Review Article

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

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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 crocin 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 underlying 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 (C₄₄H₆₄O₂₄) is a collective term of a series of hydrophilic carotenoids that are either monoglycosyl or diglycosyl polyene esters of crocetin [7]. α-Crocin (crocetin digentiobiose 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-
Crocin on neurodegenerative diseases

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

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crocin Rat</td>
<td>Protected neurons against chronic stress damages via reducing MDA level as well as elevating the levels of GPx, GR, SOD and total antioxidant capacity</td>
<td>[11]</td>
</tr>
<tr>
<td>PC-12 cell</td>
<td>Protected PC-12 cell against oxidative stress induced by deprived from serum/glucose against via preventing membrane lipid peroxidation</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>Protected PC-12 cell against ischemic stress-induced neural cell death via increasing GSH content and blocking the activation of JNK pathways</td>
<td>[13]</td>
</tr>
<tr>
<td>PC-12 cell</td>
<td>Protected PC-12 cell against ischemic stress-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</td>
<td>[14]</td>
</tr>
<tr>
<td>Rat</td>
<td>Protected hippocampus against chronic stress induced learning and memory loss by modulating oxidative stress</td>
<td>[15]</td>
</tr>
<tr>
<td>Cultured rat</td>
<td>Protected brain against acute swimming exercise induced oxidative stress by enhancing antioxidant activity and decreasing the levels of X0 and MDA</td>
<td>[16]</td>
</tr>
<tr>
<td>microglial cells</td>
<td>Protected microglial cells against LPS-induced neuroinflammation by inhibiting NF-κB activation, the levels of NO, TNF-α, IL-1β, and ROS</td>
<td>[22]</td>
</tr>
<tr>
<td>Retinal ganglion &amp; BV2 cells</td>
<td>Protected microglial cells against TNF-α-induced neuroinflammation by blocking the expression of Bcl-2S and LICE and ameliorating the Bcl-2S mRNA expression</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>[24]</td>
</tr>
</tbody>
</table>


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 (X0) 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 that protection of crocin 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 crocin is summarized in Table 1.

Neuroinflammatory 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 lba-1) and pro-inflammatory mediators (iNOS, COX-2, IL-1), 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 bilater-
Crocin on neurodegenerative diseases

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

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crocin Mice</td>
<td>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</td>
<td>[30]</td>
</tr>
<tr>
<td>Rat</td>
<td>Prevented ischemic reperfusion injury and cerebral edema by decreasing the levels of MDA and increasing the activity of SOD and GPx in the cortex</td>
<td>[31]</td>
</tr>
<tr>
<td>Mice</td>
<td>Prevented 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</td>
<td>[32]</td>
</tr>
<tr>
<td>Rat</td>
<td>Prevented brain damage after TBI by decreasing pro-inflammatory cytokines</td>
<td>[5]</td>
</tr>
<tr>
<td>Rat</td>
<td>Prevented TBI by decreasing microglial activation, several pro-inflammatory cytokines, and cell apoptosis</td>
<td>[33]</td>
</tr>
<tr>
<td>Rat</td>
<td>Protected the BBB damage in aged rats following cerebral ischemia via enhancing NADPH oxidase and blocking the induction of MMP-2 and MMP-9</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Improved chronic pain caused by SCI by reducing as a main pain and inflammatory mediators.</td>
<td>[6]</td>
</tr>
</tbody>
</table>


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 anti diabetic 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
Crocin on neurodegenerative diseases

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

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crocin Rat</td>
<td>Ameliorated chronic cerebral hypoperfusion-induced memory deficiency by modulating antioxidant system</td>
<td>[42]</td>
</tr>
<tr>
<td>Crocin Rat</td>
<td>Prevented STZ-induced memory dysfunction by modulating oxidative stress</td>
<td>[43]</td>
</tr>
<tr>
<td>Mice</td>
<td>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</td>
<td>[44]</td>
</tr>
<tr>
<td>Rat</td>
<td>Prevented sporadic Alzheimer’s disease induced by ICV-STZ</td>
<td>[47]</td>
</tr>
<tr>
<td>Rat</td>
<td>Prevented cognitive deficiency induced by ICV-STZ via decreasing MDA as well as increasing the levels of total and GPx activity</td>
<td>[48]</td>
</tr>
<tr>
<td>Rat</td>
<td>Prevented acrolein induced AD by ameliorating MDA, Abeta and p-tau levels and MAPKs signaling pathways</td>
<td>[49]</td>
</tr>
<tr>
<td>Rat</td>
<td>Improved memory deficiency by inhibiting Aβ induced apoptosis and oxidative stress</td>
<td>[50]</td>
</tr>
<tr>
<td>Mice</td>
<td>Improved memory deficiency by increasing the expression of the Aβ degrading enzyme NEP and up-regulation of the ApoE-clearance pathway</td>
<td>[51]</td>
</tr>
<tr>
<td>In vitro</td>
<td>Improved MPP induced cell injury and apoptosis and prevented mitochondrial dysfunction induced by MPP(+) via inhibiting ER stress cytotoxicity.</td>
<td>[56]</td>
</tr>
<tr>
<td>Drosophila</td>
<td>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</td>
<td>[57]</td>
</tr>
<tr>
<td>Rat</td>
<td>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</td>
<td>[58]</td>
</tr>
</tbody>
</table>


A 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
Crocin on neurodegenerative diseases

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

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crocin Rat</td>
<td>Exhibited anticonvulsant effects induced by penicillin via ameliorating GABA (A)-benzodiazepine receptor-mediated</td>
<td>[64]</td>
</tr>
<tr>
<td>Mice</td>
<td>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</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td>Improved schizophrenia-like behavioral that induced by ketamine</td>
<td>[66]</td>
</tr>
</tbody>
</table>

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, Tamaddondarfard 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 after-discharge 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.

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