Review Article

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Cognitive Improvement through Persian Medicinal Plants: A Mechanistic Overview

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Abstract

Cognition relates to the mental processes engaged in acquiring knowledge and comprehension via thought, experience, and the senses. However, cognitive abilities can progressively decline with age over time or due to certain health conditions, affecting the overall quality of life. Neurodegenerative dementia is more likely to affect older adults because of aging. Despite the availability of various conventional therapeutic approaches, they often come with high costs or unwanted side effects. So, finding new interventions to improve cognitive performance remains a hot topic of research. Recently, there has been growing interest in using medicinal plants, as abundant and affordable phytochemical compound resources. This study introduces the most prevalent and accessible medicinal plants in Persian medicine for preventing and treating cognitive impairments. Also, the scientific evidence of the plant efficacy was searched in electronic databases with keywords including the scientific plant names and cognition or memory or Alzheimer's disease (AD) or amnesia or learning, by focusing on recent credible animal and clinical studies. Every relevant clinical study was thoroughly reviewed and included in this review. Findings suggest these natural remedies may alleviate dementia and cognitive decline through key mechanisms such as antioxidant activity, anti-inflammatory effects, anti-apoptotic properties, and enhancement of cholinergic transmission. Additionally, several plants inhibit amyloid-β and tau depositions while promoting neurotrophic signaling pathways. Although these medicinal plants could be promising candidates as future drugs or adjunct therapies, further research is necessary to confirm their safety and efficacy, as well as to understand their precise underlying mechanisms of action, potential interactions and appropriate therapeutic dosages.

Keywords: cognition disorders, medicinal plants, phytotherapy, Persian medicine.

Introduction

As the global population continues to age, the rate of cognitive impairments among the elderly is increasing.[1] Neurocognitive disorders affect different cognitive disciplines, including memory, attention, language, and executive functions.[2] These impairments are categorized into dementia and non-dementia. Dementia is the more severe form and encompasses various types: AD (characterized by progressive memory loss and cognitive decline), vascular dementia (cognitive decline due to vascular deficits), and frontotemporal dementia (affecting behavior, personality, and language).

Studies show that oxidative stress, neuroinflammation, and mitochondrial dysfunction stand as the main recognized molecular mechanisms for these disorders that result in neurodegeneration and synaptic loss seen in cognitive deficits.[3,4] About 11.3% of individuals aged 65 and older have AD, the most prevalent dementia.[5] According to predictions, the number of people with AD will be doubled by 2040 in developing countries.[6] The disease not only reduces the life satisfaction of patients but also imposes a huge burden on society and the health care system. Due to the rapid growth in the prevalence of the disease and the challenges it poses for both patients and society, new treatment and prevention methods seem necessary.[7]

Different types of medicinal plants and their isolated compounds have been employed not only to boost cognitive function and memory but also to prevent related impairments.[8] Traditional medicines serve as unique and invaluable sources of medicinal plants employed in the treatment of diverse health conditions. Plants such as *Ginkgo biloba* L. and *Panax ginseng* C.A.Mey. in Chinese medicine[9], *Bacopa monniera* (L.) Pennell, *Asparagus racemosus* Willd and *Centella Asiatica* (L.) Urban in Ayurveda[9] , *Moringa oleifera* Lam. and *Mesembryanthemum tortuosum* L. in African traditional medicine[10] are all known ancient herbal remedies used as nootropics and memory enhancers.

The literature of traditional Persian medicine (TPM) proposes various candidates for addressing cognitive and memory impairments such as AD.[11,12] The neuroprotective plants, such as *Piper nigrum* and *Crocus sativus*, are examples that can reduce cognitive impairments in Alzheimer's disease, likely due to their antioxidant properties.[11]

This review aims to shed light on the most common medicinal plants used in TPM for the prevention and attenuation of memory impairments. This study is distinguished from previous works by highlighting the prevalent features of these plants, including their potent pharmacological properties, wide accessibility, and affordability. In addition, it provides a comprehensive evaluation of all relevant clinical studies of these plants, ensuring that the scientific evidence supporting their efficacy in humans is fully captured.

