Review Article

Pharmacological activity of saffron and crocin on dementia: a narrative review

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Background and Objective: This review is focused on the pharmacologically activities of saffron and crocin on dementia because rapid increase of dementia patients in the world becomes issue an alarm recently. Various kind of herbal medicines have been used widely since recorded history especially saffron has a history of over 3 thousand years. With the notable pharmacological value saffron and its constituents have been investigating widely and energetically resulting in recently anti-dementia in vivo, in vitro and in clinical trial because dementia patients drastically increase in the world.

Methods: A narrative review of data published on the pharmacological value of saffron and crocin were surveyed and collected references gathering from the Google search engine including PubMed, SciFinder and Web of Science from 1980s until April 1st 2022 and publications in English. The suitable data of investigations have been compared, analyzed and reorganized resulting in newly assembled clarification.

Key Content and Findings: The Diagnostic and Statistical Manual of Mental Disorders indicates that major dementia are Alzheimer's disease (AD) and vascular dementia (vD). In the survey of anti-dementia active medicinal plants saffron has received a lot of attention recently. Clinical trials of saffron on sleep and depression made clear the dementia therapies of saffron supported by the epidemiological survey indirectly. Oral administration of saffron was confirmed to be effective for AD by double blind analysis. The combination formula of saffron with other herb medicine such as SaiLuoTon which prescribed with ginseng and Ginkgo biloba can be used for vD patients.

Conclusions: Reported studies using saffron, crocin and the combination with other herbal medicines on dementia and AD have been surveyed, reviewed and analyzed. Clinical trial data suggest that saffron and crocin have beneficial effects to improve memory in AD without serious side effect resulting that saffron and crocin can be supported as promising candidates for future clinical AD studies.

Keywords: Saffron; crocin; neurodegenerative; dementia; clinical trial

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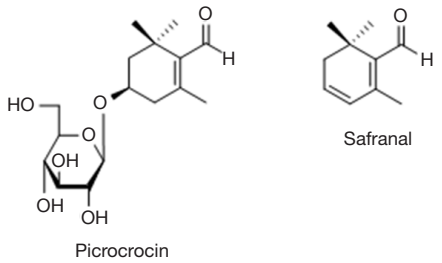
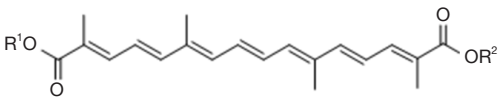
Introduction

The Diagnostic and Statistical Manual of Mental Disorders (1) specified dementia such as Alzheimer's disease (AD), vascular dementia (vD), frontal lobe hyperthermia, dementia with Lewy bodies, Parkinson's disease with dementia, and Huntington's disease with dementia. Among them AD is the most common depending on aging process. Rapid increase of dementia patients in the world becomes issue an alarm. In Japan, 7.3 million persons are speculated by 2025, and 10.2 million cases are expected by





	R^1	R^2
Crocetin digentiobioside (Crocin):	Geb	Geb
Crocin 2:	Geb	Glc
Crocin 3:	Geb	H
Crocetin diglucopyranoside (Crocin 4):	Glc	Glc
Crocetin:	H	H

Geb: gentiobiose (*β*-D-glucopyranosyl-(1–6)-*β*-D-glucopyranoside
Glc: *β*-D-glucopyranoside

Figure 1 Major constituents in saffron.

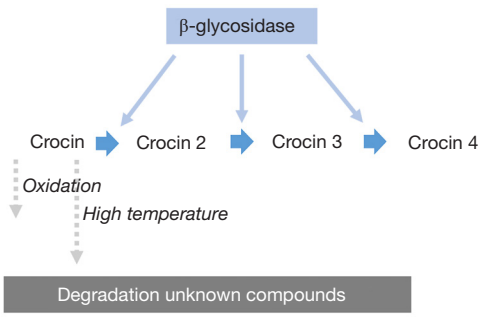


Figure 2 Degradation scheme of crocin.

