Association of *Crocus sativus* with Cognitive Dysfunctions and Alzheimer’s Disease: A Systematic Review

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**Abstract:** Alzheimer’s disease (AD) is known as a principle basis of cognitive impairment in the elderly population. Current available therapeutic approaches are not applicable enough for the reason of intolerable side effects, low patients’ compliance due to the short half-life, and biopharmaceutical limitations. Therefore discovery alternative and multi-targeted therapeutic approaches are sought. *Crocus sativus* is a distinguished medicinal plant with a wide range of biological and pharmacological belongings, exclusively antioxidant and anti-inflammatory possessions. Following PRISMA guidelines, a systematic review was conducted by search in Electronic databases comprising Scopus, PubMed, Web of Science, and Embase using the keywords **cognitive OR cognition OR memory OR nootropic OR Alzheimer OR amnesia OR dementia AND “Crocus sativus” OR saffron OR crocin OR crocetin OR safranal until 21st February 2020. The results display that saffron and its major constituents are capable of having remarkable properties on memory and cognitive deficiency. Cell signaling pathways, anti-oxidative stress experiments, modulation in inflammatory and proinflammatory mediators, tauopathy, clearance of amyloid-beta aggregation, and histopathological alterations are indicated. Cognition tests and scores allied with memory loss are specified. The administration of saffron in experimental models seems to be an encouraging attitude in AD even though it is recommended that further studies for the valuation of pharmacokinetic properties and bioavailability enhancing carriers of these phytochemicals must be directed.

**Keywords:** Alzheimer’s disease; amnesia; cognitive disorders; crocetin; crocin; dementia; memory impairment; nootropic; saffron; safranal.

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1. **Introduction**

Neurodegenerative diseases, described by irreversible neuron loss and gliosis (nonspecific changes of glial cells), including disorders such as Parkinson’s disease (PD), frontotemporal degeneration (FTD) and Alzheimer’s disease (AD) [1]. AD is postulated through the process of getting old and the most prevalent reason for dementia in aged people. AD shows, unlike clinical manifestations; however, cognitive dysfunctions and memory loss are the main hallmarks that can lead to subsequent incapability and death [2]. AD recruits with diminishing in memory, and according to its progression, AD can be classified into three phases: a. the preclinical phase, there is not any modification in cognitive ability, b. the mild cognitive impairment (MCI) phase, and c. dementia phase [3]. The global annual expenses of
dementia were assessed (US) $818 billion in 2015. Besides, AD may inflict passionate stresses on patients and their relatives. It has been appraised that 115.4 million individuals will suffer from AD until the year 2050 [3,4].

1.1. Pathogenesis of Alzheimer’s Disease.

The hippocampus is an anatomical construction in the brain medial temporal lobe that is imperative for learning and memory. It consists of four subregions, which consist of the dentate gyrus (DG), hippocampus proper (CA1, CA2, and CA3), subicular complex, and entorhinal cortex (EC). A short-term high-frequency train of inducements to major synaptic pathways raises the amplitude of the excitatory postsynaptic potentials in the target hippocampal neurons. This enablement is entitled long-term potentiation (LTP), which is substantial in the duty of memory deficiencies. Abundant convoluted mechanisms anticipated in the pathogenesis of AD [5]. There is a low chance (5–10%) for the incidence of genetic history. AD is associated with mutations in three different genes: presenilin-1 (PS1), presenilin-2 (PS2), and amyloid-β precursor protein (APP-β) [6-10]. Aggregation of β-amyloid protein (Aβ) in neuritic plaques (NPs) and hyper-phosphorylation of tau (τ) protein (tauopathy) in neurofibrillary tangles (NFTs) are the most momentous pathophysiological changes [11-14]. The formation of Aβ deposits leads to an immune response with the contribution of astrocytes and microglia [5,11]. Reactive microglia can produce free radicals, which can be fatal for neurons. Activation of some T-cells has been observed in brain parenchyma of AD sufferings. Such cells release inflammatory mediators, including: interleukin (IL)-1, IL6, Y-interferon, and tumor necrosis factor-alpha (TNF-α). It has approved that usage of non-steroidal anti-inflammatory drugs (NSAIDs) modulates the inflammatory factors responsible in AD through inhibition of cyclo-oxygenase (COX). Evidence-based studies are endorsed effects of oxidative stress on augmentation of formation and accumulation Aβ and hyper-phosphorylation of tau. It was observed that alteration in levels of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and total antioxidant status (TAS) in erythrocyte and the plasma could be considered as a marker for pathological distinctions in the brain of patients with AD [15]. Environmental factors and apolipoprotein-E are claimed as other probable causes of AD [16,17].

1.2. Therapeutic Strategies in Alzheimer’s Disease.

As a reason for the intervention of multiple factors in the initiation of AD, a multi-target-directed ligand strategy will be an effective therapeutic approach [18]. There are two groups of FDA-approved medications for the management of AD symptoms. These drugs act through two mechanistic pathways; Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists (memantine) and cholinesterase inhibitors (ChEIs) (donepezil, galantamine, and rivastigmine) [19,20]. These chemicals, synthetic therapeutic agents, have some side effects, short half-life, and fluctuated bioavailability, which leads to narrow indications [18]. There is a growing demand for the usage of phytochemicals, nutraceuticals, and phytochemical components for the control and management of numerous diseases such as AD. Phosphatidylerine, Ginko, huperzine, and vinpocetine are obtainable natural-based products in the market, which can ameliorate mental functions in patients who have dementia. By considering the tendency to discover novel drugs and the opulent therapeutic potential of
phytochemicals, investigation of the anti-AD or memory-enhancing effects of those would be well-intentioned [16,21-24].

1.3. Phytochemical Properties of Saffron.

Saffron is botanically named as *Crocus sativus* L. (Iridaceae) has three major components; crocins, (the source of coloring pigment), the glycoside picrocrocin (a precursor of safranal and contributed its explicit flavor), and safranal (the deglycosylated form of picrocrocin and the major organoleptic principle of the stigmas) [25,26]. Crocin, crocetin are carotenoids of saffron, and safranal is a monoterpene aldehyde [27,28]. Carotenoids are bioactive components with great antioxidant potential [29]. The high-performance liquid chromatography (HPLC), ionization-mass spectrometry (APCI-MS), (Fourier transform near-infrared) FT-NIR, and ultraviolet-visible (UV-Vis) spectrometry analytical procedures are chiefly applied for qualitative and quantitative analysis of saffron components [30,31].

1.4. Biological and Pharmaceutical Aspects of Saffron.

Numerous pharmacological effects have been endorsed to saffron and its components including; anticancer [32,33], neuroprotective (anti-Alzheimer’s disease, anti-Parkinson, anticonvulsant, antidepressant, anxiolytic, and anti-schizophrenia) [34-37], anti-ischemic (heart, muscular, kidney, and brain ischemia, ) [38], antioxidant [39], antinociceptive, antitusssive, hypolipidemic, anti-diabetic [40], antidote (against snake venom, acrylamide, etc.), anti-obesity and anorectic, Aphrodisiac, nephroprotective [41], anti-hypertensive, anti-genotoxic, cardioprotective [42], antimicrobial, hepatoprotective, gastroprotective [43] and anti-inflammatory effects [44-46]. Saffron is wildly used in food flavoring and coloring, antipruritic and emollient, cosmetics, textile dye, perfume, and pharmaceutical industry [47,48].