Search strategy

In this review, herbal remedies mentioned in TPM textbooks were derived and used as the keywords for subsequent search. Therefore, the most important TPM medicinal books and pharmacopeias including Ghanoon fel-teb (The Canon of Medicine, written by Avicenna in 1025 AD), Gharabadin kabir (written by Aghili Alavi Khorasani in 1772 AD), Makhzan Al-adviah (the largest phamacopeia of Persian medicine written by Aghili Alavi Khorasani in 1771 AD), and Exir azam (a comprehensive medical encyclopedia written by Azam khan in 1868 AD) were explored to identify relevant prescriptions for enhancing memory, learning and attention as well as amnesia treatment. Ten commonly cited and accessible medicinal plants were selected based on our search strategy, and their scientific names were identified using authentic references. Subsequently, the evidence for their efficacies was searched in electronic databases (including PubMed, Scopus, and Google Scholar) using combination of plant names and the keywords 'cognitive*', 'cognition', 'amnesia', 'memory', 'learning', and 'AD'. Data were collected from 2000 to 2024. The analysis was restricted to English-language publications, with a primary focus on clinical studies. In addition, relevant *in-vitro* and *in-vivo* studies were reviewed to clarify pharmacological mechanisms. Clinical studies evaluating pharmaceutical products were excluded from the analysis. Major Pharmacopeias were also reviewed to provide documentation for the selected medicinal plants.

Results

The ten most frequently cited medicinal plants in TPM references and their associated details (including ethnobotanical information, main compound classes and ingredients, and pharmacologic effects) for the prevention and treatment of cognitive disorders are presented in Table 1. The captured images of medicinal plants are presented in Figure 1. Searching scientific

databases supported the anti-inflammatory, antioxidant and anti-AchE activity properties of these plants by *in-vitro*, animal and clinical studies. The comprehensive list of relevant clinical evidence on the pharmacologic effects of the plants is represented in Table 2. Each paragraph concerning related plants outlines the mechanisms underlying the efficacy of these plants in AD and cognitive disorders.

To demonstrate the significance of these selected plants, their coverage in the "WHO International Pharmacopoeia (Ph. Int.)" [13] as well as in several prominent national pharmacopoeias, including the "British Pharmacopoeia (BP)" [14], "United States Pharmacopeia (USP)" [15], "European Pharmacopoeia (EP)" [16], "Ayurvedic Pharmacopoeia of India (API)" [17], and the "Pharmacopoeia of the People's Republic of China (ChP)" [18] was evaluated. The summarized findings are presented in Table 3. The analysis revealed that all ten plants were found in at least one major pharmacopeia. Species with dual culinary-medicinal use such as garlic, ginger, and saffron appeared across nearly all pharmacopeias, while others including frankincense, cardamom, lavender, lemon balm, black seed, and Damask rose, were represented more selectively. The results illustrate how variations in global use and traditional medicinal practices affect pharmacopeial coverage.

Table 1. Prominent pharmacological effects of selected medicinal plants in TPM for cognitive disorders.

Scientific name	Family	Common name	Traditional name	Part used	Major phytochemical classes	Main active ingredients	Pharmacologic Effect	References
***Allium sativum* L.**	Amaryllidaceae	Garlic	Soum	Rizhome	Organosulfur compounds	Allicin, S-allyl cysteine, di-allyl disulfide	Anti-AchE, anti-oxidant, anti-AD, anti-neuroinflammatory	[19-21]
***Boswellia* spp.**	Burseraceae	Frankincense, olibanum	Kondor	Oleo-gum-resin	Triterpenoids	Incensole acetate, Boswellic acid,	Anti- AchE, anti- AD, anti-oxidant	[22-24]

***Crocus sativus* L.**	Iridaceae	Saffron	Zafaran	Stigma	Carotenoids, Monoterpenoids	Crocin, crocetin, safranal	Anti- Alzheimer, anti-oxidant	[25-27]
***Elettaria cardamomum* (L.) Maton**	Zingiberaceae	Green cardamom	Hel	Fruit	Monoterpenoids	1,8-cineole, α-Terpinyl acetate	Anti-inflammatory, Anti-oxidant, anti- AD	[28-30]
***Lavandula angustifolia* Mill.**	Lamiaceae	True lavender	Ostokhoddus	Aerial part	Monoterpenoids, phenolic compounds	linalool, rosmarinic acid, caffeic Acid, luteolin	Anti- AD, antioxidant, anti-AchE	[31-34]
***Melissa officinalis* L.**	Lamiaceae	Lemon balm	Badranjbouyeh	Aerial part	Monoterpenoids, phenolic acids	Citral, rosmarinic acid	antioxidant, anti-AchE, anti-AD	[27,35,36]
***Nigella sative* L.**	Ranunculaceae	Black cumin	Sian daneh	Seed	Quinones, phenolic compounds	Thymoquinone, carvacrol	Anti-inflammatory, antioxidant, anti- AchE, anti- AD	[37-39]
***Piper nigrum* L.**	Piperaceae	Black pepper	Felfel e siah	Seed	Alkaloids, lignans	Piperine, sesamin	Neuroprotective, Antioxidant, Anti- AchE, anti-AD	[40-42]
***Rosa damascena* Mill.**	Rosaceae	Iranian or Damask rose	Gol e sorkh	flower	Monoterpenoids	Citronellol, geraniol, nerol	Neuroprotective, Antioxidant, Anti- AchE, anti-AD, anti-inflammatory	[43-45]
***Zingiber officinale* Rosc.**	Zingiberaceae	Ginger	Zanjebil	Rhizome	Phenolic ketones	6-shogaol, 6-gingerol	Anti-inflammatory, anti-apoptosis, neuroprotective, anti- AD, and Antioxidant	[46,47]

AchE: Acetylcholinesterase, AD: Alzheimer's disease.