2050 (2). This tendency is the same with the world (3). The population of dementia patients aged 60 years and over in the world was indicated the higher in Europe, United State and Japan, and lower in Asia and Africa countries (4). It might be important issue to determine the reason why such difference occurred. Epidemiological surveys confirmed that lifestyle and eating habits influence, suggesting that wine (5) or fish (6) decrease the occurrence of AD in aged people. From this evidence, the world hopes for finding of prevention method and/or preventive phytomedicines.

Several studies have shown that numerous pure compounds have anti-dementia activities (7-19), but no compounds have been clinically approved. The anti-dementia activities of saffron and crocin were well known by the protection of neuronal cell death because of strong anti-oxidation related to glutathione-dependent inhibitory mechanism, anti-inflammation activities (20) and the enhancement of learning-memory and long-term potentiation (LTP) inhibited by ethanol (21). Saffron is one of the most highly secure phytomedicine because saffron has the long food experience as spices. In fact saffron has been used longer for phytomedicine, coloring agent and spice from the thousand years (22) and is now permitted as Generally Recognized as Safe (GRAS) by the American Food And Drug Administration (FDA) (23) resulting that the most important issue for clinical use of saffron and crocin is safety without adverse effect. Therefore, saffron and crocin were administrated in healthy volunteers and confirmed their side effects (24). Stability of crocin in saffron (see *Figure 1*) has been discussed because the basic skeleton is polyene structure and has glycoside linkages in a molecule easily hydrolyzed by an inner β-glycosidase as shown in *Figure 2*. Therefore, saffron and saffron extractives should be stored under cool and dry condition (25) and confirmed the exact crocin concentration just before use in clinical trials resulted that the quality control of saffron is necessary for the constant pharmacological efficacy. Therefore, the quality control of saffron will be discussed at the first section in this review.

Since the relation between sleep disorder and depression, and dementia has been evaluated by epidemiological studies (26), clinical trials of saffron on sleep and anti-depression activity will be discussed. Recently anti-dementia activity of saffron has been investigated widely in clinical trials to confirm its efficacy. From these results the combination of saffron and other herb medicine is groped for more efficient and effective efficacy. These new prescriptions will be also discussed in this review. We present the following article in accordance with the Narrative Review reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-22-7/rc).

Methods

This article identified the publications between 1980 and 2021 on saffron and crocin in anti-dementia and neuroprotection administration via several library search engines such as PubMed, Web of Science and SciFinder

Table 1 The search strategy summary

Item	Specification
Date of search	December 15th 2021 and February 2nd 2022
Databases and other sources searched	PubMed, SciFinder, Web of Science
Search terms used	"Crocus sativus" AND "safety" AND "Saffron" AND "safety" AND "toxicity"
	"Crocin" AND "safety" AND "toxicity"
	"Crocus sativus" AND "quality control"
	"Saffron" AND "quality control"
	"Saffron" AND "stability"
	"Crocin" AND "stability"
	"Crocus sativus" AND "anti-dementia"
	"Saffron" AND "anti-dementia"
	"Crocin" AND "anti-dementia"
	"Crocus sativus" AND "neuroprotection"
	"Saffron" AND "neuroprotection"
	"Crocin" AND "neuroprotection"
Timeframe	1980–2021
Inclusion and exclusion criteria	Inclusion criteria: Research articles and reviews in English about themes such as Crocus sativa/saffron/crocin and dementia/neuroprotection/mechanism/clinical trial
	Exclusion criteria: Papers which the authors considered with low reliability
Selection process	Yukihiro Shoyama promoted the selection, all authors discussed on the research articles selection and reached to the consensus
Any additional considerations, if applicable	Some papers were shown by reviewing reference lists of relevant publications if applicable

for over 200 journal articles in the English language. The search strategy was indicated in *Table 1*.