2. Study Design

Herein we conducted the systematic review coincident to the established PRISMA guidelines [49]. A literature search was targeted on the electronic databases of Scopus, PubMed, Embase, and Web of Science. Other databases were searched to avoid missing related articles. There was no time limitation for the searched articles. The search was accomplished by using the following search strings in the title/abstract/keywords: cognitive OR cognition OR memory OR nootropic OR Alzheimer OR amnesia OR dementia AND “Crocus sativus” OR saffron OR crocin OR crocetin OR safranal. Reclaimed articles were imported to EndNoteX6 reference management software. All articles were separately screened for, duplicity, and eligibility by authors individually.

2.1. Inclusion Criteria.

Articles were included with the following properties; I) original research articles, II) articles published in English, III) use of any form of *Crocus sativus* and its major constituents (crocin, safranal, and crocetin), IV) researches with sufficient outcomes associated with objectives of the study and V) published and in press articles before 21st February 2020.
2.2. Exclusion Criteria.

Articles were excluded with the following properties; I) the study did not evaluate AD, cognitive disorders, and any related conditions of memory loss, II) no related experimental assays were used III) *Crocus sativus* or its constituents were used as a positive control or as bio-enhancers IV) only abstract was available V) the study directly claimed that crocin was originated from *gardenia*.

2.3. Data Extraction.

In total, the search yielded 451 articles of those 92 met inclusion criteria (Figure 1). In total, 60 studies were based on animal-based experiments, 29 studies were based on cellular or in vitro studies, and 8 studies were based on human clinical trials. Some of the selected articles had in vitro and in vivo studies both. In vivo studies containing nonspecific experiments were not categorized as a separate result. Studies evaluating AD, other cognitive incapacities due to neuronal disturbances, and examining healthy cognition performance were included.

![Figure 1. Study Selection Diagram.](https://biointerfaceresearch.com/)

3. Mechanisms Involved in Memory Enhancing and anti-Alzheimer’s Disease Potential of *Crocus sativus*

This is the first systematic review for evaluation of the association between consumption of saffron and its therapeutic approach in Alzheimer management and cognitive dysfunctions. Characterized extracted data of in vivo, in vitro, and clinical studies are collected in (Table 1-3), respectively.

In animal-based studies, some cognition measuring experiments were performed, and associated results show memory enhancement. Open Field Test (OFT) has indicated an increase in a. the number of square crosses, b. the number of rearings, c. time spent in the center.
and number of center entries. Y-Maze Test has demonstrated an elevation in a. spontaneous alterations (%) and b. the number of arm entries. Passive Avoidance Test (PAT) has shown a. increase in Step-Through Latency (STL) and b. the decrease in Initial Latency (IL). Morris Water Maze (MWM) is used for examination of spatial learning and memory, which has indicated a. attenuation in Escape Latency (EL), b. increase in Time Spent in Target Quadrant (TSTQ), and c. increase in swimming speed. Radical 8-Arm Maze (RAM) has demonstrated a reduction in working memory errors and reference memory errors. Novel Object Recognition Test (NORT) is shown elevation in a. Discrimination Index (DI) and b. Exploration time of the novel object. Other memories assessing behavioral experiments such as; Novel Object Location Test (NOLT) Elevated Plus Maze (EPM), Barnes Maze, T-Maze, and Sucrose Performance Test were also used (142)[50-53]. Improvement of the cognitive dysfunctions or memory impairments through pretreatment with saffron and its constituents is demonstrated apparently in preclinical studies [45].

Clinical trials, in vivo and in vitro, showed that Aβ acts a main function in the pathogenesis of AD. Aβ accumulation is responsible for senile plaques formation, activation of oxidative damage, neuronal inflammation, apoptotic death, and cognitive impairments. Mitigating the ROS formation via the consumption of saffron, safranal, crocin, and crocetin is one of the significant mechanisms in the AD therapeutic approach. Increase SOD, CAT, GSH, oxidized glutathione (GSSG), and TAC and alleviation of Malondialdehyde (MDA), nitric oxide (NO), Lactate dehydrogenase (LDH), carbonyl proteins and DNA damage are desired (143) [54-56]. Obtaining free radical scavenging capacity is probable through 2,2,1-diphenyl-1-picrylhydrazyl (DPPH), Thiobarbituric acid reactive substances (TBARS) and ferric reducing antioxidant power (FRAP), as well. Attenuation of the β-cleavage of APP may lead to protection combat AD (144, 145). The balance of pro- and anti-apoptotic Bcl-2 family proteins (e.g., Bcl-2 and Bcl-w versus Bad, Bim, and Bax) plays a pivotal function in apoptosis neuronal cells. Thus expression levels of these proteins are seemingly changed in the vulnerable neurons in AD [57].

Exposure to Aβ peptide initiates the activation of astrocytes and microglia leads to proinflammatory chemokines and cytokines such as IL-8, IL-6, IL-1β, and TNF-α [58]. Elevation in IL-1β level is accompanied by over activation of c-jun-N-terminal kinases (JNK), caspase-3, and mitogen-activated protein kinase (MAPK),; all of these contributed to apoptosis and synapse loss. IL-1β also attenuates the release of acetylcholine in synaptic space, which contributes to further cognitive impairments in AD. The release of chemokines can induce the migration of monocytes from the peripheral circulation into the brain and initiates inflammatory responses (146), whereas pretreatment with saffron attenuated its activations and regulation of p38 MAPK, and AKT pathways [59]. Lipocalin-2 (LCN2) is a principle molecule that acts in cell viability, inflammation, and many other biological reactions. LCN2 manipulations may be a potential therapeutic target in CNS inflammatory conditions for instance, AD [60]. Activation of the 78-kDa glucose-regulated protein (GRP78) of the endoplasmic reticulum may participate in phosphatidylinositol 3-kinase (PI3K)/AKT pathway of management the neurological disorders [61]. Transcription factor nuclear factor-kappa B (NF-κB) is a crucial regulator of innate immunity. NF-κB may regulate AD pathophysiology caused by apolipoprotein-E, metabolic syndrome, APP, ROS production, and environmental factors [62]. Neurotrophin BDNF plays the role of regulating diversified neuronal structure and function in the development of the adult CNS and has known as one of the most significant signaling molecules for the development of the nervous system. It has been
reported that BDNF plays a critical role in neuronal survival, synaptic plasticity, and memory [63]. Cyclic AMP (cAMP)-responsive element-binding protein (CREB) is a nuclear transcription factor that contributed to AD [64].