***Allium Sativum* L. (Amaryllidaceae)**

A. Sativim L., known as garlic, is one of the most common herbs used both as flavor and herbal medicine since ancient times. Garlic is widely cultivated around the world, with major production regions including East and South Asia, South Asia, and parts of Europe and North America.[20] It is one of the memory enhancing herbs used in TPM. Allicin (diallyl thiosulfinate) is the major organosulfur compound found in garlic, which is activated when garlic is crushed or chopped.[21] It is proposed that organosulfur derivatives of *A. Sativum* L., including allicin, diallyl disulfide, and diallyl trisulfide which all exert anti-oxidant and anti-apoptosis activity as well as anti-gliosis properties contribute to its neuroprotective and pro-cognitive effects.[21] The aged form of garlic, a processed product rich in stable organosulfurs such as S-allylcysteine and di-allyl-disulfide, has been shown in vivo to exhibit potent antioxidant and anti-inflammatory effects. These compounds also modulate neurotransmitters, including cholinergic, glutamatergic, and GABAergic pathways. This evidence suggests that aged garlic may be an effective candidate for preventing cognitive decline in AD.[48,49]

It has been shown that *A. sativum* powder could alleviate monosodium glutamate-induced neurotoxicity by improvement of short-term memory dysfunction, oxidative stress burden, and gliosis in rats.[19] Interestingly, in the smoker rat model of inflammation, the ethanol extract of garlic significantly reduced pro-inflammatory cytokine levels, highlighting its potential for suppressing inflammatory reactions linked to molecular changes in the brain of AD patients.[20]

Moreover, findings showed that taking 400 mg of encapsulated garlic powder led to significant improvements in visual memory tests and the rapid visual Information Processing (RVP) test for attention in healthy volunteers compared to the placebo group, indicating its ability to enhance higher levels cognitive abilities.[50] According to different studies, Allicin and S-allylcysteine compounds could inhibit Aβ Aggregation via direct interaction with Aβ peptides, suggesting garlic's Potential in preventing and treating age-related Aβ accumulation such as in AD.[51,52]

Boswellia Spp. (Burseraceae)

Frankincense oleo-gum-resin, which is obtained from trees of genus Boswellia, is called Kondor in TPM. Boswellia spp. are native to Northeast Africa, the Arabian Peninsula, India, and parts of Sudan.[53] Avicenna, proposed that Kondor resin could improve memory function and prevent

amnesia in elderly.[54] Several clinical studies have shown the effectiveness of formulations containing this resin on cognitive impairment experienced by AD patients.[55-57] Evidence from rat model of AD demonstrated that *B. serrata* methanolic extract could not only significantly inhibits the neuroinflammatory procedures via normalization of machineries including C-reactive protein, nuclear factor kappa B, monocyte chemotactic protein-1, and leukotriene B4 levels, but also restored cerebral acetylcholine content to normal levels and eliminated amyloid-β plaques in the hippocampus samples.[58] Moreover, it has been shown that chronic administration of *B. serrata* gum in type 2 diabetic rats, which mimic the learning and memory impairments seen in AD, improved cognitive abnormalities partly via modulation of glutamate receptors, increasing acetylcholine content and anti-oxidant enzymes activities, suppression of oxidative stress, inflammatory cytokines, and Glycogen synthase kinase-3 beta (GSK-3β) as well as reduction of p-tau and amyloid-β accumulation in the hippocampus.[53] Additionally, findings indicated that incensole acetate, one of the major derivatives of Boswellia resin, restores hippocampal-related learning and memory deficits in lipopolysaccharide-treated rats. This improvement is primarily resulted through the increase in hippocampal brain-derived neurotrophic factor (BDNF) levels and the inhibition of gliosis, which in turn leads to elevated levels of pro-inflammatory cytokines, nitric oxide, and oxidative stress markers.[59] Moreover, findings indicated that boswellic acid, an active compound derived from *B. serrata*, effectively improves antioxidant abilities and mitigates mitochondrial dysfunction in a rat model of AD. In the boswellic acid-treated AD group, there was a significant decrease in hippocampal levels of glucose, L-malondialdehyde, tau protein, and glutathione peroxidase. Additionally, boswellic acid exerts potential therapeutic effects in management of both AD and type 2 diabetes, emphasizing its relevance in metabolic and neurodegenerative disorders.[60,61]

