The Journal of Biomedical Research

Crocus sativus (Saffron): A potential multifunctional therapeutic agent for neurodegenerative disorders

Khazdair M.R.

Cite this article as:
Khazdair M.R.. *Crocus sativus* (Saffron): A potential multifunctional therapeutic agent for neurodegenerative disorders[J]. *Journal of Biomedical Research*, In press. doi: 10.7555/JBR.38.20240131

View online: https://doi.org/10.7555/JBR.38.20240131

Available online at www.jbr-pub.org.cn

Open Access at PubMed Central

Journal of Biomedical Research, 2024 38(0): 1–3

JBR

Letter to the Editor

Crocus sativus (Saffron): A potential multifunctional therapeutic agent for neurodegenerative disorders

Dear Editor,

Neurodegenerative disorders (NDDs) are age-related disorders characterized by the deposition of abnormal forms of proteins or progressive loss of neurons in the brain. NDDs are classified according to their pathophysiology properties including cognitive dysfunctions, Alzheimer's disease (AD) and other dementias, Parkinson's disease, and motor neuron disease. The increased oxidative stress and neuro-inflammatory events contribute to neuronal atrophy and death in NDDs[1]. Nitric oxide in the central nervous system has several functions, including the regulation of synaptic plasticity and neurosecretion. The physiological amount of nitric oxide is neuroprotective, whereas its higher doses are noticeably neurotoxic[2].

The nuclear factor erythroid 2-related factor 2 (NRF2), the main regulator of redox status, regulates cellular oxidative and inflammatory balance by interacting with the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[3]. In hippocampal neurons from AD brains, NRF2 is principally localized in the cytoplasm rather than in the nucleus, whereas in the normal human hippocampus, NRF2 protein is detected in both the nucleus and the cytoplasm of neurons[4].

Crocus sativus L. (Iridaceae), or saffron, is commonly cultivated in Asia and Spain and has been used as dietary spices, food additives, and for various medicinal purposes for the treatment of different diseases in Iranian traditional medicine[5]. Saffron suppresses the activation or production of a protein complex (NF-κB) that controls the transcription of DNA, cytokine production, and cell survival. Saffron and its ingredients also inhibit inflammatory enzymes, such as cyclooxygenase-2, myeloperoxidase, and inducible nitric oxide synthase, to play a critical role in the pathophysiology of diseases[6]. Saffron and its active constituents exhibit neuroprotective effects through several mechanisms, such as inhibiting amyloid-β (Aβ) aggregation and deposition in AD, protecting dopaminergic cells, modulating the cholinergic system, increasing the levels of glutathione and its dependent enzyme, and suppressing the increase in malondialdehyde (MDA), glutamate, and aspartate levels[7].

The administration of safranal, a saffron constituent, was found to significantly attenuate rotenone-induced cell death in dopaminergic neurons and markedly restore the protein expression levels of B-cell lymphoma 2-associated X protein and B-cell lymphoma 2; in addition, the pretreatment of the cells with safranal markedly decreased the expression levels of Kelch- like ECH- associated protein 1 and upregulated the expression of nuclear NRF2 that changed by rotenone[8]. These data suggest that safranal has a protective effect on rotenone-induced cell death in dopaminergic neurons.

The results of a systematic review of clinical trials (SRCT) indicated that saffron might be an antidepressant because of its serotonergic, anti-inflammatory, antioxidant, and neuroprotective effects similar to the prescribed antidepressant drugs[9]. Another systematic review and meta-analysis also showed that saffron possessed a better efficacy for improving depressive symptoms, compared with the placebo treatment, and it was as effective as synthetic antidepressants; furthermore, the incidence of adverse effects between saffron and antidepressants was not significantly different[10]. One systematic review of randomized controlled trials (RCTs) with 325 individuals showed that saffron was well-tolerated and

Received: 05 May 2024; Revised: 27 July 2024; Accepted: 05 August 2024;

CLC number: R741, Document code: B

The authors reported no conflict of interests.

significantly improved scores on the AD assessment scale-cognitive subscale (ADAS-cog) or mini-mental state examination, compared with placebo, and that these effects did not differ significantly, compared with donepezil or memantine[11].

