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

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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.
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 underlying 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.

Ethanol 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, intraperitoneal (i.p.), 3 weeks] for antagonizing performance deficits induced by intracerebroventricular (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 synergic 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-Kasmae et al., 2018).
A study was also performed to evaluate the effect of *C. sativus* hydro-alcoholic extract on D-galactose and sodium nitrite (NaNO₂)-induced amnestic mice. Prolonged systemic administration of the extract (30 mg/kg/d, i.p., 15 days) and induction of amnesia produced preventive and ameliorative effects against learning and memory impairments, examined by one way passive and active avoidance tests (Dashhi-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 (Yousefzand 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 pentylentetrazol-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) isofoms 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 isofoms 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 Aβ1-40 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 Aβ42-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 Aβ42 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 Aβ1-42-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 intracerebral 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$_2$O$_2$-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) |

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 aluminum-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 Aβ$_{42}$ 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...
**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-
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 countering 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.

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