Aβ consists of 36-43 amino acids and is a natural product of sequential cleavage of an integral membrane protein, the amyloid precursor protein (APP). APP can undergo cleavage in one of two non-amyloidogenic and amyloidogenic pathways. In the first pathway, cleavage by the enzyme α-secretase prevents Aβ formation. It leads to the production of the sAPPα fragment that has some beneficial properties such as promoting neuronal growth and neuroprotective effects. However, the sequential cleavage by γ-secretase (containing presenilin 1 at its catalytic core) and β-secretase, a beta-site amyloid precursor protein-cleaving enzyme 1 (BACE-1) lead to the formation of Aβ. Then Aβ releases into the extracellular spaces. Mediation APP and BACE-1 are considered as effective pathways in the mitigation of memory impairment by saffron [65]. Inhibition of activator and signal transducer of transcription 3 (STAT3) is a molecular mechanistic target combat AD and cognitive dysfunctions [66]. Consequently, JAK/STAT3 cascade and Glial Fibrillary Acidic Protein (GFAP) run as a dominant controller in astrocyte goings-on [67]. Postsynaptic density protein 93 (PSD-93) and PSD-95 are significant scaffolding proteins in the regulation of Aβ-persuaded synaptic dysfunctions [68]. Neutralization caspases activities or expression are considered as therapeutic targets combat neurodegenerative disorders like AD [69]. Peripheral blood mononuclear cells are considered as Aβ plaque suppressors through modulating BBB penetration by chemokines such as CXCL-10 [70]. CHOP gene (C/EBP-homologous protein) is a pro-apoptotic transcriptional factor that may cause AD in vivo, then deactivating this gene will be an option for the discovery of novel drugs with anti-AD properties [71]. It has been demonstrated by augmentation in levels of corticosterone risk of AD induction increased through Aβ plaque formation [72]. Matrix metalloproteinases (MMPs) are responsible for neuroinflammation in the pathogenesis of AD, MMP-2, MMP-3, and MMP-9 are the most important ones that are correlated with Aβ plaque formation [73]. An extracellular signal-regulated kinase (ERK) plays a functional role in restoring neuronal damages [74]. Insulin-like growth factor 1 (IGF-1) may play a pivotal role in the progression and pathogenesis of AD [75]. The p53 protein has appeared to intermediate programmed cell death in neurons of AD by regulating levels of Bcl2 family proteins [76].

TAU hyperphosphorylation can alter various synaptic proteins via inhibition of PP2A and activation of GSK-3β. Therefore synaptic proteins and their levels of expression may cause an anti-inflammatory effect in the hippocampus of AD [77]. Mammalian target of rapamycin (mTOR) may correlate in Aβ plaque formation and tauopathy induced neurodegeneration [78]. Machine learning and pattern recognition techniques are appropriate for diagnosing AD and MCI from individual MRI scans. Another application of such methods is to predict clinical scores from individual scans. Relevance vector regression (RVR), the Mini-Mental State Examination (MMSE), Dementia Rating Scale (DRS), and Auditory Verbal Learning Test (AVLT) are the basic methods. Prediction and actual clinical scores are evaluated by Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-cog), MMSE, and DRS tests. This result underscores their utility for screening and tracking disease. In clinical practice, we visualize the usage of RVR to help practitioners diagnose and predict clinical outcomes. Individual MMSE items, especially those with some type of episodic memory referent, were the best predictors of incident cases of AD. Moreover, MMSE items displayed fluctuation, especially in the incidence of AD (147).
Table 1. Results of in vivo studies.

