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Der Pharmacia Lettre, 2016, 8 (13):25-29
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Neuroprotective effects of *Crocus Sativus L.* and its main constituents

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ABSTRACT

Crocus sativus L. (C. sativus), commonly known as saffron, is used as a food additive, preservative and medicinal herb. It has been considered as an alternative treatment for neurodegenerative diseases. C. sativus' medicinal effects are associated to its major ingredients including crocin, crocetin and safranal. This study found that the neuroprotective effects of C. sativus and its major ingredients may be related to their antioxidant and anti-inflammation effects.

Keywords*: Crocus sativus*; crocins; crocetin; safranal; neuroprotective

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INTRODUCTION

C. sativus is the main part of the plant which used in traditional medicine for treatment of various diseases and recent biomedical finding has been focused on its therapeutic effects. Based on the traditional and modern biomedical findings, the plant and its constituents may be effective treatments for neurodegenerative disorders. The therapeutic effects of *C. sativus* stigma could be related to its main ingredients such as crocins, crocetin, picrocrocin and safranal [1].

MATERIALS AND METHODS

Online literature resources were checked using different search engines such as Medline, Pubmed, Iran medex, Scopus, and Google Scholar from 1980 to 2016 to identify articles, editorials, and reviews about the neuroprotective effects of *C. sativus* and its main constituents.

NEURODEGENERATIVE DISEASES

Medicinal herbs and their active ingredients contain bioactive substances that act through antioxidants activities [2-31]. Recently, numerous traditional medicines have been found to possess potential neuroprotective effects by scavenging ROS and detoxifying potent genotoxic oxidants, and have attracted considerable interest as potential candidates for the development of novel neuroprotective drugs [32-37]. Saffron, the dried stigmas of the flowers of saffron (Crocus sativus L., Iridaceae), is widely used in human applications and has commercial value for a long time. Greece, along with India, Iran, Spain, Azerbaijan and Morocco, is one of the principal world saffron producers [5]. It has been reported that saffron and its ingredients have hypolipidemic, anti-inflammatory, antioxidant and anticancer effects, moreover, this is applicable for the treatment of neurodegenerative diseases [5]. Neuroinflammation is associated to the activation of microglia and release of cytokines. Microglial cells acts main roles in immune and inflammatory responses in the central nervous system. α-Crocin (20 mg/kg) had protective effects against traumatic brain injury (TBI) in mice, by amelioration of neurological severity score (NSS) and brain edema, decrease in microglial activation, release of several pro-inflammatory cytokines, and decrease in cell apoptosis [38]. A neuroprotective effect of crocins was also observed by a decrease in production of TNF-α and IL-