***Crocus sativus* L. (Iridaceae)**

C. sativus L. commonly known as Saffron, is widely cultivated in Iran and countries such as India and Greece. The floral stigma of saffron is a precious spice and a potent ancient medicine used for treatment of conditions including depression and memory impairments.[62,63]

In various studies, saffron and its phytoconstituents (mainly crocin, crocetin, and safranal) have been shown to exhibit significant neuroprotective effects through their antioxidant and anti-

inflammatory properties.[64] Additionally, saffron extracts not only inhibited the aggregation of Aβ plaques and tau protein tangles but also suppressed the acetylcholinesterase (AchE) activity.[65-67] Collectively due to involvement of these procedures in Ad pathophysiology, it seems that saffron may help to control the symptoms of AD.

In animal models of cognitive dysfunction, saffron administration has improved performance in memory-related tasks, suggesting its potential as a pro-cognitive compound. Moreover, studies indicate that crocin counteracts memory impairments induced by neurotoxic agents such as ethanol and aluminum chloride, possibly in part by enhancing long-term potentiation and promoting synaptic plasticity in the hippocampus, a critical region for learning and memory.[68,69] Interestingly, crocin has been shown to increase the expression of BDNF and cAMP response element-binding protein (CREB). Both of which are crucial for synaptic plasticity and memory consolidation. [70]

Safranal, the compound responsible for the aroma of saffron, indirectly improves cognitive functions via exhibiting anxiolytic effects and improving impairments in learning and memory. It seems that its regulatory effects on mood and cognitive processes origins from its influence on catecholamines, including dopamine and serotonin.[71,72] Crocetin, a water-soluble pigment in saffron, has been shown to enhance mitochondrial function and reduce inflammation, which contributes to its protective effect against cognitive decline. In a rat model of vascular dementia, administration of crocetin has improved spatial learning and memory by decreasing escape latency in the Morris water maze and protecting cerebrocortical and hippocampal neurons from ischemic damage.[73] The cognitive-enhancing effects of *C. sativus* and its active components which are supported by clinical studies are presented in table.2.

***Elettaria cardamomum* (L.) Maton (Zingiberceae)**

E. cardamomum, with the common name cardamom, is among the most popular spices. It is predominantly produced in India, Sri Lanka, and Nepal, with Guatemala serving as the largest global producer and exporter. In Traditional Persian Medicine (TPM), cardamom is recognized for its impact on the central nervous system.[74] The mechanisms underlying these effects are primarily attributed to its antioxidant, anti-inflammatory, and neuroprotective properties, which are mediated by various phytochemical constituents present in the plant.

In rat models of cerebral hypoperfusion, the essential oil of *E. cardamomum*, notably its component 1,8-cineole, exhibited anti-neurodegenerative effects by reducing pro-inflammatory cytokines such as Interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and inhibiting apoptosis.[28] Other animal models exhibited the nootropic effect of the ethanol extract possibly due to its antioxidant properties, anti-cholinesterase activity, and ability to lower glucose levels.[29] The neuroprotective activity and central cholinergic system modulation makes cardamom the potential adjunct in the management of cognitive decline in AD.[75] Although direct clinical evidences is still limited, inflammatory pathways modulation by cardamom affirms its benefits in AD.[76]

***Lavandula angustifolia* Mill. (Lamiaceae)**

L. angustifolia (lavender) is a famous medicinal plant native to the Mediterranean basin and was historically cultivated in regions such as Turkey, the Levant, Iran, Afghanistan, and parts of the United Kingdom. In TPM, it is known as the great cleanser of the nervous system.[11,77] A substantial body of evidence indicate that lavender extracts and essential, primarily containing linalool, rosmarinic acid, caffeic Acid and luteolin, enhance memory function and reduce AD related cognitive impairments, largely mediated by their antioxidant properties.[32,78] In one study, the spatial performance of AD rats in Morris water maze task was normalized following treating with lavender aqueous extract. Findings revealed that while AD rats initially struggled to locate a hidden platform, administration of lavender extract, particularly at 200 mg/kg, resulted in significant improvement in their spatial learning and memory performance compared to the control group.[34]

It seems that Lavender's pro-cognitive effects originate from its potential to reduce beta-amyloid production, as well as its antioxidant, anti-inflammatory, anti-apoptotic properties, and anti-acetylcholinesterase activity.[31,79] This is consistent with research by Li et al[33] which demonstrated that lavender extracts show neuroprotective properties against accelerated dementia caused by D-galactose and aluminum trichloride in a zebrafish model, showing their capability as a treatment for AD. The study introduced linalool, a key bioactive compound in lavender, as a potential contributor to mitigating cognitive decline.[33]

