, herbal drugs prevent oxidative damage induced by Aβ aggregation.

Potential efficacy of saffron in seizure

Experimental studies performed in rodents using pentylenetetrazole (PTZ) and the maximum electroshock seizure tests demonstrate aqueous and ethanolic extracts of

C. sativus and safranal have anticonvulsant activity (*C. sativus*: 0.8 and 2 g/kg, i.p., respectively; safranal: 0.15 and 0.35 mL/kg, i.p., respectively), as indicated by delayed onset of tonic convulsions and reduced seizure periods and number of mortalities. However, crocin (200 mg/kg, i.p.) did not demonstrate any protective effect (Hosseinzadeh and Khosravan, 2002; Hosseinzadeh and Talebzadeh, 2005).

Safranal (72.75, 145.5, and 291 mg/kg, i.p.) decreased the frequency of minimal clonic and generalized tonic-clonic seizures in a dose-dependent manner, in addition to mortality resulting from seizures induced by PTZ. Since flumazenil and naloxone may antagonize the anticonvulsant effect of safranal, $GABA_A$-benzodiazepine receptor complexes may be involved in the protective effects of safranal against the tonic and clonic phases of PTZ-induced seizures (Hosseinzadeh and Sadeghnia, 2007). In contrast to the previous study, safranal showed dose-dependent antiabsence seizure activity, elicited by either γ-butyrolactone, baclofen, picrotoxin (1.5 mg/kg), bicuculline (5 mg/kg), or low dose of PTZ in C57BL/6 mice, suggestive of modifications on the benzodiazepine binding sites of $GABA_A$ receptor complexes. (Sadeghnia et al., 2008).

Similarly, it was revealed that both *C. sativus* ethanolic (250 and 500 mg/kg, i.p.) and aqueous (200, 400, and 800 mg/kg, i.p.) extracts reduce convulsions induced by PTZ or maximal electroshock seizures in rats (Sunanda et al., 2014; Dalu and Kalakotla, 2017).

This evidence demonstrates the neuroprotective role of saffron and its constituents acting via molecular mechanisms on biological processes such as interacting with $GABA_A$-benzodiazepine receptor complexes.

CLINICAL STUDIES

Herein, we will discuss clinical literature regarding therapeutic abilities of saffron on cognitive dysfunction. A number of trials have been carried out to assess the effects of saffron in human memory disorders.

A study conducted in healthy volunteers showed that consumption of green tea and saffron facilitated learning and memory, and subsequently enhanced memory function (Kumar et al., 2009). In a single-blind randomized clinical trial, therapeutic efficacy and safety of *C. sativus* in management of cognitive dysfunction was suggested (Tsolaki et al., 2016).

In a 16-week double-blind and placebo-controlled clinical trial study, 46 patients with the mild-to-moderate AD randomly received saffron capsules (15 mg) or placebo twice daily. Psychometric measures were assessed using AD assessment scale-cognitive subscales (ADAS-cog) and clinical dementia rating scale-sums of boxes (CDR) moni-

