# Cognitive functions of saffron and its major constituent crocin, a narrative review

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**Background and Objective:** Saffron is the most well-known herb medicine from 3,000 years ago and has been investigated widely to make evident its activities like anticancer, antioxidant, anti-inflammation, anti-apoptosis, learning and memory, non-REM sleeping and antidementia and so on.

**Methods:** A narrative review of data published on the pharmacological value of saffron was surveyed and collected references gathered from the Google search engine from the 1980s until April 1st 2022 and publications in English. The pertinent data of the investigations have been compared, analyzed, and reorganized, resulting in newly assembled clarification.

**Key Content and Findings:** It became evident that the saffron extract improved the error increase induced by ethanol significantly, resulting in the saffron extract ameliorating the ethanol-induced memory registration impairment. This evidence was confirmed using scopolamine or hyoscine instead of ethanol. Activity-guided purification of the saffron extract confirmed that the active constituent is crocin and that crocin is approximately 40% concentrated in the saffron extract. Expression of long-term potentiation (LTP) in the CA1 district of hippocampal slices in rats was investigated, indicating that ethanol inhibited the LTP induced by strong tetanic stimulation resulting that crocin directly prevents the LTP-suppression by ethanol in the hippocampus area suggests that crocin functions on learning and memory via LTP.

**Conclusions:** It became clear that crocin can specifically ameliorate the inhibition by ethanol related to N-methyl-D-aspartate (NMDA)-receptor-entertained reply in neuronal cells of the hippocampal area. Such evidence suggested that crocin is a preventive and/or therapeutic drug for dementia, supported by clinical trials.

Keywords: Saffron; crocin; learning and memory; long-term potentiation (LTP); antidementia

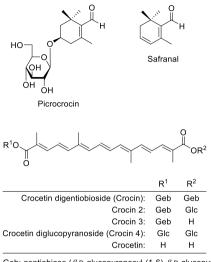
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# Introduction

Saffron has been used for 3,000 years or more as a spice with a bitter taste, picrocrocin, a spicy scent, safranal, a colorant, diterpenoid pigment, and herbal medicine. Crocetin-diglucoside, crocin-2, crocin-3, crocin-4, and crocetin di-( $\beta$ -D-digentiobiosyl)-ester (crocin) (*Figure 1*) are

diterpenoid components of saffron.

Saffron can be used as an antispasmodic, anti-catarrhal, and tranquilizing folk medicine, making it an essential treatment for blood and heart diseases (1,2). Crocin, a significant diterpenoid glycoside, has been proven to have antioxidant (3-5), antitumor (6-10), anti-hyperlipidemia (11,12), anti-atherosclerotic (13), and anti-inflammatory



Geb: gentiobiose ( $\beta$ -D-glucopyranosyl-(1-6)- $\beta$ -D-glucopyranoside) Glc:  $\beta$ -D-glucopyranoside



properties (14,15). Crocin has been extensively studied in the field of neuroprotection using *in vivo* models to be effective for cerebral ischemia (16), Alzheimer's disease (AD) (17), Parkinson's disease (18-20) and memory impairment (21,22).

Several processes are associated with neuroprotective activities in dementia, including antioxidant activity, inhibition of neuro-inflammation, enhancement of nerve growth factor (NGF) secretion, choline acetyltransferase (ChAT) activity and its mRNA levels, inhibition of  $\beta$ -amyloid secretion, promotion of energy metabolism in neurons via protection from mitochondrial damage, sirtuin 1 (SIRT1) protein activation, N-methyl-D-aspartate (NMDA) antagonist, memory impairment and conjugated activities (23). Natarajan et al. systematically surveyed many plant species and discovered numerous pharmacologically active components with antidementia properties (24). Many of these plants, such as Acorus gramineus Ayton, Angelica daburica (Hoffm.) Benth. & Hook. f. ex Franch. & Sav., Aralia cordata Thunb., Codonopsis pilosula (Franch.) Nannf., Crocus sativus L., Curcuma longa L., Epimedium brevicornu Maxim., Gardenia jasminoides J. Ellis, Glycyrrhiza glabra L., Lycium chinense Mill., Magnolia officinalis Rehder & E.H.Wilson, Panax ginseng C.A.Mey., Perilla frutescens (L.) Britton, Polygala tenuifolia Willd., Zingiber offinale Roscoe, Rhodiola rosea L., Salvia miltiorrhiza Bunge, and Uncaria rhynchophylla (Mig.) are used in traditional Chinese medicine and/or Kampo formulations (Miq.) (25).