Anti-dementia active compounds from medicinal plants

C. sativus L. (Iridaceae) was first cultivated in Greek 3,000 years ago. Currently it is cultivated in Iran, Spain, Greece and China. Saffron is obtained from only stigmas of saffron flowers resulting in too expensive herb medicine and/or spice. Typical constituents of saffron are monoterpene, safranal, monoterpene glycoside, picrocrocin and crocetin glycosides called as crocin and crocin 2, 3 and 4 as indicated in *Figure 1*.

Compared the long-term potentiation (LTP) blocking effect of ethanol *in vivo* for crocins, crocin is the most active and gradually weaken depend on sugar number and crocin 4 is negligible (21). From these results the quality control of saffron and its extractives is important in *in vivo* and clinical investigations. These results will be discussed in the following section.

Galantamine was originally isolated from *Galanthus nivalis* L and is a global anti-dementia drug for mild and moderate AD. Synthetic therapeutic drugs including galantamine for dementia are donepezil, rivastigmine and memantine.

Nakanishi reported the isolation of diterpenes and flavonoids from *Ginkgo biloba* L and their structure elucidation (27). Their pharmacological activities were investigated in Germany and developed to an over the counter (OTC) drug for vD prevention in Europe (28). *Valeriana officinalis* L. *root, an OTC medicine for sleep disorders is expected to be anti-dementia active herb medicine in Europe* (29,30). *Polygala tenuifolia* Willd. root extract is also marketed as an OTC drug for memory improvement from 2016 in Japan. Natarajan *et al.* and Ho *et al.* reported

Table 2 Herb medicine, active constituent and their mechanism

Herb medicine	Active constituent	Mechanism	Ref.
Atractylodes lancea	β-Eudesmol	Increase of intracellular Ca^{2+} level induced by PI-PLC activation	(9)
Bupleurum falcatum	Saikosaponin C	Suppression of Aβ1-40 Aβ1-42 release in various models and inhibiting tau hyperphosphorylation	(10)
Citrus unshiu	Nobiletin	Inhibiting H_2O_2-induced cytotoxicity through suppression against activation of JNK and P38	(11)
Coptis chinensis	Coptisine	Inhibition of AChE and BChE activity	(12)
Cornus officinalis	Loganin	Improvement of scopolamine-induced memory impairment and inhibition of AChE activity	(13)
Dioscorea japonica	Coreajaponin B	Upregulation of NGF nothing of cell toxicity	(14)
Glycyrrhiza glabra	2,2',4'-trihydroxychalcone	Extenuation of memory impairment in the APP-PS1 doble transgenic mouse through reduction of producing Aβ	(15)
Paeonia suffruticosa	Paeonol	Improvement of impaired learning and memory behavior induced by Aβ injection in hippocampus	(16)
Rehmannia glutinosa	Catalpol	Improvement of Aβ-induced memory and learning damage through reducing Aβ	(17)
Scutellaria *baicalensis*	Baicalein	Improvement of spatial learning and memory impairment induced by gamma-ray radiation	(18)
Uncaria rhynchophylla	Rhynchophylline	Protection of Aβ-induced cytotoxicity through inhibition of intracellular Ca^{2+} overloading and tau hyperphosphorylation	(19)

PI-PLC, phosphoinositide phospholipase; AChE, Acethycholinesterase; BChE, Butyrylcholinesterase; NGF, nerve growth factor.

the many plants having pharmacological activities such as acetylcholine esterase and monoamine oxidase inhibition related to anti-dementia effects, anti-inflammatory activities, and learning and memory effects in animal models (7,8). In traditional Chinese medicine (TCM) and Kampo medicines the following are prescribed in formula related to dementia patients such as *Acorus gramineus* Aiton, *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., *Aralia cordata* Thunb., *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, *P. tenuifolia* Willd., *Zingiber offinale* Roscoe, *Salvia miltiorrhiza* Bunge and *Uncaria rhynchophylla* (Miq.) MFiq. (31). Further survey confirmed the active constituents and their active mechanism in herb medicines prescribed in TCM, Korean and Kampo medicines as indicated in *Table 2*.