Similarly, one systematic review and meta-analysis of RCTs also revealed that saffron significantly improved cognitive function measured by the ADAS-cog, compared with the placebo groups; furthermore, the cognitive scales such as ADAS-cog were not significantly different between saffron and conventional medicine treatment[12]. Saffron supplementation in unhealthy patients in RCTs significantly decreased MDA levels but concurrently increased the total antioxidant capacity[13]. The results of another systematic review and meta-analysis in RCTs also indicated that saffron caused a significant reduction in MDA and total oxidant status levels, while significantly increasing total antioxidant capacity and glutathione peroxidase. Moreover, the subgroup analysis indicated a significant reduction in MDA levels in those with age of < 50 years, saffron dosage of > 30 mg/day, and study duration of < 12 weeks[14]. The characteristics of the included SRCT studies are summarized in ***Table 1***.

The results of the reviewed studies have indicated that the consumption of saffron and its constituents in basic and clinical studies are capable of having significant properties on memory and cognitive deficiency through cell signaling pathways, such as the modulation of inflammatory and pro-inflammatory mediators and clearance of Aβ aggregation. Treatment with saffron significantly represents the generation of ROS, oxidative stress, and cell apoptosis in *in vitro* studies.

Results of *in vivo* studies have indicated that saffron and its constituents show neuroprotective effects through various mechanisms, such as modulating neurotransmitters, enhancing neurogenesis, reducing neuro-inflammation, regulating oxidative stress, activating the NRF2 signaling pathway, and modulating epigenetic factors[15–16]. Several clinical and preclinical studies have demonstrated the efficacy and safety of saffron and its constituents in improving cognitive function, mood, and other neurological outcomes[17–18]. Although the exact mechanisms for the neuroprotection of saffron are not explicitly known, the results of several systematic reviews or/ meta-analyses indicated that saffron showed beneficial effects on NDDs *via* different mechanisms, including cell signaling pathways, the modulation in pro-inflammatory mediators, and the inhibition of

Table 1 **Study characteristics of the included studies**

References	Location	Study population	Sample size	Number of studies	*Crocus sativus* dosage	Study duration (weeks)	Main outcome
Lopresti *et al*, 2014[9]	Iran	Depression	230	6	30 mg/day delivered in two and equal doses	6	Showing large treatment effects compared with a placebo and was as effective as the antidepressants (fluoxetine and imipramine).
Dai *et al*, 2020[10]	Iran	Depression	612	12	30 mg/day and 50 mg/day in one study	6 to 12	Saffron was effective for treating mild to moderate depression and had comparable efficacy to antidepressant drugs.
Avgerinos *et al*, 2020[11]	Iran and Greece	Cognitive function	325	5	10 to 30 mg/day	12 to 48	Showing similar efficacy in improving cognitive scores as common anti- Alzheimer's disease drugs
Ayati *et al*, 2020[12]	Iran and one in Greece	Cognitive function	203	4	30 mg per day	16 to 48	Saffron showed beneficial effects to improve cognitive function in patients with Alzheimer's disease and mild cognitive impairment.
Morvaridzadeh *et al*, 2021[13]	Iran	Oxidative stress parameters	651	10	30 and 100 mg/day and 1,000 mg/day in one study	4 to 12	Saffron intake significantly decreased malondialdehyde levels, while significantly increased total antioxidant capacity. Saffron showed beneficial properties in improving OS in unhealthy patients.
Abedi *et al*, 2023[14]	Iran	Oxidative stress parameters	468	16	30 to 100 mg/day	4 to 12	Saffron and its active ingredients were able to establish a balance of oxidants/antioxidants in various disease conditions in trial studies.

oxidative events. Thus, regarding the safety and efficacy of saffron as a food additive, it may be considered a complementary therapy for reducing or treating NDDs.

Yours Sincerely,
M.R. Khazdair✉

Pharmaceutical Science and Clinical Physiology, Cardiovascular Diseases Research Center,
Birjand University of Medical Sciences,
Birjand 9717853111,
Iran.
✉Corresponding authors: M.R. Khazdair, E-mail: M.khazdair@yahoo.com.

References

[1] Kovacs GG. Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine[J]. *Int J Mol Sci*, 2016, 17(2): 189.

