Pharmacognosy Reviews, 2023; 17(34):382-391.
www.phcogrev.com

Review Article

Neuroprotective Potency of *Crocus sativum* L. for Alzheimer's Disease

Sharada L. Deore[1], R. C. Vighne[1], Bhushan A. Baviskar[2], Anjali A. Kide[1], Bhavana A. Shende[2]

[1]Department of Pharmacognosy, Government College of Pharmacy, Amravati, Maharashtra, INDIA.
[2]Department of Pharmaceutical Chemistry, Government College of Pharmacy, Amravati, Maharashtra, INDIA.

ABSTRACT

"Alzheimer's disease (AD) is recognised as the main cause of cognitive decline in the elderly." Due to unpleasant complicacy, low patient compliance, short $t_{1/2}$ and biologic restrictions these current therapeutic techniques are insufficiently effective.In AD decrease the level of acetylcholine (ACh) in the brain. Presently available drugs for AD temporarily relieve dementia symptoms by acting as an AChEI and NMDA receptor antagonist, but they cannot prevent or cure disease progression. The current emphasis of Alzheimer's research is on creating antibodies to eliminate Aβ and tau protein clumps. Some medicinal plants, either in their raw form or as isolated compounds has been found to reduce the degenerative symptoms linked to Alzheimer's illness. As a result, researchers are looking for novel, multi-targeted therapy strategies. The plant *Crocus sativus* is rich in biological and pharmacological properties, primarily antioxidant and anti-inflammatory. The findings show that *C. sativum* and its chemical ingredients might result to improve memory and cognitive impairment. Traditional medicine has defined the major qualities of this plant to the chemical constituents of saffron like colouring pigment also known as crocin, a natural apocarotenoid crocetin, aromatic saffranal and few phenolic components. Anti-convulsant, antioxidant, anti-diabetic, anti-apoptotic, anti-bacterial, anti-cancer, antigenotoxic, angiogenesis, anti-depressant, anti-inflammatory and other properties are found in *C. sativus*. Crocin is a water-soluble carotenoid, making it a unique antioxidant. It has been demonstrated to boost learning and memory while also protecting brain cells.

Keywords: Saffron, Neuroprotective, Alzheimer's disease, Crocin, Carotenoid, Neurotransmitter, Neurodegenerative, Amyloid beta, Dementia, Antioxidant.

Correspondence:
Mr. R. C. Vighne
Department of Pharmacognosy,
Government College of Pharmacy,
Amravati-444604, Maharashtra, INDIA.
Email: rampharmacy14@gmail.com

Received: 21-04-2023;
Revised: 08-05-2023;
Accepted: 28-05-2023.

INTRODUCTION

Saffron is a dried red stigma and style top of *Crocus sativus* L. belonging to family Iridaceae. It is angiosperm-containing plant. It is cultivated in region of Iran, India, Italy and Spain. saffron is important as the world's costliest spice. Traditional uses of *Crocus sativum* include its numerous health advantages and use as a natural food colourant. More than 90% of the saffron consumed worldwide is currently supplied by Iran. Iranian saffron are the three subcategories. Pushal, Negin, and Sargol are three characters, Pushal is saffron's dried stigma and style. The primary distinction between Negin and Sargol is that the red stigma in Sargol has been removed.[1] *C. sativus* has a high concentration of carotenoids, including crocin and crocetin. According to a phytochemical study, saffron stigmas contain more than 150 phytochemical components. Proteins, amino acids, gums, mucilage, minerals, carbohydrates, vitamins (particularly riboflavin and thiamine), pigments, anthocyanins, flavonoids, carotenoid degradation products like crocin, crocetin and safranin are the fragrant of terpene species and picrocrocin glucoside, which adds bitterness.[2] It is based on the analysis of marker compounds in *Crocus sativum* for dietary supplements or pharmaceuticals, particularly safranal, picrocrocin and crocin. The distinct flavour and aroma of *C. sativum* samples are the primary indicators of their high grade.[3] Dementia is the memory problem, confusion behaviour changes, loss of ability in day-to-day life is the primarily cause of Alzheimer disease, it happens in people over the age of 65, and it is defined pathologically as protein clump development and neurofibrillary tangles, which are accumulations of paired helical filaments that cause cognitive impairment and memory loss. The hydrophobic amyloid-peptides of roughly 4 kDa that produce the extremely insoluble amyloid fibrils are created by proteolytic severance of a longer precursor protein called the amyloid-protein precursor.[4] Mild Behavioural Impairment (MBI), which was recently announced by researchers at the Alzheimer's Association International Conference 2016 (AAIC 2016) in Toronto, was thought to be a precursor to

