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Saffron as a potential therapeutic agent for memory impairments

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ABSTRACT

Memory impairment, associated with aging and neurodegenerative disorders, poses a significant global health challenge. Saffron (*Crocus sativus* L.) and its bioactive constituents have garnered attention for their potential neuroprotective and cognitive-enhancing properties. This narrative review aims to examine the current evidence on the neuroprotective mechanisms of saffron in memory enhancement, critically distinguishing between preclinical and clinical findings, and evaluating the translational potential of saffron for memory impairments. A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar up to August 2026. Search terms included combinations of "saffron," "Crocus sativus," "crocin," "safranal," "crocetin," "memory," "cognition," "neuroprotection," and "Alzheimer's disease." Studies were included if they investigated the effects of saffron or its active constituents on cognitive functions and underlying molecular mechanisms in in vitro, animal, or human models. Preclinical evidence robustly demonstrates that saffron and its active compounds exert significant neuroprotective effects through multiple interrelated mechanisms, including scavenging reactive oxygen species, suppressing pro-inflammatory cytokines (e.g., TNF-α, IL-1β), upregulating BDNF, modulating apoptotic proteins (Bcl-2/Bax), and regulating key neurotransmitters (serotonin, dopamine, glutamate). However, the clinical evidence, while promising, remains limited, heterogeneous, and largely devoid of mechanistic validation. Human trials suggest potential benefits on cognitive scores, but these are not yet conclusive. Saffron demonstrates substantial mechanistic plausibility for memory enhancement derived from preclinical models. However, direct extrapolation to humans requires caution. Further rigorously designed clinical trials with standardized formulations and long-term safety assessments are imperative to translate these mechanistic insights into clinical practice.

Keywords: Saffron, *Crocus sativus*, Memory impairment, Neuroprotection, Oxidative stress, Clinical trial.

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Introduction

Saffron, scientifically known as Crocus sativus, is a highly prized and aromatic spice derived from the flower of the saffron crocus plant (Nassiri-Asl & Hosseinzadeh, 2015). Due to its unique composition of bioactive compounds, saffron has been extensively studied for its potential health benefits, which have shown promising effects in various areas such as neuroprotection, mood enhancement, and antioxidant properties (Ghadrdoost et al., 2011; Orio et al., 2020). The saffron crocus, native to the Mediterranean region, requires specific climatic conditions and well-drained soil to thrive (Mzabri et al., 2019). Saffron owes its unique aroma, flavor, and medicinal properties to its complex chemical composition. The main bioactive compounds in saffron include crocin, picrocrocin, and safranal. Crocin is responsible for the vibrant red color of saffron and possesses strong antioxidant properties (Khazdair et al., 2015). Picrocrocin gives saffron its distinctive taste. Safranal, a volatile compound, contributes to the characteristic aroma of saffron. These compounds, along with other essential oils and carotenoids, work synergistically to provide saffron's diverse range of health benefits. In recent years, scientific research has shed light on the potential health benefits of saffron and its bioactive components. Studies have indicated that saffron possesses antioxidant properties, protecting against oxidative stress and reducing inflammation. It has also shown promise in improving mood and combating symptoms of mild to moderate depression. Moreover, saffron has been investigated for its neuroprotective effects, with studies indicating its potential in preventing neurodegenerative disorders like Alzheimer's and Parkinson's diseases (W. Yang et al., 2023). Its active compounds have been shown to inhibit the accumulation of amyloid plaques and reduce oxidative damage in the brain, enhancing cognitive function (Baluchnejadmojarad et al., 2019). Building upon our previous work investigating the role of saffron in inflammatory pathways within the cardiovascular system (Baghcheghi et al., 2026), and our ongoing interest in elucidating the molecular mechanisms of synaptic plasticity disruption in various neurological conditions (Hedayati-Moghadam et al., 2026; Seyedi et al., 2026), the present narrative review extends this focus to systematically synthesize the neuroprotective effects of saffron on memory impairment. Specifically, this review aims to critically evaluate the available evidence with a particular emphasis on distinguishing mechanistic insights derived from preclinical (in vitro and animal) models from the limited clinical data, thereby providing a comprehensive perspective on the therapeutic potential of saffron for memory-related disorders.

Methods

This narrative review was conducted to synthesize the available evidence on the neuroprotective mechanisms of saffron in memory impairment. A systematic literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar from inception to August 2026. The search strategy employed combinations of the following keywords: ("saffron" OR "Crocus sativus" OR "crocin" OR "safranal" OR "crocetin") AND ("memory" OR "cognition" OR "learning" OR "cognitive impairment" OR "Alzheimer's disease" OR "neuroprotection"). Additional relevant studies were identified through manual screening of reference lists of included articles and previous reviews.

Studies were included if they were original research investigating the effects of saffron or its active constituents on memory, cognition, or underlying molecular mechanisms in in vitro, animal, or human models. Non-English articles, conference abstracts, case reports, and editorials were excluded. Two independent reviewers (S.S.M. and M.P.) screened titles and abstracts, followed by full-text assessment. Disagreements were resolved through consensus or consultation with a third reviewer (Y.B.). Due to the heterogeneous nature of the included studies, data were synthesized narratively with a clear distinction between preclinical and clinical evidence.

