Am J Neurodegener Dis 2018;7(1):1-10
www.AJND.us /ISSN:2165-591X/AJND0063575

*Review Article*

# The protective effects of crocin in the management of neurodegenerative diseases: a review

Tahereh Farkhondeh[1], Saeed Samarghandian[2], Hanieh Shaterzadeh Yazdi[3], Fariborz Samini[4]

*[1]Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran; [2]Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran; [3]Research Center of Pardis Hospital, Mashhad, Iran; [4]Department of Neurosurgery, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

Received August 13, 2017; Accepted January 6, 2018; Epub February 5, 2018; Published February 15, 2018

**Abstract:** Flavonoids have been used in traditional medicine to promote human health. Crocin has been proposed to be effective in the management of the various diseases including the neurodegenerative diseases. Antiepileptic and anti-Alzheimer effects of crocin have also been indicated. The efficacy of crocis in the treatment of cerebral ischemia and traumatic brain injury was also confirmed by using animal models. Crocin treatment increased dopamine levels in the brain of experimental model of Parkinson's disease. In addition, crocin modulates the opioid system to decrease the withdrawal syndrome. Thus, the present study highlighted the effects of crocin on the nervous system and the underling mechanisms. This review also indicated that crocins can be considered as an effective candidate in the management of nervous system diseases due to their antioxidant and anti-inflammation effects.

**Keywords:** Crocins, antioxidant, anti-inflammation, nervous system

## Introduction

Medicinal plants contain bioactive ingredients that act as major candidates for the production of safe neuroprotective drugs [1-5]. Crocin is the water soluble carotenoid found in saffron and the primary ingredient involving in the bright red color of saffron [6]. Crocin ($C_{44}H_{64}O_{24}$) is a collective term of a series of hydrophilic carotenoids that are either monoglycosyl or diglycosyl polyene esters of crocetin [7]. α-Crocin (crocetin digentibiose ester) is the main crocin of saffron and gardenia [8]. The safety study indicated that α-crocin (3 g, p.o. and i.p. as well as 15-180 mg/kg, i.p.) did not show the toxic effects on hematological, biochemical and pathological parameters of the animal models [9]. In addition, Ames/*Salmonella* test indicated that α-crocin has not mutagenic or toxic effects [10]. It has been found that crocin has many beneficial protective effects against neurodegenerative diseases due to its anti-apoptotic, anti-inflammatory, and antioxidant activities. The present study aimed to critically review the recent studies from 2004 to 2017 that regarding the protective effects of crocins in the management of neurodegenerative diseases

## Materials and methods

Online literature resources were checked using different search engines such as Medline, PubMed, Iran Medex, Scopus, and Google Scholar from 2004 to 2017 to identify articles, editorials, and reviews on the neuroprotective effects of crocins. Crocins, neurodegenerative diseases, anti-inflammation, antioxidant and brain were key words which used to search the literature.

## Results

### *Antioxidant effects*

Traditional medicine indicated that natural flavonoids possess neuroprotective activities by modulating oxidative stress, and have been considered as candidates for the production of novel neuroprotective drugs [1-5]. The protective effects of crocin against chronic stress-

**Table 1.** A summary of antioxidant and anti-inflammatory effects of crocin

| | Experimental model | Effect | Ref. |
|---|---|---|---|
| Crocin | Rat | Protected neurons against chronic stress damages via reducing MDA level as well as elevating the levels of GPx, GR, SOD and total antioxidant capacity | [11] |
| | PC-12 cell | Protected PC-12 cell against oxidative stress induced by deprived from serum/glucose against via preventing membrane lipid peroxidation | [12] |
| | | Protected PC-12 cell against ischemic stress-induced neural cell death via increasing GSH content and blocking the activation of JNK pathways | [13] |
| | | Protected PC-12 cell against ACR induced neural cell death via blocking down-regulation of Bcl-2, up-regulation of Bax as well as decreasing apoptosis and ROS generation in the treated cells | [14] |
| | Rat | Protected hippocampus against chronic stress induced learning and memory loss by modulating oxidative stress | [15] |
| | | Protected brain against acute swimming exercise induced oxidative stress by enhancing antioxidant activity and decreasing the levels of XO and MDA | [16] |
| | | Protected brain against haloperidol-induced orofacial dyskinesia by increasing GSH and decreasing MDA | [17] |
| | Cultured rat microglial cells | Protected microglial cells against LPS-induced neuroinflammation by inhibiting NF-κB activation, the levels of NO, TNF-α, IL-1β, and ROS | [22] |
| | | Protected microglial cells against TNF-α-induced neuroinflammation by blocking the expression of Bcl-XS and LICE and ameliorating the Bcl-XL mRNA expression | [23] |
| | Retinal ganglion & BV2 cells | Protected retinal ganglion cells against LPS-induced microglial activation and progression of glaucoma by decreasing the expression of microglial markers (CD11b and Iba-1) and pro-inflammatory mediators (iNOS, COX-2, IL-1β, and TNF-α). Suppressing CX3CR1 expression by modulating NF-κB/YY1 signaling | [24] |

Abbreviations: MDA: malondialdehyde, GPx: glutathione peroxidase, GR: glutathione reductase, SOD: superoxide dismutase, GSH: glutathione peroxidase, JNK: c-Jun NH2-terminal kinases, ACR: acrylamide, ROS: reactive oxygen species, XO: xanthine oxidase, LPS: lipopolysaccharide, NO: nitric oxide, TNF: tumor necrosis factor alpha, IL-1β: interleukin-1β, NOs: nitric oxide synthase, COX-2: cyclooxygenase-2, NF-Kb: Nuclear factor-κB.