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DOI: 10.5530/phrev.2023.17.14

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neurodegeneration and the development of Alzheimer's disease or dementia.[5] Five different types of behavioural symptoms in a patient were evaluated using an MBI check list and the screening may have helped identify early signs of neurodegeneration. In the US, there is sixth most common cause of death by AD. The patients suffering from AD have typically lived for eight years. A patient's chance of living might vary from four to twenty years depending on their age, level of care and other medical issues. Alzheimer's disease currently has no cure.[6] To deal with cognitive difficulties five drugs have been created, with numerous more in the works. Memantine is an NMDA receptor blocker and Donepezil (for improvement of mental function by inhibiting the cholinesterase enzyme), rivastigmine (improve the ability to remember, think clearly, communicate, and perform day to day activities by inhibiting cholinesterase enzyme), galantamine (for mild to moderate AD) and tacrine (improve thinking ability but not treat AD) are four acetylcholinesterase inhibitors. Tacrine, the first drug that approved drug for Alzheimer's disease. It has been largely abandoned due to its poor efficacy and significant side effects. Current FDA-approved drugs for Alzheimer's disease are still mixtures of memantine and donepezil standard or formulations. That drugs attempt to improve function of memory by enhancing synaptic activity (increase probability of synaptic terminals), but they do not provide neuronal protection. Anticholinesterase prevents the neurosis that led to increase the amount of Ach level in brain. Memantine is an NMDA receptor antagonist that works by influencing the activity of glutamate, a critical neurotransmitter in brain functions related to learning and memory. Excess glutamate is released in Alzheimer's patients, causing neuronal damage and cell death. Memantine regulates glutamate levels by partially inhibiting NMDA receptors.[7] For the treatment of Alzheimer's disease, long-term therapy with donepezil, galantamine, memantine, and rivastigmine or a combination of donepezil and memantine is now preferred. Some medications have low effectiveness but can have serious negative effects. Alzheimer's disease is characterised pathologically by the formation of extracellular amyloid-A peptide production and plaque deposition, as well as intracellular aggregation of microtubule-associated tau protein as neurofibrillary tangles and neuron and synapse loss. In recent years, a huge attempt has been made to develop vaccination therapies based on the Aβ and tau proteins. Clinical investigations have shown that vaccination therapy does not significantly enhance cognition in Alzheimer's disease patients. Although the causes underlying Alzheimer's disease are unknown, some risk factors exist, including genetic predisposition, oxidative stress, environmental stress, inflammation, a history of severe head injuries, depression or hypertension. To delay or prevent the cognitive, behavioural, and psychiatric symptoms of dementia associated with Alzheimer's disease, clearly practical and safe techniques or therapies are necessary. while also preserving or protecting neurons during ageing. In recent years, numerous studies using herbs that conducted to find options for the prevention and treatment of AD.[8] Among the herbal plants historically used for enhancement of memory and brain health, including *Huperzia serrata* (which contain acetylcholinesterase inhibiter huperzine), *Salvia officinalis* (reduce stress and anxiety neuroprotection, *Ginkgo biloba*, *Melissa officinalis*, and *Crocus sativus* (saffron), saffron and its primary ingredient crocin have been widely investigated for AD. Crocin is thought to be the primary cause of saffron positive properties. Early studies in clinical trials suggests that crocin improves cognition in people with AD in the same way that memantine and donepezil are used against moderate-to-severe Alzheimer's disease respectively. According to *in vitro* and animal research, crocin may provide neuroprotection as well as memory and cognition improvement.

