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A REVIEW ON NEUROPROTECTIVE POTENCY OF CROCUS SATIVUM L FOR ALZHEIMER'S DISEASE

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Abstract

Regarding cognitive impairment in people suffering from Alzheimer's disease (AD), crocus sativus L., or saffron, appears to have neuroprotective properties. Reviewing the data and mechanisms underlying saffron-induced therapeutic advantages and quantifiable cognitive gains in AD is the aim of this investigation. Preclinical and clinical trials were found after a review of the literature. The following criteria were used to choose preclinical in vitro and in vivo studies: 1) establishing a pharmacological profile for saffron based on biological or biophysical endpoints; 2) assessing the effectiveness of saffron using animal screens as an AD model; and 3) keeping the trials open for a minimum of three months. The patient's age was one of the selection criteria for the clinical research.3) suitable methods to evaluate cognitive, functional, and clinical state; and 4) a diagnosis of AD based on the National Institute on Aging-Alzheimer's Association (NIAAA) criteria. During an initial phase, a total of 1477 studies published up until November 2020 were discovered, 24 of which satisfied the inclusion criteria and were chosen for this review.

Keywords: Saffron; airway inflammation; smooth muscle relaxant effect.

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Introduction

Worldwide, Alzheimer's disease (AD) is the major prevalent neurodegenerative disease related to aging, accounting for 60-70% of overall dementia cases (1). Currently, the available treatments for AD are only supportive, namely the following four: memantine (a glutamate receptor antagonist), which are acetylcholinesterase inhibitors. These drugs seem to provide a limited symptomatic improvement in the cognitive impairment and neuropsychiatric symptoms linked to AD, but none of them can provide a real disease modifying effect.AD symptomatic changes are associated with reduced acetylcholine production, excessive glutamate release (2), deposition of extracellular amyloid-β (Aβ) peptide as plaques in brain tissue and blood vessels neurofibrillary tangles (intracellular aggregation of hyperphosphorylated tau protein). Considering that the chemical components can vary according to the environmental conditions in the country of origin, Safran's chemical composition is made of around 63% sugars (comprising starch, gums, reducing sugars, dextrin's, pectin, and pentosans), 12% protein, 10% moisture, 5% crude fiber, 5% minerals, 5% fat (3) and traces of riboflavin and thiamine vitamins .Saffron's sensory profile (colour, aroma, and taste) and its health promoting properties mainly come from its major bioactive compounds, which are the following: 1) crocin (mono-glycosyl/di-glycosyl polyene esters), 2) crocetin (carotenoid dicarboxylic acid precursor of crocin), 3) safranin (product of the carotenoid zeaxanthin degradation) and 4) picrocrocin.

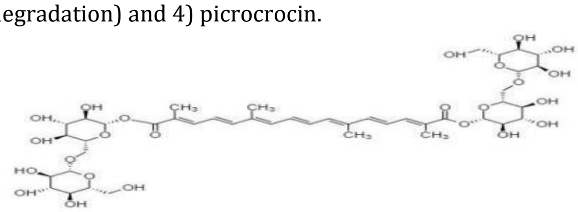
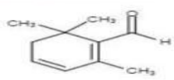


Fig. (1a). Chemical structures of crocin.

Fig. (1b). Chemical structures of crocetin.



Numerous studies have considered saffron for its anticancer (4) and anti-atherosclerosis properties. It prevents gastric ulcers, and insulin resistance and enhances digestion. Saffron also produces anti-oxidative, anti-inflammatory, anti-convulsion, anti-nociceptive, anti-depressive and anxiolytic effects. In addition to these properties, saffron has neuroprotective effects all the studies have shown that it slightly enhances cognitive function in patients with AD .The purpose of this study was to review evidence and mechanisms through which Crocus sativus L. (saffron)

Phytochemical Properties of Saffron:

The important chemical constituents present in saffron are crocin (a coloring pigment), picrocrocin (a unique flavour), safranin Crocin and crocetin, as well as the monoterpene aldehyde safranin, are carotenoids found in saffron. The bioactive substances known as carotenoids have a strong antioxidant capability (5). The most popular scientific methods for the determination of active principle include HPLC, UV-visible spectroscopy, ionization-mass spectrometry, and FT-NIR.

The oxidative stress degree is considered a risk factor for AD progression, whichis characterized by brain cell death and synaptic activity loss. It is generally thought that streptococci (STZ)-induced neurotoxicity does not contribute to changes in functional NMDA response and is associated with free radical generation causing cognitive impairment (6). A study has demonstrated that the treatment with crocin (30 mg/kg) for 3 weeks significantly improved cognitive impairment caused by intracerebroventricular injection of STZ, which induced a model of sporadic AD in male rats.