induced oxidative damage in the rat brain were studied by measuring malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-px), glutathione reductase (GR) and total antioxidant capacity. The findings indicated that crocin may be useful against chronic stress-induced oxidative damage by decreasing the MDA level as well as increasing the levels of GPx, GR, SOD and total antioxidant capacity [11]. Ochiai et al. indicated that crocin (10 μM) treatment protected PC-12 cells against oxidative stress induced by deprived from serum/glucose against [12]. In addition, Ochiai et al. and also Soeda et al. indicated that crocin was effective on ischemic stress-induced neural cell death through the elevating GSH content and blocking the activation of c-Jun NH2-terminal kinases (JNK) pathways [12, 13]. The effect of crocin (total crocins were extracted from saffron stigmas using crystallization method) against acrylamide (ACR) was assessed by using PC12 cells. Crocins (10-50 μM) blocked down-regulation of Bcl-2, up-regulation of Bax as well as decreased apoptosis and ROS generation in the treated cells [14]. Ghadrdoost et al. indicated that crocin improved chronic stress-induced learning and memory loss by modulating oxidative stress in the hippocampus of rats [15]. Altinoz and co-workers (2016) investigated the effects of crocin in a rat model of an acute swimming exercise induced oxidative stress in brain. The results indicated that crocin decreased the MDA and xanthine oxidase (XO) levels and also increased GSH levels in the brain of treated groups. The study also confirmed that crocin protected brain against the exercise induced oxidative stress by enhancing antioxidant activity [16]. Another study showed theat the protective effect of coercion against haloperidol-induced orofacial dyskinesia. Haloperidol elevated vacuous chewing movements (VCMs) and tongue protrusions (TPs) in rats and co-administration of crocin (20 and 40 mg/kg) significantly ameliorated them. Additionally, haloperidol decreased the locomotor and exploratory activities (rearing) and decreased the percentage of entries into open arms. Pretreatment with crocin (10 mg/kg) changed haloperidol effects on these behavioral parameters. Haloperidol induced lipid peroxidation in three brain regions, whereas crocin co-administration decreased the MDA and increased GSH levels in these regions. The finding suggested that crossing showed protective effects against haloperidol induced tardive dyskinesia, due to its antioxidant effects [17]. The antioxidant effect of corrosion is summarized in **Table 1**.

*Neuroinflammtory effects*

Microglial cells have a main role in the inflammatory responses of the central nervous system (CNS) [18, 19]. Chronic microglial activa-

tion disturbs neuronal survival via increasing proinflammatory cytokine. Flavonoids have been considered for the treatment of neurodegenerative disorders in traditional medicine [20, 21]. Nam et al. showed that crocin inhibited NF-κB activation, the levels of NO, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and intracellular reactive oxygen species (ROS) release from cultured the rat brain microglial cells induced by LPS [22]. It was indicated that α-crocin reduced the effect of TNF-α on neuronally differentiated PC-12 cells and also blocked the TNF-α-induced expression of Bcl-XS and LICE and ameliorated the cytokine-induced decrease of Bcl-XL mRNA expression in the rat brain microglial cells [23]. Other study investigated the effect of crocin against lipopolysaccharide (LPS)-induced microglial activation in retinal ganglion cells (RGCs) and BV2 cells. Microglial activation has been indicated to be deleterious to RGCs and may participate in the progression of glaucoma. Crocin has been shown to inhibit microglial activation. Crocin decreased the expression of microglial markers (CD11b and Iba-1) and pro-inflammatory mediators (iNOS, COX-2, IL-1β, and TNF-α) induced by LPS in a dose-dependent manner. In addition, crocin increased the CX3CR1 expression through the suppression of NF-κB/Yin Yang 1 signaling in BV2 cells. The results suggested that crocin suppressed the microglial activation and upregulated CX3CR1 expression by modulating NF-κB/YY1 signaling [24]. Anti-inflammatory effect of crocin is summarized in **Table 1**.