Taxonomical classification

Kingdom	Plantae	Order	Asparagales
Division	Magnoliophyta	Family	Iridaceae
Class	Liliopsida	Genus	Crocus
Subclass	Monocot	Species	*C. sativus*

Geographical Region of Saffron

It is cultivated in region of Iran, India, Italy and Spain. saffron is important as the world's costliest spice. More than 90% of the saffron consumed worldwide is currently supplied by Iran. Iranian saffron are the three subcategories. Pushal, Negin, and Sargol are three characters, Pushal is saffron's dried stigma and style.

METHODOLOGY

Data used in this review was gathered from several of the databases available from Web of Science (WOS), Google Scholar, PubMed and Scopus up until the end of May 2023. "Neuroprotective" or "neurotoxicity" and "*Crocus sativus*" were among the search terms used. Any research that resulted in alterations in neurotransmitter release, behavioural changes, or anti-oxidant factors was considered, including *in vitro* research, animal studies, and clinical trials included in the review papers.

Phytochemical Properties of Saffron

The important chemical constituents present in saffron are crocin (a colouring pigment), picrocrocin (a unique flavour), safranal (the deglycosylase version of picrocrocin and it is main active principle of the stigmas).[9,10] Crocin and crocetin, as well as the monoterpene aldehyde safranal, are carotenoids found in saffron. The bioactive substances known as carotenoids have a strong antioxidant capability.[11-13] The most popular scientific methods for determination of active principle include HPLC, UV-visible spectroscopy, ionisation-mass spectrometry and FT-NIR.[14,15]

Medicinal properties of *C. sativus*

C. sativus is used to treat cognitive difficulties in conventional Persian medication. *C. sativus* components now a days widely used to treat various neurological illnesses and to relax smooth muscle.[16] *C. sativus* have efficacy to treat mild to moderate depression. *Crocus sativus* contain major active constituent is crocin and it's had strong antioxidant properties via lowering MDA levels.[17] *Crocus sativus* extract (100 mg/kg) lowered glutamate and aspartate concentrations, as well as K-ATPase and SOD, catalase activity produced by ischemia.[18,19] The extract of *Crocus sativum* at about 200 mg/kg and honey syrup administration it decreased aluminium chloride-induced neurotoxicity.[20,21] For six weeks, saffron extract (30 mg/day) was equally showing the result as fluoxetine and imipramine (100 mg/day) mild-to-moderate depression treatment.[22-24]

Bioactive Principles of Saffron

There are a number of bioactive constituents present in *Crocus sativum*, including Nitrogenous matter, flavonoids, anthocyanins, vitamins, raw fibres, gums, volatile oil, proteins, glycosides, amino acids, carbs, minerals, monoterpenes, and aldehydes are the primary components of saffron.[25] The primary bioactive components are also thought to be picrocrocin (which gives apocarotenoids their bitter taste), crocetin, crocin (which gives them their colour), and safranal (which gives them their flavour and perfume).[26] High-quality saffron contains 2.5% volatile compounds, including safranal, and about 30% crocins, 5 to 15% picrocrocin, etc.[27]

Biological and Pharmaceutical Aspects of Saffron

Saffron and other active chemical constituents associated with neuroprotective properties against neurogenerative disorders include Parkinson's, anticonvulsant, antidepressant, anxiolytic, and anti-schizophrenia, antioxidant, antitussive, hypolipidemic, Alzheimer's and anti-ischemic (heart, muscle, renal, and brain ischemia); hypolipidemic.[28,29] *In vivo* study of Crocus sativum on different animals model for Alzheimer that are summerized in Table 2. The term "anti-perfume" refers to the usage of dyes in the textile industry.[30,31]

Structure

The major components of Crocus sativus stigma are the apocarotenoids like, picrocrocin (responsible for bitter taste), crocin, crocetin (responsible for bright natural color), and the odor-active safranal. Some basic structure of saffron are summarized in Figure 1.