| Animal/ Sample size (No. of groups) | Model of Study | Targeted compound /Duration/ Dosage/ Route of Administration | Cognition Test | Major Outcomes | Ref. |
|-----------------------------------|---------------|---------------------------------------------------------------|---------------|----------------|------|
| Rat/ 42, 6                         | malathion     | Crocin/14 days/10, 20 and 40 mg/kg/ i.p.                     | MWM           | ↓EL, ↑TSTQ, ↑swimming distance, AChE activity=>NSD, ↓MDA, ↑GH, ↓TNF-α, ↓ IL-6, ↓ PSD93 protein level, ↓TAU protein level at Thr205 and Ser404, phosphorylated and total GSK-3β=> NSD, ↓PP2A at the pY307-PP2AC protein level, ↓TAU mRNA expression, ↑PP2A mRNA level, ↓Bax/Bcl2 ratio, caspases (3, 8 and 9)=inhibited | [77] |
| Mouse/ 56, 3                       | C57BL/6 J     | Trans-crocin-4 (TC4)/50 , 150 mg/kg/ i.p.                    | N.M.          | 25 metabolites have been interpreted; 1) 3 of them had a potential role in neuroprotection closely related to AD 2) 5 of them contributed in the pathway of the steroid (Estrogen-Receptor beta (ERβ), 11-deoxycorticosterone (21-hydroxyprogesterone), corticosterone (11β,21-hydroxyprogesterone) and other corticosteroids) biosynthesis, even though 2 of them might be considered as neuroprotective agents | [79] |
| Rat/ 46, 4                         | Lipocalin-2    | Saffron in a combination/ 28 days/ 16.5, 33 mg/kg p.o.       | MWM           | ↓Neurological score after 2 h, ↓Neurological score after 24 h, ↓Brain Damage after Surgery, ↓number and size of infarcts, nerve cell degeneration, and Necrosis in the infarcts=Were not observed, necrotic substances=were absorbed, ↓EL, ↑TSTQ, ↑platform crossings, ↑IL-1α, ↑IL-12, ↑CXCL10, ↑LCN2 secretion, ↑p-STAT3 and p-JAK2 staining in astrocytes, ↑OGD-Induced Injury in Astrocytes | [80] |
| Mouse/ 60                          | AICI3          | Crocin/ 4 weeks 5 or 20 mg/kg p.o.                           | MWM, OFT      | ↑ the circulation around the periphery, ↑time to locate the platform, ↑serum levels of Aβ1-42, ↑cerebral cortex levels of Aβ1-42, deposition of Aβ1-42 in the hippocampal area=suppressed, pathological changes of the levels of Ach, AchE and ChAT in the serum, cerebral cortex, and hypothalamus of the AD mice=restored, ↑SOD, ↑GH-Px levels in the serum, cerebral cortex, and hypothalamus | [81] |
| Rat/ 37, 5                         | 6-OHDA        | Crocin alone or accompanied by treadmill exercise/ 100 mg/kg/ i.p. | PAT, EPM      | total net No. of rotations↑, STL↑, transfer latency↑, TNF-α levels in the striatum↑, TBARS levels in the hippocampus↑, total thiol concentration↑ | [82] |
| Rat/ 56, 4                         | Trimethylti n chloride (TMT) | Crocin/ 30 days/ 25, 50 mg/kg/ i.p. | N.M.          | ↑Bax, ↑Caspase-9 levels, ↑Bel-2, Pt and Aβ40 levels↑, BDNF levels↑, ↑IL-6, ↑IL-1β, ↑TNF-α, ↑the neuronal density of CA1, CA2, and CA3 | [83] |
| Rat/ 30, 4                         | TMT            | Crocin alone or accompanied by                               | N.M.          | ↑IGF1, Glycogen↑ | [84] |
| Animal/ Sample size (No. of groups) | Model of Study | Targeted compound /Duration/ Dosage/ Route of Administration | Cognition Test | Major Outcomes | Ref. |
|-----------------------------------|----------------|---------------------------------------------------------------|---------------|---------------|------|
| Rat/ 60, 5                        | Methamphetamine | Crocin/ 21 days/10, 20, 40, and 80 mg/kg/ i.p. | MWM | ↓EL, ↑TSTQ, swimming speed =>NSD, ↑GSH, ↑GSSG levels, ↓MDA, ↑SOD, ↑GSH-Px, ↑GR, ↓IL-1β, ↓TNF-α, ↑Bcl-2 expression, ↓Bax protein expression, ↑BDNF, and CREB protein expression | [85] |
| Rat/ 48, 4                        | Aβ25–35         | crocin 14 days/ 40 mg/kg/ i.p. | Y-maze, sucrose preference test | ↓Attempting times, ↑correct reaction rate, ↑sucrose preference, ↓number of apoptotic cells, ↑Bcl-2, ↓Bax, ↓Caspase-3, ↓CHOP, ↓GRP78, endoplasmic reticulum stress in hippocampus and PFC | [86] |
| Rat/ 70, 7                        | methylphenidate | Crocin/ 21 days/ 10, 20, 40, and 80 mg/kg/ i.p. | MWM, OFT | ↓EL ↓ traveled distance, swimming speed =>NSD, ↑TSTQ, ↑ frequency of central square entries, ↑time spent in the central region, ↑ambulation distance and rearing number, ↑ GSH content, ↓GSSG, ↑SOD, ↓GSH-Px, and ↑GR, ↓MDA, ↓IL-1β, ↓ TNF-α, ↑Bcl-2, ↓ Bax protein expression, ↑protein expression in BDNF and CREB total and phosphorylated forms | [87] |
| Rat/ 66, 6                        | Aβ1–40          | Safranal/ 7 days/ 0.025, 0.1, or 0.2 ml/kg/ p.o. | Y-maze, NORT, RAM, PAT | reduction of alternation score => prevented, ↑discrimination ratio, ↑STL, IL =>NSD, ↓ working memory errors, ↓reference memory errors, ↓MDA, ↓Nitrite, ↓protein carbonyl, ↓ROS, ↑CAT, ↑SOD, ↑GSH, ↓IL-1β, ↓IL-6, ↓TNFα, ↑NF-kB, ↓caspase 3 activity, ↓DNA fragmentation, ↓GFAP in the hippocampus, ↓AChE activity, ↑MMP, ↑number of CA1 neurons | [88] |
| Rat/ 48, 5                        | TMT             | Crocin alone or accompanied by treadmill exercise/ 8 weeks/ 25 mg/kg/ i.p. | EPM | ↓weight levels, ↑% Open Arm Entry, ↑%Elapsed Time in the Open Arm, ↑Aerobic Power | [89] |
| Rat/ 48, 6                        | Post-traumatic stress disorder | Saffron and Crocin/ 28 days/ 10 µg/ ICV | Barnes Maze | ↑corticosterone concentration, ↑Freezing Behavior, Search Strategies (direct, random and serial) =>NSD, ↓ No. of Errors in finding the target hole, ↑Traveled Distance, Latency Times =>NSD | [90] |
| Rat/ 36, 6                        | Hyoscine        | Crocin/ 5 days/ 10, 20, and 40 mg/kg/ i.p. | MWM | ↓EL, ↑TSTQ, swimming speed =>NSD, NMDA and AMPA protein expression =>NSD, CaMKII, pCaMKII and ERK proteins =>NSD, a decrease of pERK protein level =>inhibited, ERK, CaMKII, NMDA and AMPA RNA expression => NSD | [91] |