*Effect on cerebral ischemia, ischemic stroke and traumatic brain injury*

Ischemic and traumatic brain injury (TBI) caused by induction of oxidative stress, apoptosis and inflammation responses [25-27]. In both injuries, flavonoids may acts as effective pharmacological agents to protect the brain and improve behavioral changes [28, 29]. In this context, Zheng et al. indicated that crocin-crocin has protective effect against ischemia/reperfusion (I/R) injury-induced oxidative and nitrosative damage in cerebral micro vessels of the mice. It is found that crocin ameliorated increased nitric oxide (NO), nitric oxide synthase (NOS) and MDA, as well as decreased the activities of SOD and GPx in cortical microvascular homogenates of mice with 20 min of bilateral common carotid artery occlusion (BCCAO) followed by 24 h of reperfusion *in vivo*. Crocin also prevented the translocation of the G protein-coupled receptor kinase 2 (GRK2) expression from the cytosol to the membrane and decreased phosphorylation of extracellular signal-regulated kinase 1/2 ERK1/2 phosphorylation and MMP-9 expression in the cortical micro vessels. The study suggested that crocin may be effective against transient global cerebral ischemia by modulation of oxidative stress [30]. Another study investigated the effect of crocin (15, 30, 60, and 120 mg/kg) against ischemic reperfusion injury and cerebral edema in a rat model of stroke by decreasing the levels of MDA and increasing the activity of SOD and GPx in the cortex [31]. In addition, Oruc et al. confirmed the antioxidant and anti-apoptotic effects of crocin against the global cerebral IR induced by four-vessel occlusion. They showed that pre-treatment with crocin (40 mg/kg/day orally for 10 days) decreased oxidative stress indices (TAS, TOS, OSI), hypoxia-inducible factor-1 alpha (HIF-1α), TUNEL-positive cell and caspase-3 in IR-mediated brain injury induced by four-vessel occlusion [32]. Wang et al. studied the effects of crocin against brain damage after traumatic brain injury (TBI) in mice. Pretreatment with crocin (20 mg/kg) had protective effects against TBI, by ameliorating neurological severity score (NSS) and brain edema, reducing microglial activation and release of several pro-inflammatory cytokines as well as cell apoptosis [5]. It was also indicated that α-crocin (20 mg/kg) protected mice brain against traumatic brain injury (TBI) by decreasing microglial activation, several pro-inflammatory cytokines, and cell apoptosis. It was also indicated that α-crocin (20 mg/kg) protected mice brain against traumatic brain injury (TBI) by decreasing microglial activation, several pro-inflammatory cytokines, and apoptotic molecules [33]. The potential effect of crocin on blood-brain barrier (BBB) damage in aged rats following cerebral ischemia has been investigated. The result indicated that the middle cerebral artery occlusion (MCAO)-induced brain injury was ameliorated by the pretreatment of crocin. Crocin-treated animals also indicated the preserved BBB function in the presence of ischemic injury. Crocin improved the loss of tight junction proteins and enhanced NADPH oxidase in the ipsilateral brains of the MCAO-treated rats. In addition, crocin blocked the

**Table 2.** A summary of the protective effect of crocin on cerebral ischemia, ischemic stroke, traumatic brain and spinal cord injury

| | Experimental model | Effect | Ref. |
|---|---|---|---|
| Crocin | Mice | Protected I/R injury-induced oxidative and nitrosative damage in cerebral micro vessels by decreasing NO, NOS, MDA, phosphorylation of extracellular signal-regulated kinase 1/2 ERK1/2 phosphorylation and MMP-9, increasing the activities of SOD and GPx and also inhibiting translocation of the GRK2 from the cytosol to the membrane | [30] |
| | Rat | Prevented ischemic reperfusion injury and cerebral edema by decreasing the levels of MDA and increasing the activity of SOD and GPx in the cortex | [31] |
| | | Prevented the global cerebral IR induced by four-vessel occlusion via modulating oxidative stress indices (TAS, TOS, OSI), HIF-1α, TUNEL-positive cell and caspase-3 in brain | [32] |
| | Mice | Prevented brain damage after TBI by decraesing pro-inflammatory cytokines | [5] |
| | | Prevented TBI by decreasing microglial activation, several pro-inflammatory cytokines, and cell apoptosis | [33] |
| | Rat | Protected the BBB damage in aged rats following cerebral ischemia via enhancing NADPH oxidase and blocking the induction of MMP-2 and MMP-9 | [34] |
| | | Improved chronic pain caused by SCI by reducing as a main pain and inflammatory mediators. | [6] |

Abbreviations: I/ R: ischemia/reperfusion, NO: nitric oxide, NOs: nitric oxide synthase, MDA: malondialdehyde, MMP: matrix metalloproteinases, SOD: superoxide dismutase, ERK1/2: extracellular signal-regulated kinase 1/2, GPx: glutathione peroxidase, TOS: Total Oxidant Status, TOS: total oxidant status, OSI: Oxidative Stress Index, HIF-1: hypoxia-inducible factor 1, TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling, TBI: traumatic brain injury, BBB: blood-brain barrier, NADPH: Nicotinamide adenine dinucleotide phosphate, SCI: spinal cord injury.

induction of matrix metalloproteinase-2 (MMP-2) and MMP-9 by cerebral ischemia in the aged rats. The findings indicated that crocin protected against cerebral ischemia by maintaining the integrity of BBB in the aged rats, an effect likely through repressing the activation of matrix metalloproteinase pathway [34]. The protective effect of crocin on cerebral ischemia, ischemic stroke and traumatic brain injury are summarized in **Table 2**.

*Effect on spinal cord injury*

A spinal cord injury (SCI) is damage to the spinal cord that causes changes in its function, either temporary or permanent [35, 36]. Karami and co-workers showed the beneficial effects of crocin on chronic pain caused by SCI that may be related to calcitonin-gene related peptide (CGRP) reducing as a main pain and inflammatory mediators. It is indicated that treated with corrosion (150 mg/kg) improved locomotor and mechanical, behavioral tests in the rats involved in spinal cord damage [6]. The protective effect of crocin on spinal cord injury is summarized in **Table 2**.