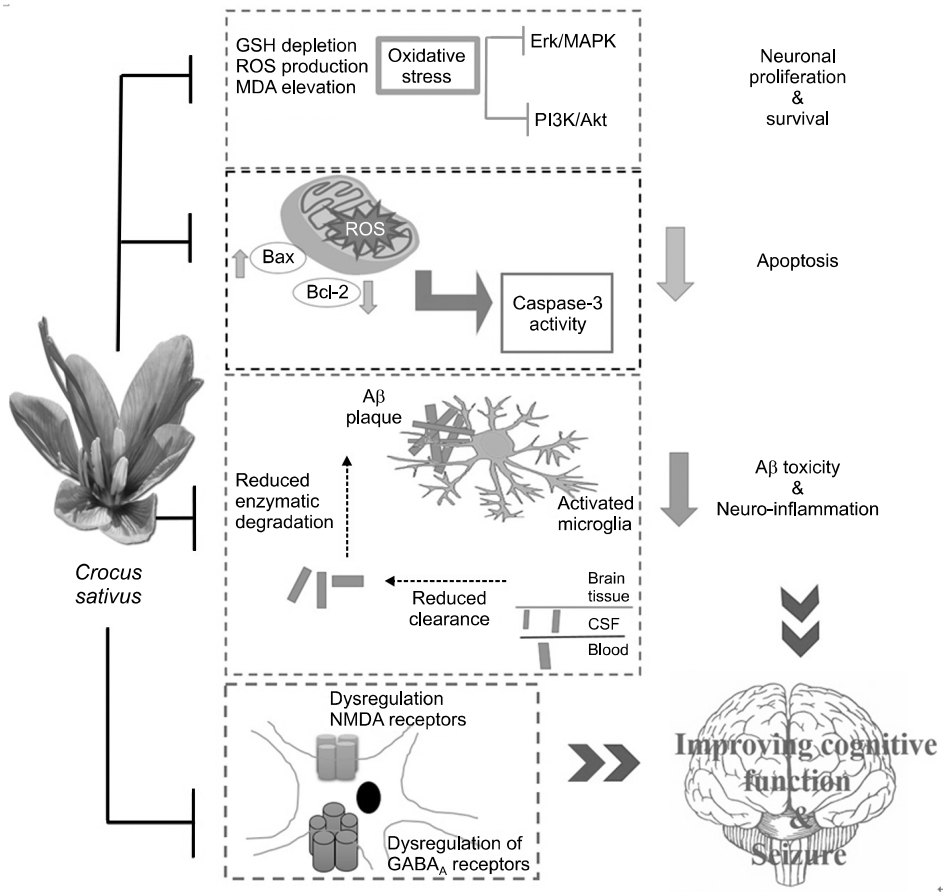

Fig. 1. Schematic diagram summarizes the potential effects of saffron in neurological disorders including seizure and Alzheimer's disease associated with learning and memory impairment. Saffron targets the direct and indirect pathways involved in brain injury and resultant cognitive disturbances. GSH, glutathione; ROS, reactive oxygen species; MDA, malondialdehyde; ERK, extracellular signal-regulated kinases; MAPK, mitogen-activated protein kinases; PI3K, phosphoinositide 3-kinase; Bax, B-cell lymphoma 2 (Bcl-2)-associated X protein; Aβ, amyloid beta; CSF, cerebrospinal fluid; NMDA, *N*-methyl-D-aspartate; GABA, gamma-aminobutyric acid.

tor global cognitive profiles. In this study, saffron showed a significantly better outcome on cognitive function than placebo. However, no significant differences in adverse events were observed between the two groups (Akhondzadeh et al., 2010a).

In a multicenter, double-blind controlled phase II clinical trial of 46 patients (adults 55 years of age or older) with mild-to-moderate AD, patients randomly received saffron (30 mg/d) or an acetylcholine esterase inhibitor donepezil (10 mg/d) for 22 weeks. Results showed that saffron was safe and well tolerated and had a similar efficacy to donepezil (as measured by ADAS-cog and CDR) for treatment of mild-to-moderate AD (Akhondzadeh et al., 2010b; Pitsikas, 2015).

In a double-blind clinical trial performed to compare the efficacy and safety of *C. sativus* with memantine, an NMDA receptor antagonist, in the patients with moderate-to-severe AD, 68 patients randomly received saffron (30 mg/d, orally) or memantine (20 mg/d, orally) for 12 months. Patients were evaluated every month using severe cognitive impairment rating scales and functional assessment staging, and probable adverse events were recorded. The efficacy and safety of *C. sativus* for reducing cognitive deterioration was found to be comparable to memantin (Farokhnia et al., 2014).

In a further study of 30 patients with mild-to-moderate AD, the effect of honey, saffron (*C. sativus*), and sedge (*Cyperus rotundus*) on cognitive dysfunction was assessed. Cognitive status was measured by the standard scale ADAS-cog. Based on the findings, the investigators concluded treatment with a combination of the above did not improve cognitive function compared to placebo (Jivad et al., 2015).

However, during a 3-week double-blind assessment of visual short-term memory of 20 volunteers, saffron ethanolic extract was shown to improve short-term memory capacity (Ghodrat et al., 2014).