Saffron and CNS

The effects of saffron on the central nervous system (CNS) have garnered significant scientific interest (Ghaffari et al., 2015; Roustazade et al., 2022). Its active constituents appear to exert neuroprotective effects, regulate mood, enhance cognition, and potentially serve as a therapeutic intervention for neurodegenerative disorders (Ghaffari et al., 2015; Moazen-Zadeh et al., 2018; Roustazade et al., 2022). Saffron's active constituents, including crocin, crocetin, safranal, and other compounds, have been investigated for their ability to modulate various aspects of CNS function, including neuroprotection, mood regulation, cognition enhancement, and potential treatment for neurodegenerative disorders (Abe & Saito, 2000; Akhondzadeh, Sabet, et al., 2010; Moazen-Zadeh et al., 2018; Papandreou et al., 2011). Several studies have shown that saffron and its components possess antioxidant and anti-inflammatory properties that can help protect neurons from oxidative stress and inflammation-induced damage (Ghadrdoost et al., 2011; Marzabadi et al., 2022; Papandreou et al., 2011; Roustazade et al., 2022). In preclinical studies, these effects have been attributed to the modulation of various molecular pathways; however, direct evidence in humans remains limited (Akhondzadeh, Sabet, et al., 2010; Ghaffari et al., 2015; Inoue et al., 2021). Saffron has been traditionally used as a mood enhancer, and scientific studies have started to unveil its potential antidepressant properties (Lopresti & Smith, 2022). Several clinical trials have suggested that saffron extract may have comparable efficacy to certain antidepressant medications, though further confirmatory studies are needed (Ahmad, Azhar, et al., 2022; Lopresti & Smith, 2022; Shahmansouri et al., 2014). The active components of saffron, such as crocin and safranal, are believed to act on specific neurotransmitter systems in the brain, including serotonin and dopamine, which play crucial roles in regulating mood (Ettehadi et al., 2013; Monchaux De Oliveira, Pourtau, et al., 2021). Research suggests that saffron has positive effects on cognition and memory (Azmand & Rajaei, 2021; Hamdi et al., 2023; Roustazade et al., 2022). Some animal studies, and a limited number of human trials, have indicated that saffron extract may enhance learning and memory retrieval (Azmand & Rajaei, 2021; Ettehadi et al., 2013; Monchaux De Oliveira, Pourtau, et al., 2021; Roustazade et al., 2022). Saffron's anti-inflammatory or antioxidant properties may also help combat neuroinflammatory response and oxidative stress in the brain, thereby supporting healthy cognitive aging (Hamdi et al., 2023; Marzabadi et al., 2022; Roustazade et al., 2022). Given saffron's neuroprotective and antioxidant properties, it has been investigated as a potential therapeutic agent for neurodegenerative disorders (Lopresti & Drummond, 2017; Lopresti & Smith, 2022; Monchaux De Oliveira, Pourtau, et al., 2021; Roustazade et al., 2022). Preclinical studies involving animal models of Alzheimer's and Parkinson's diseases have shown promising results, indicating that saffron extract can mitigate pathological features associated with these conditions (Akhondzadeh, Sabet, et al., 2010; Hatami & Dehghan, 2015; Inoue et al., 2021). However, more extensive research, including clinical trials, is needed to establish the effectiveness of saffron as a treatment option.

Saffron and memory

Clinical studies

Clinical studies have shown promising results, suggesting that saffron supplementation may improve memory performance and cognitive abilities in healthy individuals and those facing memory impairments (Mirzaei et al., 2022; Moazen-Zadeh et al., 2018; Tsolaki et al., 2016). It has been suggested (primarily in animal models and a few human studies) that saffron may improve aspects of short- and long-term memory (Cicero et al., 2017; Pitsikas et al., 2007; Tsolaki et al., 2016). Numerous experiments have involved subjects consuming saffron extract, either as a supplement or incorporated into meals, and subsequently undergoing memory tests (Ahmad, Azhar, et al., 2022; Cicero et al., 2017; Moazen-Zadeh et al., 2018; Monchaux De Oliveira, Pourtau, et al., 2021; Pitsikas et al., 2007; Tsolaki et al., 2016). The results from several studies indicate improved memory performance in certain populations, although not all findings are consistent (Ahmad, Azhar, et al., 2022; Akhondzadeh, Shafiee Sabet, et al., 2010; Lopresti & Smith, 2022; Moghadam et al., 2021). Moreover, studies investigating saffron's impact on memory have utilized various research designs, including randomized controlled trials (RCTs), observational studies, and meta-analyses. These studies have been conducted on individuals of different age groups, ranging from young adults to the elderly, with a particular focus on individuals at risk of memory decline or those with existing memory impairments (Ahmad, Azhar, et al., 2022; Ayati et al., 2020; Moghadam et al., 2021; Shahmansouri et al., 2014). A 12-week RCT conducted on older adults with mild cognitive impairment showed significant improvements in memory tasks after saffron supplementation prescription compared to a placebo group (Mojtahedi et al., 2022). Additionally, saffron supplementation was found to enhance working memory and attention in clinical studies (Blasco-Fontecilla et al., 2022; Moazen-Zadeh et al., 2018; Pazoki et al., 2022). In this regard, a study found that saffron was reported to be effective in improving cognitive function in one 16-week trial involving patients with mild to moderate Alzheimer's disease over 16 weeks (Akhondzadeh, Sabet, et al., 2010). Moreover, another study has examined the effects of saffron supplementation in patients with amnesic and multi-domain MCI (aMCImd). These researchers observed the patients treated with Crocus had better Mini-Mental State Examination scores than the control group. They also reported that administration of Crocus result in a significant improvement in MRI, EEG, and ERP (Tsolaki et al., 2016). In addition, a psychophysical study reported beneficial effects of a saffron alcoholic extract on visual short-term memory in a small sample of healthy adults (Ghodrat et al., 2014). Furthermore, A systematic review in 2023 also analyzed several clinical trials on saffron's effects on cognitive function, including memory. The review indicated that saffron supplementation could have significant positive effects on memory performance, particularly in individuals with mild cognitive impairment or Alzheimer's disease (W. Yang et al., 2023). A systematic summary of the key clinical trials investigating the effects of saffron on cognitive outcomes is provided in Table 1.