Curcumin, a significant constituent of C. longa, was

Table 1 The search terms used
("Crocus sativus"[Mesh]) AND "Learning and memory"[Mesh]
("Saffron"[Mesh]) AND "Learning and memory"[Mesh]
("Crocin"[Mesh]) AND "Learning and memory"[Mesh]
("Crocus sativus"[Mesh]) AND "Long-term potentiation"[Mesh]
("Saffron"[Mesh]) AND "Long-term potentiation"[Mesh]
("Crocin"[Mesh]) AND "Long-term potentiation"[Mesh]
("Crocus sativus Saffron Crocin"[Mesh]) AND "NMDA receptor"[Mesh]

Table 1 The second terms used

carefully examined in randomized controlled trials for its cognitive function (26) and phase 1 investigation was performed to confirm its safety and suitable dose (27). Although *Ginkgo biloba* L. extract for vascular dementia prevention, St John's wort for depression, *P. tenuifolia* Willd. root for memory improvement and *Valeriana officinalis* L. root for sleep disorders are over-the-counter drugs; these findings suggest that curcumin could be developed as a new drug from herb medicines,

Saffron emerged as a multipotent target in dementia treatment due to neuroprotective activities by antiapoptosis *in vitro* (28) and reducing ethanol-induced impairment of learning and memory behavior *in vivo* (29). Recent phytochemical studies have opened the door to the aforementioned neurogenerative processes, which physicians and researchers eagerly await. The benefit of saffron and a constituent, crocin, in terms of learning, memory, and long-term potentiation (LTP), resulting in antidementia, is discussed in this article.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-22-5/rc).

#### Methods

Studies published over the last 20 years were identified via a PubMed search using different combinations such as "Crocus sativus", "Saffron", "Crocin", "Learning and memory", "Long-term potentiation", "N-methyl-D-aspartate receptor". Most of the search formulas are shown in *Table 1*.

Additional articles were identified by checking reference lists of publications. Publications with poor credibility and not written in English are eliminated. Data are gathered on the basis of the justness of the topic, and the details are

 Table 2 The search strategy summary

Item	Specification			
Date of search	2021/12/15-2022/02/20			
Databases and other sources searched	PubMed			
Search terms used	In Table 1			
Timeframe	1980–2021			
Inclusion and exclusion criteria	Inclusion criteria: research articles and reviews in English about themes such as Crocus/saffron/ crocin and learning and memory/long-term potentiation/NMDA receptor			
	Exclusion criteria: some papers, which we considered low reliability			
Selection process	Yukihiro Shoyama conducted the selection. Authors attended a discussion on the literature selection and obtained the consensus			
Any additional consideration	Some papers were identified by reviewing reference lists of relevant publications			

shown in Table 2.

# Effects of saffron ethanol extract on memory registration

Saffron was extracted with 50% ethanol 3 times and evaporated in vacuo to give SE (30).

According to Papandreou et al., the activity of SE on memory in aged mice was related to the antioxidant activity (31). Furthermore, several groups demonstrated the antioxidant activity of SE in vitro and in vivo (32-35), indicating its association with SE memory enhancement. Zhang et al. examined the SE activity for the ethanolinduced damage of passive avoidance reactions in mice based on these findings. There was no difference between SE administered groups and the control groups when the step through test (ST) or step down (SD) test was used. Based on this finding, it is easy to conclude that SE has no memory promotion potential in normal mice. None of the positive effects of SE treatment of mice was found to be successful. However, there was evidence of latency shortening (29). Roustazade et al. discovered that the dose of SE reflects various brain activities in stressed rats, suggesting changes in the latency period of passive avoidance tasks and that a high dose of SE reduced anxiety (36). According to the evidence presented above, saffron can counteract the inhibitory activity of ethanol on learning and memory achievement.

# Learning and memory activities induced by crocin

To separate and identify the active principle of saffron, SE

was purified by silica-gel chromatography using activityguided separation to reach crocin as active principle. This is easily assumed, given that crocin is a major constituent, accounting for around 40% of the SE (30).

The activity of SE appeared from 125 mg/kg, which contained approximately 50 mg of crocin, and dosedependently increased (37). Further studies have indicated that the oral administration of at least 50 mg/kg of crocin ameliorated memory induced by ethanol, indicating that crocin and SE are proportionally effective for memory behavior, resulting in crocin being confirmed as one of the active constituents (38). No effect on memory acquisition by a single-oral manipulation of crocin in normal mice was found in ST and SD tests, respectively. If crocin was administered 10 minutes before the ethanol injection, the latency in the ST test dose-dependently increased compared with that of ethanol-injected mice. When 200 mg/kg of crocin was administered, the number of successful mice increased compared to the ethanol-treated group in the test trial. Furthermore, 200 mg/kg crocin increased the number of successful mice and decreased the error numbers compared to the negative control (38).

