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REVIEW

Cognitive Effects of Almond Consumption: A Review of Animal Studies

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Video abstract

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Aim and Background: Learning and memory are fundamental processes essential to human cognition. Memory disorders can greatly impact cognitive abilities and overall quality of life. Synthetic drugs are not always completely effective in the treatment of memory disorders and can have diverse side effects. As a result, the use of plants for treating various diseases, including those related to memory disorders, is common. Almond is a highly nutritious nut and has been used as a traditional remedy for a long time. They contain active compounds that have numerous biological effects on the entire body, particularly the nervous system. Therefore, the purpose of this study is to review animal studies that have investigated the effects of almond intake on memory and its related disorders.

Methods: In this study, a comprehensive search in several databases including PubMed, Web of Science, Scopus, Science Direct, and Cochrane Library was performed. The study included published articles featuring preclinical studies conducted on healthy animals or models with memory impairments. These studies employed specific controlled groups and evaluated memory-related parameters through behavioral tests or molecular investigations. Eleven original papers that met the criteria were selected from a total of 1190 identified articles and included in the study.

Results: Almond consumption has been shown to have beneficial effects on learning and memory in healthy animals. Additionally, evidence suggests that consuming almonds can positively impact scopolamine-, cadmium-, chronic stress-, and high-fat diet-induced memory impairment in animal models.

Conclusion: Based on available evidence, consuming dietary supplementation of almonds may have a significant role in brain processes, specifically the neuromodulatory systems. Consequently, incorporating almonds into one's diet could potentially enhance memory function, making them a readily available and useful natural resource with both nutritional and therapeutic benefits.

Keywords: Almond, *Prunus amygdalus*, *Prunus dulcis*, learning, memory, neuromodulatory systems

Introduction

Cognitive functions, including learning and memory, are complex and intricate processes that occur within the human mind. Learning enables us to obtain new knowledge about the world, while memory encompasses the essential functions of storing, processing, and reconstructing this acquired knowledge over time. These processes greatly contribute to our conscious and unconscious behaviors.[1] Memory is a dynamic trait that relies on the complex interactions between networks of neurons in the brain. The storage of memories involves structural changes that take place at the cellular level, particularly within neurons and synapses, a phenomenon known as synaptic plasticity.[2,3] This process occurs primarily through two major forms, long-term potentiation (LTP) and long-term depression (LTD), wherein synaptic efficacy and connections between neurons are strengthened or weakened, respectively. Memories are encoded by such modifications of the synaptic strength. Disruptions in synaptic plasticity can contribute to memory disorders and impact cognitive function.[2,4] Memory disorders encompass a range of conditions that affect an individual's ability to remember, learn, and process information. Conditions such as normal aging, dementia, obesity, exposure to toxins, and stress can disrupt the physiological conditions

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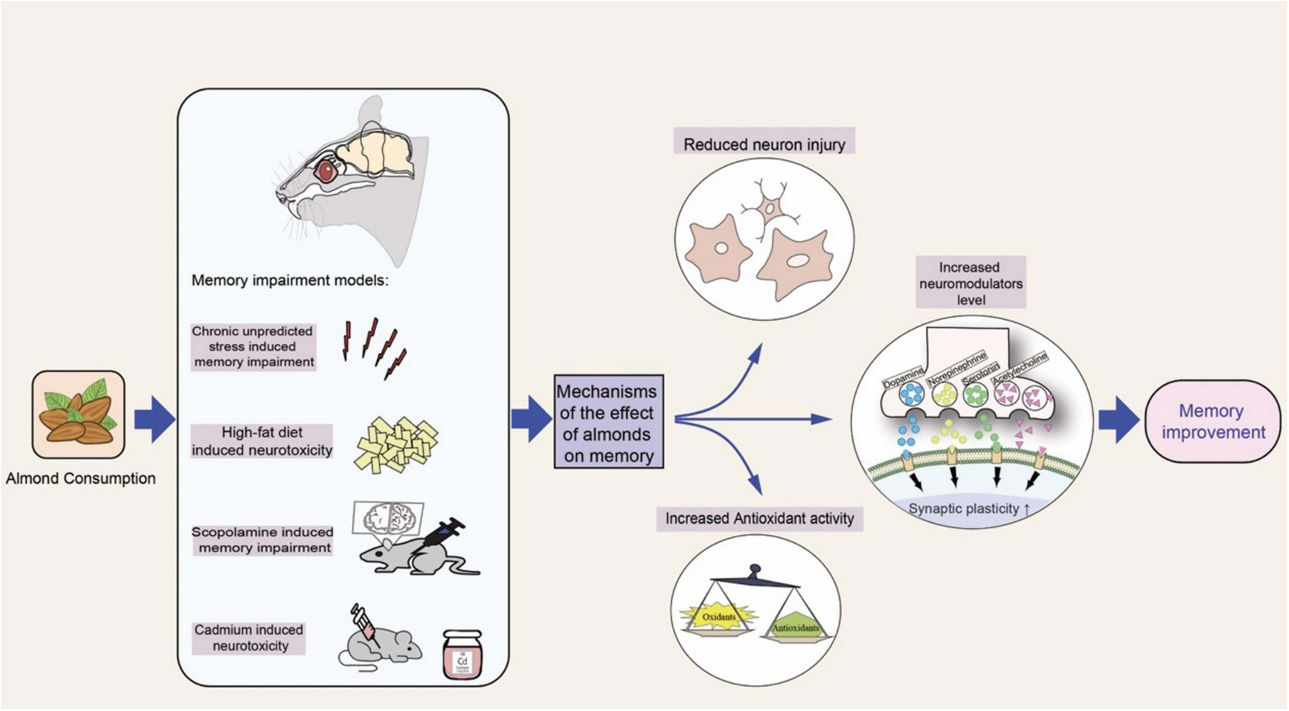
Graphical Abstract



necessary for optimal memory function.[5–9] Mild cognitive impairment (MCI) serves as an intermediate stage between normal age-related cognitive decline and more severe dementia.[10] Dementia, a broad term, refers to a decline in mental ability severe enough to interfere with daily life, which can be caused by various conditions, such as Alzheimer's disease.[11] In Alzheimer's disease, the accumulation of amyloid-beta plaques and tau tangles disrupts synaptic plasticity, leading to memory loss and cognitive decline.[12] Synaptic plasticity disturbances are also implicated in other memory disorders, such as dementia and MCI, highlighting the importance of this process in maintaining cognitive health.[13]

Memory is also a part of the developmental process, so it may be affected by various environmental factors such as climate, various stresses, exercise, and also nutrition.[1,14] Nutrition is one of the environmental factors that play a crucial role in brain health and the prevention of memory impairment.[15] Essential micronutrients and macronutrients found in natural products, such as nuts, are vital for regulating brain processes, including memory.[15,16] Different types of nuts, such as walnuts, almonds, and Chehelghoza pine nuts, have been found to have significant benefits for brain health and memory. Numerous studies have highlighted the positive impact of these nuts on cognitive functioning, emphasizing their potential as protective measures against memory decline.[15,17,18] Almonds, scientifically known as *Prunus dulcis* (syn. *Prunus amygdalus*) belonging to the *Rosaceae* family, are widely recognized as one of the most popular tree nuts in the world. Originating in Central Asia, almonds have been cultivated in the Middle East, South-Western Asia, the Mediterranean Basin, the USA, and Australia.[19] Afghanistan is ranked fourth in almond production globally.[20] Recognizing regional diversities, variations exist in the content of almonds grown across different regions. These distinctions can influence the taste, nutritional profile, and potential health benefits of almonds, making each variety unique.[21,22] Nevertheless, reports indicate that certain constituents of Afghan almonds, such as tocopherols and fatty acid compositions are comparable to those from other countries, but it is important to note that some other contents may vary in quantity.[20] This suggests that the overall biological effects of the same almond species from different regions may be similar, although variations in effective doses could be expected.

Almonds are known for their nutritional value and used as a traditional herbal medicine for a long time. The almond species contain plant protein, choline, phytosterols, fiber, carbohydrates, vitamins (vitamin E, especially alpha-tocopherol, vitamin B6, and folate), minerals (manganese, copper, potassium, calcium, iron, zinc, and selenium), and antioxidants including polyphenols such as flavanones, isorhamnetin, kaempferol, quercetin, catechin, epicatechin, anthocyanins (cyanidins and delphinidins), procyanidins, and phenolic acids (caffeic acid, ferulic acid, p-coumaric acid, and vanillic acid). Specifically, almonds like other nuts are rich in unsaturated fatty acids including polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA).[20,23–27] Almonds with their diverse essential constituents, have been shown to elicit various biological effects, such as lowering blood cholesterol, improving heart health, inducing sedation, and enhancing memory function.[27–29] Research has indicated that the presence of beneficial compounds in almonds, particularly PUFAs, minerals, phytosterol and polyphenols, may be associated with memory enhancing effects of almonds. Studies have shown that PUFAs found in nuts, including almonds,[30] pine nuts[18] or walnuts[31] can enhance synaptic transmission and plasticity, thereby reducing cognitive decline. Nuts are also known for their phytosterol content, which has been linked to benefits for memory disorders, such as Alzheimer's disease.[32] Additionally, the minerals,[33] tocopherols, and polyphenols including flavonoids in nuts like almonds are believed to protect neural cells from oxidative stress, a significant factor in memory loss.[34–36] Therefore, it is expected that incorporating almonds into the diet may help enhance memory function and potentially improve memory-related disorders.

Despite the positive reputation of almonds, there have been limited studies investigating their specific effects on brain health, memory, and related disorders. Particularly, the specific mechanisms through which almonds affect brain processes and cognitive functions are not fully understood. Recent studies point towards the interactions between almonds and neuromodulatory systems, as well as oxidative stress pathways. Neuromodulatory systems, which include cholinergic, serotonergic, noradrenergic, and dopaminergic systems, as well as the balance of oxidants and antioxidants, play crucial roles in brain physiology and memory processes. Disturbances in these systems and increased oxidative stress can contribute to the development of various learning and memory disorders.[37–41] It is widely recognized that neuromodulator systems play crucial roles in modifying synaptic strength and enhancing plasticity within neural circuits during memory processing. For example, cholinergic transmission increases cellular excitability, potentiates glutamatergic synapses and facilitates LTP.[42,43] Similarly, noradrenaline and dopamine modulate neuronal excitability and influence molecular components essential for promoting synaptic plasticity.[44,45] Serotonergic transmission interacts with other neurotransmitters to regulate learning and memory processes.[46] Additionally, the antioxidant compounds in almonds are thought to counteract the oxidative stress-induced dysregulation of synaptic plasticity. These antioxidants may preserve memory function by protecting neurons from oxidative damage, scavenging reactive nitrogen and oxygen species, and regulating signaling pathways.[47] Nevertheless, the existing literature lacks a comprehensive assessment of the available evidence related to the impact of almonds on modulating neuromodulatory systems, oxidative stress, and, consequently, memory function. On the other hand, animal models provide valuable information about the molecular targets and mechanisms of action of drugs, which aids the identification and development of new treatments.[48,49] Therefore, this study aims to evaluate the mechanisms by which almonds may potentially improve memory, with a specific focus on their interactions with neuromodulatory systems and oxidative pathways, through a comprehensive review of relevant animal studies. As the prevalence of memory disorders continues to rise and therapeutic options remain limited, investigating the effects of nutritious and traditional herbal remedies like almonds may offer a promising treatment strategy.