Neuroprotective effects of Crocus sativum

Saffron is grown in a few nations, including Iran, Spain, Turkey, and Afghanistan. A little bit of the yellowish style from the *C. sativus* plant is linked to the dried, dark-red stigma that makes up saffron. In many parts of the world, it is primarily

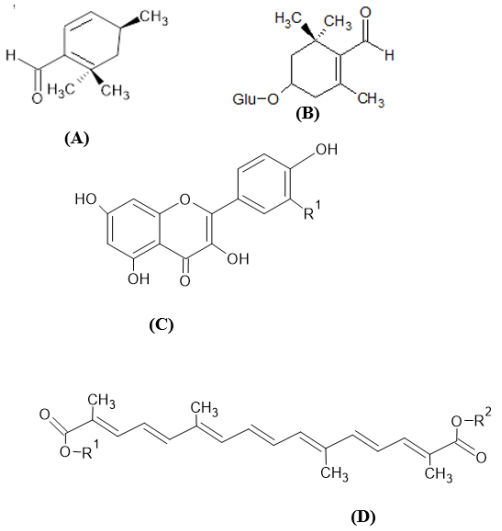


Figure 1: The basic structure of saffron contain (A) Safranal (monoterpenoid) (B) Picrocrocin (monoterpenes glycoside precursor) (C) Flavanol (D) Crocin (water soluble carotenoid compounds).

used as herbal medication.[32] There are 150 distinct chemicals in saffron, including sugars, vitamins, polypeptides, lipids, water, and minerals. The primary biologically active components of *C. sativum* are crocins, a group of carotenoids that are all red, water-soluble, and glycosides of crocetin. Moreover, saffron contains the bioactive substances crocin, crocetin, picrocrocin, and safranal in four primary amounts. These bioactives substances and its pharmacogogical activity summerised in Table 1. Picrocrocin, another component of saffron, has a bitter flavour.[33]

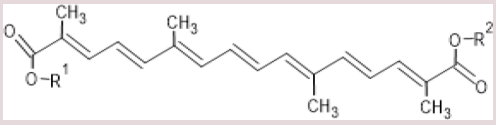
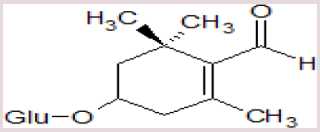
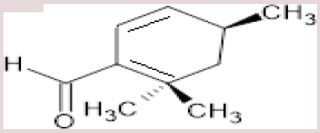
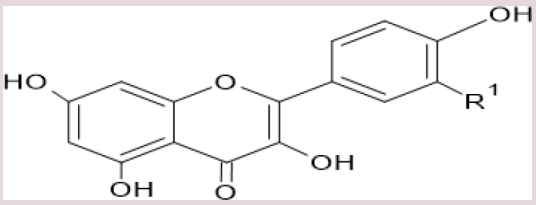
FDA Approved drug for AD

As per investigation, there is no proper available treatment for AD, but one medication may help to delay clinical degeneration and improve cognition function. AD symptoms such as memory loss and confusion can be alleviated. In the US, the FDA has approved pharmaceuticals in two ways: drugs that may help people with Alzheimer's disease see a gradual clinical decline and treatments that may temporarily relieve some of the illness's related symptoms. Before initiating any treatment, it is necessary to consult with a health care professional to determine its relevance. To ensure that the necessary guidelines are carefully followed, patients who use these medications must be continuously consult with physician.

Medicines that could impede the progression of Alzheimer's

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

Table 1: Secondary metabolites of Saffron and its pharmacological activities.

Molecular Formula	Structure	Characterized constituent	Pharmacological activity
$C_{44}H_{64}O_{24}$		Crocin	Strong antioxidant activity.
$C_{16}H_{26}O_7$		Picrocrocin	Anticancer and memory enhancer properties.
$C_{10}H_{14}O$		Safranal	Anticonvulsant effects, Hypnotic effect.
$C_{15}H_{14}O_2$		4 - Flavanol	Anticancer, Antioxidant, Anti-inflammatory and antiviral properties.