Furthermore, saffron will be focused on this session because saffron is also used to be a sleep accelerator (26) and an anti-depressing active herb (32). Insufficient sleep (26) and depression symptom (33) are closely related to dementia supported by epidemiological survey (34).

Stability of crocin in saffron and the quality control of saffron

Crocin seems to be unstable depend on polyenes structure in crocetin molecule suggesting that the auto-decomposition of crocins (see *Figure 1*) might be stimulated by storage conditions such as temperature, air, humidity and light. Saffron was stored under the combining conditions in the long-term storage period resulting that the existence of air and higher temperature promoted degradation of crocin (25). Moreover, we revealed that inner β-glucoside is stable and reactive under moisture condition to cleavage the glycoside linkage in crocetin glycosides resulting in crocin 4 via crocins 2 and 3 (25). *Figure 2* indicated the degradation steps of crocin. We confirmed that the improved activity of individual crocins against the inhibition of LTP blocking activity by ethanol was proportional to the sugar numbers like crocin having four glucose in a molecule indicating the strongest improving activity and negligible activity of crocin 4 (21). This tendency was found in the biologically active natural saponins such as cardiac steroids (35), streptozotocin (36), ginsenosides (37), saikosaponins (38),

and hemolytic saponins (39). From the results saffron and saffron extractives should be stored under cool and dry condition (25) until use and assessed the exact crocin concentration before use in clinical trials because crocin in saffron is changeable as discussed. Therefore, the quality control of saffron and its extractives is necessary *in vitro*, *in vivo* and clinical investigations although the nanoparticle preparation of crocin using chitosan-alginate was investigated (40). To establish the quality control of crocin in saffron we prepared anti-crocin monoclonal antibody (MAb) and set up the enzyme-linked immune sorbent assay (ELISA) system (41).

Safety of saffron and its constituent crocin

An important issue regarding medical use of saffron in humans is safety without side effects although saffron has been used for herb medicine, spice and coloring agent from the ancient years and is now approved as Generally Recognized as Safe (GRAS) by the American Food And Drug Administration (FDA) (23). In this section saffron and crocin were administrated in healthy volunteers under a double-blind, placebo-controlled study and confirmed their side effects.

Modaghegh *et al.* investigated the safety of saffron (200 and 400 mg tablet) during 7 days for short term safety and tolerability in healthy volunteers. In this study, saffron decreased slightly red blood cell, hemoglobin, hematocrit and platelets, and merely increased sodium, blood urea nitrogen and creatinine in blood. The authors concluded that such fluctuations were not important for clinical use although the above hematological and biochemical parameter's differences were found (24). Ayatollahi *et al.* also found that saffron (200 and 400 mg tablets) are safe drug on coagulation system such as the plasma levels of fibrinogen, factor VII in healthy volunteers under a double-blind, placebo-controlled study for 1 week (42). The study of crocin tablet was administrated a randomized, double-blind, placebo-controlled design in healthy volunteers for one month. Volunteers received crocin tablet (20 mg) or placebo. During treated period biochemical, hematological, urinary and hormonal parameters were analyzed. From these results it became clear that the crocin tablet showed no major side effect except decreases of amylase, white blood cells and partial thromboplastin time (43).

We summarize the side effects of saffron and crocin. As side effects of saffron dizziness, dry mouth, fatigue, hypomania, nausea and vomiting, confusion, agitation and sedation are confirmed (44). As hematological parameter the decreases of red blood cell, hemoglobin, hematocrit and platelets, and increases of sodium, urea nitrogen and creatinine in blood and the decreases of amylase, white blood cells and partial thromboplastin time are reported. However, these side effects were same in both saffron extract and placebo groups except vomiting (45). Bloody diarrhoea, hematuria, bleeding from the nose, uterine bleeding and yellowing of the skin are occurred as side effects by the uptake of higher amount of saffron (46,47).