However, crocin, at doses higher than 50 mg/kg, decreased the number of errors as against ethanol-treated mice in the SD test. However, the crocin treatment did not alter the number of successful mice in the testing trial. Sugiura *et al.* also checked the effects of crocin on motor activity in ethanol-treated mice, which was performed immediately after ST and SD tests both in the learning and testing trials. Oral manipulation of 30% ethanol 20 min just before the learning trial increased the amount

of motor activity as on the control group. But the increasing effect of ethanol was not recognized after 24 h of the testing trial. Oral pre-administration of crocin (50 and 100 mg/kg) before ethanol treatment did not affect the increasing effect of 30% ethanol on motor activity in the learning trial. However, at a 200 mg/kg dose, crocin attenuated the increasing effect of ethanol on the treated group. In the testing trial, the amount of motor activity in the crocin (50 to 200 mg/kg) and 30% ethanol-treated groups did not differ from that in the control group. Oral manipulation of 40% ethanol 20 min just before the testing trial also increased the amount of motor activity in the testing trial.

The administration of crocin (50–200 mg/kg) did not affect the increasing effect of 40% ethanol on motor activity in the testing trial. A single-oral crocin uptake did not show any activity on memory in normal mice. Conversely, the ethanol-induced learning impairment in passive avoidance performance was improved (38).

Since it was discovered that ethanol could impede the memory performance of crocin, cholinergic receptor antagonists scopolamine and hyoscine have been used to validate crocin behavior instead of ethanol. Ghadami and Pourmotabbed used a Morris water maze (MWM) to evaluate the action of crocin in rats with learning and memory impairment caused by scopolamine. Injection of crocin (1-10 mg/kg, i.p.) for 6 days consecutively 30 min after injection of scopolamine improved the scopolamine-induced impairment of learning behavior dose-dependently (39). In hyoscine crocin (20 and 40 mg/kg, i.p.), saline and rivastigmine were administered 30 min before hyoscine for 5 days as a positive control. Crocin 20 mg/kg injection improved memory impairment induced by hyoscine and dramatically enhanced brainderived neurotropic factor (BDNF) and cAMP response element binding (CREB) protein and their transcript levels compared with hyoscine. This evidence suggests that crocin might ameliorate memory impairment by cholinergic receptor antagonists such as scopolamine and/or hyoscine via increased BDNF and CREB (40).

Crocin (40 mg/kg) was administered continuously for 14 days to AD rats prepared by injection of  $A\beta_{25-}$  $_{35}$  resulted in considerably higher learning and memory reactions compared with the control group. Furthermore, while the apoptotic cell number in the CA1 region of hippocampal and prefrontal cortical neurons in the AD model group was higher compared to the control group, crocin administration significantly reduced the apoptotic cells in the AD group. Increased Bcl2 in PFC and hippo of the AD model group occurred, and the expression of Bax and Caspase3 was decreased by crocin administration. This evidence suggests that crocin improves learning and memory and decreases neuronal apoptosis (41).

# Effect of crocin on long-term potentiation (LTP)

Saffron was extracted with 90% of methanol 3 times. The methanol extract was repeatedly purified by silicagel chromatography, eluting ethyl acetate-ethanol-water (10:3:2) mixture to give crocin, crocin-2, -3, and -4, respectively (21). It became clear that the SE improved the ethanol blocking effect on the hippocampal LTP dose-dependently (21). Since previous, the active principle of SE related to brain function was confirmed to be crocin, the activity of crocin against the ethanol blocking effect on the hippocampal LTP is discussed in this section. By injecting of 51.2 nm i.c.v. crocin before the ethanol administration, strong LTP occurred compared to the control, easily suggesting that the LTP blocking effect of ethanol was improved by crocin (21,22).

Hippocampal LTP is involved in learning and memory. Blockade of NMDA receptors by specific antagonists or channel blockers not only inhibit the induction of hippocampal LTP but also impair the spatial cognition of the rats in WMW. The LTP size in the dentate gyrus is related to associative learning in rats (42).