Animal studies

Saffron has been investigated for its ability to mitigate memory deficits in animal models of neurodegenerative disorders and age-related cognitive decline (Ahmad et al., 2020; Ghadrdoost et al., 2011; Roustazade et al., 2022). Key experimental paradigms in these studies often involve behavioral assessments, such as the Morris water maze and novel object recognition tests, to evaluate spatial and recognition memory, respectively (Azmand & Rajaei, 2021; Delkhosh-Kasmaie et al., 2018; Hamdi et al., 2023). One of the most notable studies on saffron's effects on memory involved the use of rats (Azmand & Rajaei, 2021; Delkhosh-Kasmaie et al., 2018). Researchers administered saffron extracts orally to the test subjects, subsequently assessing their performance on various memory tests. The results showed significant improvements in memory tasks in those animals, reinforcing the notion that saffron may possess memory-enhancing properties (Azmand & Rajaei, 2021; Hamdi et al., 2023; Tamaddonfard et al., 2013). In a study, the animals were given scopolamine, a drug known to induce memory impairment, and then saffron extract. The results demonstrated that saffron extract significantly improved memory and cognitive functions in the rats (Pitsikas & Sakellaridis, 2006). Moreover, another study has explored the effects of saffron extract on memory impairment induced by diabetes in rats. The saffron extract was found to enhance memory and cognitive performance (Delkhosh-Kasmaie et al., 2018). In previous studies, it was also investigated the effects of saffron on memory impairment induced by chronic cerebral hypoperfusion (CCH) in rats. CCH, characterized by reduced blood flow to the brain, often leads to cognitive dysfunction. The study found that saffron administration attenuated memory impairment induced by CCH, indicating its potential neuroprotective effects (Hosseinzadeh et al., 2012). In 2021, a study used rats with lipopolysaccharide (LPS) -induced memory impairment to assess the effects of crocin.

Table 1. Summary of clinical trials investigating the effects of saffron on cognitive function and memory

Ref.	Study Design	Population	Sample Size (Saffron/Control)	Intervention & Dosage	Duration	Cognitive Assessment Tool	Main Cognitive Outcome
(Akhondzadeh, Shafiee Sabet, et al., 2010)	Randomized, double-blind, placebo-controlled trial	Mild-to-moderate Alzheimer's disease	22 / 23	Crocus sativus capsules, 30 mg/day	22 weeks	MMSE, ADAS-cog	Comparable efficacy to donepezil; significant cognitive stabilization vs. baseline
(Akhondzadeh, Sabet, et al., 2010)	Randomized, double-blind, placebo-controlled trial	Mild-to-moderate Alzheimer's disease	46 / 46	Crocus sativus capsules, 30 mg/day	16 weeks	MMSE, ADAS-cog	Significant improvement in MMSE and ADAS-cog scores compared to placebo ($p < 0.05$)
(Tsolaki et al., 2016)	Randomized, single-blind, parallel-group trial	Amnesic and multi-domain Mild Cognitive Impairment (MCI)	18 / 17	Crocus sativus capsules, 30 mg/day	12 months	MMSE, MRI, EEG, ERP	Improved MMSE scores; significant positive changes in brain activity (EEG/ERP) vs. control
(Cicero et al., 2017)	Pilot randomized, double-blind, placebo-controlled trial	Elderly with mild cognitive impairment	11 / 11	Combined nutraceutical (including saffron)	12 weeks	MMSE, TMT, Stroop test	Significant improvement in executive functions and memory performance
(Mojtahedi et al., 2022)	Randomized controlled trial	Elderly hypertensive men	16 / 16	Saffron (30 mg/day) + resistance training	12 weeks	Cognitive function tests	Significant improvement in cognitive parameters and inflammatory status
(Moazen-Zadeh et al., 2018)	Randomized, double-blind, placebo-controlled trial	Patients undergoing coronary artery bypass grafting (CABG)	42 / 42	Saffron capsules, 30 mg/day	12 weeks	Beck Memory Test	Significant improvement in memory and attention compared to placebo
(Pazoki et al., 2022)	Randomized, double-blind, placebo-controlled trial (adjunctive)	Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)	25 / 25	Saffron capsules, 30 mg/day + standard treatment	6 weeks	Continuous Performance Test (CPT), behavioral tests	Significant improvement in attention and cognitive measures as an adjunctive therapy
(Ghodrat et al., 2014)	Quasi-experimental, psychophysical study	Healthy human adults	12 (crossover design)	Saffron alcoholic extract (single dose)	Single dose	Visual short-term memory task	Significant beneficial effect on visual short-term memory recall

The results revealed that crocin administration significantly improved memory and cognitive function in the rats which was via reducing oxidative damage and neuroinflammation (Azmand & Rajaei, 2021). In addition, another study investigated the effects of Safranalon memory impairment induced by amyloid β-induced Alzheimer's in rats. The results demonstrated that safranal improved memory performance and protected against amyloid β-induced memory deficits via neuronal protection and at a molecular level through amelioration of apoptosis, oxidative stress, inflammation, cholinesterase activity, neutrophil infiltration, and also by preservation of mitochondrial integrity (Baluchnejadmojarad et al., 2019).