***Melissa officinalis* L. (Lamiaceae)**

M. officinalis, commonly known as lemon balm, is a medicinal plant belonging to the Lamiaceae family. It is native to the Mediterranean and Western Asia and is now widely cultivated in Europe, North America, and parts of Asia. Lemon balm is traditionally used for its diverse therapeutic properties, particularly for neurological and gastrointestinal effects.[11,77] The evidences showed that *M. officinalis* extract, which is high in phenolics and flavonoids, considerably improved cognitive performance in rat models. As experimental study showed, *M. officinalis* exerted free radical scavenging effects which makes it as a suitable candidate for treatment of cognitive dysfunction.[35,80] Furthermore, the ability of lemon balm for protection of neural cell from oxidative stress induced apoptotic death, have been established both in *in-vivo* and *in-vitro* models. Apparently, this effect is mediated in part via decreasing malondialdehyde levels and cysteine-aspartic proteases-3 (caspase-3) activity.[36,81] In healthy individuals acute administration of lemon balm extract has been associated with enhanced mood and cognitive function.[82,83] Moreover, results of a randomized controlled trial revealed that chronic administration of *M. officinalis* extract in patients with mild to moderate AD resulted in significant improvement in their cognitive abilities.[84]

***Nigella sativa* L. (Ranunculaceae)**

N. sativa, often known as black cumin, is a well-known medicinal plant and spice. It is native to Southwest Asia, northern Africa, and the Mediterranean region and is now widely cultivated in countries such as India, Pakistan, Egypt, and parts of the Middle East. In TPM, it used for its neurological and general health-promoting effects. The seeds contain bioactive compounds such as thymoquinone and beta-caryophyllene, which are believed to improve learning and memory.[85,86] A study on the effect of oral black seed oil on motor skill learning in mice, using a single pellet reaching task, revealed its beneficial impact on improving learning outcomes. The observed effect may be attributed to thymoquinone and carvacrol, which are potent antioxidants and have ability to increase synaptic strength and boost experience-dependent motor skill learning.[39] As animal studies suggested, thymoquinone's neuroprotective effect in improving the cognitive functions may be mediated by the anti-oxidant activity and inhibitory effects on degeneration of pyramidal cells in the hippocampus.[37,38] Confirming prior reports, daily administration of 500 mg *N. sativa* capsules, once daily for 4 weeks in healthy young

volunteers and twice daily for 9 weeks in healthy older adults, improved emotional and cognitive outcomes in both groups.[87,88] These findings support *N. sativa* as a preferred herb for daily use.

***Piper nigrum* L. (Piperaceae)**

Black pepper is a valuable medicinal plant and spice, native to southern India and now widely cultivated throughout tropical regions worldwide.[89] *P. nigrum* is regarded as one of the most effective enhancers of memory and mental performance.[90] Piperine, the main bioactive ingredient in black pepper, has been identified as an essential element for neuroprotective and cognitive-enhancing properties. A result of animal study showed that cold-pressed oil from black pepper fruits, (rich in sesamin and piperine), improved cognitive performance in scopolamine induced rat model of dementia. On the basis of in silico molecular docking and histopathological investigations, it considerably enhanced the rat cognitive behaviors as compared to the donepezil received group, modified the activity of antioxidant enzymes such as catalase, while reducing the levels of malondialdehyde and hippocampus acetylcholinesterase.[40] According to evidence from animal studies, *P. nigrum* is able to decrease AchE levels and amyloid plaque, emphasizing on its effectiveness for management of memory loss in AD.[41,42] Limited clinical studies represented the efficacy of mixed herbal therapies containing *p. nigrum* in the improvement of memory in mild-to-moderate AD patients and enhancement of sustained attention and motivation to do cognitive works in low energy young adults.[91,92] For instance, a double-blind, randomized clinical trial by Tajadini et al. evaluated the efficacy of a traditional herbal compound containing *Piper nigrum*, *Cyperus rotundus*, *Zingiber officinale*, *Acorus calamus*, and *Boswellia carterii*, in mild-to-moderate AD patients. After 12 weeks, the intervention group demonstrated significantly greater improvements in cognitive function compared to the placebo group.[91]

***Rosa damascena* Mill. (Rosaceae)**

R. damascena, an appealing perennial shrub, is renowned for its aromatic and flavoring properties. It is extensively cultivated in Iran, especially in Kashan region and also grows in temperate regions across the world including Turkey, Bulgaria, and parts of Europe and the