aducanumab (AduhelmTM) is given Intravenously (IV). A diagnostic test that has been approved by the FDA is typically recommended prior to initiating treatment. It is a monoclonal antibody (mAb) with high affinity that is exclusively human. It primarily binds parenchymal amyloid over vascular amyloid. It was created using a reverse translational medical technique, from which the antibody was derived. from elderly people who had not yet gotten Alzheimer's disease in the hopes that they might have exceptional resistance to the condition. When aducanumab was given intraperitoneally to Tg2576 mice, it was discovered that it showed parenchymal plaques and aided in their elimination without generating microhaemorrhages. Also, the researchers discovered an increase of brain macrophages surrounding the remaining plaques, implying that phagocytosis could be a route to exceptional disease resistance.[34] A monoclonal IgG1 anti-body called aducanumab is attached to the amyloid's amino acids 3-7.1-6.6. Most of the interactions between beta amyloid and the Fab region of aducanumab lead to the formation of amyloid residues like His6, Glu3, Arg5, and Phe4. Animal studies have shown that aducanumab therapy reduces amyloid-, while human trials have not shown any appreciable changes in amyloid-40 and amyloid-42.[35] Novel approch for treating to Alzheimer disease. some novel formulation of saffron and its activity for neuroprotection summerized in Table 3.

Available medication for Alzheimer's disease

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

Acetylcholinesterase inhibitors

FDA-approved drugs are Donepezil and rivastigmine for the treatment of mild, moderate and severe Alzheimer's disease respectively. Galantamine also FDA approved drug only for mild and moderate Alzheimer's disease. AChE activity is

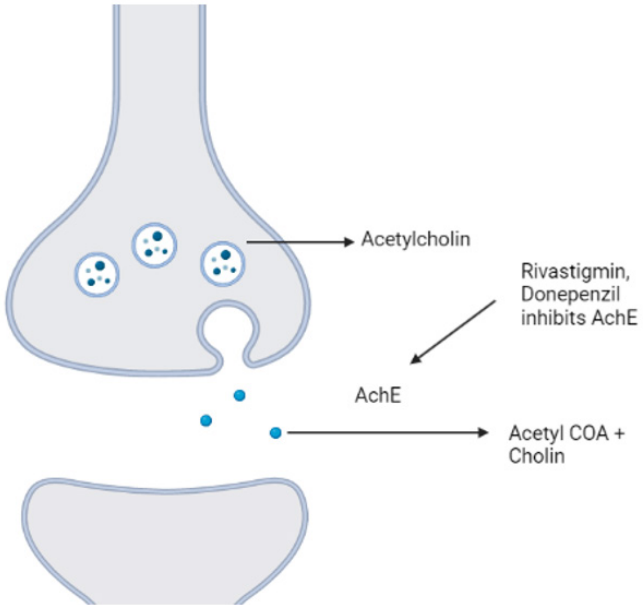


Figure 2: Acetylcholinesterase inhibitors mechanism of action.

Table 2: *In vivo* study of *Crocus sativum* on animals, dose and outcome occur in different models.

Animal	Model	Drug/ Route of Administration/ Dose	Outcome	References
Male mice	50mgAlCl3/kg/day (5 week) - Control. Aluminum + saffron (60 mg)/ kg/day) 6 days - (Treated) i.p route	60 mg SE i.p	AChE and BuChE activity in the Al + saffron group provide evidence for the neuroprotective properties of saffron in toxic environments.	[41]
Meriones shawi	Pb 25 mg / kg for 3 days i.p	50 mg / kg *C. sativus*	Pb disrupts dopaminergic and noradrenergic systems, *Crocus sativus* reversed 90% of the reduction in locomotor activity in Pb-intoxicated meriones.	[2]
(Drosophila melanogaster) Drosophila head/body regions of flies	Rotenone (500mM) (ROT)	saffron and crocin	The anti-oxidative activity of saffron may be primarily responsible for the neuroprotective advantages seen in the fly model.	[42]
Wistar rats	Model of middle cerebral artery blockage,	*C. sativum* (100 mg/kg) for seven day Given through i.p route	Sodium, potassium-ATPase, and superoxide dismutase (SOD) activity were reduced. The antioxidant properties of CS are most likely responsible for its efficacy in localised ischemia.	[21]
Adult male NMRI rats (200-300 g)	four vessel occlusion method to induse global cerebral ichemia	Safranal i.p. (Dose-727.5, 63.75, 145.5, 72.75 mg/kg3 body weight)	Safranal reduced oxidative damage caused by cerebral ischemia in the rat hippocampus.	[43]
Male mice	C57BL/6J wild-type mice aged 8 weeks	crocetin's orally via the gavage technique (60 mg/kg) or i.v route through the artery 60mg/kg	absorption through the mouth Crocin from aqueous extract of saffron was rapidly hydrolysed in the GI tract.	[44]
Albino Wistar rats	stereotaxic apparatus Morris water maze	Xylazine-20 mg/kg by i.p route + ketamine (100 mg/kg),	Crocin prevents beta amyloid-induced apoptosis, which may be due to its antioxidant qualities.	[44]
Male mice (4-months-old)	SH-SY5Y cell	Saffron extract (i.p)	In SH-SY5Y cells, in response to H_2O_2-induced toxicity, saffron extract increased total brain antioxidant activity while decreasing caspase-3 activity.	[45]
Male adult Wistar rats (310-350 g)	intracerebroventricular streptozotocin induce rat model	*Crocus sativus* extract (60 mg/kg; i.p)	*C. sativus* extract was found to be effective in reducing cognitive deficits caused by STZ in rats, and it has the potential to cure neurodegenerative illnesses such as Alzheimer's.	[46]
Male Wistar rats aged (weighing 200–250 g)	Morris water maze (MWM) test	crocin Dose – 30 and 60 mg/kg	Crocin is a viable therapy for ischemic cerebrovascular accidents due to its memory-preserving, Ach-increasing, and neuroprotective effects.	[47]