CONCLUSION

This review focuses on therapeutic potential and applications of saffron and its active constituents (crocin, crocetin, and safranal) alone or in combination with other compounds on learning, memory, cognitive impairment, neurodegeneration, and other neurological disorders including epilepsy. We further discuss underlying mechanisms examined during many *in vitro*, *in vivo*, and clinical studies (Fig. 1).

A combination of saffron, crocin, crocetin, or safranal with other medicinal plants and compounds may exert additive and/or synergistic effects, thus amplifying their pharmacological anti-inflammatory, neuroprotective, antioxidant, and cognition-enhancing activities.

These phytochemicals may interact with GABA, cholinergic, glutamatergic, and dopaminergic systems in animal and cell culture models of neurological diseases, suggesting these systems may be involved in mediating their beneficial effects. The antioxidant activity of saffron may be an important mechanism in counteracting learning and memory disturbances caused by oxidative stress.

Together, these findings show the pharmacological basis for use of saffron in the treatment and prevention of neurodegenerative diseases. Further phytochemical and mechanistic investigations, *in vivo* experiments, and clinical studies should be carried out before saffron can be used for treatment of patients with neurological disorders.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

REFERENCES

Abdel-Zaher AO, Abdel-Rahman MS, Elwasei FM. Protective effect of *Nigella sativa* oil against tramadol-induced tolerance and dependence in mice: role of nitric oxide and oxidative stress. Neurotoxicology. 2011. 32:725-733.

Abe K, Sugiura M, Shoyama Y, Saito H. Crocin antagonizes ethanol inhibition of NMDA receptor-mediated responses in rat hippocampal neurons. Brain Res. 1998. 787:132-138.

Abe K, Sugiura M, Yamaguchi S, Shoyama Y, Saito H. Saffron extract prevents acetaldehyde-induced inhibition of long-term potentiation in the rat dentate gyrus *in vivo*. Brain Res. 1999. 851:287-289.

Ahmadi M, Rajaei Z, Hadjzadeh MA, Nemati H, Hosseini M. Crocin improves spatial learning and memory deficits in the Morris water maze via attenuating cortical oxidative damage in diabetic rats. Neurosci Lett. 2017. 642:1-6.

Akbari G, Ali Mard S, Veisi A. A comprehensive review on regulatory effects of crocin on ischemia/reperfusion injury in multiple organs. Biomed Pharmacother. 2018. 99:664-670.

Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, et al. 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. 2010a. 35:581-588.

Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, et al. A 22-week, multicenter, randomized, double-blind controlled trial of *Crocus sativus* in the treatment of mild-to-moderate Alzheimer's disease. Psychopharmacology. 2010b. 207:637-643.

Akhondzadeh S. Herbal medicines in the treatment of psychiatric and neurological disorders. In: L'Abate L, editor. Low-Cost Approaches to Promote Physical and Mental Health: Theory, Research, and Practice. Springer, New York, NY, USA. 2007. p 119-138.

Baghishani F, Mohammadipour A, Hosseinzadeh H, Hosseini M, Ebrahimzadeh-Bideskan A. The effects of tramadol administration on hippocampal cell apoptosis, learning and memory in adult rats and neuroprotective effects of crocin. Metab Brain Dis. 2018. 33:907-916.

Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011. 377:1019-1031.

Batarseh YS, Bharate SS, Kumar V, Kumar A, Vishwakarma RA, Bharate SB, et al. *Crocus sativus* extract tightens the blood-brain barrier, reduces amyloid β load and related toxicity in 5XFAD mice. ACS Chem Neurosci. 2017. 8:1756-1766.

Berger F, Hensel A, Nieber K. Saffron extract and trans-crocetin inhibit glutamatergic synaptic transmission in rat cortical brain slices. Neuroscience. 2011. 180:238-247.

Brem AK, Ran K, Pascual-Leone A. Learning and memory. Handb Clin Neurol. 2013. 116:693-737.

Christodoulou E, Kadoglou NP, Kostomitsopoulos N, Valsami G. Saffron: a natural product with potential pharmaceutical applications. J Pharm Pharmacol. 2015. 67:1634-1649.