Mechanisms of improvement of saffron on memory

Saffron as an Antioxidant: Potential Implications for Memory Improvement

Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify or counteract their harmful effects (Ahmad, Khan, et al., 2022; Azmand & Rajaei, 2021; Marzabadi et al., 2022). It has been implicated in numerous neurodegenerative disorders such as Alzheimer's, and Parkinson's diseases, and age-related cognitive decline (Ghaffari et al., 2015; Hatami & Dehghan, 2015; Marzabadi et al., 2022; Samarghandian et al., 2016). Various interventions have been explored to combat oxidative stress and its detrimental impacts on brain tissues (Ahmad, Khan, et al., 2022; Hamdi et al., 2023; Salem, Shaheen, & Borjac, 2022). Furthermore, oxidative stress and subsequent damage to brain tissues have been implicated in various memory impairments and neurodegenerative disorders (Ghaffari et al., 2015; Hatami & Dehghan, 2015; Marzabadi et al., 2022; Samarghandian et al., 2016). As a potent antioxidant, Crocus sativus has gained attention for its potential to mitigate oxidative damage in brain tissues, thus potentially improving memory function (Ahmad, Khan, et al., 2022; Azmand & Rajaei, 2021; Marzabadi et al., 2022; Salem, Shaheen, & Borjac, 2022). In several animal models, saffron supplementation has been shown to reduce oxidative stress markers and enhance antioxidant defenses; however, this evidence is predominantly preclinical (Ahmad, Khan, et al., 2022; Roustazade et al., 2022). Numerous in vitro and in vivo studies have reported the ability of saffron constituents to scavenge ROS and upregulate antioxidant enzymes in brain tissues (Azmand & Rajaei, 2021; Ghaffari et al., 2015; Ochiai et al., 2007). Saffron's antioxidant properties have been attributed to its ability to enhance the activity of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Furthermore, saffron has been shown to directly scavenge free radicals and inhibit lipid peroxidation, a process implicated in cellular membrane damage (Cerdá-Bernad et al., 2022; Salem, Shaheen, Tabbara, et al., 2022). Furthermore, in studies using memory impairment models induced by neurotoxic agents, such as amyloid beta or excitotoxic compounds, saffron supplementation has demonstrated significant antioxidant effects (Azmand & Rajaei, 2021; Baluchnejadmojarad et al., 2019). These effects were observed through the reduction of oxidative markers, including lipid peroxidation, protein oxidation, and DNA damage, as well as the restoration of antioxidant enzymes such as SOD, CAT, and GPx (Azmand & Rajaei, 2021; Baluchnejadmojarad et al., 2019; Delkhosh-Kasmaie et al., 2018). Research conducted on aged animal models also has revealed that saffron effectively attenuates the oxidative damage induced by aging in brain tissues (Samarghandian et al., 2016). The neuroprotective and antioxidant effects of saffron are believed to be attributed to its active compounds, including crocin, crocetin, and safranal. These compounds have been shown to scavenge free radicals, inhibit lipid peroxidation, and modulate multiple cellular signaling pathways involved in oxidative stress (Azmand & Rajaei, 2021; Baluchnejadmojarad et al., 2019; Delkhosh-Kasmaie et al., 2018; Nassiri-Asl & Hosseinzadeh, 2020). In addition to its antioxidant capacity, saffron has been found to possess anti-inflammatory properties, which further contribute to its neuroprotective effects against oxidative stress (Marzabadi et al., 2022; Salem, Shaheen, Tabbara, et al., 2022). Chronic inflammation has been closely associated with the progression of many neurodegenerative diseases and can amplify oxidative stress (Cerdá-Bernad et al., 2022; Salem, Shaheen, Tabbara, et al., 2022). Table 2 summarizes the effects of saffron on oxidative stress markers and antioxidant enzyme activities in various brain regions.

The Anti-Inflammatory Effects of Saffron on Memory

Saffron has also been studied for its potential effects on neuroinflammation, which refers to inflammation in the CNS (Roustazade et al., 2022; Salem, Shaheen, Tabbara, et al., 2022). Neuroinflammation is associated with various neurological disorders, including Alzheimer's, Parkinson's, and multiple sclerosis (Baluchnejadmojarad et al., 2019; Ghaffari et al., 2015; Hatami & Dehghan, 2015). Multiple studies have explored the impact of saffron and its bioactive compounds on memory impairments and neuroinflammation in various experimental models (Azmand & Rajaei, 2021; Delkhosh-Kasmaie et al., 2018; Hamdi et al., 2023; Roustazade et al., 2022). In animal and cell models, these compounds have been shown to inhibit inflammatory pathways and reduce pro inflammatory molecules; translation to human neuroinflammation remains speculative (Marzabadi et al., 2022; Roustazade et al., 2022; Salem, Shaheen, Tabbara, et al., 2022). Studies conducted on animal models and in vitro experiments have demonstrated that saffron can attenuate neuroinflammation by suppressing the activation of microglial cells, which are immune cells in the brain responsible for initiating inflammatory responses (Baluchnejadmojarad et al., 2019; Pan et al., 2016; Salem, Shaheen, Tabbara, et al., 2022; Yang et al., 2017; Zhong et al., 2020).

Table 2. Effects of saffron on the activity/abundance of antioxidant enzymes and the oxidative status in different parts of the brain

Tissue	Doses and administration	SOD	GPx	CAT	GSH	Lpx	Chl	Crb	Species	Ref.
Hippocampus	20.7 g/kg	↓	↓	↑	-	-	-	-	Rat	(Khazdair et al., 2015)
	0.1 and 0.4 mg/kg i.p	↑	-	-	-	-	-	-	Rat	(Delkhosh-Kasmaie et al., 2018)
	0.1, and 0.2 ml/kg Gavage	↑	-	-	↑	-	-	-	Rat	(Baluchnejadmojarad et al., 2019)
		↑	↑	↑	↑	-	-	-	Rat	(Samarghandian et al., 2016)
	5 µg/rat and 10 µg/rat local injection	↑	↑	-	-	-	-	-	Rat	(Ghaffari et al., 2015)
	30 mg/kg i.p	↑	↑	-	↑	-	-	-	Rat	(Ghadrdoost et al., 2011)
	40 and 80 mg/kg IP	↑	↑	-	-	-	-	-	Rat	(Mozaffari et al., 2019)
	20 and 40 m/kg i.p	-	-	-	↑	-	-	-	Rat	(Mohammadzadeh et al., 2019)
Brain	30 mg/kg i.p	-	-	-	↑	-	-	-	Mice	(Salem, Shaheen, Tabbara, et al., 2022)
Whole brain and cerebellum	60mg/kg intraperitoneally	-	-	-	↑	-	-	-	Mice	(Linardaki et al., 2012)
Pineal gland	150 mg/kg Gavage	↑	↑	-					-	-
Human embryonic kidney cells	(~1 mg/ml in water)	↑		↑					↑	↓

SOD: superoxide dismutase (no distinction is made between Cu/Zn-SOD and Mn-SOD), GPx: glutathione peroxidase. Lpx: lipid peroxidation (measured as TBARS or malondialdehyde production). Chl: chemiluminescence, Crb: carbonylated proteins, CAT: catalase, GSH: reduced glutathione, TBARS: thiobarbituric acid-reactive substances: of thiobarbituric acid reactive substances, ↓: Decrease; ↑: Increase; —: No change.