Sugiura *et al.* investigated the effect of crocin on the LTP induction in the CA1 region of rat hippocampal slices. Ethanol (50–75 mM) blocked the LTP with strong tetanic stimulation (51 pulses at 100 Hz) in the *vitro* assay system. Crocin significantly improved the inhibition of LTP by ethanol in a concentration (10–30  $\mu$ M)-dependent manner, although crocin (20  $\mu$ M) alone showed no effect similar to the baseline synaptic responses. This *in vitro* evidence indicated that crocin directly prevents the LTP-suppression by ethanol in the hippocampus area, suggesting that crocin functions on learning and memory via LTP (22). Dastgerdi *et al.* found the similar results of crocin on LTP by chronic stress (43,44).

The effects of saffron and/or crocin on cognitive activity were summarized in *Table 3*.

# Sleep quality improvement by saffron and crocin for good memory

We found that non-rapid eye movement (REM) sleeping occurred when crocin (100 mg/kg) was received in mice by

Component	Dose concentration	Animals	Inhibition impairment	Evaluation method	Reference
Saffron extract	125–500 mg/kg	Mice	Ethanol	STSD	(29)
	125, 250 mg/kg	Rat	Ethanol	LTP	(37)
	30, 60 mg/kg	Rat	Restrain stress	PA, NOR/OL	(36)
Crocin	50–200 mg/kg	Mice	Ethanol	STSD	(38)
	1–10 mg/kg	Rat	Scopolamine	MWM	(39)
	30 mg/kg	Rat	Chronic stress	LTP	(43)
	51.2 nmol	Rat/in vitro	Ethanol	LTP	(21)
	20 mmol	Rat/in vitro	Ethanol	LTP	(22)

Table 3 The effect of saffron and/or crocin on cognitive activity

STSD, step through and step down test; LTP, long-term potentiation; PA, passive avoidance; NOR, novel object recognition test; OL, object location test; MWM, Morris water maze test.

intraperitoneal administration in the evening. The intensity increased immediately after injection, and the potency continued significantly for 4 hours after the injection compared with the control. The increase in non-REM sleeping times was induced by the reduction of the period awake. However, crocin showed no REM sleeping, and the control mice remained awake between 20:00 and 01:00, confirming that crocin gave non-REM sleep without typical side effects, such as rebound insomnia. A 30 mg/kg crocin injection also gave the shorter non-REM sleeping for around 1-2 hours after the injection, although crocin at 10 mg/kg had no effect on the cumulative amount of non-REM and REM sleep after injection. From the evidence, the injections of 30 and 100 mg/kg crocin statistically increased total non-REM sleep to 160% and 270%, respectively, and significantly decreased total awoke time to 20% and 50%, respectively, without changing REM sleep levels during 4 hours as compared with the control (45).

To confirm sleep quality during saffron uptake, we conducted a double-blind clinical trial using 21 healthy adults randomly attributed to either a saffron extract group (crocin: 0.6 mg/day) or a placebo group. This result indicated a significant reduction in the Pittsburgh sleep quality index scores in the extract group. Moreover, a significant positive effect of the saffron group was shown on daytime dysfunction in the saffron extract group compared with the placebo group (46).

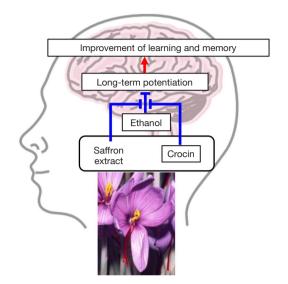
The Hisayama epidemiological study in Fukuoka, Japan, reported that sleep obstacles and sleeping pills increased the risk of dementia in elderly individuals. Comparing 5 h and 10 h daily sleeping terms, the risk of dementia like

vascular dementia and AD increased in the short sleeping group approximately 2-fold rather than that of the 10 h cohort. This finding explained that the quality of poor sleep might bring brain aging resulting in  $\beta$ -amyloid accumulation progressing into AD (47). Recently, the relationship between sleep and dementia has been searched widely. These results suggest that sleep disorders affect inflammatory induction in the brain resulting in AD (48). Several meta-analyses and systematic reviews have shown that sleep disturbance might be an important risk factor resulting in an important target for AD prevention (49-51).

# Safety of saffron and its constituents

Regarding safety of saffron and crocin, saffron extract of 400 mg/kg/day and 20 mg/kg/day of crocin showed slightly biological parameter's differences, respectively using healthy volunteers (52,53). The saffron extract of 30 mg/d showed week vomiting compared to memantine group (54,55). From these findings above levels of saffron and crocin can be used for the clinical trials.