Dalu D, Kalakotla S. Anticonvulsant activity of ethanolic root extract of *C. sativus* on experimental animals. Adv Pharmacol Toxicol. 2017. 18:19-26.

Dashti-R MH, Zeinali F, Anvari M, Hosseini SM. Saffron (*Crocus sativus* L.) extract prevents and improves D-galactose and $NaNO_2$ induced memory impairment in mice. EXCLI J. 2012. 11:328-337.

Dastgerdi AH, Radahmadi M, Pourshanazari AA, Dastgerdi HH. Effects of crocin on learning and memory in rats under chronic restraint stress with special focus on the hippocampal and frontal cortex corticosterone levels. Adv Biomed Res. 2017. 6:157.

Del-Angel DS, Martínez NLH, Cruz MEG, Urrutia EC, Riverón-Negrete L, Abdullaev F. Saffron extract ameliorates oxidative damage and mitochondrial dysfunction in the rat brain. Acta Hortic. 2006. 739:359-366.

Delkhosh-Kasmaie F, Farshid AA, Tamaddonfard E, Imani M. The effects of safranal, a constitute of saffron, and metformin on spatial learning and memory impairments in type-1 diabetic rats: behavioral and hippocampal histopathological and biochemical evaluations. Biomed Pharmacother. 2018. 107:203-211.

Domingo JL. Aluminum and other metals in Alzheimer's disease: a review of potential therapy with chelating agents. J Alzheimers Dis. 2006. 10:331-341.

Farokhnia M, Shafiee Sabet M, Iranpour N, Gougol A, Yekehtaz H, Alimardani R, et al. 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. 2014. 29:351-359.

Finley JW, Gao SA. Perspective on *Crocus sativus* L. (Saffron) constituent crocin: a potent water-soluble antioxidant and potential therapy for Alzheimer's disease. J Agric Food Chem. 2017. 65:1005-1020.

Georgiadou G, Grivas V, Tarantilis PA, Pitsikas N. Crocins, the active constituents of *Crocus sativus* L., counteracted ketamine-induced behavioural deficits in rats. Psychopharmacology. 2014. 231:717-726.

Geromichalos GD, Lamari FN, Papandreou MA, Trafalis DT, Margarity M, Papageorgiou A, et al. Saffron as a source of novel acetylcholinesterase inhibitors: molecular docking and *in vitro* enzymatic studies. J Agric Food Chem. 2012. 60:6131-6138.

Ghadrdoost B, Vafaei AA, Rashidy-Pour A, Hajisoltani R, Bandegi AR, Motamedi F, et al. Protective effects of saffron extract and its active constituent crocin against oxidative stress and spatial learning and memory deficits induced by chronic stress in rats. Eur J Pharmacol. 2011. 667:222-229.

Ghaeni FA, Mohajeri S, Hosseinzadeh H, Motamedshariaty V. Effects of saffron (*Crocus sativus* L.) and its active constituent, crocin, on recognition and spatial memory after chronic cerebral hypoperfusion in rats. Res Pharm Sci. 2012. 7:S823.

Ghaffari S, Hatami H, Dehghan G. Saffron ethanolic extract attenuates oxidative stress, spatial learning, and memory impairments induced by local injection of ethidium bromide. Res Pharm Sci. 2015. 10:222-223.

Ghodrat M, Sahraei H, Razjouyan J, Meftahi GH. Effects of a saffron alcoholic extract on visual short-term memory in humans: a psychophysical study. Neurophysiology. 2014. 46:247-253.

Gohari AR, Saeidnia S, Mahmoodabadi MK. An overview on saffron, phytochemicals, and medicinal properties. Pharmacogn Rev. 2013. 7:61-66.

Haghighizad H, Pourmotabbed A, Sahraei H, Ghadami MR, Ghadami S, Kamalinejad M. Protective effect of Saffron extract on morphine-induced inhibition of spatial learning and memory in rat. Physiol Pharmacol. 2008. 12:170-179.

Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain. 2018. 141: 1917-1933.