1β in cultured rat brain microglia and inhibited LPS-induced apoptosis in organotypic hippocampal slice cultures [39]. Crocins improved locomotor function and mechanical behavior in a rat model of contused spinal cord injury via decreasing calcitonin gene-related peptide (CGRP), an important mediator of inflammation and pain [40]. Ethanolic and aqueous *C. sativus* extracts ameliorated neuropathic pain in the chronic constriction injury (CCI) model through attenuation of pro-inflammatory factors including TNF-α, IL-6 and IL-1β [41]. The neuro-protective effects of safranal and their underlying mechanism in spinal cord injury (SCI) models have been investigated. Safranal treatment decreased immunoreactivity and expression of the inflammatory cytokines TNF-α, IL-1β, and p38 MAPK, and elevated expression of IL-10 after SCI, proposing an anti-inflammatory activity. Safranal administration ameliorated edema via decreasing the expression of aquaporin-4. These results suggest that safranal improves neuronal function after SCI in rats which were associated with anti-inflammatory, anti-apoptotic, and edema-attenuating effects [42]. The anti-allodynia effect of safranal and its underlying mechanism in spinal nerve transection model of rats was also investigated [43]. Safranal improved pain sensitivity and suppressed the expression of glial activation markers (GFAP and OX-42) and inflammatory cytokines (TNF-α and IL-1β) in ipsilateral dorsal horn of lumbar enlargement post-surgery. These results showed that the anti-allodynia effect of safranal after nerve injury is due to safranal's inhibitory effect on glial activation and inflammatory cytokine generation in central nervous system [43]. Crocetin ($C_{20}H_{24}O_2$, (all-E)-2 ,6, 11, 15-tetramethyl-2, 4, 6, 8, 10, 12, 14-hexadecaheptaenedial crocetin-dial-8, 8'-diapo-ψ,ψ-carotenedial) treatment reduced LPS-stimulated production of TNF-α and IL-1β in cultured rat brain microglia and inhibited LPS-induced apoptosis in organotypic hippocampal slice cultures. This study proposed that the neuroprotective effects of crocetin may be related to reduction of inflammatory cytokines production by activated microglia [39]. The effect of ethanolic extract of *C. sativus* treatment in the experimental autoimmune encephalomyelitis (EAE) in mice was also assessed. Results indicated that saffron significantly reduced the clinical symptoms in C57BL/6 mice with EAE [44]. The plant significantly reduced leukocyte infiltration in spinal cord as compared with control mice. These results suggest that *C. sativus* is effective in the inhibition of oxidative stress and leukocyte infiltration to CNS and may be potentially useful for the treatment of multiple sclerosis (MS) [45]. The protective role of crocins in the immune and inflammatory responses was examined in rat brain microglial cells. It was reported that α-crocin decreased the effect of TNF-α on neuronally differentiated PC-12 cells and also blocked the TNF-α-induced expression of Bcl-XS and LICE mRNAs and repaired the cytokine-induced reduction of Bcl-XL mRNA expression [46]. Crocetin inhibited LPS-induced TNF-α, IL-1β, NO and ROS production as well as NF-κB activation in cultured cells. It also decreased NO production in microglia stimulated with IFN-γ and amyloid-β. This finding suggests that crocins and crocetin provide neuroprotection by decreasing the production of pro-inflammatory and neurotoxic factors from activated microglia [39]. The protective effects of *C. sativus* extract (30 mg/kg) on chronic stress-induced oxidative damage in the brain, liver and kidneys was also studied. Chronic stress has been reported to induce oxidative damage in the tissue. In the stressed animals, the plant extract (30 mg/kg) treatment caused amelioration of the increased levels of MDA, and the activities of GPx, GR, and SOD as well as the decreased total antioxidant capacity. These observations indicate that *C. sativus* may be useful against chronic stress damage via oxidative stress system modulation [47]. The effect of *C. sativus* extract in striatal synaptosomes isolated from the brain of rats against nitropropionic acid (3-NPA) has been studied. *C. sativus* extract (1 mg/kg/day, i.p.) caused neuroprotective effect by decreasing lipid peroxidation and improving mitochondrial function [48]. It was reported that the plant extract (60 mg/kg/day, for the last 6 days) ameliorated the neurotoxic effect of aluminum (Al) intake in animals. *C. sativus* extract significantly reversed Al-induced changes in MAO activity and the levels of MDA and GSH in brain. In addition, the expression of A Disintegrin and metalloprotease, AChE, P53, Bcl-2 andIL-4 and IL-12 genes was disturbed in animal exposed to $AlCl_3$. *C. sativus* aqueous extract (200 mg/kg/day) also ameliorated these damages in rat brains [49]. It was reported that the plant exerts nephroprotective effect against ceftazidime by decreasing lipid peroxidation [50]. The effects of saffron on learning and memory loss and the induction of oxidative stress in the hippocampus by chronic stress were also examined. These observations indicated that *C. sativus* ameliorated learning and memory function as well as the oxidative stress damages (increased lipid peroxidation products and decreased antioxidant enzymes levels including GPx, GRx, SOD, and total antioxidant capacity) in the rat hippocampus induced by chronic stress. The effects of *C. sativus* on learning and memory loss and the induction of oxidative stress in the hippocampus by chronic stress was investigated. Water-maze study indicated that treatment with *C. sativus* blocked the ability of chronic stress to impair spatial learning and memory retention via decreasing lipid peroxidation and increasing the activity of antioxidant enzymes in hippocampus [51]. The effects of saffron treatment on cognitive functions were examined in healthy adult and aged mice. Results indicated that *C. sativus*-treated mice significantly ameliorated learning and memory by decreased lipid peroxidation and caspase-3 activity as well as increased total brain antioxidant activity in age mice [52]. The protective activities of saffron were evaluated in diabetic encephalopathy. This study indicated that saffron at 40 and 80 mg/kg significantly increased body weight and serum TNF-α and decreased blood glucose levels, glycosylated serum proteins, and serum advanced glycation endproducts (AGEs) levels. Furthermore, significant increase in HDL and decrease ($P<0.05$) in cholesterol, triglyceride, and LDL were observed after 28 days of treatment. At the end of experiments, the hippocampus tissue was used for determination of glutathione content (GSH), superoxide dismutase (SOD), and catalase (CAT) activities. Furthermore, saffron significantly increased