| Rat/ 30, 5                        | hypoxia         | Crocin/ 3 days/ 25, 50, 100 mg/kg/ i.m. | MWM | ↓EL, ↑TSTQ, ↑ No. of crossings, ↑mitochondria of nerve cells, mitochondria swelling and cristae blurring =>improved, ↑SIRT1 and PGC-1α proteins distribution, ↑the hippocampal density of SIRT1 and PGC-1α | [92] |
| Animal/ Sample size (No. of groups) | Model of Study | Targeted compound /Duration/ Dosage/ Route of Administration | Cognition Test | Major Outcomes | Ref. |
|-----------------------------------|----------------|---------------------------------------------------------------|----------------|----------------|------|
| Mouse/ 26, 3                      | APPsw          | Crocetin/ 6 months/ 10, 30 mg/kg/ p.o.                       | MWM, NORT     | ↓ insoluble Aβs in the hippocampus, the cerebral cortex, and the cerebellum, ↓ EL, ↑TSTQ, ↑ time spent exploring the novel object, ↓ NF-kB-p65, ↓ p53 levels, ↓Aβ plaques, ↑TNF-α, ↓IL-1β, ↓IL-8, ↓IL-6, ↑ IL-10 levels | [93] |
| Rat/ 40, 5                        | morphine       | Crocin/ 21 days/ 12.5, 25 mg/kg/ i.p.                        | N.M.          | ↓glucose level, serum cholesterol=>NSD, serum triglyceride level=>NSD, ↑BDNF and CREB gene expression in the VTA area, ↑serum BDNF level | [94] |
| Rat/ 32, 4                        | normal         | Crocins alone and in combination with memantine/ 5, 15, and 30 mg/kg/ i.p. | NORT          | ↑Discrimination (D) index, Total exploration times=>NSD, Total motor activity=>NSD | [95] |
| Rat/ 40, 5 Island stress          | Aβ peptide (1-42) | Crocin/ 12 days/ 30mg/kg/ i.p. | Barnes maze, PAT | ↓ latency time to achieve the target hole, ↓number of errors to find the target hole, ↓STL, ↓c-Fos, ↓number of TUNEL-positive cells in the CA1 region, cell death=>prevented, ↑PS amplitude, ↑fEPSP slope, LTP induction=>prevented | [96] |
| Rat/ 88, 8 Streptozotocin (STZ)   | Safranal alone and in combination with metformin/ 37 days/ 0.025, 0.1 and 0.4 mg/kg/ i.p. | MWM          | ↓hyperglycemia, ↓EL, ↑TSTQ, ↓distance swam, hippocampal neuron loss=> recovered, ↓MDA, ↓TNF-α, ↓Caspase-3, ↑SOD | [98] |
| Rat/ 48, 6 Chronic unpredictable Stress | Crocin/ 21 days/ 30 mg/kg/ i.p. | PAT           | ↑STL, ↑ IL to enter the darkroom, total dark compartment stay time=>NSD | [99] |
| Mouse, rat 5XFAD, STZ, scopolamine | IIIM-141 trans-4- GG-crocin (36 % w/w)/ 28 days/ 12.5, 25, 50, 100 mg/kg/ p.o. | MWM (STZ-rat), PAT (Scopolamine-mouse) | MWM; ↑transfer latency time, ↓% change in transfer latency PAT; ↑transfer latency time, ↑ % change in transfer latency | [100] |
| Rat/ 35, 5 Tramadol               | Crocin/ 28 day/ 30 mg/kg/ p.o. | MWM, PAT      | TSTQ=>NSD, ↑traveled distance, ↑time delay for entering the dark compartment, ↑total time spent in the dark compartment, No. of entries to the dark compartment=>NSD, ↑total time spent in the light compartment, ↓No. of TUNEL positive cells in CA1, CA3 and DG of the hippocampus, DNS No. per unit area in CA3 and DG of the hippocampus | [101] |
| Rat/ NORT; 60/ NOLT; 48           | Apomorphine    | Crocins/ 3 days/ 15 and 30 mg/kg/ i.p.                       | NOLT, NORT    | ↑index D, exploration times=>NSD, NOLT; D index=>NSD, exploration | [102] |
| Animal/ Sample size (No. of groups) | Model of Study | Targeted compound /Duration/ Dosage/ Route of Administration | Cognition Test | Major Outcomes |
|-----------------------------------|----------------|---------------------------------------------------------------|----------------|----------------|
| Mouse/ 40, 5 pentylenetetrazol | Crocin/ 36 days/ 5, 10 and 20 mg/kg/p.o. | T-maze, NORT | Seizure severity score, ↑(%)spontaneous alternation, ↑(%)preference index, ↑ discrimination ratio, ↑SOD, ↓ number of Nissl-stained dark neurons, ↓ NF-KB expression, ↓p-NF-KB expression | [103] |
| Mouse/ 32, 4 aflatoxin B1 | Saffron tea/ 2 weeks 90 mg styles/200 mL (3.6 mg saffron/ mouse)/ p.o. | PAT | body weight gain, food and liquid intake=>NSD, ↑STL, IL=>NSD, ↓SS- and DS-AChE activity in whole brain and cerebellum, ↑ the activity of whole-brain DS-BuChE was at control levels, ↓ liver SS- AChE and BuChE activity, ↓ liver DS-BuChE, ↓ MAO-A and MAO-B, ↓MDA in the whole brain, cerebellum, and liver | [104] |
| Rat/ 30, 6 D-galactose | Crocin/56 days/ 7.5, 15, 30 mg/kg/i.p. | MWM | ↓EL, ↑TSTQ, swimming speeds=>NSD, ↓MDA, ↓CML expression, ↑phosphorylation of Akt protein, MAPK activity through the elevation of pErk/Erk ratio↑, ↓NF-κB p65 protein level in the hippocampus, ↓ IL-1β and TNFα formations | [105] |
| Rat/ 40, 5 Chronic Restraint Stress | Crocin/ 21 days/ 30 and 60 mg/kg/ i.p. | PAT | ↑STL, ↑ IL, ↓corticosterone levels in the hippocampus and frontal cortex | [106] |
| Rat/ 60, 6 Aβ(25-35) | Saffron / 21 days/ 5, 10 mg/kg/ i.p. | The Y-maze task, RAM | In vitro antioxidant; ↑DPPH scavenging, ABTS•+ scavenging (general experimental tests)/ In vivo; ↑short working memory, ↑(%)spontaneous alternation, ↑ No. of arms entries, ↑ Working memory errors, ↓reference memory errors | [107] |
| Rat/ 36, 6 hyoscine | Crocin/ 5 days/ 10, 20, 40 mg/kg/ i.p. | MWM | ↑TSTQ, Swim Speed in the Target Quadrant and Total Swim Speed=>NSD, ↓Latency Time to Find Platform, ↑ BDNF, ↑ p-CREB, ↑CREB | [108] |
| Mouse/ 18, 2 5XFAD | 1 month/ Saffron; 50 mg/kg/Crocin; 10 mg/kg/ p.o. | N.M. | ↓total Aβ and Aβo levels in the brain, ↓levels of monomeric Aβ40 and Aβ42 in the brain, ↑ LR1P1 and P-gp expressions, expression of the Aβ-degrading enzyme NEP in brain homogenates↑, expression of IDE levels=>NSD, ↑ABCA1 expression, ↑ PPARγ expression, ↓IgG extravasation, ↑ claudin-5 expression in brain microvessels, ↑PSD-95 expression, ↑SNAP-25 expression, ↓ brain levels of IL-1β, ↓GFAP optical intensity | [109] |
| Rat/ 35, 5 streptozotocin | Crocin/ 6 weeks/ 15, 30 and 60 mg/kg/ i.p. | MWM | ↓serum glucose levels, ↓EL, ↓traveled distance, ↑TSTQ, ↓TBARS level in the cortex, total thiol concentration in the cortex=>NSD | [110] |