Heidari S, Mehri S, Hosseinzadeh H. Memory enhancement and protective effects of crocin against D-galactose aging model in the hippocampus of Wistar rats. Iran J Basic Med Sci. 2017. 20: 1250-1259.

Hosseini A, Razavi BM, Hosseinzadeh H. Pharmacokinetic properties of saffron and its active components. Eur J Drug Metab Pharmacokinet. 2018. 43:383-390.

Hosseinzadeh H, Khosravan V. Anticonvulsant effects of aqueous and ethanolic extracts of *Crocus sativus* L. stigmas in mice. Arch Irn Med. 2002. 5:44-47.

Hosseinzadeh H, Sadeghnia HR, Ghaeni FA, Motamedshariaty VS, Mohajeri SA. Effects of saffron (*Crocus sativus* L.) and its active constituent, crocin, on recognition and spatial memory after chronic cerebral hypoperfusion in rats. Phytother Res. 2012. 26:381-386.

Hosseinzadeh H, Sadeghnia HR, Rahimi A. Effect of safranal on extracellular hippocampal levels of glutamate and aspartate during kainic acid treatment in anesthetized rats. Planta Med. 2008. 74:1441-1445.

Hosseinzadeh H, Sadeghnia HR. Protective effect of safranal on pentylenetetrazol-induced seizures in the rat: involvement of GABAergic and opioids systems. Phytomedicine. 2007. 14:256-262.

Hosseinzadeh H, Sadeghnia HR. Safranal, a constituent of *Crocus sativus* (saffron), attenuated cerebral ischemia induced oxidative damage in rat hippocampus. J Pharm Pharm Sci. 2005. 8: 394-399.

Hosseinzadeh H, Talebzadeh F. Anticonvulsant evaluation of safranal and crocin from *Crocus sativus* in mice. Fitoterapia. 2005. 76:722-724.

Hosseinzadeh H, Ziaei T. Effects of *Crocus sativus* stigma extract and its constituents, crocin and safranal, on intact memory and scopolamine-induced learning deficits in rats performing the Morris water maze task. J Med Plants. 2006. 3:40-50.

Hritcu L, Ciobica A, Artenie V. Effects of right-unilateral 6-hydroxydopamine infusion-induced memory impairment and oxidative stress: relevance for Parkinson's disease. Cent Eur J Biol. 2008. 3:250-257.

Javed H, Vaibhav K, Ahmed ME, Khan A, Tabassum R, Islam F, et al. Effect of hesperidin on neurobehavioral, neuroinflammation, oxidative stress and lipid alteration in intracerebroventricular streptozotocin induced cognitive impairment in mice. J Neurol Sci. 2015. 348:51-59.

Jivad N, Zare-Hassanabadi N, Azizi M. Effect of combination of honey, saffron (*Crocus sativus* L.) and sedge (*Cyperus rotundus* L.) on cognitive dysfunction in patients with Alzheimer's disease. Adv Herb Med. 2015. 1:11-16.

Kanakis CD, Tarantilis PA, Tajmir-Riahi HA, Polissiou MG. Crocetin, dimethylcrocetin, and safranal bind human serum albumin: stability and antioxidative properties. J Agric Food Chem. 2007. 55:970-977.