Clinical trials of saffron on sleep and relation between sleep and dementia

A double-blinded clinical trial randomly allowed to the saffron alcohol extractives (0.6 mg/day) or a placebo group using 21 healthy adult volunteers was investigated. The saffron extractives group significantly reduced the Pittsburgh Sleep Quality Index scores. Moreover, when compared with the placebo group a significant positive effect of saffron extractives (0.6 mg/day) on daytime dysfunction was appeared over 4 weeks in the saffron extractives group (48).

Recently Irwin indicated that sleep disorders induced inflammatory phenomenon becoming AD (26). Moreover, sleep disorder was suggested to be an important risk factor resulting in an important target for AD prevention supported by several meta-analyses and systematic reviews (49-51). Ohara *et al.* indicated that sleep disturbances and the hypnotic drug use increased the risk of dementia in especially aged people reported by the Hisayama epidemiological study in Fukuoka, Japan (34). The people having daily sleep durations shorter than 5.0 h have 2-fold of risk for vD and AD compared with more than 10 h cohort. This result indicated that the short sleep may influence the aging of brain and β-amyloid accumulation inducing AD. Ohara *et al.* also suggested that the sleep disorder induced inflammation related phenomenon and then dementia via depression (34). As we reported saffron and crocin improve non-LEM sleeping (52), the sleep time extension may be able to prevent dementia.

In the several clinical disciplines the combinations of Kampo formulas with saffron have been prescribed like that 100 mg per day of saffron was clinically used together with Chitosan, Daijyokito, Hangekobokuto, Saikokaryukotuboreito and Sansoninto which are used for sleep disorders and mental disease (53). From this evidence the combination of saffron and Kampo medicine may open

a possibility of new therapeutic methodology for dementia patients.

Activities of saffron and crocin for anti-depression activities and relation between depression and dementia

The neuroprotective activities of crocin were surveyed by *in vivo* models, like cerebral ischemia (20), AD (54), depression (55), and memory loss (56) that are clearly associated with dementia. Depression was considered to be an omen of early stage of dementia and then confirmed as a risk factor of dementia by 2–17 years of meta-analysis. The analysis of 10,189 depression patients in the Whitehall Study in the UK showed the increase of dementia patients with the years (33). Cognitive healthy people of 4,922 around 70–80 years old were observed in 14 years resulted that the dominant number of dementia patients developed via depression (57). From above evidence it is clear that the indirect relation between saffron/crocin and dementia via sleeping and/or depression disorders was confirmed in this session.

Saffron for anti-dementia in clinical trials

The occurrence of neurodegenerative disorders such as dementia has been increasing with increased life expectancy. Among them AD is the most common, with aging the most important single risk factor and estimated to be 67.6% of dementia in the old age population. Therefore, methods to prevent dementia are needed. Among its therapeutic benefits, saffron has been reported to have neuroprotective effects (58). Data on crocin, a major constituent in saffron has shown *in vivo* and *in vitro* neuroprotective activities such as on neuronal antioxidant (59-61), anti-inflammatory (62-64), related to β-amyroid peptide, neuronal cell anti-apoptosis (65), anti-hyperlipidemia (66,67), anti-atherosclerotic (68) and anti-autophagy properties (69), resulting in reduced neuronal damage. Recently several clinical trials for AD patients as following.