Methods

The present study conducted a comprehensive review of the literature investigating the impact of consuming almond nuts on memory and related disorders in animal models. The main objective was to evaluate the relationship between almond consumption and parameters related to memory and related disorders, based on evidence from behavioral and molecular studies.

To conduct this review, a systematic search strategy was developed and presented in a flowchart in Figure 1. The search involved searching several databases including PubMed, Web of Science, Scopus, Embase, and Cochrane Library. The search was limited to studies published between 2000 and 2023. The keywords used for the search were ("Prunus Dulcis" OR "Prunus Amygdalus" OR "Almond" OR "Badam") AND ("Memory" OR "Learning" OR "Cognition" OR

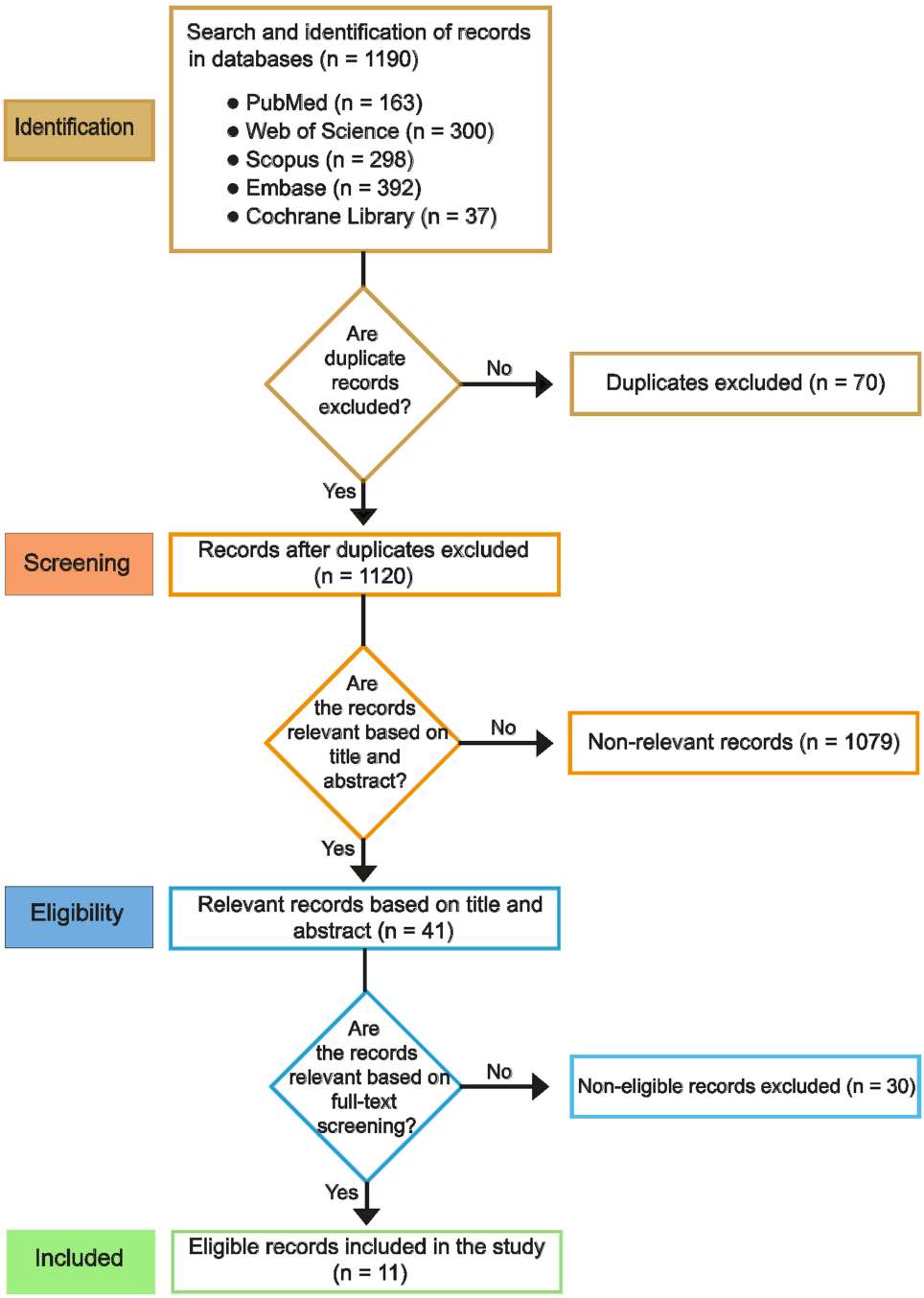


Figure 1 Flowchart representing the current study's article selection process. Out of 1190 articles, eleven were chosen through a four-stage process: identification, screening, eligibility, and inclusion.

"Brain" OR "Amnesia" OR "Dementia" OR "Alzheimer's disease" OR "Memory Enhancement" OR "Neuroprotection" OR "Memory disorder" OR "Neuroinflammation" OR "Neuroprotective" OR "Neurodegeneration").

The inclusion criteria for articles in this study were as follows: (1) the articles had to be published in English; (2) the studies had to have been conducted on animal, preclinical, experimental, or nonhuman models; (3) almond nuts (species *Prunus Dulcis* syn. *Prunus Amygdalus*) should have been orally administered in the studies; (4) the articles should have mentioned the connection between almond and memory or related disorders; (5) memory-related parameters should have been examined using behavioral tests or molecular investigations; and (6) the studies should have used specific controlled groups. On the other hand, the exclusion criteria for articles in this study were as follows: (1) human studies; (2) studies

conducted on cell models; (3) review articles, case reports, posters, conference abstracts, books, theories, and unpublished articles; (4) articles in languages other than English; and (5) articles that did not mention the connection between almond and memory or related disorders.

After searching, any duplicate articles found in all databases were removed. Subsequently, two authors independently evaluated the titles and abstracts of the remaining articles based on the predetermined inclusion and exclusion criteria. The articles that met these criteria were selected for a thorough review of the full text. In the event of any disagreements regarding the selection of articles, a third author was consulted to reach a consensus among the authors.

Following the article selection process, data from each one of the chosen articles were collected and organized in Table 1. The collected information includes (1) author and year of study; (2) species, sex, age and weight of animals; (3) animal model for memory impairment; (4) form of almond administration; (5) dose of almond administrated; (6) duration of treatment; (7) behavioral tests conducted; (8) the direction of change in behavioral indices; (9) the sample used for molecular and chemical investigations; (10) the direction of change in molecular and chemical indices, and (11) main results.

Results

The study selection process is presented in Figure 1, illustrating the details. Initially, a search of scientific databases resulted in 1190 articles. However, after applying the inclusion and exclusion criteria, only 11 articles were deemed relevant to include in this study. Most of the selected articles were from PubMed and WoS databases. Unrelated articles were excluded primarily due to the absence of investigation or mention of the relationship between almonds and memory, as well as studies conducted on humans. The available data from the included articles in this study has been categorized into the impact of almonds on memory enhancement in healthy animals and various models of memory impairment, as follows:

Effect of Almonds on Memory Enhancement in Healthy Animals

The following section provides a comprehensive overview of the evidence and results from studies conducted on the impact of almonds on memory enhancement in healthy adult animals and pregnant rat offspring.

Nootropic Effect of Almonds

Nootropics or cognitive enhancers are substances that are used to improve memory, increase mental alertness and concentration, as well as increase energy levels and alertness. Studies have reported the nootropic effects of almonds in rats. In 2012, Haider et al conducted a study to investigate the potential nootropic effect of almonds on the memory of healthy rats. This study involved administrating almond suspension (80 mg/day) to the rats for 28 days. The results of the study indicated that the rats that consumed almonds exhibited improvements in learning and memory consolidation indices in elevated plus maze (EPM) (decrease in transfer latency for entering closed arms), and also spatial working memory index in radial arm maze (RAM) (decrease in time elapsed before the rat entered the baited arm). In addition, investigations using the electrochemical detection in high-performance liquid chromatography (HPLC-EC) technique showed that the levels of tryptophan, 5-hydroxytryptamine (serotonin), and 5-hydroxyindoleacetic acid (5-HIAA), as indices of tryptophan metabolites and compounds involved in serotonin synthesis, increased in the brain of rats receiving almond. Therefore, the authors suggest that long-term consumption of almonds may have beneficial effects on learning and memory processes by affecting the overall metabolism of tryptophan and enhancing serotonergic transmission.[51]

In another study conducted by Batool et al in 2016, the researchers aimed to investigate the effect of repeated administration of almonds on memory enhancement in healthy rats. They administered almond suspension (200, 400, and 800 mg/kg) orally to the rats for 28 days. The results showed that almond consumption can significantly increase learning and memory consolidation indices in EPM, spatial memory indices in Morris water maze (MWM) (decrease in escape latency), as well as cognitive index in novel object recognition (NOR) (increase in time spent with new object). In addition, molecular investigations revealed a decrease in the activity of acetylcholinesterase, an enzyme involved in the breakdown of acetylcholine, and an increase in the level of acetylcholine in the frontal cortex and hippocampus of rats