Khalili M, Hamzeh F. Effects of active constituents of *Crocus sativus* L., crocin on streptozocin-induced model of sporadic Alzheimer's disease in male rats. Iran Biomed J. 2010. 14:59-65.
Khalili M, Roghani M, Ekhlasi M. The effect of aqueous *Crocus sativus* L. extract on intracerebroventricular streptozotocin-induced cognitive deficits in rat: a behavioral analysis. Iran J Pharm Res. 2009. 8:185-191.
Khan MB, Hoda MN, Ishrat T, Ahmad S, Moshahid Khan M, Ahmad A, et al. Neuroprotective efficacy of *Nardostachys jatamansi* and crocetin in conjunction with selenium in cognitive impairment. Neurol Sci. 2012. 33:1011-1020.
Khazdair MR, Boskabady MH, Hosseini M, Rezaee R, Tsatsakis AM. The effects of *Crocus sativus* (saffron) and its constituents on nervous system: a review. Avicenna J Phytomed. 2015. 5:376-391.
Kong Y, Kong LP, Luo T, Li GW, Jiang W, Li S, et al. The protective effects of crocetin on $A\beta_{1-42}$-induced toxicity in HT22 cells. CNS Neurol Disord Drug Targets. 2014. 13:1627-1632.
Kumar P, Saraswathy N, Kulkarni KS. Evaluation of effect of green tea and saffron on learning process and memory in healthy human volunteers. Pharmacologyonline. 2009. 2:782-796.
Kumar V, Bhat ZA, Kumar D, Khan NA, Chashoo IA, Shah MY. Pharmacological profile of *Crocus sativus*—a comprehensive review. Pharmacologyonline. 2011. 3:799-811.
Lautenschläger M, Sendker J, Hüwel S, Galla HJ, Brandt S, Düfer M, et al. Intestinal formation of trans-crocetin from saffron extract (*Crocus sativus* L.) and *in vitro* permeation through intestinal and blood brain barrier. Phytomedicine. 2015. 22:36-44.
Li ZG, Sima AA. C-peptide and central nervous system complications in diabetes. Exp Diabesity Res. 2004. 5:79-90.
Linardaki ZI, Lamari FN, Margarity M. Saffron (*Crocus sativus* L.) tea intake prevents learning/memory defects and neurobiochemical alterations induced by aflatoxin B_1 exposure in adult mice. Neurochem Res. 2017. 42:2743-2754.
Linardaki ZI, Orkoula MG, Kokkosis AG, Lamari FN, Margarity M. Investigation of the neuroprotective action of saffron (*Crocus sativus* L.) in aluminum-exposed adult mice through behavioral and neurobiochemical assessment. Food Chem Toxicol. 2013. 52:163-170.
May BH, Feng M, Hyde AJ, Hügel H, Chang SY, Dong L, et al. Comparisons between traditional medicines and pharmacotherapies for Alzheimer disease: a systematic review and meta-analysis of cognitive outcomes. Int J Geriatr Psychiatry. 2018. 33:449-458.
Mazumder AG, Sharma P, Patial V, Singh D. Crocin attenuates kindling development and associated cognitive impairments in mice via inhibiting reactive oxygen species-mediated NF-κB activation. Basic Clin Pharmacol Toxicol. 2017. 120:426-433.
Mehri S, Abnous K, Khooei A, Mousavi SH, Shariaty VM, Hosseinzadeh H. Crocin reduced acrylamide-induced neurotoxicity in Wistar rat through inhibition of oxidative stress. Iran J Basic Med Sci. 2015. 18:902-908.
Mehri S, Abnous K, Mousavi SH, Shariaty VM, Hosseinzadeh H. Neuroprotective effect of crocin on acrylamide-induced cytotoxicity in PC12 cells. Cell Mol Neurobiol. 2012. 32:227-235.
Muriach M, López-Pedrajas R, Barcia JM, Sanchez-Villarejo MV, Almansa I, Romero FJ. Cocaine causes memory and learning impairments in rats: involvement of nuclear factor kappa B and oxidative stress, and prevention by topiramate. J Neurochem. 2010. 114:675-684.
Naghibi SM, Hosseini M, Khani F, Rahimi M, Vafaee F, Rakhshandeh H, et al. Effect of aqueous extract of *Crocus sativus* L. on morphine-induced memory impairment. Adv Pharmacol Sci. 2012. 2012:494367.