Totally 54 patients of 55 years old or more old AD patients were administered saffron extractives (30 mg) or donepezil (10 mg) as a positive control in a day for 22 weeks under a double-blinded/phase II study conducting Alzheimer's Disease Assessment Scale, Cognitive Subscale and Clinical Dementia Rating Scale and Sums of Boxes Scores compared with baseline. Adverse events (AEs) were systematically recorded. From this trial the outcome of saffron extractives was evaluated to be the same with donepezil for mild to moderate AD patients resulting in possible therapeutic effect of saffron extractives. The major adverse effect of saffron, vomiting was lower than that of donepezil (70). The double-blinded randomized clinical trial of saffron extract (30 mg per day) was performed on 46 mild to moderate AD patients for 16 weeks. The authors confirmed a significant efficacy comparing cognitive function and no side effect compared with the placebo group (71). Saffron extract (30 mg per day) capsules or memantine (20 mg per day) as a positive control was investigated as the randomized double blind parallel-group study for 68 moderate to severe AD (Mini-Mental State Examination score of 8–14) patients during one year. Patients were judged every month using Severe Cognitive Impairment Rating Scale (SCIRS) and Functional Assessment Staging (FAST). The saffron extract capsule indicated the same outcomes with memantine in decreasing cognitive phenomena without the side effect. However, the authors suggested that more large scale sample size and more long investigation terms are desired for more clear differences in the two score changes (72). Thirty five and 18 mild cognitive impairment (MCI) patients were administrated saffron alcohol extracts (125 mg/day) and placebo, respectively for one year in single-blind randomized clinical trial. Patients treated with saffron extractives improved cognitive performance judging by Mini-Mental State Examination score, event-related potential, channel electroencephalogram and magnetic resonance imaging. From these evidence the authors suggested that saffron is a good choice for treatment of mild cognitive impairment patients (73). Akhondzadeh *et al.* reported that 55 mild-to-moderate AD patients uptook 30 mg/day of saffron capsule or donepezil 10 mg/day for 22 weeks resulting that saffron and donepezil showed effectiveness without the side effect (70). Ayati *et al.* reviewed the relevant randomized clinical trials measuring AD Disease Assessment Scale-cognitive subscale and Clinical Dementia Rating Scale-Sums of Boxes in 2020 resulted that saffron significantly improved the cognitive function in AD patients compared to placebo groups and further no significant difference on daily living function and quality of life compared to the ordinary medicine (45). Recently Zandi *et al.* also reviewed the clinical trials of saffron for AD patients together with the mechanisms of AD onset such as neuronal oxidation, accumulation of

amyloid-β and its induced inflammation, neuronal cell apoptosis, tau phosphorylation and apolipoprotein E, and the inhibiting effect of saffron and its constituents *in vitro* and *in vivo* (73).

Combination of saffron and other herb medicine for dementia

Three herbal medicines such as saffron, ginseng and Gingko biloba were prescribed together to prepare a new formula, SaiLuoTong (SLT) in China. Among them the effects of saffron were discussed previously. Lee *et al.* investigated that ginseng and its constituents enhanced cell survival, neurite growth, and rescued the death of neurons both *in vivo* and *in vitro* (74). Ginseng was found to increase the level of choline acetyltransferases in animal brains, indicating that they might ameliorate central cholinergic role resulting to treat dementia (75). Ginsenosides enhanced dopamine and norepinephirine in the cerebral cortex, indicating that the ginseng extract affected attention, auditive reaction time, sensory-motor function, and mental processes in healthy persons (76). Further studies have also shown positive effects on learning and memory either in aged and/or brain damaged gnawing animals (77). The effect of ginsenoside Rg1 on the proliferation of neural precursor cells may be a necessary mechanism in its cognitive enhancer and anti-aging effects (78). Recently Li *et al.* reviewed preclinical and clinical evidences (79). When the red ginseng steamed (4.5 g/day) was administrated for 24 weeks, behavioral symptom and learning and memory functions are promoted in moderately severe AD patients at 12 weeks resulting in the next 12-week follow-up (80). AD patients administrated high-dose (9 g/day) Korean red ginseng show significant promotions on the AD assessment scale (ADAS) and Clinical Dementia Rating scales after 12-week administration than that of placebo group (81).

On the other hand, *G. biloba* is also well known anti-dementia herb. Another similar product, EGb761 extract fraction of the dried leaves of *G. biloba*, containing flavone glycosides and diterpene lactones is an OTC drug for the prevention of vD in Europe (28).