Table 1 Summary of the Data Collected from Studies Included in the Present Study

Reference	Species (Sex, Age, Weight)	Animal Model	Form of Almond	Almond Dose (Treatment Period)	Behavioral Tests	Behavioral Indices, Direction of Change	Samples for Molecular and Chemical Tests	Measured Molecular and Chemical Indices, Direction of Change	Main Results
(Kulkarni et al, 2010)[50]	Wistar rats (Male, N/A, 150–180 g)	Scopolamine-induced memory impairment	Suspension in water	150, 300, and 600 mg/kg/day (7 and 14 days)	EPM	Transfer latency, ↓	Blood serum, Whole brain	Total cholesterol, ↓ Triglyceride, ↓ Glucose, ↑ Acetylcholine esterase activity, ↓	Prevention of amnesia; increase in cholinergic system activity; decrease in blood cholesterol level; a slight increase in blood glucose level
					PAT	Step-down latency during acquisition and retention, ↑			
					Actophotometer	Locomotor activity, ↔			
(Haider et al, 2012)[51]	Wistar rats (Male, N/A, mean 200 g)	Healthy	Suspension in water	80 mg/day (28 days)	EPM	% of time spent in open arms, ↓	Whole brain	5-hydroxytryptamine/5-hydroxyindoleacetic acid, ↑ Tryptophan, ↑	Memory enhancement, increase in blood tryptophan, increase in the metabolism of serotonin
					RAM	Time elapsed before the rat entered the baited arm, ↓			
(Batool et al, 2016)[29]	Wistar rats (Not mentioned, 5–6 m, 180–200 g)	Healthy, Scopolamine-induced memory impairment	Suspension in water	200, 400*, and 800 mg/kg (28 days)	EPM	Transfer latency, ↓	Frontal cortex and hippocampus	Acetylcholine, ↑ Acetylcholine esterase activity, ↓	Memory enhancement; improve scopolamine-induced memory impairment; increase in cholinergic activity of frontal cortex and hippocampus
					MWM	Escape latency, ↓			
					NOR	Recognition index, ↑			
(Batool et al, 2017)[35]	Wistar rats (Not mentioned, N/A, 150–200 g)	Cadmium-induced memory impairment	Suspension in water	400 mg/kg/day (28 days)	MWM	Escape latency, ↓	Frontal cortex and hippocampus	Acetylcholine, ↑ Acetylcholine esterase activity, ↔ Malonaldehyde, ↓	Ameliorating cadmium-induced memory impairment; improve antioxidant activity and reduce oxidative stress in frontal cortex and hippocampus; increase in cholinergic activity of frontal cortex and hippocampus
					OFT	Number of square crossings, ↓ Time of rearing, ↓ Number of rearing, ↔			
					NOR	Recognition index, ↑			
(Arslan et al, 2017)[34]	Sprague-Dawley rats and C57Bl/6 (Male and female, 4–6 m, 180–200 g)	Scopolamine-induced memory impairment High-fat diet-induced memory impairment	Whole, soaked, and blanched almond	3, 6 and 12* g/kg (14 days)	OFT	Locomotor activity, ↔	Frontal cortex and hippocampus	Acetylcholine esterase activity, ↓ alpha-tocopherol content, ↑	The beneficial effect of consuming soaked almond during fasting, rather than a whole form of almond, on prevention of scopolamine-induced amnesia and high fat diet-induced memory impairment; increase in cholinergic activity and tocopherol content of frontal cortex and hippocampus
					NOR	Discrimination index, ↔			
					MWM	Escape latency, ↓			
			Whole, soaked, and blanched almond	1, 2, and 4* g/kg (6 weeks)	OFT	Locomotor activity, ↔			
					MWM	Escape latency, ↓			

(Batool et al, 2018)[52]	Wistar rats (Male, 5–6 m, 180–200 g)	Scopolamine-induced memory impairment	Suspension in water	400 mg/kg/day (28 days)	PAT	Step through latency, ↓ Step-down latency, ↓	Whole brain	Malonaldehyde, ↓ superoxide dismutase activity, ↑ Catalase activity, ↑ Glutathione peroxidase activity, ↑	Delaying or preventing the onset of memory impairment; decrease in scopolamine-induced oxidative stress; increase in antioxidant activity of the brain
(Batool et al, 2019)[36]	Wistar rats (Male, N/A, 180–200 g)	Cadmium-induced memory impairment	Suspension in water	400 mg/kg/day (28 days)	FST	Immobilization time, ↓ Struggling time, ↑ Swimming time, ↔	Whole brain	Serotonin, ↑ Noradrenaline, ↑ Dopamine, ↑ Dihydroxyphenyl acetic acid, ↑ Homo vanillic acid, ↓ 5-hydroxyindoleacetic acid, ↓	Preve ntion of memory impairment, depression, and anxiety caused by cadmium neurotoxicity; increase in cholinergic, serotonergic, and noradrenergic activity of the brain
					LDT	Latency to move into dark room, ↑ Time spent in light box, ↑			
					EPM	Transfer latency in training and test sessions, ↓			
					MWM	Escape latency in training and test sessions, ↓			
					NOR	Discrimination index, ↑			
(Agha et al, 2020)[53]	Wistar rats (Male, N/A, 180–200 g)	Cadmium-induced memory impairment	Suspension in water	400 mg/kg/day (28 days)	EPM	% of memory retention, ↑	Whole brain	Lipid peroxidation, ↓ Superoxide dismutase activity, ↑ Catalase activity, ↑ Glutathione peroxidase activity, ↑	Memory enhancement; prevention of cadmium-induced memory impairment; improvement of antioxidant activity and reduction of oxidative stress of the brain
					MWM	% of memory retention, ↑			
(Shrivastava et al, 2021)[54]	Wistar rats (Not mentioned, 10–12 w, 150–210 g)	Scopolamine-induced memory impairment	Alcoholic extract	250 and 500 mg/kg/day (7–8 days and 10–11 days)	EPM	Transfer latency in acquisition and retention trials, ↓	Whole brain	Acetylcholine esterase activity, ↓ Acetylcholine, ↑ Thiobarbituric acid, ↓ Lipid peroxidation, ↓	Improvement of cognitive function; improve antioxidant activity, decrease in oxidative stress; increase in cholinergic activity of the brain
					MWM	Escape latency in acquisition and retention trials, ↓			

(*Continued*)

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Table 1 (Continued).

Reference	Species (Sex, Age, Weight)	Animal Model	Form of Almond	Almond Dose (Treatment Period)	Behavioral Tests	Behavioral Indices, Direction of Change	Samples for Molecular and Chemical Tests	Measured Molecular and Chemical Indices, Direction of Change	Main Results
(Bhatia et al, 2022)[55]	Wistar rats (Male and female, N/A, 230–250 g)	Chronic unpredicted stress-induced memory impairment	Methanolic extract	25 and 50 mg/kg/day (10 days)	MWM	Transfer latency, ↓ Time spent in target quadrant, ↑	Whole brain	Thiobarbituric acid, ↓ Glutathione, ↑ Catalase, ↑	Ameliorating chronic unpredicted stress-induced memory impairment; ameliorating chronic unpredicted stress-induced neuroinflammation; increase in antioxidant activity; decrease in oxidative stress
(Bahaeddin et al, 2022)[56]	Wistar rats (Male, 2–3 m, 200±20 g)	Healthy	Mixed with diet	5% (23 days during mating and gestation period)	Y-maze	% of spontaneous alternation, ↑ Locomotor activity, ↔	The prefrontal cortex, Amygdala, and hippocampus	CREB phosphorylation, ↑ BDNF, ↑ MAO-A, ↓ MAO-B, ↓	Memory enhancement; decrease in anxiety-like behavior; increase in adaptation to stress; increase in phosphorylation of CREB and BDNF in frontal cortex and decrease in MAO-A and MAO-B level in both frontal cortex and hippocampus
					EPM	% of open arms entries, ↑ % of time spent in open arms, ↔ Locomotor activity, ↔			
					FST	Immobility time, ↓			

Notes: ↑, Increase; ↓, Decrease; ↔, No change; *Effective dose.

Abbreviations: EPM, Elevated plus maze; PAT, Passive avoidance task; RAM, Radial arm maze; MWM, Morris water maze; NOR, Novel object recognition; OFT, Open field Task; FST, Forced swimming task; LDT, Light dark task; CREB, Cyclic AMP response element-binding proteins; BDNF, Brain-derived neurotrophic factor; MAO-A, Monoamine oxidases-A, MAO-B, Monoamine oxidases-B.

receiving almonds. Therefore, the authors suggested that the repeated administration of almonds enhanced memory in healthy rats by increasing the levels of acetylcholine in the specific brain regions involved in memory function.[29]

Effect of Almond Consumption During Pregnancy on Memory Enhancement in Offspring

In a study conducted by Bahaeddin et al in 2022, the authors examined the impact of almond consumption during pregnancy on the cognitive activity of male rat offspring. The study administered a diet consisting of almonds (5%) to female rats during mating and gestation periods. The results of this study showed that this dietary intervention resulted in improved working memory performance in the Y-maze test (increase in spontaneous alternations), as well as reduced anxiety- and depression-like behaviors in EPM (increase in percentage of open arms entries) and forced swimming test (FST) (decrease in immobility time) in male offspring. Also, molecular studies showed an increase in cAMP-response element binding protein (CREB) phosphorylation and brain-derived neurotrophic factor (BDNF) (as molecules involved in synaptic plasticity) levels and a decrease in monoaminoxidase-A (MAO-A) and MAO-B (as enzymes that breakdown the monoamines such as serotonin, noradrenaline and dopamine) activity in the hippocampus and prefrontal cortex of the offspring. Therefore, the authors of this study concluded that the consumption of almonds during pregnancy, through changes in memory-related molecules and the activity of enzymes involved in the metabolism of monoamines, improves working memory performance, increases adaptation to stress and survival, and slightly reduces anxiety- and depression-like behavior in adult male offspring.[56]

Effect of Almonds on the Improvement of Memory Impairment in Some Animal Models

The effects of almonds on animal models of memory impairment, including memory impairment induced by scopolamine, cadmium, high-fat diet, and chronic unpredicted stress, are detailed below.

Almonds and Scopolamine-Induced Memory Impairment

Scopolamine, as an anticholinergic drug, is used to induce memory impairment in animals. Studies provided evidence of the effect of almonds on scopolamine-induced memory impairment in animals. In a study conducted in 2016 by Batool et al, the researchers aimed to investigate the effect of repeated administration of almonds on an animal model of scopolamine-induced memory impairment. They administered almond suspension orally to healthy rats at various doses (200, 400, and 800 mg/kg) for 28 days. Based on behavioral assessments, the dose of 400 mg/kg was identified as the most effective dose on memory performance. Subsequently, the impact of the effective dose of almonds on scopolamine-induced memory impairment was investigated. The findings demonstrated that the 28-day administration of the effective dose of almond improved learning and memory consolidation indices in EPM, cognitive index in NOR, and spatial memory index in MWM behavioral test in animals that received scopolamine (0.5 mg/kg). Moreover, neurochemical examinations indicated a decrease in the activity of the acetylcholinesterase enzyme and an increase in the level of acetylcholine in the hippocampus and frontal cortex. The authors concluded that the long-term consumption of almonds can alleviate the scopolamine-induced memory deficit by reducing the activity of acetylcholinesterase and increasing the levels of acetylcholine in the frontal cortex and hippocampus.[29]