In a more recent study, the neuroprotective effects of crocin against AD were investigated in l-glutamate (L-Glu)- induced HT22 apoptotic cells and in aluminium trichloride ($AlCl3$) and d-galactose (d-gal)-induced AD mice, from which three fundamental results emerge:

- crocin substantially improved the cognition and memory abilities of the mice as measured by their coordination of movement in an open field test and Reduced their escape time in the Morris water maze test compared with untreated mice;
- moreover, the biochemical analysis confirmed that crocin was able to reduce the Aβ1-42 content in the mouse brains, increase the levels of glutathione peroxidase, superoxide dismutase, acetylcholine, and choline acetyltransferase,and reduce the levels of ROS and acetylcholinesterase in the serum, cerebral cortex, and hypothalamus compared with untreated mice(6);

safranal (the deglycosylase version of picrocrocin and is the main active principle of the stigmas). (9) Crocin and crocetin, as well as the monoterpene aldehyde safranal,are carotenoids found in saffron. The bioactive substances known as carotenoids havea strong antioxidant capability. The most popular scientific methods for the determination of active principle include HPLC, UV-visible

Medicinal properties of C. Sativus

C. Sativus is used to treat cognitive difficulties in conventional Persian medication. C. Sativus components are nowadays widely used to treat various neurological illnesses and to relax smooth muscle. C. Sativus has efficacy in treating mild to moderate depression. Crocus sativus contains a major active constituent crocin and it has strongantioxidant properties via lowering MDA levels. Crocus sativus extract (100 mg/kg) lowered glutamate and aspartate concentrations, as well as ATPase and SOD, catalase activity produced by ischemia. The extract of Crocus Sativum at about 200 mg/kg and honey syrup administration decreased aluminium chloride-induced neurotoxicity. For six weeks, saffron extract (30 mg/day) was equally showing the same result as fluoxetine and imipramine (100 mg/ day) mild-to-moderate depression treatment. Clinical Studies

A successive double-blind placebo-controlled study was realized with 46 mild-
tomoderate AD patients (9) who were casually allocated to take a capsule of saffron 30 mg/- day (15 mg twice a day) or a capsule of placebo (two capsules a day) for 16 weeks. The results of this study indicated that saffron produces a significant improvement in cognitive performance

Bioactive Principles of Saffron

There are several bioactive constituents present in Crocus Sativum, including Nitrogenous matter, flavonoids, anthocyanins, vitamins, raw fibers, gums, volatile oil, proteins, glycosides, amino acids, carbs, minerals, monoterpenes, and aldehydes the primary components of saffron.(9) The primary bioactive components are also thought to be picrocrocin (which gives apocarotenoids their bitter taste), crocetin, crocin (which gives them their color), and safranal (which gives them their flavor and perfume). High-quality saffron contains 2.5% volatile compounds, including safranal, and about 30% crocins, 5 to 15% picrocrocin, etc.

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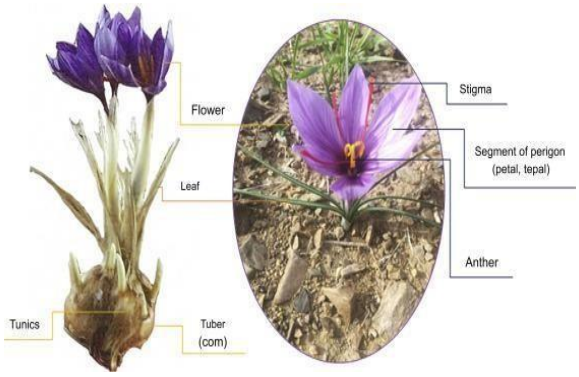

day) mild-to-moderatedepression treatment. (5)

Figure no: 1Antioxidant activities of bioactive compounds and various extracts obtained from saffron

Biological and Pharmaceutical Aspects of Saffron

Saffron and other active chemical constituents associated with neuroprotective properties against neurogenerative disorders include Parkinson's, anticonvulsant, antidepressant, anxiolytic, anti- schizophrenia, antioxidant, antitussive, hypolipidemic, Alzheimer's, and antiischemic (heart,
muscle, renal, and brain ischemia); hypolipidemic (3)

- there is no proper available treatment for AD, but one medication may help to delay clinical degeneration and improve cognition function.
- AD symptoms such as memory loss and confusion can be alleviated.
- In the US, the FDA has approved pharmaceuticals in two ways:
- drugs that may help people with Alzheimer's disease see a gradual clinical decline and treatments that may temporarily relieve some of the illness's related symptoms.
- Before initiating any treatment, it is necessary to consult with a healthcare professional to determine its relevance.
- To ensure that the necessary guidelines are carefully followed,
- patients who use these medications must continuously consult with a physician.
- The major components of Crocus sativus stigma are the apocarotenoids like, picrocrocin (responsible for bitter taste), crocin, crocetin (responsible for bright natural color), and the odor-active safran.

Phytochemistry, pharmacology, and potential clinical applications of saffron: A Morethan 150 chemical compounds, including carotenoids, flavonoids and flavonoid glycosides, monoterpenes and monoterpenoid derivatives, monocyclic aromatic hydrocarbons, amino acids,alkaloids and others, were revealed (11).