Naghizadeh B, Mansouri MT, Ghorbanzadeh B, Farbood Y, Sarkaki A. Protective effects of oral crocin against intracerebroventricular streptozotocin-induced spatial memory deficit and oxidative stress in rats. Phytomedicine. 2013. 20:537-542.
Naghizadeh B, Mansouri MT, Ghorbanzadeh B. Protective effects of crocin against streptozotocin-induced oxidative damage in rat striatum. Acta Med Iran. 2014. 52:101-105.
Nam KN, Park YM, Jung HJ, Lee JY, Min BD, Park SU, et al. Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells. Eur J Pharmacol. 2010. 648:110-116.
Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981-2002. J Nat Prod. 2003. 66: 1022-1037.
Pandit S, Kim HJ, Kim JE, Jeon JG. Separation of an effective fraction from turmeric against *Streptococcus mutans* biofilms by the comparison of curcuminoid content and anti-acidogenic activity. Food Chem. 2011. 126:1565-1570.
Papandreou MA, Kanakis CD, Polissiou MG, Efthimiopoulos S, Cordopatis P, Margarity M, et al. Inhibitory activity on amyloid-β aggregation and antioxidant properties of *Crocus sativus* stigmas extract and its crocin constituents. J Agric Food Chem. 2006. 54:8762-8768.
Papandreou MA, Tsachaki M, Efthimiopoulos S, Cordopatis P, Lamari FN, Margarity M. Memory enhancing effects of saffron in aged mice are correlated with antioxidant protection. Behav Brain Res. 2011. 219:197-204.
Pitsikas N, Sakellaridis N. *Crocus sativus* L. extracts antagonize memory impairments in different behavioural tasks in the rat. Behav Brain Res. 2006. 173:112-115.
Pitsikas N, Tarantilis PA. 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. 2017. 644:37-42.
Pitsikas N, Tarantilis PA. Effects of the active constituents of *Crocus sativus* L. crocins and their combination with memantine on recognition memory in rats. Behav Pharmacol. 2018. 29:400-412.
Pitsikas N, Zisopoulou S, Tarantilis PA, Kanakis CD, Polissiou MG, Sakellaridis N. Effects of the active constituents of *Crocus sativus* L., crocins on recognition and spatial rats' memory. Behav Brain Res. 2007. 183:141-146.
Pitsikas N. The effect of *Crocus sativus* L. and its constituents on memory: basic studies and clinical applications. Evid Based Complement Alternat Med. 2015. 2015:926284.
Purushothuman S. Oxidative stress in neurodegenerative conditions and the protective potential of a natural antioxidant, dietary saffron. Oxid Antioxid Med Sci. 2015. 4:112-118.
Rajaei Z, Hosseini M, Alaei H. Effects of crocin on brain oxidative damage and aversive memory in a 6-OHDA model of Parkinson's disease. Arq Neuropsiquiatr. 2016. 74:723-729.
Ranjbar H, Radahmadi M, Alaei H, Reisi P. Effect of different durations of stress on spatial and cognitive memory in male rats. J Isfahan Med Sch. 2014. 32:1933-1943.
Rao RV, Descamps O, John V, Bredesen DE. Ayurvedic medicinal plants for Alzheimer's disease: a review. Alzheimers Res Ther. 2012. 4:22.
Rushing BR, Selim MI. Aflatoxin B1: a review on metabolism, toxicity, occurrence in food, occupational exposure, and detoxification methods. Food Chem Toxicol. 2019. 124:81-100.
Sadeghnia HR, Cortez MA, Liu D, Hosseinzadeh H, Snead OC 3rd. Antiabsence effects of safranal in acute experimental seizure models: EEG and autoradiography. J Pharm Pharm Sci. 2008. 11:1-14.
Sadeghnia HR, Kamkar M, Assadpour E, Boroushaki MT, Ghorbani A. Protective effect of safranal, a constituent of *Crocus sativus*, on quinolinic acid-induced oxidative damage in rat hippocampus. Iran J Basic Med Sci. 2013. 16:73-82.
Sadeghnia HR, Shaterzadeh H, Forouzanfar F, Hosseinzadeh H. Neuroprotective effect of safranal, an active ingredient of *Crocus sativus*, in a rat model of transient cerebral ischemia. Folia