*Effects on memory deficit and cognitive impairment*

Dysfunction of memory is one of the most disabilities of neurological diseases such as strokes, hypoxia, head injuries, depression, heart surgery, anxiety and neurodegenerative diseases which may cause usual daily activities impairments [37-39]. Saffron extract or its active components, crocin and crocetin could be helpful for treatments of neurodegenerative problems accompanying memory deficit [40, 41]. In this context, Hosseinzadeh and co-workers have indicated that crocin (25 mg/kg) ameliorated chronic cerebral hypoperfusion-induced memory deficiency by using Morris water maze test. They also showed crocin protected behavioral deficits by modulating antioxidant system in rat brain [42]. Other study investigated the effect of crocin on improving spatial memory deficits and cerebral oxidative damage in streptozotocin-induced diabetic rats. The result indicated that treatment with crocin (15, 30 and 60 mg/kg, ip, 6 weeks) improved cognitive performance and lowered hyperglycemia and oxidative stress in diabetic rats. The results suggested that the beneficial effects of corrosion on streptozotocin-induced memory dysfunction may be related to its antidiabetic and antioxidant activity [43]. Mazumder and co-workers investigated the effect of crocin on pentylenetetrazol (PTZ)-induced kindling development and its associated cognitive deficit in mice. The results indicated that crocin treatment (5, 10 and 20 mg/kg p.o. doses) decreased the severity of PTZ-induced seizures. Crocin also increased percentage spontaneous alternations in T-maze test. Histopathological examination indicated that crocin decreased dark neurons in the hippocampal pyramidal layer of mice. The results showed that crocin increased SOD activity and decreased ROS level as well as nuclear factor-κB (NF-κB) expression in the hippocampus of animals. The results of this

**Table 3.** The protective effect of crocin on memory deficit and cognitive impairment, AD and PD

| | Experimental model | Effect | Ref. |
|---|---|---|---|
| Crocin | Rat | Ameliorated chronic cerebral hypoperfusion-induced memory deficiency by modulating antioxidant system | [42] |
| | Rat | Prevented STZ-induced memory dysfunction by modulating oxidative stress | [43] |
| | Mice | Prevented PTZ-induced kindling development and its associated cognitive deficit by increasing SOD activity and decreased ROS level as well as NF-κB expression in the hippocampus | [44] |
| | Rat | Prevented sporadic Alzheimer's disease induced by ICV-STZ | [47] |
| | | Prevented cognitive deficiency induced by ICV-STZ via decreasing MDA as well as increasing the levels of total and GPx activity | [48] |
| | Rat | Prevented acrolein induced AD by ameliorating MDA, Abeta and p-tau levels and MAPKs signaling pathways | [49] |
| | Rat | Improved memory deficiency by inhibiting Aβ induced apoptosis and oxidative stress | [50] |
| | Mice | Improved memory deficiency by increasing the expression of the Aβ degrading enzyme NEP and up-regulation of the ApoE-clearance pathway | [51] |
| | In vitro | Improved MPP induced cell injury and apoptosis and prevented mitochondrial dysfunction induced by MPP(+)-via inhibiting ER stress cytotoxicity. | [56] |
| | Drosophila | Prevented ROT induced parkinsonism by increasing the levels of GSH and TSH in head/body regions and ameliorated mitochondrial dysfunctions and the activity of AChE by modulating oxidative stress | [57] |
| | Rat | Ameliorated 6-OHDA model of Parkinson's disease by decreasing MDA and nitrite levels in the hippocampus, and improved aversive memory by modulating oxidative and inflammatory responses | [58] |

Abbreviations: STZ: streptozotocin, PTZ: pentylenetetrazol, SOD: superoxide dismutase, ROS: reactive oxygen species, NF-Kb: nuclear factor-κB, ICV: intracerebroventricular, MDA: malondialdehyde, GPx: glutathione peroxidase, AD: alzheimers disease, p-tau: phospho-tau, MAPKs: mitogen-activated protein kinases, Aβ: beta amyloid, ApoE: Apolipoprotein E, ER: endoplasmic reticulum, ROT: rotenone, GSH: reduced glutathione, TSH: total thiols, AChE: acetylcholinesterase, OHDA: hydroxydopamine.

study indicated that crocin treatment inhibited PTZ-induced kindling development and improving cognitive function via suppressing ROS generation and NF-κB expression in the hippocampal pyramidal layer of mice [44]. The protective effect of crocin on memory deficit and cognitive impairment is summarized in **Table 3**.

*Effects on alzheimer's disease*

Alzheimer's disease (AD) is a chronic progressive, degenerative disease of the central nervous system with cognitive dysfunction and mental disorder [45, 46]. The effect of flavonoids such as crocins in the management of learning and memory deficiency has been found. In this context, the effect of crocins (15 and 30 mg/kg) on sporadic Alzheimer's disease induced by intracerebroventricular (ICV) injection of streptozotocin (STZ) in male rats has been studied. The study indicated the protective of crocin (30 mg/kg) against cognitive deficits induce by ICV-STZ in rats [47]. The effects of crocin (100 mg/kg) on cognitive performance in ICV-STZ-lesioned rats has been also studied by using Morris water maze task. Results indicated that crocin treatment improved cognitive deficiency via decreasing MDA as well as increasing the levels of total and GPx activity [48]. Rashedinia and co-workers investigated the neuro-protective effects of crocin against acrolein toxicity. Acrolein, as a by-product of lipid peroxidation, is involved in the pathogenesis of neurodegenerative disorders including Alzheimer's disease (AD). They investigated the protective effects of crocin against acrolein induced cerebral cortex damage in rat. The study indicated that crocin ameliorated MDA, Abeta and phospho-tau (p-tau) levels by modulating mitogen-activated protein kinases (MAPKs) signaling pathways. They suggested that crocin may be a suitable agent for treatment of neurodegenerative diseases, such as AD [49]. Asadi and co-workers investigated the effect of crocin on memory deficiency by using in vivo models of Alzheimer's disease. Results indicated that crocin ameliorated spatial memory indicators including escape latency, traveled distance and time spent in target quadrant. In addition, it was observed that crocin decreased Bax/Bcl-2 ratio and cleaved Caspase-3 level. They indicated that crocin prevented AD by inhibiting beta amyloid (Aβ) induced apoptosis and oxidative stress [50]. Crocin (10 mg/kg/day) decreased Aβ levels in brain homogenates from mice by increasing the expression of the Aβ degrading enzyme NEP and up-regulation of the ApoE-clearance pathway [51]. The protective effect of crocin on AD is summarized in **Table 3**.