Kulkarni et al in 2010 investigated the effect of almonds on amnesia induced by scopolamine. Rats were orally administered almond suspension (150, 300, and 600 mg/kg) for 7 or 14 consecutive days. Results showed that all three doses of almond, regardless of the treatment duration, improved learning and memory consolidation indices in the EPM test, as well as avoidance memory in passive avoidance task (PAT) (increase in step-down latency for entering the dark room) in rats receiving scopolamine (1 mg/kg). In addition, molecular investigations revealed decreased activity of the acetylcholinesterase enzyme and increased levels of acetylcholine in the whole brain, as well as a significant reduction in triglyceride levels upon almond consumption. However, all three doses of almonds also caused a slight increase in blood glucose levels. Based on the findings, the authors suggested that almond consumption may counteract scopolamine-induced learning and memory impairment through the enhancement of cholinergic transmission.[50]

Another experimental study conducted by Arslan et al in 2017 aimed to investigate the protective effect of soaked almonds on a scopolamine-induced memory impairment model. They administered multiple doses of almonds (3, 6, and

12 g/kg) to C57BI/6 mice in both fasting and non-fasting conditions for 6 to 14 days. The almonds were administered in three different forms: whole, soaked, and blanched. The results of the study showed that the administration of whole almonds (12 mg/kg), and soaked almonds (6 and 12 mg/kg) in fasting and non-fasting states improved spatial memory impairment caused by scopolamine (2 mg/kg) in the MWM test. However, three doses of almonds did not affect the cognitive index in NOR and locomotor activity in the open field test (OFT). In addition, the results of molecular studies showed that only the highest dose of whole almonds (12 mg/kg) inhibited the activity of the acetylcholinesterase enzyme only in the cortex. Soaked almonds with doses of 6 and 12 mg/kg inhibited the activity of acetylcholinesterase enzyme in both frontal and prefrontal cortices. However, blanched almonds did not affect the activity of this enzyme. Furthermore, authors found that soaked almonds with all three doses (3, 6, and 12 mg/kg) administered in the fasting state inhibited the activity of acetylcholinesterase enzyme in the hippocampus and with doses of 6 and 12 mg/kg in the frontal cortex, similar to the drug physostigmine. However, soaked almonds consumed in the non-fasting state did not significantly affect the activity of this enzyme. Likewise, HPLC results also showed that the concentration of vitamin E (α-tocopherol) was 119.4 mg/kg in whole almonds, 259 mg/kg in soaked almonds, and 189 mg/kg in blanched almonds. Therefore, the authors of this study concluded that soaked almonds prevent scopolamine-induced memory impairment by increasing the vitamin E content and improving cholinergic function in memory-related brain regions.[34]

In addition, in 2018, Batool et al conducted a study to investigate the antioxidant effect of almonds on oxidative stress and the prevention of memory impairment in male rats induced by scopolamine. The study involved administrating almond suspension at different doses (200, 400, and 800 mg/kg) to animals for 28 days. They found that the dose of 400 mg/kg was the most effective in improving the memory of healthy rats. The results also showed that the administration of an effective dose of almond suspension for 28 days improved learning and avoidance memory in animals receiving scopolamine (0.5 mg/kg). Additionally, almond administration reduced the activity of lipid peroxidation and the level of malondialdehyde (MDA) (as residue of oxidate stress) and increased the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) (as enzymes with antioxidant activity) in the whole brain. Furthermore, a significant correlation was observed between the percentage of memory consolidation and the level of malondialdehyde, as well as between catalase activity and the malondialdehyde level. Therefore, the authors concluded that long-term administration of almonds reduces oxidative stress and improves learning and memory performance.[52]

In 2021, Shrivastava et al investigated the impact of repeated administration of almonds on a scopolamine-induced memory impairment animal model. The researchers administered almond alcoholic extract (250 and 500 mg/kg) for a period of 7 to 11 days. The study revealed that this treatment improved learning and memory consolidation indices in EPM, and spatial memory index in MWM in animals receiving scopolamine (1 mg /kg). The effects of almonds were comparable to piracetam, a known cognitive enhancer, administered at a dose of 120 mg/kg. In addition, the molecular studies conducted in this research indicated that almonds were able to significantly decrease the levels of Thiobarbituric acid, a biomarker of oxidative stress, as well as inhibit the activity of acetylcholinesterase enzyme in the whole brain. These findings suggest that almond consumption may prevent scopolamine-induced memory impairment by reducing the acetylcholinesterase activity, alleviating oxidative stress, decreasing lipid peroxidation, and increasing the acetylcholine levels in the brain.[54]

Almonds and Cadmium-Induced Neurotoxicity

Cadmium is a heavy metal that repeated exposure to it induces memory impairment in animals. Studies have provided evidence of the effect of almonds on cadmium-induced memory impairment. In a study conducted by Batool et al in 2017, the researchers investigated the effects of repeated administration of almonds and walnuts on a cadmium-induced memory impairment animal model. The study found that administering almond (400 mg/kg/day) and walnut (400 mg/kg/day) suspensions orally for 28 days led to improvements in non-associative memory indices in OFT (decrease in the number of rearing and crossing), spatial memory index in MWM, and cognitive index in NOR in animals receiving cadmium. In addition, the neurochemical investigation conducted as a part of the study revealed that neither almonds nor walnuts had a significant effect on the activity of the acetylcholinesterase enzyme in the frontal cortex and hippocampus. However, the levels of acetylcholine were significantly increased after the administration of almond and walnut

treatments. Furthermore, the study discovered that administering almonds or walnuts alongside cadmium can prevent the increase of malondialdehyde, which is caused by exposure to cadmium, in rats. Therefore, the authors concluded that the concurrent administration of almonds or walnuts with cadmium can improve cadmium-induced memory impairment. This improvement is attributed to the antioxidant properties of almonds, which affect the cholinergic system and reduce oxidative stress.[35]

In an experimental study conducted by Batool et al in 2019, the potential of almonds to prevent cadmium-induced neurotoxicity was investigated. The study involved administering an almond suspension (400 mg/kg/day) orally for 28 days. The results of the study demonstrated that the administration of almonds significantly improved learning and memory consolidation indices in EPM, spatial memory index in MWM, and cognitive index in NOR in animals exposed to cadmium. Furthermore, almond consumption reduced depressive and anxiety-like behaviors in the FST and light-dark test (LDT) (increase in transfer latency for entering into dark room). Also, neurochemical analysis using HPLC showed that almonds administration led to a decrease in the levels of 5-hydroxytryptamine (5-HT), 5-hydroxyindole acetic acid (5-HIAA), homovanillic acid (HVA) (as compounds resulting from the metabolism of monoamines), and increase in noradrenaline (NA), dopamine (DA), dihydroxyphenylacetic acid (DOPAC) levels in the brain. Therefore, it was suggested that treatment with almond supplements may improve spatial and cognitive memory function and significantly reduce anxiety and depressive-like behaviors in the cadmium-induced memory impairment model. It could potentially be attributed to the increase in serotonin, dopamine, and noradrenaline levels.[36]

An experimental study was conducted by Agha et al in 2020 to examine the impact of almond supplementation on the oxidative status and brain function of male rats. They administered almond suspension (400 mg/kg) for 28 days in animals exposed to cadmium (50 mg/kg/week). The findings of the study demonstrated that administering almond suspension led to a significant improvement in the indices of learning in EPM and spatial memory in the MWM behavioral test. Additionally, the results of the biochemical study indicated a decrease in lipid peroxidation and an increase in superoxide dismutase, catalase, and glutathione peroxidase in the whole brain following almond administration. In conclusion, the study suggests that the long-term inclusion of almonds in the diet can contribute to the prevention of memory impairment caused by cadmium. The positive effects are believed to be due to the reduction of oxidative stress and the increase in the restoration of antioxidant enzyme activity. As a result, almond supplementation can improve cadmium-induced memory impairment.[53]

Almonds and Chronic Unpredicted Stress-Induced Memory Impairment

Chronic stress is one of the factors that lead to memory loss. Bhatia et al in 2020 conducted an experimental study to investigate the protective effects of the almond extract on chronic unpredicted stress (CUS)-induced memory impairment and related biochemical changes in rats. They administered almond methanolic extract (25 and 50 mg/kg) orally to animals subjected to the CUS protocol for 10 days. The study found that the administration of almond extract improved short-term (decrease in escape latency) and long-term memory (increase in time spent in target quadrant) indices in the MWM behavioral test. In addition, the histopathological examination of brain tissue showed that the almond extract reduced inflammation and migration of microglia, particularly in the hippocampus. This effect was more pronounced with the higher dose of almond extract. Additionally, the results of the neurochemical analysis revealed that almond extract, especially at the higher dose, prevented the increase of Thiobarbituric acid reactive substance (TBARS) and restored the levels of GSH and catalase. Therefore, the authors of this study suggested that consuming almond extract could be beneficial in counteracting memory impairment induced by chronic unpredicted stress, primarily due to its antioxidant and anti-inflammatory properties.[55]

Almonds and High-Fat Diet-Induced Memory Impairment

It is well known that high-fat diet consumption causes memory impairment. Arslan et al in 2017 investigated the protective effect of soaked almonds on memory impairment induced by a high-fat diet. The study examined the effects of different doses of almonds (1, 2, and 4 g/kg) administered in three different forms (whole, soaked, and blanched) in both fasting and non-fasting conditions over 6 weeks. The results showed that whole almonds (2 g/kg), as well as soaked almonds (2 and 4 g/kg), improved spatial memory impairment in the MWM test in animals on a high-fat diet.

Furthermore, the protective effect of soaked almonds was found to be greater when administered in the fasting state compared to the non-fasting state. Therefore, the study concluded that soaked almonds in higher doses and the fasting state can significantly prevent memory impairment caused by a high-fat diet.[34]

Discussion

Memory, the ability to retain and recall information, is a fundamental biological function necessary for survival. It helps integrate our conscious and unconscious behaviors.[1] Memories are stored in the brain through structural changes at the level of neurons and synapses, known as synaptic plasticity. This process plays a crucial role in creating and reinforcing memories.[2,3] Memory disorders are often caused by a wide range of neurological pathologies that affect synaptic plasticity in different brain regions.[57] Despite the increasing prevalence of these disorders, effective treatments have not yet been identified.[58,59] This has prompted researchers to explore alternative approaches, such as nutrition, to enhance memory function and manage related disorders. Diet has been extensively studied in both animal and human research for its role in preventing and managing cognitive disorders. Nuts, including almonds, have been shown to have cognitive benefits, including enhancing memory and preventing memory disorders.[15,18] One well-known nut is almonds, which are consumed worldwide. As mentioned, various studies have shown that almonds can be effective in enhancing memory function and improving related disorders. Like many other plants and nuts, almonds are rich in various compounds, such as polyunsaturated fatty acids, proteins, minerals, vitamins, and polyphenols, which contribute to their positive effects on memory.[15,29,35,53]