| Animal/ Sample size (No. of groups) | Model of Study | Targeted compound /Duration/ Dosage/ Route of Administration | Cognition Test | Major Outcomes | Ref. |
|---|---|---|---|---|---|
| Rat/ 60 | | Crotcin/2, 5 or 10 mg/kg/ i.p. | PAT | STL=>NSD, the performance of the rats in the shuttle box=>improved | [111] |
| Rat/ 32, 4 | 6-OHDA | Crotcin/6 weeks/30 and 60 mg/kg/ i.p. | PAT | ↓TBARS levels in the hippocampus, ↓ nitrite levels in the hippocampus, total thiol concentrations in the hippocampus and cortex=>NSD, GSH-Px=>NSD, ↑STL | [112] |
| Rat/ 10, 2 | aging | safranal /30 days/ 0.5 mg/kg /i.p. | N.M. | ↓MDA, ↑GSH-Px, ↑ SOD, ↑ GST | [113] |
| Rat/ 24, 4 | acrolein | Crotcin/ 2 weeks/ 12.5, 25, 50 mg/kg/day/ i.p. | N.M. | ↓MDA, ↑ GSH-Px, ↓Aβ1–42, ↓T231 phosphorylation state, ↓ phosphorlated and total GS-3β at Ser9 GSK-3β=>NSD, ↓ p-ERK1/2, ↓ p-JNK, level of p-p38=>NSD | [114] |
| Rat/ 40, 5 | ethidium bromide | Saffron/1 week/ 5 and 10 µg/ i.p. | MWM | ↓EL, ↑traveled the distance to find the platform, ↓ FRAP value, ↓TBARS levels, ↓ GSH-Px activity, ↑SOD | [115] |
| Rat | Aβ (1–42) | Crotcin/ 21 days/i.h.; 150, 300, 600 nmol/ i.p.; 30 mg/kg | MWM | ↑traveled distance, ↓EL, swimming speed=>NSD, ↑TSTQ, ↑Bcl-2, ↑Bcl-2/LC3-I ratio=>NSD, ↓Bax, ↑Bcl-2, ↑ Bax/Bcl-2 ratio, ↑ Caspase-3 | [116] |
| Rat/ 50, 5 | STZ | Saffron/ 4 weeks/ 20, 40, and 80mg/kg/ i.p. | MWM | ↑Bodyweight, ↑ Blood Glucose Levels, ↓EL, ↑TSTQ, ↓TNFα, ↓serum levels of total Lipids, ↓ triglycerides, ↓total cholesterol, ↓ LDL, ↑ GSH, ↑SOD, ↑CAT, ↓ iNOS | [117] |
| Rat/ 20, 4 | STZ | Crotcin/21 days/ 100 mg/kg/ p.o. | N.M. | ↓MDA levels in the striatum, ↑total thiol, ↑ GSH-Px activity | [118] |
| Rat/ 60, 6 | ketamine | Crotins/ 3 days/ 30, 50 mg/kg/ i.p. | NORT | ↑discrimination index D; ↑ataxia, total object exploration times=>NSD | [119] |
| Rat/ 30, 5 | ketamine | Crotetin/ 7 days/ 2,4, 8 mg/kg/ i.p. | MWM | ↑EL, ↑TSTQ, swimming speed=>NSD, the morphology of neurons in cortex and hippocampus CA1, CA2, CA3 regions=>protected | [120] |
| Rat/ 48, 8 groups | STZ | Crotcin/ 27 days/ 7.5, 15 and 30 mg/kg/ i.p. | EPM | ↑Transfer latency, ↓ Blood glucose, ↑ serum insulin, ↑ TAC, ↓ MDA, a decrease of neurons in the hippocampus=> prevented | [121] |
| Rat/ 35, 5 | Quinolinic Acid | Safranal/ 72.75, 145.5, and 291 mg/kg/i.p. | N.M. | (general antioxidant tests were assessed in vitro), ↓MDA, ↑antioxidant power (FRAP value) of brain homogenate samples, ↑ total thiol content, ↑ DNA damage | [122] |
| Mouse/ 30, 3 | AlCl3 | Saffron/ 6 days/ 60 mg/kg/ i.p. | PAT | Step through latency=>NSD, Initial latency=>NSD, ↓SS- and DS-AChE activity in whole brain and cerebellum, cerebral BuChE=>NSD, ↓SS- and DS-liver BuChE and SS-AChE, ↓ MAO-A and MAO-B activity of the whole brain, ↑MAO-B activity of cerebellum, ↓MDA, ↑ GSH | [123] |
| Animal/ Sample size (No. of groups) | Model of Study | Targeted compound / Duration/ Dosage/ Route of Administration | Cognition Test | Major Outcomes | Ref. |
|-----------------------------------|---------------|---------------------------------------------------------------|---------------|----------------|------|
| Mouse/ 24, 3                      | Morphine      | Saffron/ 3 days/ 50, 150, and 450 mg/kg/ i.p.                | PAT           | ↑total time spent in the light compartment, ↓total time spent in the dark compartment | [124] |
| Rat/ 32, 4                        | STZ           | Crocin in a combination/ 15 days/ 25 µg/kg/ p.o.            | MWM, PAT      | ↑STL, IL=>NSD, ↓EL, ↑TSTQ, ↓TBARS level in rat hippocampus and frontal cortex, ↑GSH, ↑GPx, ↑GST, ↑SOD, ↑CAT | [125] |
| Rat/ 70, 8                        | chronic cerebral hypoperfusion | 5 days/ saffron (50, 100 and 250mg/kg , crocin (5, 10, 25mg/kg/ i.p. | MWM           | ↓EL, ↑TSTQ    | [126] |
| Mouse/ 70, 8                      | D-galactose and NaNO2 | Saffron/ 15 days/ 30 mg/kg/ i.p. | AAT, PAT      | ↑avoidance responses, ↑STL          | [127] |
| Mouse/ 20, 4                      | APP/PS1       | Saffron in combination/ 3 months/ 30, 44 mg/kg/ p.o.         | MWM           | ↓EL, ↑TSTQ, cytoplasmic and nuclear membranes=>NSD, ↑cytoplasmic swelling and vacuolation, ↓Aβ immunoreactivity, deformed mitochondrion detected with cristae residues, rare autophagosomes, and dilated Golgi complex and reticulum | [128] |
| Mouse/ 16, 2                      | Balb-c, aging | Saffron/ 6 days/ 60mg/kg/ i.p.                                | PAT           | IL=>NSD, ↑STL, ↓ SS and DS AChE-specific activity, ↓MDA, ↑GSH, ↓caspase-3 | [130] |
| Rat/ 150, 8                       | chronic stress | 21 days/ Crocin; 15, 30 mg/kg, Saffron; 30 mg/kg/ i.p.      | MWM           | ↓corticosterone levels, ↓EL, ↑TSTQ, swimming speed=>NSD, ↑FRAP levels, ↑TBARS levels, ↑SOD, ↓GSH, ↓GSH-Px | [131] |
| Rat/ 45, 3                        | STZ           | Saffron/ 3 weeks/ 30 mg/kg/ i.p.                              | PAT           | ↓IL, ↑STL, pathohistolocal effects=>NSD | [132] |
| Rat/ 90, 6                        | STZ           | Crocin/ 2 days/ 15 and 30 mg/kg/ i.p.                        | Y-maze, PAT   | ↓body weight, ↑step-through latency, ↑(% Alteration behavior, ↑No. of animals falling | [133] |
| Rat/ NORT:4 0,4/PAT; 80, 8        | scopolamine   | Saffron/ 10, 30, 60 mg/kg/ i.p.                              | NORT, PAT     | Total motor activity=>NSD, Total exploration times=>NSD, ↑exploration time of the novel object, ↑Discrimination index D, ↑Retention latencies to enter the dark chamber | [135] |
| Rat                              | acetaldehyd e | Saffron/ 62.5, 125, 250 mg/kg/ p.o.                          | N.M.          | inhibition of long-term potentiation (LTP) in the rat dentate gyros=>inhibited | [136] |
| Mouse                            | ethanol       | Crocin/ 50, 100, 200 mg/kg/ p.o.                             | PAT           | ↓No. of errors, ↑STL            | [137] |