*Effects on parkinson's disease*

Parkinson's disease (PD) is caused by the degeneration of dopaminergic neurons in the

**Table 4.** The protective effect of crocin on epilepsy and schizophrenia

| | Experimental model | Effect | Ref. |
|---|---|---|---|
| Crocin | Rat | Exhibited anticonvulsant effects induced by penicillin via ameliorating GABA (A)-benzodiazepine receptor-mediated | [64] |
| | Mice | Inhibited hippocampal electrical ignition of epilepsy by promoting the secretion of BDNF in the hippocampus and further enhancing the function of the downstream TrkB receptor and inhibiting inflammatory cytokines production | [65] |
| | | Improved schizophrenia-like behavioral that induced by ketamine | [66] |

Abbreviations: GABA: gamma-amino butyric acid, BDNF: Brain-derived neurotrophic factor, TrkB: Tropomyosin receptor kinase B.

substantia nigra of the midbrain and aggregation of alpha synuclein (αS) in the brain [52, 53]. In addition, induction of inflammation and oxidative stress responses has been suggested to play a main role in the pathogenesis Parkinson's disease [27, 54, 55]. Zhang et al. investigated the protective effects of crocin by using an in vitro model. They observed that crocin ameliorated 1-methyl-4-phenylpyridinium (+)-MPP induced cell injury and apoptosis. Crocin also prevented mitochondrial dysfunction induced by MPP(+)-, which related to inhibited endoplasmic reticulum (ER) stress cytotoxicity [56]. The neuroprotective effect of crocin has been studied in a Drosophila model of parkinsonism by using rotenone (ROT)-induced neurotoxicity in this model. It was observed that crocin decreased mortality, locomotor phenotype and the levels of oxidative stress indices as well as increased the levels of GSH and TSH in head/body regions of flies exposed to ROT [57]. In addition, crocin ameliorated mitochondrial dysfunctions and the activity of acetylcholinesterase (AChE) in head/body regions. This study indicated that crocin may be effective agent for treatment of PD by modulating oxidative stress [57]. Rajaei and co-workers (2016) also investigated the effect of crocin on brain oxidative damage and memory deficits in a 6-hydroxydopamine (6-OHDA) model of Parkinson's disease. The results indicated that crocin decreased MDA and nitrite levels in the hippocampus, and improved aversive memory in the 6-OHDA lesioned rats, which was accompanied by memory deficits in a passive avoidance test at the end of week 6. The study suggested that crocin improved aversive memory due to its antioxidant and anti-inflammatory properties [58]. The protective effect of crocin on PD is summarized in **Table 3**.

*Antiepileptic effects*

Epilepsy is a central nervous system disease that characterized by periods of uncommon behavior, loss of consciousness and sensations [59-61]. Treatment of seizures is necessary because of risks that may occur during some activities such as swimming or driving [62, 63]. Epileptic patient can be treated with traditional medicine. In this regard, Tamaddonfard et al. showed that crocin exhibited anticonvulsant effects in rats exposed to penicillin. Electrocorticographic (ECOG) recordings indicated that intracerebroventricular (ICV) injection of crocin (25, 50 and 100 μg) enhanced the latency time to start of first spike wave and reduced periodicity and amplitude of spike waves. The result indicated that GABA (A)-benzodiazepine receptor-mediated mechanism has a main role in the anti-seizure effect of crocin [64]. The protective effect of crocin on the progression and generalized seizure of temporal lobe epilepsy in mice has been investigated. The results indicated that crocin (20 mg/kg) significantly ameliorated behavioral seizure stages and shortened cumulative afterdischarge duration (ADD) during hippocampus rapid kindling acquisition in mice. Crocin (100 or 200 mg/kg) significantly decreased the incidence of generalized seizure (GS) and reduced average seizure stages in fully-kindled mice. The findings indicated that Low-dose crocin improved the progression in hippocampus rapid kindling acquisition in mice, while high-dose crocin ameliorated the GS in fully-kindled mice. The study suggested that the inhibitory effect of crocin on the hippocampal electrical ignition of epilepsy in mice may be caused by promoting the secretion of BDNF in the hippocampus and further enhancing the function of the downstream TrkB receptor. In addition, the study proposed that some inflammatory mediators such as TNF-α, IL-1β, IL-6 and so on have a significant role in the development of epilepsy; while crocin has an inhibitory effect on these inflammatory cytokines [65]. The antiepileptic effect of crocin is summarized in **Table 4**.

*Effects on schizophrenia*

Schizophrenia is a main psychic problem, which can cause signs such as illusion, hallucinations, avolition, anhedonia and memory deficits in patients [66]. Georgiadou and co-workers investigated the effect of crocin against schizophrenia-like behavioral that induced by ketamine injection in rats. The non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine impairs cognition negative symptoms of schizophrenia in rats. They investigated the ability of crocin against ketamine-induced memory deficits using the novel object recognition task (NORT). In addition, the social interaction test was done to study the effects of crocin on ketamine-induced social withdrawal. Crocin (50 mg/kg) ameliorated ketamine-caused hyper motility, stereotypies, ataxia and social interaction. Post-training crocin treatment (15 and 30 mg/kg) ameliorated ketamine-caused performance deficits in the NORT. This study indicated that crocin improved schizophrenia-like behavioral deficits caused by ketamine in rats [67]. The protective effect of crocin on schizophrenia is summarized in **Table 4**.