continued...

Table 2: Cont'd.

Male and female mice (C57BL/6 J)	Normal	Trans-crocin 4 (TC4) intraperitonially.	potential activity against Alzheimer's Disease (AD) increase circulating steroids.	[48]
Rat/ 32, 4	Normal (Novel Object Recognition Test)	Crocins + memantine combination 5, 15, and 30 mg/kg Intraperitoneal route	Increase Discrimination index, Total exploration times, Total motor activity increases.	[49]
Rat/ 48, 6	Barnes Maze	Saffron + Crocin for 28 days Dose - 10 µg/ ICV	Increase behavior, locating latency time.	[50]
Mouse/ 24, 3	Passive Avoidance Test (PAT)	Saffron Dose at about 50,150 and 450 mg/kg/ i.p. for 3 days.	The amount of time spent in the light compartment grows, while the amount of time spent in the dark area diminishes.	[51]
Mouse / hippocampal HT22 cells	hippocampal HT22 cells	crocetin	HT22 cells were protected against A1-42, reactive oxygen species (ROS) were reduced, and a neuroprotective effect was seen.	[52]
Rat/ 48, 4	Aβ25–35 Y-maze, sucrose preference test	Crocin 40 mg/kg for 14 day intraperitoneal route.	Reduce the number of attempts, raise the rate of correct reactions, and boost sucrose preference. Reduce the number of apoptotic cells while increasing Bcl-2 and also ↓ Caspase-endoplasmic reticulum stress in the hippocampus and PFC.	[53]
Rat/ 48, 5	EPM (elevated plus maze)	Crocin 25 mg/kg Intraperitoneal route For 8 weeks	Decreased weight levels, increased percentage of Open Arm Entrance, and Aerobic Ability, increased proportion of Elapsed Time in the Open Arm.	[54]
Mouse	D-galactose and NaNO2	Saffron/ 15 days/ 30 mg/ kg / i.p.	↑ Avoidance responses, ↑STL	[55]
Wistar rats/ 4	Morris water maze (MWM) test 4-vessel occlusion brain ischemia	Crocin Doses - 30, 60 mg/kg for 7 days	↑ Ach- and ↑ Neuronal antiapoptotic ↓ Ischemic cerebrovascular ↑ neuroprotective effects.	[49]
Rat 90, 6	STZ, Y-maze, PAT	Crocin Dose - 15 and 30 mg/kg Intraperitoneal route for 2 day	Reduce body weight, ↑ step-through delay, increase (%) Alternation behaviour and ↑ number of animals that fall.	[56]
Rat 32, 4	Normal	Crocins, + memantine Dose -5, 15 30 mg/kg/i.p	Increases Discrimination index, Total exploration times, Total motor activity.	[51]

Table 3: Novel formulation of saffron and its activity for neuroprotection.