The role of neuromodulatory systems is considered to be a crucial factor in understanding synaptic plasticity. Neuromodulators, such as dopamine, acetylcholine, noradrenaline, and serotonin have been found to play a specific role in regulating the induction of synaptic plasticity.[60] These neuromodulators enable the precise regulation of neural network activities.[61] Evidence suggests that neuromodulators are involved in coupling rhythmic activity and synaptic plasticity.[62] Various neuromodulators can interact with glutamatergic transmission, potentiating the response of N-methyl-D-aspartate (NMDA) receptors. These receptors are primarily involved in synaptic plasticity changes in specific brain regions, notably the hippocampus. At the network level, neuromodulators help regulate the synchronized activity of neurons, meeting the first requirement for inducing plasticity known as associativity, which involves simultaneous activity between pre- and post-synaptic neurons.[60] Disruptions in neuromodulatory systems can lead to memory disorders, while certain compounds that affect memory can enhance memory function by modulation of these systems.[63]

Additionally, maintaining a balance between oxidative stress and antioxidant pathways is essential for normal brain function. Imbalances in this system have been found to contribute to pathological processes underlying memory disorders.[64] Oxidative stress can impair memory by damaging essential brain structures and functions. Reactive oxygen species (ROS) generated during oxidative stress can damage neurons, particularly in the hippocampus and frontal lobe, which are critical for memory and cognitive functions. This damage leads to mitochondrial dysfunction, abnormal accumulation of synaptic vesicles, and a decline in neurotransmitter release, ultimately impairing synaptic plasticity and memory consolidation.[65] Furthermore, oxidative stress causes DNA damage and disrupts epigenetic modifications, resulting in the downregulation of genes necessary for cognitive functions and promoting neuronal cell death.[66] On the other hand, almonds, known for their medicinal and nutritional properties, have been found to possess strong antioxidant properties.[67] Based on the previous studies, it is expected that almonds may have an impact on memory and synaptic plasticity through their influence on neuromodulatory systems and oxidative stress pathways.

Studies have shown that consuming almonds can improve memory in healthy animals.[29,51] Evidence suggests that this improvement may be mediated by the involvement of both the serotonergic and cholinergic systems.[29,51,56] The serotonergic system is an important neuromodulatory system and controls various functions, such as sensory and motor modulation, emotion regulation, and cognitive control.[68,69] Its action in both normal and pathological situations is largely dependent on the action of enzymes, transporters, and specific subtypes of expressed receptors (5-HTR) and their localization, which all affect local serotonin concentration and neurotransmission.[70] The important role of serotonin receptors in learning and memory has been well established.[71,72] There is evidence that 5-HTR may enhance glutamatergic transmission and subsequent plasticity.[70] The serotonergic transmission also deals with other neurotransmitters, such as dopamine, acetylcholine, and gamma-aminobutyric acid (GABA) to regulate learning and memory.[46] Serotonin is synthesized from the amino acid tryptophan in the presynaptic terminal of serotonergic neurons. It is then converted to 5-hydroxytryptophan or 5-HT by an enzyme called

tryptophan hydroxylase. 5-HT is further converted to serotonin.[51] When released, serotonin affects the serotonergic receptors in the postsynaptic neuron, leading to changes that enhance plasticity, synaptic transmission, and ultimately learning and memory.[73] In this regard, some evidence has reported an increase in brain serotonin following almond consumption in rats. As shown in a study in healthy rats, almond consumption increases brain serotonin levels in rats by increasing blood tryptophan levels. Almond constituents also increase the ratio of 5-hydroxyindoleacetic acid to 5-hydroxytryptamine, leading to increased transmission of the serotonergic synaptic pathway.[51] Likewise, the acetylcholine and the cholinergic system are known to play a role in learning and memory processes.[74] Acetylcholine coordinates the firing of groups of neurons, activates the intrinsic mechanisms for continuous spiking, and influences synaptic transmission. It specifically regulates glutamatergic transmission within the specific brain areas involved in learning and memory processes and induces synaptic plasticity.[75] Acetylcholine is synthesized in the presynaptic terminal using choline and is released into the synaptic space, where it binds to postsynaptic receptors to enhance memory.[76,77] On the other hand, there is evidence that almonds are rich in choline.[29] Consumption of almonds increases choline levels in the bloodstream, leading to increased production of acetylcholine. Additionally, almond consumption inhibits acetylcholinesterase, an enzyme that breaks down acetylcholine, further enhancing its effects on postsynaptic neurons.[29] Both the increase in acetylcholine production and the inhibition of its degradation, lead to heightened cholinergic transmission. This, in turn, promotes plastic changes in the brain that are associated with memory enhancement. Likewise, it has been shown that almond consumption reduces the activity of MAO-A and B in the brain.[56] By inhibiting the metabolism of monoamines, almonds can increase the transmission of synaptic pathways involving these neurotransmitters. Moreover, evidence indicates the presence of antioxidant compounds in almond nuts.[78] Research suggests that almonds may enhance memory by reducing oxidative stress, and lipid peroxidation, and increasing the expression of BDNF and CREB at the neuronal level.[56] The antioxidant compounds found in almonds have the potential to inhibit the production of ROS, which in turn can lead to the upregulation of genes essential for facilitating plastic changes in synapses. These mechanisms contribute to synaptic plasticity and memory enhancement. Therefore, the beneficial effects of almond consumption on memory may be mediated through the involvement of cholinergic and serotonergic systems, as well as by reducing oxidative stress and increasing the expression of BDNF and CREB (Figure 2).

In this regard, multiple studies have shown that consuming almonds can improve memory disorders, such as scopolamine-induced memory impairment.[29,34,51] Scopolamine is a substance that blocks muscarinic receptors in the brain, reducing the activity of acetylcholine.[79] Scopolamine blocks the release of acetylcholine and increases the activity of the acetylcholinesterase enzyme. This results in a decrease in the amount of acetylcholine in the synaptic space.[29,51] In addition, scopolamine increases oxidative stress in postsynaptic neurons by increasing the level and function of malondialdehyde and reducing the levels of antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. This imbalance leads to increased neuronal damage and memory loss.[51,80] To study memory impairment similar to Alzheimer's disease in laboratory animals, researchers use the scopolamine-induced memory disorder model.[81] On the other hand, evidence suggests that almond consumption inhibits the action of scopolamine. Almonds increase the production and release of acetylcholine in the presynaptic neuron, leading to an increase in its concentration. This also decreases the activity of acetylcholinesterase in the synaptic space, allowing more acetylcholine to bind to receptors in the postsynaptic neuron.[29,34,50–52,54] Furthermore, the constituents of almonds reduce oxidative stress in the postsynaptic neuron by increasing the levels of antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase.[51] This helps prevent neuronal damage and memory impairment caused by oxidative stress. Overall, by affecting the cholinergic system, almond consumption can prevent scopolamine-induced memory impairment and reduce the risk of memory impairment caused by oxidative stress (Figure 3).

Another common condition is memory impairment caused by chronic exposure to cadmium. Studies have shown that long-term consumption of almonds can improve the neurotoxicity and memory impairment caused by cadmium.[35,36,53] Cadmium is a heavy metal that is considered biologically harmful and can disrupt neuronal functions.[82] According to the studies, cadmium can pass through the blood-brain barrier and disrupt the production of neurotransmitters such as serotonin, noradrenaline, acetylcholine, and dopamine.[83,84] Cadmium also increases the activity of the enzyme acetylcholinesterase in different brain regions, including the hippocampus and cerebral cortex. Therefore, it leads to a reduction in neurotransmitters and disruption of synaptic activity, ultimately resulting in learning and memory impairment.[85] On the other hand, almonds have been observed to inhibit the effect of cadmium and increase the levels

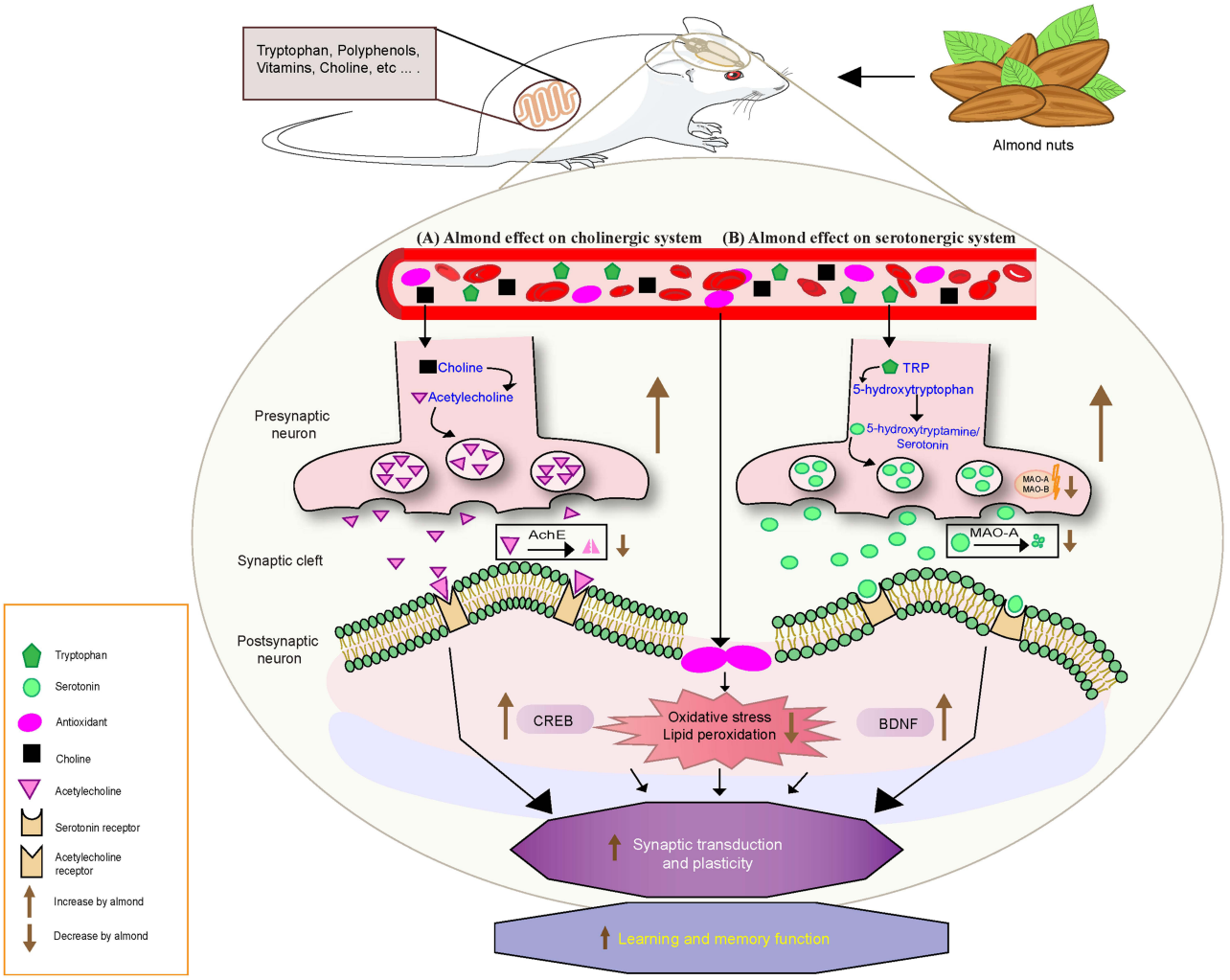

Figure 2 Memory enhancing effect of almond consumption in healthy rats. Possible impacts of almonds on cholinergic (**A**) and serotonergic synaptic transmissions (**B**) are shown. Almonds, containing tryptophan, choline, phenols, and vitamins, could enhance both cholinergic and serotonergic synaptic transmission, reduce oxidative stress and lipid peroxidation, and increase BDNF and CREB expression. These mechanisms collectively enhance synaptic transmission and plasticity, ultimately improving learning and memory function in healthy rats.