## Discussion

Natural alternatives which exhibit beneficial effects to multiple targets and pathways could be valuable options and applied in conjunction with drug therapies for neurodegenerative prevention and management. Studies presented in this review provided evidence that crocin may be effective in delaying progression of the neurodegenerative disease. The efficacy of crocin in the management of neurodegenerative disease may be related to its antioxidant and anti-inflammatory effects. According to the recent studies, protective effects of the crocin on Alzheimer and Parkinson's disease are caused by its interaction with opioid systems. It is also suggested that antiepileptic of crocin and its effects on ketamin withdrawal may be related to an interaction between crocin, GABA and opioid system. Neuroprotective effects of crocin have been shown by experimental studies, but not yet in clinical trials and more safety studies should be performed to indicate possible toxic effects of crocin in long-term administration in human.

## Conclusion

In conclusion, this review suggests that the neuroprotective effects of crocin may connect to its antioxidant and anti-inflammatory activities. Although experimental studies indicated the beneficial effects of crocin against the nervous system, well designed clinical trials in humans are needed to confirm these effects.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Saeed Samarghandian, Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran. Tel: 98-5142628523; Fax: 98-5142628524; E-mail: samarghandians@mums.ac.ir

## References

[1] Moghaddam HS, Samarghandian S, Farkhondeh T. Effect of bisphenol A on blood glucose, lipid profile and oxidative stress indices in adult male mice. Toxicol Mech Methods 2015; 25: 507-513.

[2] Samarghandian S, Afshari R, Farkhondeh T. Effect of long-term treatment of morphine on enzymes, oxidative stress indices and antioxidant status in male rat liver. Int J Clin Exp Med 2014; 7: 1449-1453.

[3] Samarghandian S, Asadi-Samani M, Farkhondeh T, Bahmani M. Assessment the effect of saffron ethanolic extract (Crocus sativus L.) on oxidative damages in aged male rat liver. Der Pharm Lett 2016; 8: 283-290.

[4] Farkhondeh T, Samarghandian S, Azimin-Nezhad M, Samini F. Effect of chrysin on nociception in formalin test and serum levels of noradrenalin and corticosterone in rats. Int J Clin Exp Med 2015; 8: 2465-2470.

[5] Wang K, Zhang L, Rao W, Su N, Hui H, Wang L, Peng C, Tu Y, Zhang S, Fei Z. Neuroprotective effects of crocin against traumatic brain injury in mice: involvement of notch signaling pathway. Neurosci Lett 2015; 591: 53-58.

[6] Karami M, Bathaie SZ, Tiraihi T, Habibi-Rezaei M, Arabkheradmand J, Faghihzadeh S. Crocin improved locomotor function and mechanical behavior in the rat model of contused spinal cord injury through decreasing calcitonin gene related peptide (CGRP). Phytomedicine 2013; 21: 62-67.

[7] Lage M, Cantrell C. Quantification of saffron (Crocussativus L.) metabolites crocins, picrocrocin and safranalfor quality determination of the spice grown under different environmental Moroccan conditions. Sci Hort 2009; 121: 366-373.

[8] Ordoudi SA, Kyriakoudi A, Tsimidou MZ. Enhanced bioaccessibility of crocetin sugar esters from saffron in infusions rich in natural