Drugs/ Extract	Model	Novel formulation	Activity/Result	References
Saffron and kaempferol extracts	Mouse fibroblasts	Antioxidant enriched hydrogels	*In vitro* grown fibroblasts demonstrated good antioxidant and biocompatibility using hydrogels loaded with kaempferol and crocin derived from saffron petals. These new hydrogel variants could be used in wound therapy and/or cosmetics.	[57]
Crocetin:PLGA (1:20)	MCF-7 cancer cells	Nanoparticle	Crocetin, in its free form, exerts greater cytotoxicity and apoptotic effects on MCF-7 cancer cells. The nanoparticles were generated by evaporating a single emulsion/ solvent, and their ideal size was 2884.22 nm, with an encapsulation efficiency of 97.20%5.39.	[58]
DSPG:Chol:DSPC/ Crocin DSPG: EPC: Chol/Crocin DOPE:Chol:DSPC/ Crocin	MCF-7 cells	Liposome (150–200nm)	Crocin kills HeLa and MCF-7 cells more effectively. DOPE, DSPC, and cholesterol nanoliposomes inhibited the most effectively. Crocin nanoliposomal formulation was also presented as a chemotherapeutic agent in cancer treatment in this study.	[59]
DSPC/Chol/DSPG/ safranal	HeLa cell	Safranal Nanoparticles	Cytotoxicity was increased as compared to safranal solution.	[60]
Safranal+Glyceryl monostearate Tween 80/safranal	Normal	SLNs (100–200nm)	Safranal topical administration via an efficient nanocarrier	[61]
Emulsions Carbitol+tween-20/ labrasol+cremophore EL+water+safranal	Normal	Emulsion	Treatment of cerebral ischemia with a more effective neuroprotective drug than free safranal	[62]
Crocin (Span80/polyglycerol polyricinoleate)	Normal	crocin loaded nano-emulsions	It creates nanoscale emulsions without the use of cosurfactants, a large amount of surfactant, or high energy methods.	[63]
Saffron	Disk diffusion method	Silver (AgNPs) nanoparticles	Effective antibacterial activity	[64]
Saffron	breast cancer cells (MCF-7)	Gold (AuNPs)	Potent anti-tumor activity Higher cytotoxicity	[65]
PEG-SeNPs and crocin	Human lung cancer cell lines (A549 cells)	Selenium nanoparticles	The acidic conditions of the tumour microenvironment promote the synergistic anticancer impact of PEG-SeNPs and crocin.	[66]
Crocetin	HT22 hippocampal cells	CuO nanoparticles (31 nm)	CuO nanoparticles are neurotoxic to HT22 hippocampus cells but in presence of crocetin, These nanoparticles inhibited the activity of certain antioxidants.	[67]
Nanostructured lipid dispersions + Crocin	Franz cells (Human melanoma cell line)	Nanostructured lipid dispersions	The MTT test was performed to investigate the antioxidant and antiproliferative activity of nanostructured lipid dispersions. This can protect the labile chemical crocin from degradation, alter its skin distribution, and extend antioxidant effect.	[68]
Saffron petals extract + graphene oxide (GO) nanosheets + selenium	4T1 and MCF7 cells	Selenium nanoparticles (180–250 nm)	The crystal structure, form, chemical composition, and potential as an antioxidant, antibacterial, and anticancer agent of rGO SeNCs were investigated.	[69]

increased in patient suffering from AD that result in an increased destruction of acetylcholine and reduced acetylcholine level in the brain region. Ach concentrations decrease, which leads to the generation of -amyloid plaques and neurofibrillary tangles. These FDA-approved drugs mechanism by inhibiting the enzyme acetylcholinesterase, which is required for the metabolic destruction of acetylcholine, and it is summerized in Figure 2 hence increasing its levels in the brains of those suffering from mild to moderate Alzheimer's disease.[36] The most prevalent side effects of AChEIs acting on the GI tract include diarrhoea, nausea, and vomiting. Donepezil and galantamine are believed to be eliminated mostly by hepatic metabolism, but rivastigmine is eliminated via both hepatic and intestinal metabolism. Rivastigmine is a "pseudo-irreversible" AChE and BuChE inhibitor, whereas donepezil and galantamine are known to inhibit acetylcholinesterase selectively and reversibly. Rivastigmine has "pseudo-irreversible" acetylcholinesterase action because it produces a covalent carbamoyl-Acetylcholinesterase complex after combining with the main active site serine, preventing it from starting acetylcholine production.[37] Galantamine has a t1/2 of about 6 to 8 hr, but donepezil has an elimination half-life of 70 hr. Half-life of Rivastigmine is short to elimination slowly but a long duration of action.[38]