Middle East.[93] In TPM, Iranian rose is recognized as a brain tonic that supports cognitive function.[94] The antioxidant and anti-inflammatory effects of the plant, which underlie its neurological benefits, are primarily attributed to its monoterpene alcohols, particularly citronellol, geraniol, and nerol.[95] In aluminum chloride induced rat model of AD, administration of aqueous extract of *R. damascena* not only resulted in the regulation of AChE activity and increase in anti-oxidant elements (glutathione and catalase) but also reduced cerebral lipid peroxidation levels, supporting its potential for treatment of AD complications.[44] In another study, administration of *R. damascena* essential oil in scopolamine received rats improved learning and memory and augmented Ach neurotransmission, increased the expression of M1 Muscarinic acetylcholine receptors, and brain-derived neurotrophic factor in cerebral tissues. The possible molecular interactions between the human M1 Muscarinic acetylcholine receptors and the main components of *R. damascena* oil, mainly citronellol, geraniol, and nerol, have been further clarified by computational modelling, indicating the potential of damask rose oil on memory impairments in neurodegenerative disorders.[43] Furthermore, it has been shown that *R. damascena* extract exhibits neuroprotective properties, including the reduction of neuroinflammation and Aβ toxicity in animal models. These findings position it as a promising candidate for a therapeutic development in AD.[45,96]

***Zingiber officinale* Roscoe. (Zingiberaceae)**

Ginger is regarded as a valuable herb not just for its role as a spice in culinary, but also for its historical use in traditional medicine. *Z. officinale* is widely cultivated in tropical and subtropical regions, including Northeast India, China, Sudan, and Taiwan.[97] It is believed to be effective in improving memory and combating the effects of aging in TPM. Ginger is a rich source of bioactive compounds, with 6-shogaol and 6-gingerol being the key constituents responsible for its health benefits.[47]

One of the primary mechanisms by which *Z. officinale* exerts its cognitive benefits is through AChE inhibitory effects. Studies have shown that ginger extracts, containing active compounds like 6-gingerol and 6-shogaol, significantly inhibit AChE which leads to improvement of memory performance in various animal models of cognitive disorders.[46,98,99] In an animal study, the 6-gingerol-rich fraction alleviated Acrylonitrile -induced brain injury in male rats by normalizing

malondialdehyde, interleukin-6, tumor necrosis factor-α, and Nitric Oxide levels as well as preserving glutathione and superoxide dismutase function. Moreover, the extract decreased cerebral cortical lesions caused by Acrylonitrile and enhanced the expression of Caspases-9 and -3, indicating its potential to prevent neuronal apoptosis induced by Acrylonitrile.[100] Overall, many *in-vitro* and *in-vivo* evidences supported that ginger's biological agents have the potential to alleviate neurological symptoms and diseases, probably via influencing brain ' monoamine and cholinergic neurotransmissions, exerting anti-oxidant activity, reducing inflammation.[47]

The underlying neuroprotective mechanisms through which the above mentioned medicinal plants improve cognitive impairments are illustrated in Figure 2.

Table 2. List of clinical studies on the pharmacological effects of the plants in populations with neurodegenerative, psychiatric, cardiovascular, and metabolic disorders, as well as in healthy or cognitively intact individuals.

Plant	Intervention		Study design	Patients	Treatment duration	Results	References (year)
	Treatment group	Control group					
***Boswellia sacra* Flueck.**	Herbal capsule, 500 mg (TID) containing *B. sacra* resin, *M. officinalis*, *Piper longum*, *Cinnamomum verum*, and *Physalis alkekengi*	Maltodextrin, 500 mg (TID)	Double-blinded, placebo-controlled trial	60 patients With mild-to-moderate AD or mild cognitive impairment	3 months	Herbal capsule was significantly more effective than placebo in improving cognitive and behavioral symptoms	[101] (2022)
***Boswellia papyrifera* (Delile ex Caill.) Hochst.**	*B. papyrifera* capsule, 300 mg (BID)	Placebo capsule 300 mg (BID)	Randomized, double-blinded, placebo-controlled clinical trial	80 patients with relapsing-remitting multiple sclerosis	2 months	Herbal capsule significantly improved visual-spatial memory, no significant effect on verbal memory (CVLT) or information processing speed	[102] (2014)
***Boswellia serrata* Roxb.**	Herbal tablet, 27 mg (BID), containing *B. serrata* and *M. officinalis* extract	Placebo capsule (BID)	Randomized, parallel, double-blinded, placebo-controlled	70 older adults with No history of psychological disorder or AD	1 month	significant increase in the total memory score of the intervention group was observed	[56] (2017)