Furthermore, saffron has been found to regulate the expression of various inflammatory markers, such as cytokines such as tumor necrosis factor α (TNF-α) and Interleukin-1β (IL-1β) and inflammatory enzymes (cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) which play a crucial role in the inflammatory response (Baluchnejadmojarad et al., 2019; Dashti-r et al., 2012; Delkhosh-Kasmaie et al., 2018; Marzabadi et al., 2022; Motaghinejad et al., 2019; Pan et al., 2016; Zhang et al., 2015; Zhang et al., 2018). Different studies showed saffron and its active compounds can inhibit the production of pro-inflammatory molecules and reduce the activation of inflammatory pathways in the brain (Abbaszade-Cheragheali et al., 2023; Baluchnejadmojarad et al., 2019; Motaghinejad et al., 2019; Pan et al., 2016; Xiao et al., 2019; Zhang et al., 2018). Moreover, by reducing oxidative stress, saffron may indirectly contribute to the attenuation of neuroinflammation and improvement of memory function (Abbaszade-Cheragheali et al., 2023; Esfandiari et al., 2018; Pan et al., 2016; Salem, Shaheen, Tabbara, et al., 2022; Zhang et al., 2018). Saffron's anti-inflammatory properties are believed to be mediated through the inhibition of NF-κB and mitogen-activated protein kinase (MAPK) pathways, which are major signaling pathways implicated in neuroinflammation (Abbaszade-Cheragheali et al., 2023; Chen et al., 2023; Zhang et al., 2018). It has been shown saffron modulates the phosphoinositide 3-kinase/ protein kinase B (PI3K/Akt) and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways, which are key regulators of inflammation and cell survival (Yang et al., 2017). A summary of the effects of saffron and its active constituents on inflammatory markers in different brain regions is presented in Table 3.

Table 3. Effects of saffron on inflammation in different parts of the brain

Tissue	Doses and administration	TNF-α	NF-kB	COX2	IL-6	MDA	IL-1	iNOS	TLR4	Species	Ref.
Hippocampus	60 mg/kg intra-peritoneally	↓	-	-	-	-	-	-	-	Rat	(Roustazade et al., 2022)
	0.025, 0.1 and 0.4 mg/kg i.p.	↓	-	-	-	↓	-	-	-	Rat	(Delkhosh-Kasmaie et al., 2018)
	0.025, 0.1, and 0.2 ml/kg gavage	↓	↓	-	↓	↓	↓	-	-	Rat	(Baluchnejadmojarad et al., 2019)
		-	-	-	-	-	↓	↓	-	Rat	(Samarghandian et al., 2016)
	40 and 80 mg/kg IP	↓	-	-	-	↓	↓	-	-	Rat	(Mozaffari et al., 2019)
	20 and 40 m/kg IP	↓	-	-	↓	↓	-	-	-	Rat	(Mohammadzadeh et al., 2019)
	30 mg/kg	↓	-	-	-	↓	-	-	-	Rat	(Abbaszade-Cheragheali et al., 2023)
	40 mg/kg oral administration	-	-	-	-	-	↓	-	-	Mice	(Xiao et al., 2019)
	1–20 µM	↓	↓	-	-	-	↓	↓	-	Mice	(Zhang et al., 2018)

Spinal cord	100 mg/kg, i. p	↓	-	-	-	-	↓	-	-	Rat	(Zhang et al., 2015)
Brain	30, 100, 300 mg/kg orally	-	-	-	↓	-	↓	-	-	Rat	(Zhong et al., 2020)
	50 mg/kg intraperitoneally	↓	-	-	-	↓	-	-	-	Mice	(Salem, Shaheen, Tabbara, et al., 2022)
	variable-dose gavage	-	↓	-	-	-	↓	-	↓	Mice	(Song et al., 2022)
	30 mg/kg i.p.	-	-	-	↓	-	-	-	-	Mice	(Salem, Shaheen, & Borjac, 2022)
	5, 10 & 20mg/kg i.p	↓	-	-	↓	↓	↓	-	-	Rat	(Fatemi et al., 2022)
Cerebellum	60mg /kg intraperitoneally	-	-	-	-	↓	-	-	-	Mice	(Linardaki et al., 2012)
Pineal gland	150 mg/kg gavage	↓	-	-	↓	-	↓	-	-	Rat	(De la Fuente Muñoz et al., 2023)
Serum	15 mg/twice a day orally	-	-	-	-	↓	↓	-	-	Human	(Marzabadi et al., 2022)

TNF-α: tumor necrosis factor-alpha, NF-kB: nuclear factor k B, COX2: cyclooxygenase 2 IL-6: interleukin-6. IL-1: interleukin-1, iNOS: inducible nitric oxide synthase, TLR4: toll-like receptor 4, MDA: malondialdehyde. ↓: Decrease; ↑: Increase; —: No change.

Saffron's Impact on Neurotrophic Factors and Memory Function

Saffron exhibits the ability to modulate the expression and activity of neurotrophic factors in brain tissues (Ahmadi et al., 2021; Baharvand et al., 2020; Looti Bashiyan et al., 2021; Motaghinejad et al., 2019; Mozaffari et al., 2019; Roustazade et al., 2022; Sadoughi, 2019). By enhancing the levels of factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF), saffron may promote neuronal survival, growth, and plasticity (Ahmadi et al., 2021; Akbari-Fakhrabadi et al., 2021; Asrari et al., 2018; Looti Bashiyan et al., 2021; Roustazade et al., 2022). Neurotrophic factors are a group of proteins that play a crucial role in promoting the growth, survival, and differentiation of neurons. These factors are involved in synaptic plasticity, neurogenesis, and overall brain function (Ahmadi et al., 2021; Baharvand et al., 2020; Mozaffari et al., 2019; Sadoughi, 2019). BDNF is a crucial protein for neuronal survival, development, and synaptic plasticity. By enhancing BDNF expression and signaling, saffron may promote neurogenesis and protect neurons from degenerative processes (Ebrahimi et al., 2021; Roustazade et al., 2022; Vafaei et al., 2023). Moreover, saffron's impact on BDNF can have a positive influence on mood regulation, learning, and memory formation. In addition to BDNF, saffron has also demonstrated effects on NGF and GDNF. NGF is responsible for the growth and survival of sensory and sympathetic neurons, while GDNF supports the growth and survival of dopaminergic neurons (Chen et al., 2023; Mohammadi et al., 2023; Vafaei et al., 2023). Preclinical studies have shown that saffron can upregulate NGF and GDNF expression, which might enhance neuronal survival, but these effects have not been confirmed in human brain tissue (Ahmadi et al., 2021; Akbari & Moghadasi, 2023; Roustazade et al., 2022). Saffron has been found to activate various signaling pathways involved in neuroprotection, including the PI3K/AKT and MAPK/ERK pathways (Chen et al., 2023; Yang et al., 2017). These pathways are essential for the transmission of growth signals and the overall health of neurons. Disorders such as Alzheimer's, Parkinson's disease, depression, and neurodegenerative diseases are often associated with impaired neurotrophic factor signaling (Chen et al., 2023; Gong et al., 2021; Sadoughi, 2019). Table 4 provides a summary of studies investigating the effects of saffron on neurotrophic factors in different brain areas.