The relation between saffron and pregnancy has been argued frequently. Nili-Ahmadabadi *et al.* reported that the saffron extract reduced the level of progesterone in all stages of rat pregnancy and the level of estradiol in the early and late stages. Progesterone levels was reduced by crocin in the late stages of pregnancy. A high dose of saffron extract and crocin increased the follicle stimulating hormone levels (56). Safranal, monoterpene having a typical flavor of saffron was confirmed to be low toxic in acute intraperitoneal uptake and non-toxic in acute oral uptake in mice and rat (57). On Page 6 of 10



**Figure 2** Mechanism of learning and memory enhancement via long-term potentiation by saffron and/or crocin.

the other hand, the study of picrocrocin on pregnancy has not been investigated although this component seems to be affected to pregnancy. From these findings it suggested that saffron and crocin uptake should be avoided in the pregnancy period although Said *et al.* investigated the readiness of uterine cervix in double-blind trial using pregnancy women (58).

# Discussion

It is easily suggested that crocetin derivatives, as shown in Figure 1, affect LTP strength. Therefore, the actions of the crocetin gentiobiose glucose ester and crocetin di-glucose ester on the LTP blocking effect of ethanol were examined at the same dose scale as crocin (19). These activities were lower than those of crocin, indicating that the improvement activity against blocking was compatible with the sugar number because crocin possessed four glucose in a molecule, indicating the greatest ameliorating effect, whereas the effect of crocetin di-glucose ester was nearly identical to that of the control, although crocetin glycosides can work synergically. This result also confirmed again that crocin is the actual active principle in saffron since crocin is the major crocetin glycoside, about 15%, and crocin 2 and 3 contain approximately 5% and 0.7%, respectively, in saffron (30).

Recently, Dastgerdi *et al.* reported that a 30 mg/kg/day intraperitoneal injection of crocin reversed the effects of

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chronic restraint stress on LTP to confirm the crocin doses on the excitability and LTP in the rat CA1 area in the hippocampus (43,44). Mohammadmehdi et al. investigated the effect of crocin on memory, LTP, and neuronal apoptosis using amyloid- $\beta$  (A $\beta$ ) model rats with AD by the administration of the A $\beta$  peptide [1–42] into the frontal cortex after surgery. Crocin of 30 mg/kg was injected i.p. for 12 days. Injection of crocin ameliorated spatial memory significantly compared with the Aß model group. The passive avoidance test showed that crocin significantly increased the ST latency compared to Aβ-treated rats, resulting in decreased learning ability in Aβ-treated rats associated with decreased LTP. Crocin was confirmed to decrease neuronal apoptosis and have neuroprotective activity compared with A $\beta$ -group (59). This evidence showed that crocin in saffron prevents the suppression action of ethanol and/or other drugs on LTP. As investigated above, the effects of chronic restraint stress and the Aβtreated rats on LTP were used to evaluate crocin. However, scopolamine (39,40), acetaldehyde (60), and ethanol, as previously discussed, were used as inhibiting drugs for LTP induction. A smaller amount of crocin can prevent the LTP inhibited by ethanol. From this, ethanol might be the quick response and easy use drug for preventing LTP rather than the other drug. Moreover, the internal cerebral vein (i.c.v.) injection is most sensitive for LTP expression when compared with the investigation by intraperitoneal (i.p.) injection of crocin. Therefore, the i.c.v. injection of crocin is recommended if possible. Figure 2 shows a diagram of the mechanism for learning and memory enhancement via LTP by saffron and/or crocin.

Recently some prophylactic phytochemicals for dementia have been required because there is no preventive medicine in Japan, although the dementia population is increasing rapidly. In these circumstances, numerous health foods have been produced rapidly without safety testing. Under this concept, saffron can be selected because saffron has a long eating experience of just about 3,000 years as a spice, coloring agent, and medicine in Europe and was listed in the Chinese Compendium of Materia Medica approximately 400 years ago.

A recent paper showed that crocin significantly improved memory, increased acetylcholine levels, and prevented hippocampal neuronal apoptosis suggesting good prevention and/or therapy for ischemic cerebrovascular diseases (61). Several processes are associated with neuroprotective activity in dementia, including antioxidant activity, inhibition of neuro-inflammation, enhancement

of NGF secretion, choline acetyltrasferase (ChAT) activity and its mRNA levels, inhibition of  $\beta$ -amyloid secretion, promotion of energy metabolism in neurons via protection of mitochondrial damage, SIRT1 protein activation, NMDA antagonist, memory impairment and conjugated activities (19). These findings suggested that crocin might be preventing and/or therapeutic drug for neuroprotection, including dementia, supported by the previous investigation that crocin has antioxidant (5) and anti-inflammation (8), resulting in anti-apoptosis activity for PC-12 cells (5,16,28,62). Therefore, depending on their pharmacological activities, saffron and/or crocin can be called a multifunctional natural product in the brain.

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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