Abbreviations: TRP, Tryptophan; AchE, Acetylcholine esterase; CREB, Cyclic AMP response element-binding proteins; BDNF, Brain-derived neurotrophic factor; MAO-A, Monoamine oxidases-A, MAO-B, Monoamine oxidases-B.

of various neurotransmitters, such as dopamine, noradrenaline, serotonin, and acetylcholine in the brain.[35,36] Almonds do not affect the activity of the acetylcholinesterase enzyme.[35] As a result, almonds improve cadmium-induced memory impairment by strengthening the effect of these neuromodulators. In addition, cadmium is known to increase oxidative stress in cells and weaken the antioxidant system,[86] by inhibiting the binding of calcium to calmodulin. An increase in the accumulation of oxidants and their residues such as malonaldehyde and a decrease in antioxidants such as superoxide dismutase, glutathione peroxidase, and catalase, resulting in DNA damage, disruption of protein production, and neuron dysfunction. This leads to the apoptosis of neurons and their dysfunction.[87–91] Almonds, on the other hand, are rich in minerals, vitamins, and antioxidant polyphenols. These compounds neutralize free radicals and reduce the neurotoxicity caused by cadmium.[36,53,92,93] Almond consumption has been shown to reduce oxidative stress and increase antioxidants in the brain.[36,53] This reduces DNA damage and apoptosis, leading to increased cell survival. Therefore, almond consumption can be effective in treating memory impairment caused by cadmium. It is suggested that almonds and their constituents can prevent neuronal dysfunction, influence neuromodulatory systems, increase neurotransmitter release, reduce oxidative stress, and increase antioxidants. The summary of the effect of almonds on cadmium-induced memory impairment is shown in Figure 4.

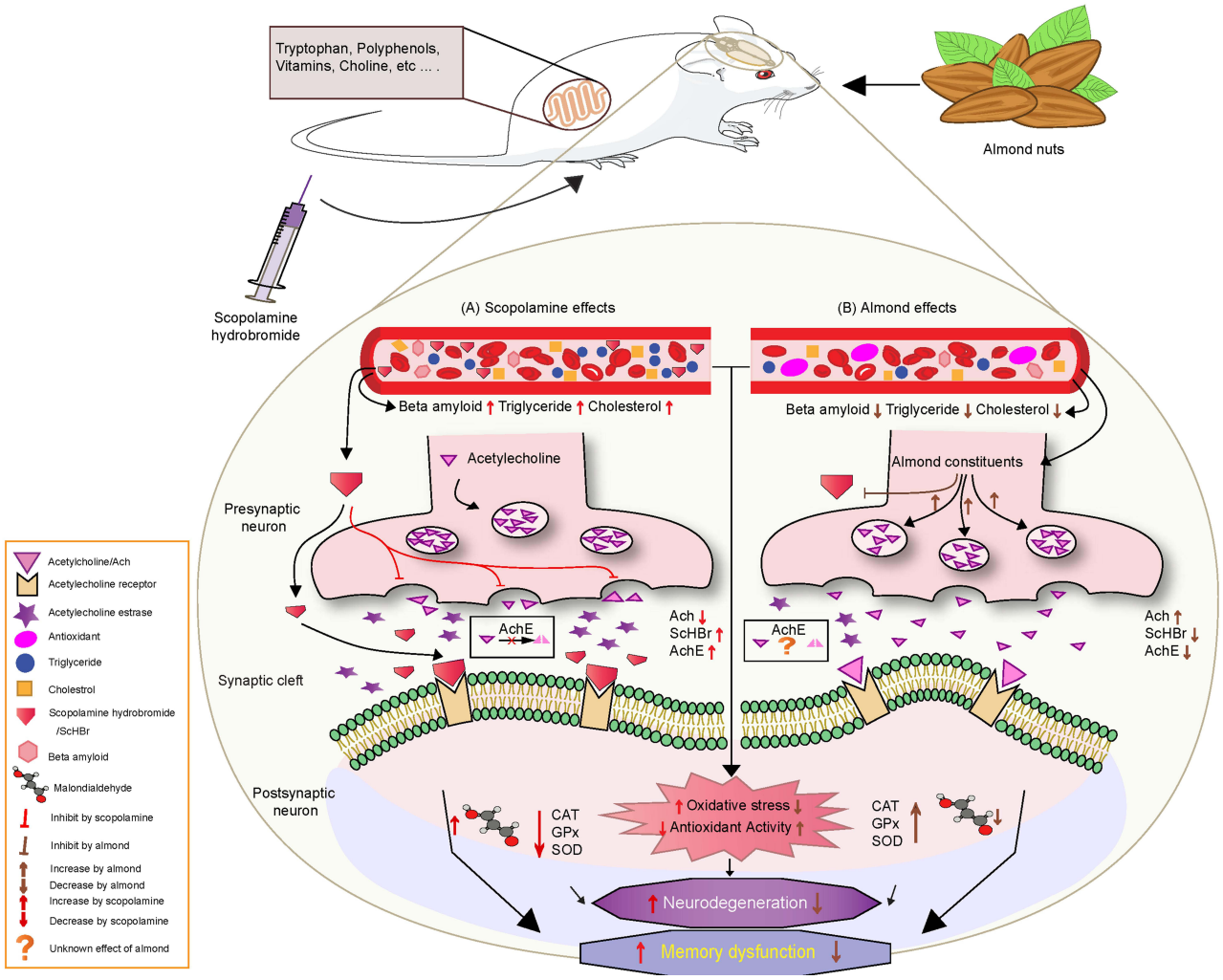

Figure 3 Effect of almond consumption on scopolamine-induced memory impairment in rats. Impacts of scopolamine administration (**A**) on cholinergic transmission and its counteraction by almond administration (**B**) are shown. Almonds attenuate scopolamine-induced memory impairment by improving cholinergic synaptic transmission, lowering oxidative stress, and boosting antioxidant activity. These mechanisms altogether help alleviate neurodegeneration and improve memory dysfunction. Key constituents such as tryptophan, choline, phenols, and vitamins play integral roles in mediating these effects.
Abbreviations: SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; Ach, acetylcholine; AchE, acetylcholine esterase; ScHBr, scopolamine hydrobromide.

Chronic stress is a major contributor to memory impairment in both humans and animals. To study the effects of different drugs on chronic stress, researchers use a laboratory model of chronic unpredicted stress.[94] There is evidence that almond consumption can improve behavioral and neurochemical changes associated with chronic unpredicted stress. Stress causes long-term damage to the brain and disrupts its ability to encode and retrieve information by affecting biochemical parameters in certain brain areas.[55] Stress also activates free radical production cascades, which can lead to oxidative stress if the stress becomes chronic.[95] The brain, with its high-fat content and oxygen consumption, is particularly vulnerable to the harmful effects of oxidative stress.[96] Oxidative stress triggers an overactivation of the pituitary-adrenal-hypothalamus (HPA) axis, resulting in the release of large amounts of corticotropin-releasing hormone. This hormone then stimulates adrenocorticotropin release from the anterior pituitary, which subsequently releases glucocorticoids from the adrenal cortex. Glucocorticoids affect the expression and regulation of various genes differently.[97,98] Excessive glucocorticoid secretion leads to memory impairment by increasing the amount of thiobarbituric acid, decreasing the level of glutathione, and reducing the level of catalase.[98] Furthermore, chronic unpredicted stress up-regulates inflammatory genes NFκB and iNOS, releases cytokines such as TNF-α, IL-1b, and IL-6, and increases microglial migration. Activation of inflammatory signals in the brain leads to impaired cognition and