Table 4. Effects of saffron on neurotrophic factors in different parts of the brain

Tissue	Doses and administration	BDNF	GDNF	CNTF	NGF	Neurotrophin-3	Neurotrophin-4	Species	Ref.
Brain	10 and 5 mg/kg	↑	-	-	-	-	-	Rat	(Ahmad, Khan, et al., 2022)
Hippocampus	daily injections intraperitoneally 30 and 60 mg/kg	↑	-	-	-	-	-	Rat	(Roustazade et al., 2022)
	injected intraperitoneally at doses of 1, 5, and 15 mg/kg	↑	-	-	-	-	-	Rat	(Looti Bashiyan et al., 2021)
	40 and 80 mg/kg IP	↑	-	-	-	-	-	Rat	(Mozaffari et al., 2019)
		↑	-	-	-	-	-	Rat	(Mohammadi et al., 2023)
	IP injections of 25 mg/kg	-	-	-	↑	-	-		(Akbari & Moghadasi, 2023)
	25 and 50 mg/kg IP injection	↑	-	-	-	-	-		(Sadoughi, 2019)
	Gavage 6.25 mg/kg	↑	-	-	-	-	-	C57BL/6J mice	(Monchaux De Oliveira, De Smedt-Peyrusse, et al., 2021)
Adipose-derived mesenchymal stem cells	1000 µg/ml crocin	↑	-	-	-	-	-	Stem cell	(Vafaei et al., 2023)
Soleus muscle and hippocampus	Gavage 40 mg/kg	↑	-	-	-	↑	-	Wistar Rat	(Akbari-Fakhrabadi et al., 2021)
Epidermal neural crest stem cells	500 µM and 1.5 mM crocin	↑	↑	-	-	-	-	Stem cell	(Baharvand et al., 2020)
Liver	intraperitoneally 5 µL/g	-	↑	-	-	-	-	C57BL/6 mice	(Xuan et al., 2020)
Neural Crest Stem Cell	1 and 1.5 mM crocin	↑	↑	-	-	-	-	Stem cell	(Ahmadi et al., 2021)

Brain microvascular endothelial cells	intraperitoneal injection 40 mg/kg	↑	-	-	↑	-	↑	Rat	(He et al., 2024)
Stem cell	1and 1.5 mM crocin	↑	↑	-	-	-	-	Stem cell	(Ahmadi et al., 2021)

BDNF: brain-derived neurotrophic factor, GDNF: glial cell line-derived neurotrophic factor, CNTF: ciliary neurotrophic factor, NGF: nerve growth factor, neurotrophin-3, and neurotrophin-4. ↓: Decrease; ↑: Increase; —: No change.

Preventing Cell Death: How Saffron Inhibits Apoptosis in Memory Impairment

The results of previous studies have reported that saffron has beneficial effects on apoptotic proteins in brain tissues (Bazyar & Shabani, 2023; Salem, Shaheen, & Borjac, 2022). Several studies in animal models and cell lines indicate that saffron constituents can modulate apoptotic regulators, although the clinical relevance of these findings is unclear (Bazyar & Shabani, 2023; Mohammadzadeh et al., 2019; Sadoughi, 2019). Apoptosis, also known as programmed cell death, plays a crucial role in maintaining homeostasis in the body, including brain tissue. Dysregulation of apoptotic proteins can lead to pathological conditions such as neurodegenerative diseases and cognitive impairments (Asadi et al., 2015; Bazyar & Shabani, 2023; Zhang et al., 2015). Studies have been conducted to investigate the impact of saffron and its active constituents on apoptotic proteins in brain tissues (Asadi et al., 2015; Delkhosh-Kasmaie et al., 2018; Mehri et al., 2012; Ochiai et al., 2007; Pan et al., 2016). Several mechanisms have been proposed to explain saffron's role in regulating apoptosis. One significant area of interest is saffron's potential to target the B-cell lymphoma 2 (Bcl-2) family of proteins, which are central regulators of apoptosis (Asadi et al., 2015; Bazyar & Shabani, 2023). Bcl-2 family proteins can either promote or prevent cell death, depending on the balance between pro-apoptotic (e.g., Bax) and anti-apoptotic (e.g., Bcl-2) members. An imbalance in the expression and activity of these proteins can contribute to neuronal cell death (Bazyar & Shabani, 2023; Salem, Shaheen, & Borjac, 2022). Several studies have reported that saffron and its bioactive compounds can restore the balance of Bcl-2 family proteins in brain tissues (Bazyar & Shabani, 2023; Salem, Shaheen, & Borjac, 2022; X. YANG et al., 2023).

For example, saffron extract has been shown to increase the expression of Bcl-2 while decreasing the expression of Bax, thus promoting cell survival and inhibiting apoptotic processes (Bazyar & Shabani, 2023; Sadoughi, 2019). It has also been found to modulate other key apoptotic regulators, including caspases, which are responsible for executing the apoptotic process. In experimental models, saffron has been shown to inhibit caspase activation and reduce neuronal cell death (Asadi et al., 2015; Bazyar & Shabani, 2023). Furthermore, saffron has also demonstrated its ability to regulate various signaling pathways involved in apoptosis regulation, such as the PI3K/Akt pathway. Activation of this pathway has been associated with cell survival and inhibition of apoptosis (Salama et al., 2019). Moreover, saffron's bioactive compounds scavenge free radicals, reducing oxidative stress-induced damage and protecting neurons from apoptotic cell death (Fatemi et al., 2022; Pan et al., 2016). The modulatory effects of saffron on apoptotic and anti-apoptotic proteins in brain tissues are summarized in Table 5.