[2] Calabrese V, Mancuso C, Calvani M, et al. Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity[J]. *Nat Rev Neurosci*, 2007, 8(10): 766–775.

[3] Yang T, Zhang F. Targeting transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) for the intervention of vascular cognitive impairment and dementia[J]. *Arterioscler Thromb Vasc Biol*, 2021, 41(1): 97–116.

[4] Kang TC. Nuclear factor-erythroid 2-related factor 2 (Nrf2) and mitochondrial dynamics/mitophagy in neurological diseases[J]. *Antioxidants*, 2020, 9(7): 617.

[5] Hosseinzadeh H, Nassiri - Asl M. Avicenna's (Ibn Sina) the canon of medicine and saffron (*Crocus sativus*): a review[J]. *Phytother Res*, 2013, 27(4): 475–483.

[6] Khazdair MR, Gholamnezhad Z, Rezaee R, et al. A qualitative and quantitative comparison of *Crocus sativus* and *Nigella sativa* immunomodulatory effects[J]. *Biomed Pharmacother*, 2021, 140: 111774.

[7] Butnariu M, Quispe C, Herrera-Bravo J, et al. The pharmacological activities of *Crocus sativus* L. : a review based on the mechanisms and therapeutic opportunities of its phytoconstituents[J]. *Oxid Med Cell Longev*, 2022, 2022: 8214821.

[8] Pan P, Qiao L, Wen X. Safranal prevents rotenone-induced oxidative stress and apoptosis in an in vitro model of Parkinson's disease through regulating Keap1/Nrf2 signaling pathway[J]. *Cell Mol Biol*, 2016, 62(14): 11–17.

[9] Lopresti AL, Drummond PD. Saffron (*Crocus sativus*) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action[J]. *Human Psychopharmacol*, 2014, 29(6): 517–527.

[10] Dai L, Chen L, Wang W. Safety and efficacy of saffron (*Crocus sativus* L.) for treating mild to moderate depression: a systematic review and meta-analysis[J]. *J Nerv Ment Dis*, 2020, 208(4): 269–276.

[11] Avgerinos KI, Vrysis C, Chaitidis N, et al. Effects of saffron (*Crocus sativus* L.) on cognitive function. A systematic review of RCTs[J]. *Neurol Sci*, 2020, 41(10): 2747–2754.

[12] Ayati Z, Yang G, Ayati MH, et al. Saffron for mild cognitive impairment and dementia: a systematic review and meta-analysis of randomised clinical trials[J]. *BMC Complement Med Ther*, 2020, 20(1): 333.

[13] Morvaridzadeh M, Agah S, Dulce Estêvão M, et al. Effect of saffron supplementation on oxidative stress parameters: a systematic review and meta - analysis of randomized placebo - controlled trials[J]. *Food Sci Nutr*, 2021, 9(10): 5809–5819.

[14] Abedi A, Ghobadi H, Sharghi A, et al. Effect of saffron supplementation on oxidative stress markers (MDA, TAC, TOS, GPx, SOD, and pro-oxidant/antioxidant balance): an updated systematic review and meta-analysis of randomized placebo-controlled trials[J]. *Front Med (Lausanne)*, 2023, 10: 1071514.

[15] Maggi MA, Bisti S, Picco C. Saffron: chemical composition and neuroprotective activity[J]. *Molecules*, 2020, 25(23): 5618.

[16] Cerdá-Bernad D, Costa L, Serra AT, et al. Saffron against neuro-cognitive disorders: an overview of its main bioactive compounds, their metabolic fate and potential mechanisms of neurological protection[J]. *Nutrients*, 2022, 14(24): 5368.

[17] Jackson PA, Forster J, Khan J, et al. Effects of saffron extract supplementation on mood, well-being, and response to a psychosocial stressor in healthy adults: a randomized, double-blind, parallel group, clinical trial[J]. *Front Nutr*, 2021, 7: 606124.

[18] Khazdair MR, Boskabady MH, Hosseini M, et al. The effects of *Crocus sativus* (saffron) and its constituents on nervous system: a review[J]. *Avicenna J Phytomed*, 2015, 5(5): 376–391.