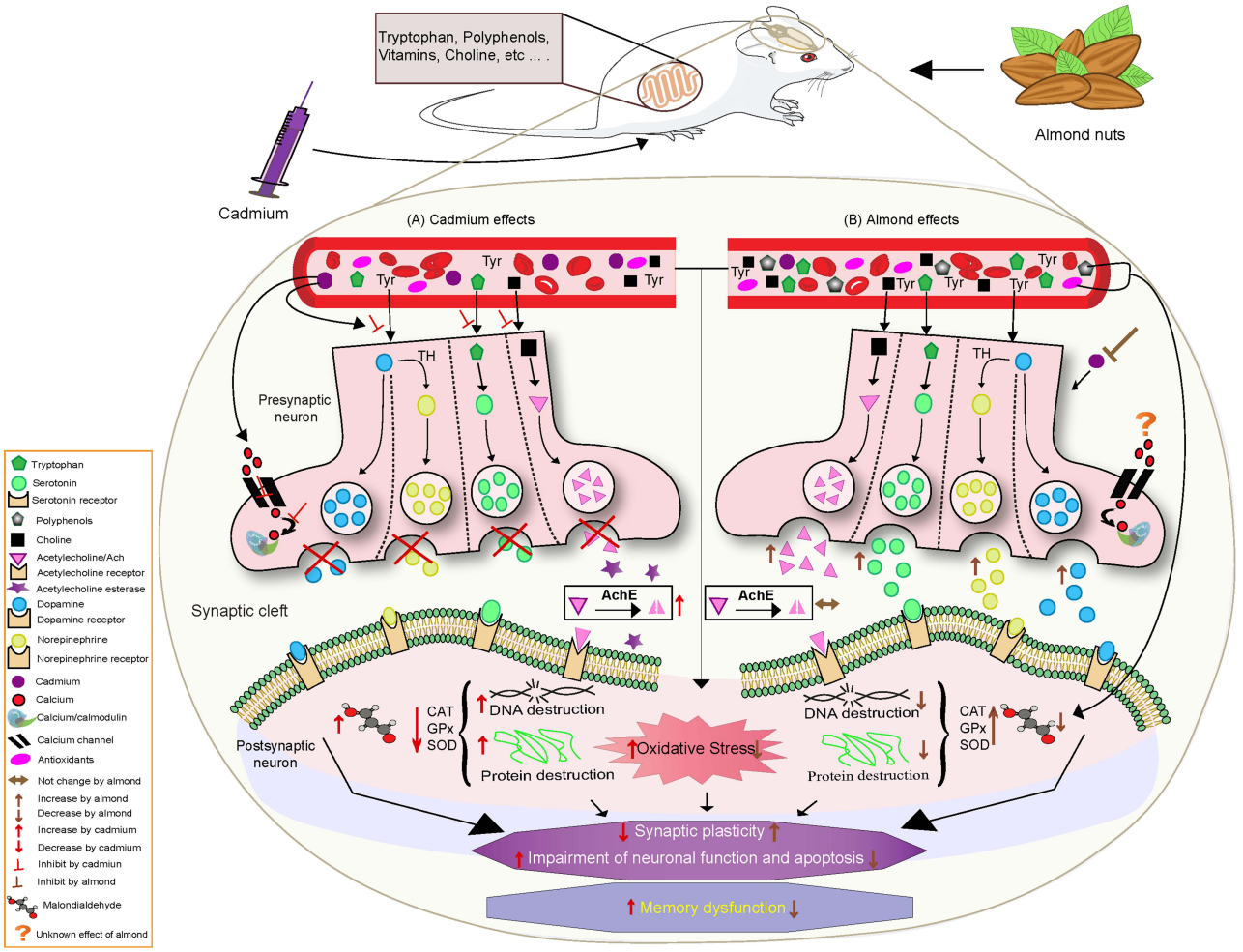

Figure 4 Effect of almond consumption on cadmium-induced memory impairment in rats. Impacts of cadmium administration (**A**) on neuromodulatory systems transmissions and its counteraction by almond administration (**B**) are shown. Almonds mitigate the memory impairment caused by cadmium by enhancing cholinergic, serotonergic, dopaminergic, and noradrenergic synaptic transmissions, lowering oxidative stress, reducing DNA and protein degradation, and boosting antioxidant activity. Collectively, these mechanisms prevent apoptosis and loss of neuronal function, increase synaptic plasticity, and improve learning and memory dysfunction in rats with cadmium-induced memory impairment. Constituents within almonds including phenols, choline, tryptophan, and vitamins are involved in mediating these mechanisms.
Abbreviations: Tyr, Tyrosine; TH, Tyrosine hydroxylase; AchE, Acetylcholine esterase; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase.

mood.[99,100] Almonds have been found to have antioxidant and anti-inflammatory effects, protecting the brain.[55,67] A study showed that the methanol extract of almonds has a high antioxidant potential and can reduce oxidative damage caused by chronic unpredicted stress. As a result, almonds probably improve memory function by reducing thiobarbituric acid levels, increasing the levels of glutathione and catalase, and decreasing microglial migration and brain inflammation.[94] In addition to oxidative stress and inflammation, chronic stress injuries also disrupt neuromodulatory systems, including the cholinergic, serotonergic, dopaminergic, and noradrenergic systems. These dysfunctions contribute to memory impairment.[101,102] However, there is no evidence of the effect of almonds on neuromodulatory systems in the chronic unpredicted stress model. As almonds predominantly modulate the activity of the cholinergic system in other memory impairment models,[35,52,53] it is possible that the cholinergic system is also involved in the effect of almonds on stress-induced memory impairment. Further research in this area is needed. A summary of the effects of almonds on memory impairment caused by chronic unpredicted stress is shown in Figure 5.

Another model of memory impairment is memory deficits caused by long-term consumption of a high-fat diet. It has been shown that almonds can improve memory deficits caused by a high-fat diet.[34] A high-fat diet can lead to memory disorders, particularly spatial memory, and other behavioral abnormalities.[103] A high-fat diet increases total cholesterol and LDL while decreasing HDL in plasma. Hypercholesterolemia is also associated with an increased risk of late-life

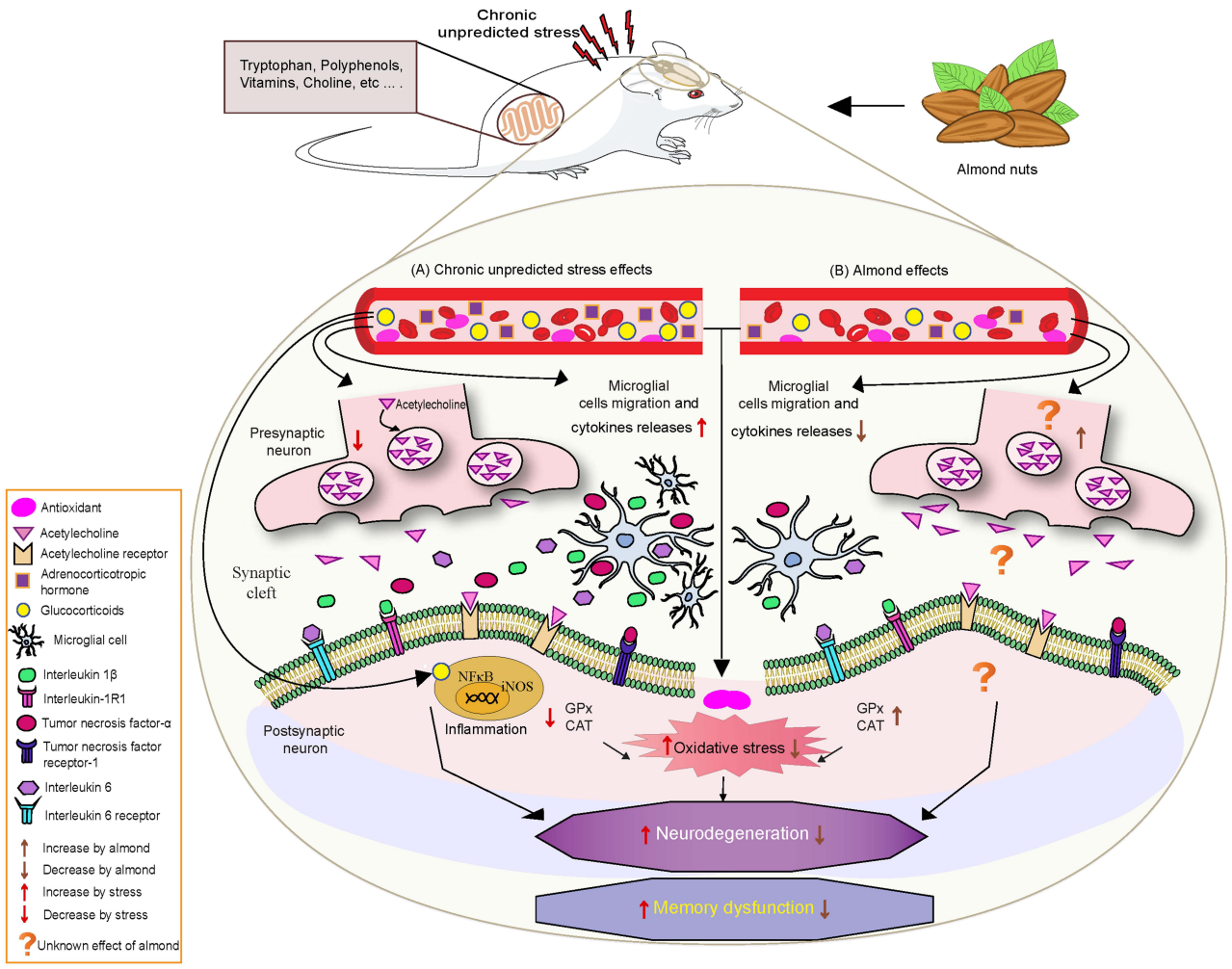

Figure 5 Effect of almond consumption on chronic unpredicted stress-induced memory impairment in rats. Impacts of stress exposure (**A**) on cholinergic transmission and inflammatory process and its counteraction by almond administration (**B**) are shown. Almonds may improve memory dysfunction caused by chronic unpredicted stress by lowering brain inflammation and microglial migration, elevating antioxidant enzymes including glutathione and catalase levels, and lowering oxidative stress. Taken together, these mechanisms protect neurons from degeneration and thus enhance learning and memory function.
Abbreviations: AchE, Acetylcholine esterase; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase; NFκB, nuclear factor kappa light chain enhancer of activated B cells; iNOS, Inducible nitric oxide synthase.

dementia.[104] Studies have indicated that a high-fat diet disrupts the cholinergic system. Long-term consumption of a high-fat diet can alter the regulation of the acetylcholinesterase gene, resulting in the accumulation and stimulation of Calcium influx due to the release of beta-amyloid pro-oxidant peptides. This leads to increased activity of acetylcholinesterase, rapid breakdown of acetylcholine, and subsequent memory loss.[105–107] The mechanism of the effect of a high-fat diet is probably the activation of oxidative stress pathways and the reduction of antioxidant enzymes. The brain is highly susceptible to damage from oxidative stress due to its oxygen consumption, relatively low antioxidant defenses, and high lipid content. Therefore, rats fed a high-fat diet have shown increased lipid peroxidation, malondialdehyde levels, and reduced GSH levels.[105,108,109] Additionally, a high-fat diet causes chronic inflammation and increases inflammatory cytokines such as IL-6, IL-1β, and TNF-α, which further contribute to an increase in free radicals.[110] On the other hand, evidence shows that almond nuts are rich in various antioxidants and can potentially reduce oxidative stress.[67] A study demonstrated that consuming whole and soaked almonds, especially in the fasting state, can improve the high-fat diet-induced memory impairment. The high content of vitamin E in soaked almonds was emphasized in this study, suggesting that the antioxidant compounds in almond nuts, particularly vitamin E, can neutralize free radicals, thereby altering synaptic plasticity and improving memory performance.[34] However, molecular studies on the effect of

almonds on neuromodulatory systems, oxidative stress parameters, or brain inflammation have not yet been conducted. As mentioned earlier, almonds by modulating the activity of neuromodulatory systems, particularly the cholinergic system, reducing oxidative stress factors, and mitigating inflammation in the brain may improve memory disorders caused by scopolamine, cadmium, or chronic stress.[35,51,53,55] Therefore, it is possible that these mechanisms also mediate the effect of almonds on memory impairment caused by a high-fat diet. However, further studies are needed in this field. A summary of the potential mechanisms of the effect of almonds on memory impairment caused by a high-fat diet is depicted in Figure 6.