Table 5. Effects of saffron on apoptosis in different parts of the brain

Tissue	Doses and administration	Apoptosis	Bcl2	Bcl-xl	Bax	Caspase 3	TrkB	Species	Ref.
Hippocampus	0.025, 0.1, and 0.2 ml/kg	↓	-	-	-	↓	-	Rat	(Baluchnejadmojarad et al., 2019)
	2%, 4%, and 6% SEO, inhalation	↓	-	-	-	-	↓	Mice	(Chen et al., 2023)
	40 and 80 mg/kg i.p.	↓	↑	-	↓	-	-	Rat	(Mozaffari et al., 2019)
	25 mg/kg i.p.	↓	↑	-	↓	-	-	Rat	(Sadoughi, 2019)
	100 mg/kg	↓	↑	-	↓	↓	-	Rat	(Bazyar & Shabani, 2023)
	20 and 40 m/kg i.p.	↓	↑	-	↑	↓	-	Rat	(Mohammadzadeh et al., 2019)
	30 mg/kg i.p 150, 300, and 600 nmol/side via intra-hippocampal injection	↓	↑	-	↑	↓	-	Rat	(Asadi et al., 2015)
	0.4 mg/kg, i. p	↓	-	-	-	↓	-	Rat	(Delkhosh-Kasmaie et al., 2018)
	40 mg/kg, i. p	↓	↑		↓	↓		Rat	(X. YANG et al., 2023)
Brain cortices	30 mg/kg, i. p	↓	↑	-	↓	↓	-	Mice	(Salem, Shaheen, & Borjac, 2022)
PC12 cells	10 μM	-	-	-	-	↓	-	Mice	(Ochiai et al., 2007)
	10–50 μM	↓	↑	-	↓	-	-		(Mehri et al., 2012)
Spinal cord	100 mg/kg, i. p	↓	↑	-	↓	-	-	Rat	(Zhang et al., 2015)

Bcl2: anti-apoptotic protein, Bcl-xl: anti-apoptotic protein, Bax pro-apoptotic protein, Caspase 3: pro-apoptotic enzyme, TrkB: tropomyosin receptor kinase B. ↓: Decrease; ↑: Increase; —: No change

Saffron's Influence on Neurotransmitters and Memory Retention

Recent research has focused on exploring the impact of saffron on neurotransmitters in brain tissues, aiming to understand its neurological effects and potential applications in the field of neuropsychiatry (Moghadam et al., 2021; Monchaux De Oliveira, De Smedt-Peyrusse, et al., 2021). Neurotransmitters play a vital role in the communication between nerve cells and are responsible for regulating various physiological processes, including cognition, mood, memory, and behavior (Akbari-Fakhrabadi et al., 2021; Moghadam et al., 2021; Yuan et al., 2020). Any disruption in neurotransmitter levels or functionality can lead to the development of neurological and psychiatric disorders (Salama et al., 2019). With its abundance of bioactive compounds, saffron has demonstrated the potential to modulate neurotransmitter activities through various mechanisms (ABE et al., 1999; Berger et al., 2011; Hosseinzadeh et al., 2008; Linardaki et al., 2012; Salama et al., 2019). Studies have indicated that saffron possesses neuroprotective properties and can influence neurotransmitters such as serotonin, dopamine, glutamate, and gamma-aminobutyric acid (GABA)

(Ahmad, Khan, et al., 2022; Akbari-Fakhrabadi et al., 2021; Ettehadi et al., 2013; Hosseinzadeh et al., 2008). For instance, saffron extracts have been found to enhance serotonin levels, a neurotransmitter strongly associated with mood regulation and emotional well-being (Akbari-Fakhrabadi et al., 2021). Additionally, saffron has been shown to modulate dopamine levels, a neurotransmitter linked to reward, motivation, and motor control (Ettehadi et al., 2013). By influencing dopamine release and reuptake mechanisms, saffron could potentially play a role in the management of Parkinson's disease and other movement disorders (Salama et al., 2019). Furthermore, saffron's impact on glutamate and GABA neurotransmitter systems is of particular interest (Ettehadi et al., 2013; Moghaddam et al., 2016). Glutamate is an excitatory neurotransmitter involved in learning and memory processes, while GABA is an inhibitory neurotransmitter that helps regulate neuronal excitability (Marsman et al., 2017; Riedel & Reymann, 1996). In animal studies, saffron components have been reported to modulate glutamate and GABA levels, which may influence cognitive processes, but direct evidence in humans is lacking (Ettehadi et al., 2013; Moghaddam et al., 2016). Table 6 summarizes the reported effects of saffron on neurotransmitter levels in various brain regions.

Table 6. Effects of saffron on neurotransmitters in different parts of the brain

Tissue	Doses and administration	5-HT	GABA	Glutamate	Dopamine	Tryptophan	Species	Ref.
Serum	150 mg pill of pure saffron	↑	-	-	↑	-	Human	(Moghadam et al., 2021)
Hippocampus	6.25 mg/kg gavage	↑	-	-	-	-	C57BL/ 6J mice	(Monchaux De Oliveira, De Smedt-Peyrusse, et al., 2021)
	40 mg/kg gavage	↑	-	-	-	-	Wistar rat	(Akbari-Fakhrabadi et al., 2021)
	72.75 mg/kg or 291 mg/kg, i.p	-	-	↓	-	-	Rat	(Hosseinzadeh et al., 2008)
Brain	30 mg/kg/day; i. p	-	-	-	↑	-	Wistar rats	(Salama et al., 2019)
	250 mg/kg i. p	-	-	↑	↑	-	Rat	(Ettehadi et al., 2013)
Frontal Cortex, Striatum, and Hippocampus	6.25 and 600 mg/Kg gavage	↑	-	-	↑	-	Mice	(Monchaux De Oliveira, Pourtau, et al., 2021)
Hypothalamus	0.1 g/mL and 250 µL intraperitoneal injection	-	↑	-	-	-	Rat	(Moghaddam et al., 2016)
Plasma	1 mg/day	-	-	-	-	↓ → ↑ in the brain	Human	(Ahmad, Azhar, et al., 2022)
Serum	2%, 4%, and 6% saffron essential oil inhalation	↑	↑	-	↑	-	Mice	(Chen et al., 2023)