Glutamate Receptor Antagonist

Memantine is an NMDA receptor antagonist that protects the brain from the detrimental effects of elevated glutamate levels summerized in Figure 3. Memantine, also for the treatment of mild to moderate Alzheimer's disease, has been shown to improve cognitive skills and outcomes in patients with the condition.[39] Since memantine and AChEIs have complementary mechanisms of action, they can be used together. Combination therapy often benefits patients by producing cumulative effects without increasing unfavourable consequences.[40] Better overall functioning and therapeutic results are associated with the length and durability of monotherapy or combinatorial treatment modalities with higher doses in intermediate or advanced dementia. Memantine can cause pharmacotoxicity and psychosis when combined with other chemically similar NMDA receptor antagonists such as amantadine, budipine, ketamine, and dextromethorphan. The most frequent symptoms in clinical trials included dizziness, agitation, hallucinations, headaches, and tiredness. The less frequent effects were anxiety, emesis, urinary tract infections, and increased perspiration.

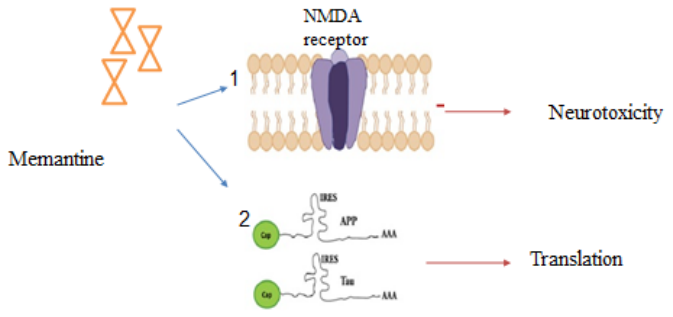


Figure 3: Mechanism of action of memantine.

Significance of work

A list of approved drugs for the treatment of Alzheimer's disease is provided in the present review. These drugs are help to enhance quality of life of Alzheimer's patients but surely not providing complete cure.

CONCLUSION

Many therapeutic targets for AD are the focus of numerous ongoing clinical trials. Given the current knowledge of a high failure rate in AD medication clinical trials, identifying a single primary outcome and developing novel trial designs are essential. The convergence of advancements in AD biomarkers tends to support most current investigations. Modern research is also concentrating on developing more thorough diagnosis tools and looking into ways to prevent diseases. Innovative healthcare needs planning, combined with the right pharmacological care. significantly enhance the Alzheimer's disease treatment plan. This would be accomplished by constructing a persuasive therapeutic alliance between the patient and healthcare professionals using complete and Psychoeducational, behavioural, psychoeducational, and environmental approaches are combined in an integrated strategy.

ACKNOWLEDGEMENT

The authors are thankful to DST, Delhi and RGSTC, Mumbai for research project funding for Alzheimer's disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AD: Alzheimer Disease; **AChEI:** Acetylcholinesterase inhibitor; **NMDA:** N-Methyl-D-aspartate; **Aβ:** Amyloid beta; **MBI:** Mild behavioural impairment; **FDA:** Food Drug Administration; **mAb:** Monoclonal Antibody; **MDA:** Malondialdehyde; **His:** Histidine; **Glu:** Glutamine; **Arg:** Arginine; **BuChE:** Butyl cholinesterase; **SOD:** Superoxide Dismutase; **GO:** Graphene oxide.

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Cite this article: Deore SL, Vighne RC, Baviskar BA, kide A, Shende B. Neuroprotective Potency of *Crocus sativum* L. for Alzheimer Disease. Pharmacog Rev. 2023;17(34):382-91.