The pharmacological activities study of saffron were focused on the antioxidant, anti-inflammatory, antitumor, antidepressant, hypoglycemic, hypolipidemic, memory-enhancing, and so on. Currently, saffron is mainly used for the treatment of diabetes, Alzheimer's disease, depression, anxiety disorders, cardiovascular diseases, learning and memory disorders, cancer, and other conditions.

Saffron, the dried stigma of the perennial herb *Crocus sativus* L. (Iridaceae), is one of the most expensive spices in the world(14). It is mainly distributed in Iran, China, Spain, Morocco, Italy, Greece, and India (Tong et al., 2015). Because of its unique color and odor, saffron is used as a coloring and flavoring agent in foods and cosmetics In China, saffron is also used as a herb medicine (Li et al., 2018), it has been included in the Chinese Pharmacopeia since 1985 (Board of Pharmacopeia of the People's Republic of China, 1985), under the Chinese name "Xinghua", "Zanghonghua" or "Fanhonghua". Using saffron in Traditional Chinese medicine has shown effects in promoting blood circulation and suppressing blood stasis, cooling blood detoxification, and relieving depression (Board of Pharmacopeia of the People's Republic of China, 2020). Along with these effects, it is mainly used to treat irregular menstruation, postpartum thrombosis, and bruises (15).

Carotenoids

Carotenoids are a class of important natural pigments that are ubiquitous in red, orange-red, or yellow pigments of higher plants, algae, fungi, and animals. Saffron is a well-known colorant in food owing to its high content of carotenoids. The carotenoids in saffron exhibit various bioactivities, such as antioxidant, anti-inflammatory, and immunomodulatory activities Notably, crocetin, crocin, and picrocrocin exhibit cardiac protective(14)

Antioxidant activity

Antioxidants effectively inhibit free radical oxidation and can potentially prevent cancer, aging, and other diseases. Many researchers have revealed the antioxidant properties of the extracts and secondary metabolites of saffron. Methanolic extract of saffron exhibits high antioxidant activity, and crocin, picrocrocin, and safranal in saffron exhibitradical scavenging activity (15).

Type 2 diabetes

Diabetes is a metabolic disease characterized by high blood sugar, which can lead to chronic damageto the heart, blood vessels, and nerves. Studies have shown that saffron may alleviate diabetes and reduce diabetic complications. Clinical studies have found that saffron can significantly reduce waist circumference and fasting plasma glucose levels (Rahmani et al., 2020). saffron intake may protect the myocardium from injuries. Saffron water extracts (1:10 g/ml) _ combined with aerobic.

Toxicity assessment

While the medicinal properties of saffron have been extensively studied, very few toxicity studies of saffron conducted to date. Literature reports include a subchronic study, where ethanolic extracts of saffron did not produce significant changes in liver and kidney functions in rats after continuous oral administration at a dose of 0.5 g/kg b.wt for eight weeks(14). When the ethanolic extracts were orally administered at doses up to 5 g/kg b.wt, no death or signs of toxicity were observed in mice

Medicines that could impede the progression of Alzheimer's

These medications may help people with AD by halting clinical deterioration and enhancing cognition and function. Aducanumab received expedited FDA approval on June 7, 2021. FDA-Approved Drug Products: Aduhelm I.V. injection (aducanumab-ava) As a treatment for Alzheimer's disease, the anti-amyloid antibody(16).

Diction for Alzheimer's disease

The following drugs are now used to treat AD. Acetylcholinesterase inhibitors include Rivastigmine, Donepezil, Galantamine, and Tacrine. Memantine functions as an NMDAantagonist (glutamate inhibitor).

Acetylcholinesterase inhibitors

FDA-approved drugs are Donepezil and rivastigmine for the treatment of mild, moderate, and severe Alzheimer's disease respectively. Galantamine is also FDA approved drug only for mildand moderate Alzheimer's disease. Anti-inflammatory properties of drugs from saffron crocus

The medicinal uses of saffron (Crocus sativus Linnaeus) have a long history beginning in Asian countries since the Late Bronze Age. Recent studies have validated its potential to lower the risk of several diseases (18). Some metabolites derived from saffron stigmas exert numerous therapeutic effects due to hypolipidemic, antitussive, antioxidant, antidiabetic activities, and many others.

Conclusion

Numerous active clinical trials are centered around a wide range of treatment targets for AD. Identifying a single primary goal and creating innovative trial designs are crucial, as we currently know that AD drug clinical studies have a high failure rate (19). The majority of ongoing studies are generally supported by the convergence of advances in AD biomarkers. Additionally, the focus of contemporary research is on creating more accurate diagnostic instruments and investigating disease prevention strategies (20). Planning is required for innovative healthcare, in addition to appropriate pharmaceutical care. considerably improve the strategy for treating Alzheimer's disease. This would be achieved by employing comprehensive behavioral, psychoeducational, and psychoeducational approaches to build a strong therapeutic bond between the patient and medical staff.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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