From above evidence the SLT prescription is easily suggested to be used for prevention and/or treatment for dementia. Three hundred twenty three patients were randomly assigned to experimental groups (SLT 360 or 240 mg/day) for 26 or 52 weeks, or placebo group. Higher dose groups (360 mg/day) at week 26 were more effective than that of lower dose group (240 mg/day) resulted that SLT can be used for the treatment of vD (82).

Kai Xin San is prescribed with *P. ginseng*, *P. tenuifolia*, *P. cocos* and *A. tatarinowii*. This formula was confirmed to be used for the senile dementia (83). From the above evidences of Kai Xin San and neuronal function of saffron such as anti-neuronal cell death (20) and learning and memory activity (70), the combination of saffron and Kai Xin San was approved as Hul Tong capsule for OTC traditional Chinese medicine for prevention of dementia in Singapore in 2018.

Discussion

In the first stage we suggested that the quality control of saffron is necessary for all investigations because its major and main active constituent, crocin is sensitive against humidity concerned to β-glycosidase, auto-oxidation and high temperature. Currently, 25% of the population has been reported sleeping disorders in Japan for which saffron was prescribed in combination with Kampo medicine (53). *In vivo* investigation we found that saffron increased the non-REM sleeping time resulting in a sleeping promoter (52). Thus, the accumulated evidence easily suggested the clinical advantage of saffron for sleeping disorder. Sleeping and/or depression disorders apparently induced neurodegenerative illness reaching dementia. Moreover, the results discussed already indicated that saffron improves AD symptomatic in clinical trials compared with dementia drug as controls. However, the large scale and more long clinical trials are required for the development of anti-dementia and/or anti-AD drug.

The authors summarized the role of saffron and its major constituent, crocin for neurodegenerative disorders especially concerned to dementia as indicated in *Figure 3*. The anti-dementia activities of saffron and crocin were well known by the protection of neuronal cell death because of strong anti-oxidation related to glutathione-dependent inhibitory mechanism, anti-inflammation activities (20) and the enhancement of learning-memory via long-term potentiation (LTP) inhibited by ethanol (21) resulting in N-methyl-D-aspartate (NMDA)-receptor-reply in hippocampal cells (84). Gathered evidence saffron can be

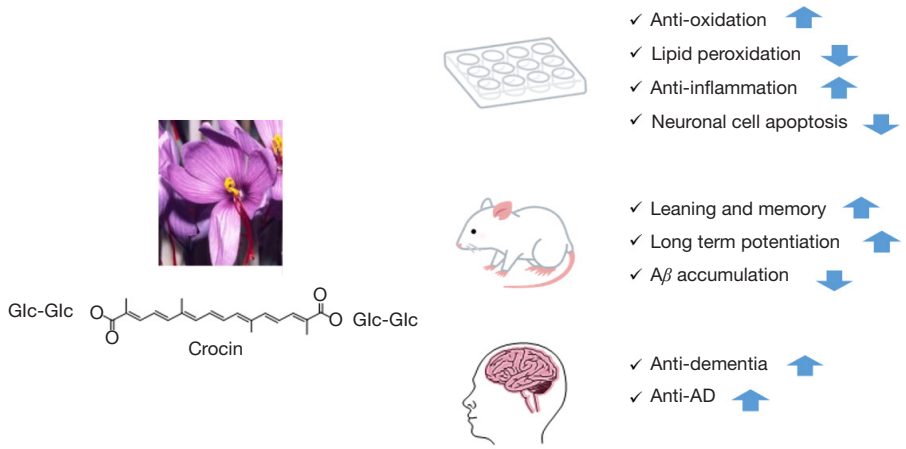


Figure 3 Neuronal activity of saffron, crocin on dementia/Alzheimer's disease. Geb, gentiobiose (β-D-glucopyranosyl-(1–6)-β-D-glucopyranoside; Glc, β-D-glucopyranoside; AD, Alzheimer's disease.

called as multifunctional herb medicine.

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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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