phenolic antioxidants. Molecules 2015; 20: 17760-17774.
[9] Hosseinzadeh H, Shariaty VM, Sameni AK, Vahabzadeh M. Acute and subacute toxicity of safranal, a constituent of saffron, in mice and rats. Iran J Pharm Res 2013; 12: 93-99.
[10] Alavizadeh SH, Hosseinzadeh H. Bioactivity assessment and toxicity of crocin: a comprehensive review. Food Chem Toxicol 2014; 64: 65-80.
[11] Bandegi AR, Rashidy-Pour A, Vafaei AA, Ghadrdoost B. Protective effects of Crocus sativus L. extract and crocin against chronic-stress induced oxidative damage of brain, liver and kidneys in rats. Adv Pharm Bull 2014; 4 Suppl 2: 493-499.
[12] Ochiai T, Ohno S, Soeda S, Tanaka H, Shoyama Y, Shimeno H. Crocin prevents the death of rat pheochromyctoma (PC-12) cells by its antioxidant effects stronger than those of α-tocopherol. Neurosci Lett 2004; 362: 61-64.
[13] Soeda S, Ochiai T, Tanaka H, Shoyama Y, Shimeno H. Prevention of ischemic neuron death by a saffron's carotenoid pigment crocin and its mechanism of action. Focus. Neurochem Res 2005; 139-56.
[14] Moghaddam HS, Samarghandian S, Farkhondeh T. Effect of bisphenol A on blood glucose, lipid profile and oxidative stress indices in adult male mice. Toxicol Mech Methods 2015; 25: 507-13.
[15] Ghadrdoost B, Vafaei AA, Rashidy-Pour A, Hajisoltani R, Bandegi AR, Motamedi F, Haghighi S, Sameni HR, Pahlvan S. 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.
[16] Altinoz E, Ozmen T, Oner Z, Elbe H, Erdemli ME, Bag HG. Saffron (its active constituent, crocin) supplementation attenuates lipid peroxidation and protects against tissue injury. Bratisl Lek Listy 2016; 117: 381-387.
[17] Kamyar M, Razavi BM, Hasani FV, Mehri S, Foroutanfar A, Hosseinzadeh H. Crocin prevents haloperidol-induced orofacial dyskinesia: possible an antioxidant mechanism. Iran J Basic Med Sci 2016; 19: 1070-1079.
[18] Li DC, Bao XQ, Wang XL, Sun H, Zhang D. A novel synthetic derivative of squamosamide FLZ inhibits the high mobility group box 1 protein-mediated neuroinflammatory responses in murine BV2 microglial cells. Naunyn Schmiedebergs Arch Pharmacol 2017; 390: 643-650.
[19] Bussi C, Ramos JM, Arroyo DS, Gaviglio EA, Gallea JI, Wang JM, Celej MS, Iribarren P. Autophagy down regulates pro-inflammatory mediators in BV2 microglial cells and rescues both LPS and alpha-synuclein induced neuronal cell death. Sci Rep 2017; 7: 43153.
[20] Costa SL, Silva VD, dos Santos Souza C, Santos CC, Paris I, Muñoz P, Segura-Aguilar J. Impact of plant-derived flavonoids on neurodegenerative diseases. Neurotox Res 2016; 30: 41-52.
[21] Cirmi S, Ferlazzo N, Lombardo GE, Ventura-Spagnolo E, Gangemi S, Calapai G, Navarra M. Neurodegenerative diseases: might citrus flavonoids play a protective role? Molecules 2016; 21.
[22] Nam KN, Park YM, Jung HJ, Lee JY, Min BD, Park SU, Jung WS, Cho KH, Park JH, Kang I, Hong JW. Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells. Eur J Pharmacol 2010; 648: 110-6.
[23] Soeda S, Ochiai T, Paopong L, Tanaka H, Shoyama Y, Shimeno H. Crocin suppresses tumor necrosis factor-α-induced cell death of neuronally differentiated PC-12 cells. Life Sci 2001; 69: 2887-98.
[24] Lv B, Huo F, Zhu Z, Xu Z, Dang X, Chen T, Zhang T, Yang X. Crocin upregulates CX3CR1 expression by suppressing NF-κB/YY1 signaling and inhibiting lipopolysaccharide-induced microglial activation. Neurochem Res 2016; 41: 1949-57.
[25] Gao Y, Zhuang Z, Gao S, Li X, Zhang Z, Ye Z, Li L, Tang C, Zhou M, Han X, Li J. Tetrahydrocurcumin reduces oxidative stress-induced apoptosis via the mitochondrial apoptotic pathway by modulating autophagy in rats after traumatic brain injury. Am J Transl Res 2017; 9: 887-899.
[26] Chen W, Guo Y, Yang W, Zheng P, Zeng J, Tong W. Connexin40 correlated with oxidative stress in brains of traumatic brain injury rats. Restor Neurol Neurosci 2017; 35: 217-224.
[27] Naghibi T, Mohajeri M, Dobakhti F. Inflammation and outcome in traumatic brain injury: does gender effect on survival and prognosis. J Clin Diagn Res 2017; 11: PC06-PC09.
[28] Bramlett HM, Dietrich WD. Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. J Cereb Blood Flow Metab 2004; 24: 133-50.
[29] Zhao S, Gao X, Dong W, Chen J. The role of 7, 8-dihydroxyflavone in preventing dendrite degeneration in cortex after moderate traumatic brain injury. Mol Neurobiol 2016; 53: 1884-95.
[30] 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.
[31] Vakili A, Einali MR, Bandegi AR. Protective Effect of crocin against cerebral ischemia in a dose-dependent manner in a rat model of ischemic stroke. J Stroke Cerebrovasc Dis 2014; 23: 106-13.