			clinical trial				
***Allium sativum* L.**	*A. sativum* capsule, 400 mg (BID)	Placebo capsule, 400 mg (BID)	Randomized controlled trial	20 healthy volunteers	5 weeks	Improvement in Visual Memory test, significant increase in attention measures, Nonsignificant Effects on Verbal Memory	[50] (2015)
***Crocus sativus* L.**	Crocin, 15 mg (BID)	Placebo, 15 mg (BID)	Randomized clinical trial	60 opioid patients undergoing methadone maintenance treatment	12 weeks	Craving and withdrawal symptoms significantly reduced, Nonsignificant effect on cognitive function	[103] (2021)
	Saffron capsule, 15 mg (BID)	Placebo capsule (BID)	Randomized, double-blinded, placebo-controlled clinical trial	76 patients undergoing coronary artery bypass grafting (CABG)	12 weeks	Nonsignificant effect on (CABG)-related Cognition, Anxiety, and Depression	[104] (2018)
	Saffron (not mentioned the form of medication)	No treatments received	Single-Blind Randomized, with Parallel Groups, Clinical Trial	35 patients with amnesic and multi domain mild cognitive impairment	12 months	beneficial effect on cognitive function by improvement of Mini-Mental State Examination (MMSE) scores	[105] (2016)
	Saffron capsule, 15 mg (BID)	Placebo capsule, 15 mg (BID)	Randomized placebo-controlled trial	46 patients with mild to moderate AD	16 weeks	Significant improvement of cognitive function in treatment group was observed	[106] (2010)
	Saffron capsule, 15 mg (BID)	Donepezil, 5 mg (BID)	Randomized, double-blinded, controlled clinical trial	54 patients with mild to moderate AD	22 weeks	Saffron effects were similar to donepezil in the treatment of mild-to-moderate AD	[26] (2010)
***Elettaria cardamomum* (L.) Maton**	Herbal capsule, 44 mg (BID) containing Cardamom, Bacopa monnieri, Gotu kola leaf, Turmeric whole	Placebo capsule, standard-use magnesium stearate (BID)	Randomized, placebo-controlled trial	128 cognitively intact older adults	3 months	Increased speed of cognitive task performance, negative effects on memory	[107] (2023)

	powder, Reishi full spectrum, Rosemary, Holy Basil, Turmeric extract, Green Tea, Seagreens						
***Lavandula angustifolia* Mill.**	2 groups: one group lavender aromatherapy and another group rosemary aromatherapy (three days in the week)	Water in diffuser (three days in the week)	Randomized, placebo-controlled trial	144 healthy volunteers	Not mentioned	No distinct effect of lavender group on cognitive performance, positive effects on mood	[108] (2003)
	Aromatherapy of rosemary and lemon essential oils in the morning, and lavender and orange in the evening	No placebo	Interventional crossover trial	28 elderly people, 17 with AD, 3 with vascular dementia, and 8 with other diagnoses	28 days	significant improvement of all patients specially AD patients in personal orientation related to cognitive function	[109] (2009)
	3 groups: aromatherapy of 3 individual essential oils: lavender, Rosemary, and Orange (30min/day, 3 days/week)	Placebo	Parallel randomized controlled clinical trial	86 patients under chronic hemodialysis	1 month	For lavender group: no significant change in prospective memory problems and decrease in retrospective memory problems, No difference between 3 groups	[110] (2022)
	2 groups: One group lavender aromatherapy and another group rosemary aromatherapy	Placebo	prospective, randomized trial	63 elderly people with diabetes	4 weeks	Lavender improved cognitive functions and sleep quality and reduced anxiety	[111] (2024)
	Aromatherapy with lavender essential oil 10min (BID)	Aromatherapy with distilled water 10min (BID)	Randomized clinical trial	60 women with multiple sclerosis	2 weeks	statistically significant enhancement in working memory	[112] (2021)

	Aromatherapy with lavender essential oil before procedure	No placebo	Clinical trial	20 healthy adults	once	significant changes in oscillatory power and behavioral performance	[113] (2024)
	Aromatherapy of rosemary-lemon oil in the mornings for one week, followed by lavender oil in the evenings for another week	No placebo	pretest-posttest clinical trial	39 older adults	2 weeks	Lavender oil reduced daytime sleepiness and improved cognitive function	[114] (2022)
***Melissa officinalis* L.**	*M. officinalis* extract supplementation, 500 mg, once per day	Placebo, 500 mg, once per day	Randomized placebo-controlled double-blind trial	232 patients with subjective or mild cognitive impairment	96 weeks	*M. officinalis* extract may help prevent cognitive decline in older adults without hypertension	[115] (2023)
	M. officinalis extract supplementation, 500 mg, once per day	Placebo, 500 mg, once per day	Randomized placebo-controlled double-blind trial	23 patients with mild dementia due to probable AD	24 weeks	*M. officinalis* extract may help prevent the worsening of AD-related neuropsychiatric symptoms	[116] (2020)
	M. officinalis powder capsules with 7 days interval, Single doses of 600, 1000, and 1600 mg	Placebo, Single dose	Randomized placebo-controlled double-blind trial	20 healthy, young participants	Testing on the same day of treatment	1600 mg doses can improve cognitive performance and mood	[117] (2003)
	M. officinalis extract, 60 drops/day	Placebo, 60 drops/day	Randomized placebo-controlled double-blind trial	42 patients with mild to moderate AD	4 months	Significant improvement in cognitive function, reduction of agitation	[84] (2003)
	M. officinalis extract capsules with 7 days interval, Single doses of 300, 600 and 900 mg	Placebo, Single dose	Randomized placebo-controlled double-blind balanced-crossover	20 healthy, young participants	Testing on the same day of treatment	improvement in mood and accuracy of attention with dose 600 mg, reductions in both Secondary memory and working memory factors	[83] (2002)