Table 2. Results based on *in vitro* assays.
| Targeted Cell Lines | Model | Targeted Compound/ Exposure Time/ Dosage | Major outcomes | Ref. |
|---------------------|-------|----------------------------------------|----------------|------|
| PC12                | Aβ(25–35), H2O2 | saffron extract, essential oil, safranal/ 120 min/ saffron extract, essential oil, safranal (2.5, 5, 10, 20, 40, 80 μM) | ↑cell survival rates, ↓fluorescence intensity, ↓ROS production, ↓amount of apoptosis, ↓Cyt, and cleaved caspase 3, increased phosphor SAPK/JNK to SAPK/JNK=>inverted, reduction in surviving and the ratio of Phospho-p44/42 MAPK (ERK1/2) to p44/42 MAPK (ERK1/2) and increase in Phospho-PI3 kinase p85/p55 to PI3 kinase p85/p55=>protected | [139] |
| HT22                | L-glutamate (L-Glu) | Crocin/ 3 h/ 0.5 and 2 μM | L-Glu-induced mitochondrial apoptosis in HT22 cells against =>protected, MMP dissipation=>restored, hyper-levels of intracellular ROS compared with the L-Glu-damaged HT22 cells=>suppressed, an overload of Ca2+=>inhibited, Bcl-xL, Bax, Bad, caspase-3=>restored to standard levels, attenuation the phosphorylation of Akt and mTOR=>reversed | [81] |
| N.M.                | N.M. | Crocin/ 50 -800 μM | AChE; IC50=0.92±0.23 | [140] |
| SH-SY5Y, PC12       | SH-SY5Y-APP, PC12-htau | trans-Crocin 4, trans-Crocin/ 24, 72 hours/ 0.1, 1, 10, 100, 1000 μM | cell viability=>NSD, Trans-crocin 4; ↑total PSEN1, ↓(γ-secretases)PSEN1 and PSEN2 complexes, ↑PSEN1-CTF and PSEN2, ↓(β-secretase)BACE1, sAPPα; APP-C83=>NSD, ▼APP-C99 Trans-crocin; total APP, ↑cellular APP and APP-C99 trans-crocin 4; total tau levels↓, ↓tau phosphorylation (pThr231 and pSer199/Thr202-tau), active and inactive forms of GSK3β (total GSK3β, pSer9-GSK3β) and ERK1/2 (total ERK2, pERK1, pERK2)=>downregulated, ERK1=>NSD, trans-crocin; ▼total and phosphorylated tau (pThr231 and pSer199/Thr202), as well as GSK3β, ERK2, pERK1 and pERK2, ▼inactive pSer9-GSK3β | [141] |
| N.M.                | N.M. | Saffron, crocin-1, crocin-2, crocetin, and safranal, and crocetin structural analogs/ 0.233, 0.669, 2.33, 6.99, 23.3 μg/mL | Saffron; inhibited αS aggregation and dissociated αS fibril; IC50=0.656 and EC50=4.17 μg/mL, fibrils of αS, Crocin-1, crocin-2, crocetin, and norbixin inhibited αS aggregation and dissociated αS fibrils, with IC50 values of 4.0, 0.541, 0.0930 (first), and 0.911 μM, respectively, and EC50 values of 4.95, 3.63, 0.0617 (first), and 0.244 μM/ safranal, hexadecanedioic acid, and trans, trans-muconic acid; did not show >50% inhibition and >50% efficacy | [142] |
| N.M.                | N.M. | Crocin/ 8 h/ 10, 20, 40 μM | cell viability=>NSD, [Aβ]42 and Aβ40 | [93] |
| HeLa cells          | APP751 | APP51 | cell viability=>NSD, [Aβ]42 and Aβ40 | [93] |
| LS-180, SH-SY5Y, and THP-1 | NLRP3 inflammasom | IIM-141/ 100 μg/mL | IL-1β=>inhibited, ↑efflux of the Rh123 dye, ↓% intracellular Rh123 levels in LS-180 cells, ↑protection of SH-SY5Y cells from amyloid-β toxicity, and protection of SH-SY5Y cells from glutamate toxicity, ↑expression of P-gp and the amyloid-β clearance | [100] |
| Targeted Cell Lines | Model | Targeted Compound/ Exposure Time/ Dosage | Major outcomes | Ref. |
|--------------------|-------|------------------------------------------|---------------|------|
| bEnd3             | BBB endothelium | Saffron/ 1.1, 2.2 μg/mL | ↑tightness of bEnd-3 cells-based BBB model, ↑transport of 125I-Ab40 from basolateral to apical compartment across the bEnd-3 cells, ↑Pgp expression, LR1P1 expression=>NSD | [109] |
| AD patients' monocytes | Aβ1-42 | trans-crocin/ 24, 48, 72, and 120 h/ 5, 10, 25, 50, 100, 150 μM | ↑cell death, ↑Aβ42 degradation, ↑Aβ42 degradation through CatB | [143] |
| EA.hy926          | H2O2 | Saffron in a combination/ 24 h/ 8.25, 16.5, 33 mg/kg | ↓ROS-related cellular damage, ↓LDH leakage, ↑SOD, Intracellular ROS Generation=>suppressed, ↓Bax/Bcl-2 ratio, ↓cleaved caspase-3 expression | [144] |
| NSCs               | Aβ1-42 | Saffron/ 26 h/ 25 μg/ml | ↑nuclear intensities of caspase-3 activation in Aβ1-treated samples, ↑total No. of ROIs indicated expression of c-fos concerning their nuclei | [145] |
| SH-SY5Y           | Aβ    | Crocin/ 24 h 1, 10, 50 μM | ↓fluorescence intensity, ↑cell viability, intracellular ROS levels=>inhibited, formation of Aβ fibrils=>inhibited | [146] |
| N.M.              | N.M. | Saffron/ 50, 250 μg/mL | β-secretase=>inhibited | [147] |
| N.M.              | N.M. | Saffron pollens in a combination in alcoholic and nonalcoholic beverage | Nonalcoholic; DPPH=> 91.95 ± 0.23 (mg trolox/100 mL beverages), FRAP=> 2.51 ± 0.01 (mmol Fe(II)/100 mL beverages) Alcoholic; DPPH=> 66.19 ± 0.17, FRAP=> 1.28 ± 0.02/ ↑AchE | [148] |
| PC12 cells        | 1N/4R human tau protein | Crocin /24 h/ 100 µg/mL. | tau aggregation=>inhibited | [149] |
| HT22 cells        | H2O2, Aβ1-42 | Crocin/ 24 h/ 3 μM | HT22 cells H2O2-induced cell death=>protected, HT22 cells Aβ1-42-induced cell death=> protected, ↓ROS production induced by Aβ1-42 | [150] |
| N.M.              | Aβ42 | Crocin/ 15.4 μM | ↓fluorescence intensity (degree of amyloid assembly), ↓ANS fluorescence intensity (hydrophobic surface exposure of Aβ42), ↓number of fibrils | [151] |
| N.M.              | Aβ1–40 | Crocin /15 μg | ↓THT fluorescence intensity, ↓ANS fluorescence, ↓number, and average fibril length | [152] |
| N.M.              | N.M. | Saffron | ↓AChE/ IC50 of crocin, dimethylcrocetin, safranal=>96.33, 107.1, and 21.09 μM respectively | [153] |
| SH-SY5Y           | H2O2 | Saffron; 1, 10, 50 125, 250 μg/mL/ Crocin; 0.1, 1, 10, 50, 125 μM/ Safranal; 0.1, 1, 10, 50, 125 μM/ 18 h | H2O2-induced toxicity on SH-SY5Y(saffron, safranal, crocin)=>prevented, rescuing cell viability, ↓ROS production, ↓H2O2-induced caspase-3 activation | [130] |
| N.M.              | Aβ    | Crocin | ThF fluorescence=>NSD, A11-positive conformational epitopes of Aβ oligomers=>preserved | [154] |
| N.M.              | α-Lactalbumin | Crocin, Safranal/ 50, 100 μM | ↓fluorescence intensity, ↓ANS fluorescence intensity, ↑cell viability | [155] |
| BV2 microglial cells | (LPS), Aβ25-35 + IFN-γ | Crocin, crocin/ 24 h/5, 10, 20 μM | ↓NO production, ↑cell viability, ↓TNF-α, ↓IL-1β, ↓ROS production, ↓NF-κB activation, neuronal damage=>protected | [156] |
| N.M.              | N.M. | saffron | AChE=>NSD | [157] |
| N.M.              | Aβ1–40 | saffron, crocin | antioxidant activity=>observed, ↓fluorescence intensity | [158] |
| PC-12 cells       | TNF-α | Crocin/ 24 h/ 1, 10 μM | ↓expression of Bcl-2, morphological changes and DNA fragmentation=>blocked | [159] |
| hippocampal slices | ethanol | Crocin/ 10 μM | inhibition of non-NMDA response=>NSD, inhibition of NMDA response=>significantly blocked | [160] |
**Targeted Cell Lines** | **Model** | **Targeted Compound/ Exposure Time/ Dosage** | **Major outcomes** | **Ref.**
--- | --- | --- | --- | ---
Hippocampal slices | Ethanol | Crocin/ 10, 20, 30 µM | ↑Spike amplitude, impairment of hippocampal synaptic plasticity=>prevented | [161]