[32] Boskabady MH, karimi GR, Samarghandian S, Farkhondeh T. Tracheal responsiveness to methacholine and ovalbumin, and lung inflammation in guinea pig exposed to inhaled lead after sensitization. Ecotoxicol Environ Saf 2012; 86: 233-8.
[33] Oruc S, Gönül Y, Tunay K, Oruc OA, Bozkurt MF, Karavelioğlu E, Bağcıoğlu E, Coşkun KS, Celik S. The antioxidant and antiapoptotic effects of crocin pretreatment on global cerebral ischemia reperfusion injury induced by four vessels occlusion in rats. Life Sci 2016; 154: 79-86.
[34] Zhang X, Fan Z, Jin T. Crocin protects against cerebral-ischemia-induced damage in aged rats through maintaining the integrity of blood-brain barrier. Restor Neurol Neurosci 2017; 35: 65-75.
[35] Rubin M. Overview of spinal cord disorders. Merck Manuel, Retrieved, October 2014.
[36] Sabapathy V, Tharion G, Kumar S. Cell therapy augments functional recovery subsequent to spinal cord injury under experimental conditions. Stem Cells Int 2015; 2015: 132172.
[37] Budson AE, Price BH. Memory dysfunction in clinical practice. Discov Med 2009; 5: 135-41.
[38] Bahraini NH, Monteith LL, Gerber HR, Forster JE, Hostetter TA, Brenner LA. The association between posttraumatic stress disorder and perceptions of deployment-related injury in veterans with and without mild traumatic brain injuy. J Head Trauma Rehabil 2017; [Epub ahead of print].
[39] Jacobs M, Hart EP, Roos RAC. Driving with a neurodegenerative disorder: an overview of the current literature. J Neurol 2017; 264: 1678-96.
[40] Abe K, Saito H. Effects of saffron extract and its constituent crocin on learning behaviour and long-term potentiation. Phyto Res 2000; 14: 149-52.
[41] Pitsikas N, Sakellaridis N. Crocus sativus L. extracts antagonize memory impairments in different behavioural tasks in the rat. Behav Brain Res 2006; 173: 112-5.
[42] Samarghandian S, Shoshtari ME, Sarolzaei J. Hossinimoghadam H, Farahzad JA. Anti-tumor activity of safranal against neuroblastoma cells. Pharmacogn Mag 2014; 10: S419-24.
[43] 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.
[44] 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: 426-33.
[45] Ringman JM, Monsell S, Ng DW, Zhou Y, Nguyen A, Coppola G, Van Berlo V, Mendez MF, Tung S, Weintraub S, Mesulam MM. Neuropathology of autosomal dominant Alzheimer disease in the national alzheimer coordinating center database. J Neuropathol Exp Neurol 2016; 75: 284-90.
[46] Shahidi S, Zargooshnia S, Asl SS, Komaki A, Sarihi A. Influence of N-acetyl cysteine on beta-amyloid-induced Alzheimer's disease in a rat model: a behavioral and electrophysiological study. Brain Res Bull 2017; 131: 142-149.
[47] 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.
[48] 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: 537-42.
[49] Rashedinia M, Lari P, Abnous K, Hosseinzadeh H. Protective effect of crocin on acrolein-induced tau phosphorylation in the rat brain. Acta Neurobiol Exp 2015; 75: 208-19.
[50] Asadi F, Jamshidi AH, Khodagholi F, Yans A, Azimi L, Faizi M, Vali L, Abdollahi M, Ghahremani MH, Sharifzadeh M. Reversal effects of crocin on amyloid β-induced memory deficit: modification of autophagy or apoptosis markers. Pharmacol Biochem Behav 2015; 139: 47-58.
[51] Batarseh YS, Bharate SS, Kumar V, Kumar A, Vishwakarma RA, Bharate SB, Kaddoumi A. Crocus sativus extract tighten the blood-brain barrier, reduces amyloid-β load and related toxicity in 5XFAD mice. ACS Chem Neurosci 2017; 8: 1756-66.
[52] Cavaliere F, Cerf L, Dehay B, Ramos-Gonzalez P, De Giorgi F, Bourdenx M, Bessede A, Obeso JA, Matute C, Ichas F, Bezard E. In vitro α-synuclein neurotoxicity and spreading among neurons and astrocytes using Lewy body extracts from Parkinson disease brains. Neurobiol Dis 2017; 103: 101-12.
[53] Ryu YK, Kang Y, Go J, Park HY, Noh JR, Kim YH, Hwang JH, Choi DH, Han SS, Oh WK, Lee CH. Humulus japonicus prevents dopaminergic neuron death in 6-hydroxydopamine-induced models of Parkinson's disease. J Med Food 2017; 20: 116-23.
[54] Csencsits-Smith K, Suescun J, Li K, Luo S, Bick DL, Schiess M. Serum lymphocyte-associated cytokine concentrations change more rapidly over time in multiple system atrophy compared to parkinson disease. Neuroimmunomodulation 2016; 23: 301-8.

[55] Xu T, Wang S, Lalchandani RR, Ding JB. Motor learning in animal models of Parkinson's disease: aberrant synaptic plasticity in the motor cortex. Mov Disord 2017; 32: 487-97.
[56] Zhang GF, Zhang Y, Zhao G. Crocin protects PC12 cells against MPP+-induced injury through inhibition of mitochondrial dysfunction and ER stress. Neurochem Int 2015; 89: 101-10.
[57] Rao SV, Yenisetti SC, Rajini PS. Evidence of neuroprotective effects of saffron and crocin in a drosophila model of parkinsonism. Neurotoxicology 2016; 52: 230-42.
[58] 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: 723-9.
[59] Fisher RS, Boas WV, Blume W, Elger C, Genton P, Lee P, Engel J. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005; 46: 470-2.
[60] Rawling GH, Jamnadas-Khoda J, Broadhurst M, Grünewald RA, Howell SJ, Koepp M, Parry SW, Sisodiya SM, Walker MC, Reuber M. Panic symptoms in transient loss of consciousness: frequency and diagnostic value in psychogenic nonepileptic seizures, epilepsy and syncope. Seizure 2017; 48: 22-7.
[61] Feng M, He Z, Liu B, Li Z, Tao G, Wu D, Xiang H. Consciousness loss during epileptogenesis: implication for VLPO-PnO circuits. Int J Physiol Pathophysiol Pharmacol 2017; 9: 1-7.
[62] Landwehr R, Liszka R. Acute symptomatic seizures in geriatric patients with multiple risk factors-a diagnostic challenge. Curr Aging Sci 2017; 10: 263-9.
[63] Shariff EM, AlKhamis FA. New onset epilepsy in the elderly: clinical, radiological and electroencephalographic features and treatment responses. Neurosciences (Riyadh) 2017; 22: 102-6.
[64] Tamaddonfard E, Gooshchi NH, Seiednejad-Yamchi S. Central effect of crocin on penicillin-induced epileptiform activity in rats. Pharmacol Rep 2012; 64: 94-101.
[65] Wang X, Tang O, Ye Y, Zheng M, Hu J, Chen Z, Zhong K. Effects of crocin on hippocampus rapid kindling epilepsy in mice. Zhejiang Da Xue Xue Bao Yi Xue Ban 2017; 46: 7-14.
[66] Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353: 1209-23.
[67] 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: 717-26.