Neuropathol. 2017. 55:206-213.
Saleem S, Ahmad M, Ahmad AS, Yousuf S, Ansari MA, Khan MB, et al. Effect of saffron (*Crocus sativus*) on neurobehavioral and neurochemical changes in cerebral ischemia in rats. J Med Food. 2006. 9:246-253.
Sgobio C, Ghiglieri V, Costa C, Bagetta V, Siliquini S, Barone I, et al. Hippocampal synaptic plasticity, memory, and epilepsy: effects of long-term valproic acid treatment. Biol Psychiatry. 2010. 67:567-574.
Shal B, Ding W, Ali H, Kim YS, Khan S. Anti-neuroinflammatory potential of natural products in attenuation of Alzheimer's disease. Front Pharmacol. 2018. 9:548.
Shati AA, Elsaid FG, Hafez EE. Biochemical and molecular aspects of aluminium chloride-induced neurotoxicity in mice and the protective role of *Crocus sativus* L. extraction and honey syrup. Neuroscience. 2011. 175:66-74.
Stuchlik A. Dynamic learning and memory, synaptic plasticity and neurogenesis: an update. Front Behav Neurosci. 2014. 8:106.
Sugiura M, Saito H, Abe K, Shoyama Y. Ethanol extract of *Crocus sativus* L. antagonizes the inhibitory action of ethanol on hippocampal long-term potentiation *in vivo*. Phytother Res. 1995a. 9:100-104.
Sugiura M, Shoyama Y, Saito H, Abe K. The effects of ethanol and crocin on the induction of long-term potentiation in the CA1 region of rat hippocampal slices. Jpn J Pharmacol. 1995b. 67: 395-397.
Sugiura M, Shoyama Y, Saito H, Nishiyama N. Crocin improves the ethanol-induced impairment of learning behaviors of mice in passive avoidance tasks. Proc Jpn Acad Ser B. 1995c. 71:319-324.
Sunanda BPV, Rammohan B, Amitabh K, Kudagi BL. The effective study of aqueous extract of *Crocus sativus* Linn. in chemical induced convulsants in rats. World J Pharm Pharm Sci. 2014. 3:1175-1182.
Tamaddonfard E, Farshid AA, Asri-Rezaee S, Javadi S, Khosravi V, Rahman B, et al. Crocin improved learning and memory impairments in streptozotocin-induced diabetic rats. Iran J Basic Med Sci. 2013. 16:91-100.
Tashakori-Sabzevar F, Hosseinzadeh H, Motamedshariaty VS, Movassaghi AR, Mohajeri SA. Crocetin attenuates spatial learning dysfunction and hippocampal injury in a model of vascular dementia. Curr Neurovasc Res. 2013. 10:325-334.
Tiribuzi R, Crispoltoni L, Chiurchiù V, Casella A, Montecchiani C, Del Pino AM, et al. Trans-crocetin improves amyloid-β degradation in monocytes from Alzheimer's disease patient. J Neurol Sci. 2017. 372:408-412.
Tsolaki M, Karathanasi E, Lazarou I, Dovas K, Verykouki E, Karacostas A, et al. 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. 2016. 54:129-133.
Yoshino Y, Ishisaka M, Umigai N, Shimazawa M, Tsuruma K, Hara H. Crocetin prevents amyloid $\beta_{1\text{-}42}$-induced cell death in murine hippocampal cells. Pharmacol Pharm. 2014. 5:37-42.
Yousefvand N, Doosti H, Pourmotabbed A, Nedaei SE. The therapeutic effect of crocin on ketamine-induced retrograde amnesia in rats. J Kermanshah Univ Med Sci. 2016. 20:68-73.
Zhang XY, Zhang XJ, Xv J, Jia W, Pu XY, Wang HY, et al. Crocin attenuates acute hypobaric hypoxia-induced cognitive deficits of rats. Eur J Pharmacol. 2018. 818:300-305.
Zhang Y, Shoyama Y, Sugiura M, Saito H. Effects of *Crocus sativus* L. on the ethanol-induced impairment of passive avoidance performances in mice. Biol Pharm Bull. 1994. 17:217-221.
Zhao WQ, Chen H, Quon MJ, Alkon DL. Insulin and the insulin receptor in experimental models of learning and memory. Eur J Pharmacol. 2004. 490:71-81.
Zheng YQ, Liu JX, Wang JN, Xu L. Effects of crocin on reperfusion-induced oxidative/nitrative injury to cerebral microvessels after global cerebral ischemia. Brain Res. 2007. 1138:86-94.