**Table 3. Results of clinical trials.**

| Clinical Trial Type | Patients’ Demographic features | Compound/ Route of Administration/ Duration/ Dosage | test | Major outcomes | Ref. |
|---------------------|--------------------------------|--------------------------------------------------|------|----------------|------|
| Randomized Double-Blind Placebo-Controlled Trial | Saffron; N=18 Placebo; N=19 Patients <70 years and who had aWMS-R score >70 | Saffron capsules/ p.o./ 12 weeks 15 mg/twice daily | WMS-R, HADS, MMSE | NSD in scores | [162] |
| Randomized Double-Blind Clinical Trial | Herbal combination; N=30 Placebo; N=30, diagnosed MCD patients, mean age of patients =66.8 years, mean age of placebo= 70.2 years | Saffron in a combination/ p.o./ 4, 8 weeks (each capsule containing 500 mg of sedge and 30 mg of saffron extract) plus a teaspoon of Astragalus honey (equal to 5 g in each take)/ 2 capsules per day | ACE, GDS | Attention, memory, language, and visuospatial function=> significant changes, fluency variable=>NSD, MMSE, ACE, GDS scores=>significant changes | [163] |
| Pilot, Double-Blind, Randomized Clinical Trial | 30 young elderly subjects (mean age 66±3), MMSE=between 20 and 27 | Saffron in a combination/ p.o./ 8 weeks/ Combined nutraceutical | MMSE, PSQ Index, SRDS | MMSE=>NSD, ↑PSQ Index, ↑SRDS | [164] |
| Single-Blind Randomized, with Parallel Groups, Clinical Trial | patient; N=17 control; N=18 mean age of patients with MDI= 71.47 mean age of control= 69.72 | Saffron/ 12 months | GDS, FRSSD, MMSE, NPI, MOCA, MRI, EEG, and ERP | MMSE=>NSD, ↑FRSSD, ↑MoCa=>NSD, ↑NPI, GDS=>NSD, MRI, EEG, and ERP=> showed improvement in specific domains | [165] |
| Phase 2 Clinical Trial, Randomized, Multicenter, Double-Blind, Placebo-Controlled Study | male and female patients, 40 years of age or older, with a diagnosis of probable mild to moderate VaD | Saffron in a combination/ 26 weeks | V-ADAS-cog, ADCS-CGIC, MMSE, CDR, ADCS-ADL, CLOX, EXIT25, NPI, MRI or CT | The results of the study will provide high-quality evidence on the effect of SLT capsule in patients with VaD and have the potential to establish a novel therapeutic approach for VaD | [166] |
| Double-Blind Randomized Clinical Trial | Male and female outpatients older than 60 years, MMSE score of 8–14 at baseline Saffron; N=34 Memantine; N=34 | Saffron/ p.o./ 12 months/ 30 mg/day | SCIRS, FAST, MMSE | Scores=>NSD between memantine and saffron groups | [167] |
| Multicenter, randomized, double-blind controlled trial | MMSE; 15–26 inclusive 54 Persian-speaking adults | Saffron / p.o./ 15 mg for 4 weeks/ 22 weeks | ADAS-cog, CDR-SB | Scores=>NSD | [168] |
Randomized and Placebo-Controlled Trial | 56 patients older than 55 years, MMSE score of 15–26 | Saffron capsules/ p.o./16-week/ 15 mg twice per day | ADAS-cog, CDR-SB | ADAS-cog, CDR-SB=>significant changes | [169]

4. Pharmacological and Pharmaceutical Aspects of Saffron

From the collected results, it is concluded that saffron and its active constituents may be a great therapeutic agent combat cognitive dysfunctions. Toxic and lethal effects of saffron can be revealed in 5g and 20 g of the daily dose, respectively. Therapeutic activities of saffron have been observed in (30-50mg/day) clinically; thus, saffron considered as a medicinal plant that possesses a wide therapeutic index (145)[170]. Clinical safety evaluation of crocin through a placebo-controlled, double-blind, randomized study has shown a safe and well-tolerated manifestation in healthy volunteers administered 20 mg/day of crocin in one month [171].

Through studying the pharmacokinetic properties of saffron, it is indicated that oral administration of crocetin is a water-soluble carotenoid of saffron stigmas crocetin is absorbed and detected in plasma faster than the other carotenoids, through its excretion take place widely through the intestinal tract, plasma concentrations of crocetin are not accumulated following repeated doses crocin, hydrolysis of crocin is taken place mostly in the intestinal tract. Crocetin can penetrate the blood barrier brain (BBB) and reach to CNS; it has a high affinity to the NMDA receptor; thus, saffron applied in the treatment of CNS disorders [172,173]. The free form of crocetin may be bound to albumin in blood plasma, this weak bind can break easily, and crocetin may be able to penetrate the tissues. To enhance the stability of crocin, chitosan, and alginate biopolymer carriers can be used for crocin delivery and encapsulation of bioactive agents [29,174].

5. Conclusions

Various health complications can be treated by the application of medicinal plants, phytochemicals, and nutraceuticals. Discovery and identification of these components with possession of numerous clinical indications can ameliorate our lives quality. Saffron and its active phytochemicals comprising crocin, crocetin, and safranal have the capacity to elucidate anti-AD and memory enhancer properties. Mostly common contributed mechanisms to combat AD are underlying oxidative stress, inflammatory process, apoptosis, beta-amyloid aggregation, and tauopathy. Saffron can be used in the prevention and treatment of clinical complications with etiologies the same as AD. Moreover, regarding the capability of saffron to penetrate BBB it can be considered in therapeutic approaches of other neurological disorders. Study particular cell signaling pathways contributed in AD is recommended following saffron administration. From all of the mentioned extracted data of original researches, memory-enhancing properties of saffron are concluded. However, some modifications in carriers, bioavailability, and route of administration will be required.

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Conflicts of Interest

The authors declare no conflict of interest.

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