In addition to the animal studies discussed here, the potential of almonds for memory enhancement has also been examined in studies involving human subjects. For instance, a study demonstrated that consuming almonds could enhance cognitive functions in healthy middle-aged/older adults, particularly when consumed in a higher dose of 3 oz/d (approximately 85 g/d).[111] This improved cognitive performance was demonstrated alongside potential benefits in alleviating symptoms of attention deficit hyperactivity disorder (ADHD) in children[112] and reducing post-lunch dip in overweight adults.[113] However, it is worth noting that another study reported no significant impact of almonds on the

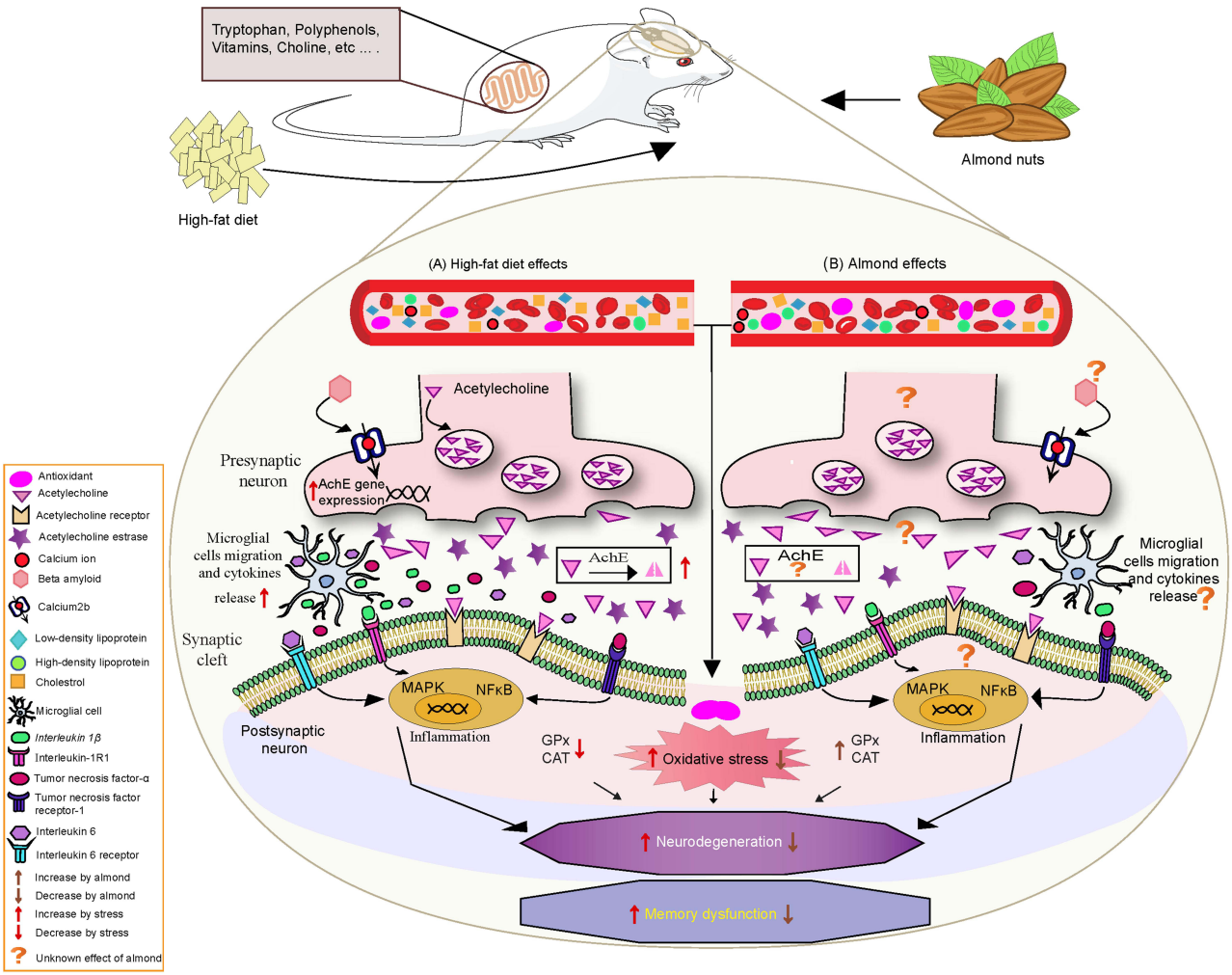

Figure 6 Effect of almond consumption on high-fat diet-induced memory impairment in rats. Impacts of high-fat diet administration (**A**) on cholinergic transmission and inflammatory process and its counteraction by almond administration (**B**) are shown. While the exact mechanisms by which almonds reduce high-fat diet-induced memory impairment are unknown, research suggests that the beneficial constituents of almonds, including tryptophan, phenols, vitamins, or choline, may increase antioxidant enzymes and reduce oxidative stress and neural inflammation. Almonds help prevent neurodegeneration and memory dysfunction in rats with high-fat diet-induced memory impairment.

Abbreviations: AchE, Acetylcholine esterase; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase; MAPK, Mitogen-activated protein kinase; NFκB, nuclear factor kappa light chain enhancer of activated B cells.

cognitive function of participants.[114] Further research involving human subjects is warranted to draw a more definitive conclusion regarding the effects of almonds on cognitive functions in humans.

Our review of studies evaluating the cognitive effect of almonds on animal models found that the effective dose of almonds varied across studies, ranging from a minimum of 25 mg/kg to a maximum of 12 g/kg. These studies generally administered the almonds for a duration of at least 7 days to up to 6 weeks in rats. To draw an integrated conclusion from the reviewed studies, it is suggested that an average dose of 6 g/kg over an average determined period of 28 days in rats may be beneficial for the enhancement of memory. Extrapolating this to a human equivalent, a 6 g/kg dose in rats would approximate about 900 mg/kg in humans, which would be roughly equivalent to consuming 54 g of almonds per day for a person weighing 60 kg. This calculation is derived using the formula described by Nair et al,[115] taking into account the weight ratios of rats used in the animal studies (150–250 g) and using the standard human weight of 60 kg as a reference point. This dose aligns closely with the effective doses of almonds observed in human studies that have shown improvements in memory function. Therefore, consuming around 54 g of almonds per day for a 60 kg individual could potentially be beneficial for memory enhancement based on the data gathered from animal studies. Moreover, according to findings,[34] the optimal timing for almond consumption appears to be fasting, potentially enhancing its beneficial effects. We propose that incorporating almonds into the diet before the first meal of the day, particularly in the morning, on a long-term basis may yield the most significant benefits. Further research and clinical trials could help validate these findings and provide more concrete evidence regarding the cognitive benefits of almond consumption.

Conclusions

This study reviewed the effect of almond consumption on memory in both healthy animals and some models of memory impairment, including memory impairment caused by scopolamine, cadmium, chronic stress, and a high-fat diet. Overall, studies showed beneficial effect of almonds on cognitive functions in animal models. Based on the reviewed studies, it is recommended that the administration of a 6 g/kg dose of almonds in rats (equivalent to 54 g/day in humans) for a long-term treatment period (28 days in rats) is optimal for enhancing memory function and potentially treating conditions associated with memory impairments. Almonds are a rich source of beneficial compounds that are known to potentiate memory processes. These compounds include unsaturated fatty acids (PUFAs and MUFAs), choline, phytosterols, polyphenols, minerals, and vitamins. PUFAs and MUFAs, found abundantly in almonds, are recognized for their ability to modulate neuromodulatory systems and promote synaptic plasticity. Moreover, the antioxidant content of almonds, such polyphenols, plays an essential role in protecting neural cells against damage associated with memory disorders. The full health benefits of almonds may result from the synergistic effects of these bioactive components. The mechanism underlying almonds' impact on memory function is not fully understood and requires further investigation. However, it is proposed that almonds may improve memory function by affecting the neuromodulatory systems, reducing oxidative stress and inflammation, and improving antioxidant defense mechanisms in the brain. Despite these promising findings, additional research is necessary to establish the optimal dose and duration of consumption for humans.

Limitations and Future Directions

This review of animal studies investigating the cognitive effects of almonds reveals a range of study designs, variations in almond doses, study durations, and diverse cognitive parameters measured. The heterogeneity in variables and particularly the lack of statistical data in many of these studies has impeded our ability to perform a thorough quantitative analysis and determine statistical effect sizes for the various interventions. Further research with standardized methodologies and robust statistical reporting is essential to better elucidate the cognitive benefits of almonds in animal models. The mechanisms underlying the cognitive effects of almonds on memory and related disorders remain incompletely understood. A comprehensive evaluation of how almonds interact with various neuromodulators and their receptors could provide valuable insights. Further research involving animal studies is crucial to gain a deeper understanding of the mechanisms through which almonds impact synaptic plasticity and enhance cognitive function. Moreover, given the significant beneficial effects of almonds on various memory disorders, further research should explore their potential therapeutic effects in conditions such as Parkinson's disease, ADHD, and autism spectrum disorders. Investigating the specific mechanisms through which almonds exert these effects could offer new avenues for the development of novel

therapeutic approaches. While animal studies provide controlled environments, their results may not directly translate to humans due to physiological and genetic differences. Therefore, conducting randomized controlled trials (RCT) in humans is essential to ascertain the cognitive effects of almonds, determine the optimal dosage and duration, and evaluate their impact across diverse populations, such as children, the elderly, and individuals with specific health conditions. To enhance the robustness and applicability of the findings, RCTs with larger sample sizes and more diverse participant groups are warranted. By expanding research efforts to include a broader range of individuals, we can refine dietary recommendations based on solid scientific evidence and potentially identify new avenues for nutritional and therapeutic interventions to enhance public health.

Abbreviations

ADHD, Attention deficit hyperactivity disorder; BDNF, Brain-derived neurotrophic factor; CAT, Catalase; CREB, Cyclic AMP response element-binding proteins; CUS, Chronic unpredicted stress; DA, Dopamine; DOPAC, dihydroxyphenylacetic acid; EPM, Elevated plus maze; FST, Forced swimming task; GABA, Gamma-aminobutyric acid; GPx, Glutathione peroxidase; HPA, Pituitary-adrenal-hypothalamus axis; HVA, Homovanillic acid; HPLC-EC, Electrochemical detection in high-performance liquid chromatography; 5-HT, 5-hydroxytryptamine; 5-HTR, 5-hydroxytryptamine receptor; 5-HIAA, 5-hydroxyindole acetic acid; HDL, High-density lipoprotein; IL-α, Interleukin- α; IL-6, Interleukin-6; LDL, Low-density lipoprotein; LDT, Light-dark task; LTP, Long-term potentiation; LTD, Long-term depression; MCI, Mild cognitive impairment; MUFA, Monounsaturated fatty acids; MWM, Morris water maze; MDA, Malondialdehyde; MAO-A, Monoamine oxidases-A, MAO-B, Monoamine oxidases-B; NOR, Novel object recognition; NA, Noradrenaline; NMDA, N-methyl-D-aspartate; OFT, Open field Task; PAT, Passive avoidance task; PUFA, Polyunsaturated fatty acids; RCT, Randomized controlled trials; RAM, Radial arm maze; ROS, Reactive oxygen species; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substance; TNF, Tumor necrosis factor.

Data Sharing Statement

No data was used for the research described in the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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