GSH, SOD, and CAT but remarkably decreased cognitive deficit, serum TNF-α, and induced nitric oxide synthase (iNOS) activity in hippocampus tissue. Our findings indicated that saffron extract may reduce hyperglycemia and hyperlipidemia risk and also reduce the oxidative stress in diabetic encephalopathy rats. This study suggested that saffron extract might be a promising candidate for the improvement of chemically induced diabetes and its complications [23]. An imbalance between production of reactive oxygen species (ROS) and its elimination by antioxidant defense system in the body has been implicated for causes of aging and neurodegenerative diseases. The changes in activities of antioxidant enzymes (superoxide dismutase (SOD), glutathione-S-transferase (GST), catalase), lipid peroxidation and reduced glutathione (GSH) levels in the brain of 2, 10 and 20 month old rats after safranal treatment was evaluated. This study demonstrated that aging caused significant increase in the level of lipid peroxidation as well decrease in the GSH level and activities of SOD and GST in the brain of aging rats. The results of this study also showed that safranal ameliorated the increased lipid peroxidation level as well as decreased GSH content of the brain of 10 and 20 month old rats. In addition, safranal treatment to the 20 month old rats, which restored the SOD and GST activities. This study suggested that safranal can be effective to protect susceptible aged brain from oxidative damage by increasing antioxidant defenses [25]. One pre-clinical study demonstrated a neuroblastoma cell line to be highly sensitive to safranal-mediated growth inhibition and apoptotic cell death [17]. The effects of safranal and vitamin E on sciatic nerve function after induction of crush injuries was also investigated. The sciatic functional index (SFI) values were accelerated, cold and mechanical allodynia were ameliorated, the severities of Wallerian degeneration and muscular atrophy were suppressed, and the increased MDA level was restored to normal with safranal and vitamin E after 10 days. These results indicated that safranal ameliorated crushed-injured sciatic nerve functions via modulation of oxidative stress pathway. The comparable effects of safranal with vitamin E on oxidative stress also indicate the anti-antioxidant effect of this natural agent [53]. The protective effects of crocin on chronic stress-induced oxidative damage in the brain, liver and kidneys were assessed which has been reported to induce oxidative damage in the tissues. In the stressed animals, crocins treatment caused amelioration of the increased MDA level and the activities of GPx, GR, SOD as well as the decreased total antioxidant capacity. These observations indicate that crocins may be useful against chronic stress damages via modulating oxidative stress system [47]. Ochiai *et al*. stated that treatment of PC-12 cells deprived from serum/glucose with 10 μM α-crocin and α-tocopherol blocked cell membrane lipid peroxidation and recovered intracellular SOD activity [54]. Crocins acts more effectively than α-tocopherol at the same concentration. According to studies conducted by Ochiai *et al*. and Soeda *et al*. crocin was effective against ischemic stress-induced neural cell death by increasing GSH levels and blocking the activation of c-Jun NH2-terminal kinases (JNK) pathways [46, 54]. The neuroprotective effects of crocin against acrolein-induced toxicity were examined. The finding suggested that exposure to acrolein triggers oxidative stress system which mediated brain aging and neurodegenerative disorders such as Alzheimer's disease (AD). Moreover, this study indicated that administration of crocin significantly attenuated decreased the concentration of glutathione (GSH) and increased levels of malondialdehyde (MDA), amyloid-β (Aβ) and phospho-tau in the brain. According to these data, crocins may be considered as a therapeutic agent for neurodegenerative disorders because of its antioxidant effect [55]. The effect of crocins (total crocins was extracted from saffron stigmas using crystallization method) on neurotoxic agent and acrylamide (ACR), was studied using PC12 cells. Pretreatment of cells with 10–50 μM crocins significantly decreased ACR cytotoxicity in a dose-dependent manner. Crocin inhibited down-regulation of Bcl-2, the up-regulation of Bax and reduced apoptosis in treated cells. Results indicated that crocins also inhibited ACR neurotoxicity by decreasing ROS generation in the exposed cells [56]. Ghadrdoost *et al.* indicated that α-crocin ameliorated learning and memory loss and the induction of oxidative stress in the hippocampus by chronic stress [51]. Papandreou *et al.* indicated that crocetin protected human neuroblastoma cells viability against H_2O_2 through decreasing ROS production and caspase-3 activation [52]. The neuroprotective effects of combination of certain natural antioxidants, *Nardosatchys jatamansi* (N), crocetin and selenium (Se), were investigated against STZ-induced cognitive impairment in rats. Behavioral functions, markers of oxidative stress and antioxidant enzymatic as well as non-enzymatic defense systems were ameliorated in animals pretreated with the combination of antioxidants [57-59].

CONCLUSION

This review proposes that the neuroprotective effects of *C. sativus* and its constituents may be associated to the antioxidant and anti-inflammatory activities.

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