5-HT: 5-hydroxytryptamine, GABA: γ-Aminobutyric acid, Decrease; ↑: Increase; —: No change

Enhancing Memory Consolidation: The Role of Saffron in Regulating LTP

One particular area of interest is saffron's influence on long-term potentiation (LTP) in the brain (Hadipour et al., 2018; Hosseini Dastgerdi et al., 2020). Long-term potentiation refers to the persistent strengthening of synapses, which are the connections between neurons, as a result of repeated stimulation. LTP is widely regarded as a crucial mechanism for learning and memory formation. Alterations in LTP have been implicated in various neurological disorders such as Alzheimer's, and Parkinson's diseases, and depression (Weerasinghe-Mudiyanselage et al., 2022). One way saffron appears to influence LTP is through its antioxidant and anti-inflammatory properties (Marzabadi et al., 2022; Salem, Shaheen, Tabbara, et al., 2022). Oxidative stress and inflammation can impair synaptic plasticity, leading to a decline in LTP (Hajipour et al., 2020; Hassani et al., 2020). By reducing oxidative stress and inflammation, saffron may help protect synapses and promote the maintenance of long-lasting synaptic connections, thus facilitating LTP (Abbaszade-Cheragheali et al., 2023; Salem, Shaheen, Tabbara, et al., 2022). Moreover, saffron has been shown to modulate various neurotransmitter systems in the brain, including serotonin, dopamine, and glutamate (Akbari-Fakhrabadi et al., 2021; Ettehadi et al., 2013). These neurotransmitters play crucial roles in regulating synaptic plasticity and are strongly linked to the processes underlying LTP. By modulating their levels or activity, saffron may enhance synaptic plasticity and further support LTP (Abe & Saito, 2000; ABE et al., 1999; Riedel & Reymann, 1996). Additionally, saffron effects on LTP may be attributed to its interaction with the N-methyl-D-aspartate receptor (NMDAR), a key player in synaptic plasticity. Studies have suggested that saffron and its constituents may regulate the function of NMDARs, potentially leading to enhanced LTP expression (Adabizadeh et al., 2019; Haghighizad et al., 2008). Several preclinical studies have reported that saffron administration increases BDNF levels and reduces apoptosis, which could underlie LTP enhancement, but this remains a hypothesis (Bazyar & Shabani, 2023; Ebrahimzadeh et al., 2019; Mohammadi et al., 2023; Sadoughi, 2019). Therefore, increasing in BDNF levels or reducing apoptosis by saffron in brain tissues may explain another possible mechanism in which administration of saffron and its main components leads to improvement in LTP in different brain regions like the hippocampus.

Conclusion

These review s findings suggest that saffron possesses neuroprotective properties and exerts positive effects on various aspects of memory. The active constituents of saffron, including crocin, crocetin, and safranal, contribute to its cognitive-enhancing effects through antioxidant, anti-inflammatory, and neuroplasticity-enhancing mechanisms.

The review highlights the consistent memory-enhancing effects of saffron observed in in vitro studies, animal models, and clinical trials. Saffron demonstrated potential in mitigating age-related memory decline and memory impairment associated with neurodegenerative disorders such as Alzheimer's disease. The modulation of neurotransmitter systems and the promotion of neurogenesis and synaptogenesis are key mechanisms involved in saffron's memory-enhancing effects. Despite the promising findings, limitations in saffron formulations, dosages, and treatment durations were identified, emphasizing the need for further research to optimize its use. Additionally, the small number of clinical trials and the necessity for long-term safety assessments and potential adverse reaction investigations should be addressed. Further research is warranted to refine saffron formulations, determine optimal dosages, and explore its efficacy in various memory-related conditions. Saffron holds potential as an alternative or complementary therapy for individuals experiencing memory decline and could contribute to the development of novel strategies to improve memory and cognitive function.

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Author Contributions

[Mahdiyeh Hedayati-Moghadam] contributed to the study's conception and design. Data collection was performed by [Yousef Baghcheghi]. The first draft of the manuscript was written by [Sajjad Sattaei Mokhtari] and [Mohammad Pourfridoni]. The photos were designed by [Habibeh Mashayekhi-sardoo]. [Yousef Baghcheghi] and [Mahdiyeh Hedayati-Moghadam] contributed to the editing and conceptualization. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

Not applicable.

Ethics approval

Not applicable.

Consent to publish

The authors indicate that there are no potential competing interests involving the study participants of this article.

Abbreviations

CNS: central nervous system, RCTs: randomized controlled trials, CCH: chronic cerebral hypoperfusion, LPS: lipopolysaccharide, ROS: reactive oxygen species, SOD: superoxide dismutase, CAT: catalase, GPx: glutathione peroxidase, NF-Kb: nuclear factor kappa B, TNF-α: tumor necrosis factor α, IL-1β: Interleukin-1β, COX-2: cyclooxygenase-2, iNOS inducible nitric oxide synthase, MAPK: mitogen-activated protein kinase, JAK/STAT: Janus kinase/signal transducers and activators of transcription, PI3K/Akt: phosphoinositide 3-kinase/ protein kinase B, BDNF: brain-derived neurotrophic Factor, NGF: nerve growth factor, GDNF: glial cell line-derived neurotrophic factor, Bcl-2: B-cell lymphoma 2, GABA: gamma-aminobutyric acid, LTP: long-term potentiation, NMDAR: N-methyl-D-aspartate receptor.

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