			trial				
	Mixed extract of *M. officinalis* L., *Salvia officinalis* L., *Rosmarinus officinalis* L., 50 ml/day	*Myrrhis odorata* extract with non-cognitive effects, 50 ml/day	Randomized double-blind placebo-controlled pilot trial	44 normal healthy subjects	2 weeks	Improvement of verbal episodic memory	[118] (2018)
***Nigella sativa* L.**	*N. sativa* capsule, 500 mg, once daily	placebo capsule, 500 mg, once daily	Randomized placebo-controlled double-blind trial	48 healthy adolescent human males	4 weeks	Mood stabilization, decrease in anxiety and cognition improvement	[88] (2014)
	N. sativa capsule, 500 mg (BID)	Placebo capsule, 500 mg (BID)	Randomized placebo-controlled double-blind trial	40 healthy elderly	9 weeks	Significant enhancement in memory, attention and cognition	[87] (2013)
***Piper nigrm* L.**	*P. nigrum* capsule, 500 mg, in three mixed herbal orders: *P. nigrum* then placebo, Rosemary then *P. nigrum*, Rosemary then placebo	Rice flour capsule, 500 mg	Double-blind, randomized, placebo-controlled crossover experiment	40 young adults with lower feeling of energy	Testing after 2 days	Significant short-term enhancement of sustained attention, motivation to do cognitive work	[92] (2013)
	Herbal capsule, 500 mg (TID), containing: *P. nigrum, Cyperus rotundus, Zingiber officinale, Acorus calamus, and Boswellia carterii,*	Placebo capsule, 500 mg (TID)	Randomized double-blind placebo-controlled clinical trial	44 older patients with mild to moderate AD	12 weeks	improvement of memory in patients with mild-to-moderate AD	[91] (2015)
***Rosa damascena* Mill.**	Donepezil and *R. damascena* extract capsules	Placebo and *R. damascena* capsules	Randomized double-blind, placebo-controlled clinical trial	40 elderly patients with dementia	3 months	Improved cognitive impairment, depression and behavioral problems	[96] (2018)

***Zingiber officinale* Rosc.**	Ginger extract capsule, once daily, 2 groups of 400 mg and 800 mg	Placebo capsule, once daily	Randomized double-blind, placebo-controlled clinical trial	60 healthy, middle-aged women	2 months	enhanced working memory and cognitive functions	[119] (2012)

mg: milligrams, TID: three times a day, AD: Alzheimer's disease, BID: twice a day.

Table 3. Presence of selected medicinal plants across major pharmacopeias.

Plant Name	Ph. Int.	BP	USP	EP	API	ChP.
***Allium sativum* L.**	☑	☑	☑	☑	☑	☑
***Boswellia* spp.**	☑	_	_	_	☑	_
***Crocus sativus* L.**	☑	☑	☑	☑	☑	☑
***Elettaria cardamomum* (L.) Maton**	☑	_	_	_	☑	_
***Lavandula angustifolia* Mill.**	☑	☑	_	☑	_	_
***Melissa officinalis* L.**	☑	☑	_	☑	_	_
***Nigella sative* L.**	☑	_	_	_	☑	_
***Piper nigrum* L.**	☑	☑	☑	☑	☑	_
***Rosa damascena* Mill.**	_	☑	☑	_	_	_
***Zingiber officinale* Rosc.**	☑	☑	☑	☑	☑	☑

☑: means the presence, _: means the absence, Ph. Int.: WHO International Pharmacopoeia, BP: British Pharmacopoeia, USP: United States Pharmacopeia, EP:European Pharmacopoeia, API:Ayurvedic Pharmacopoeia of India, ChP: Pharmacopoeia of the People's Republic of China.

Discussion

This review demonstrated the effectiveness of selected medicinal plants in alleviating cognitive dysfunction and memory impairments. The primary mechanisms involved were antioxidant and anti-inflammatory properties that restore redox balance, inhibit microgliosis, and reduce pro-inflammatory mediators such as TNF-α, IL-1β, and nuclear factor kappa B (NF-κB).[120] Many of these plants also enhance cholinergic neurotransmission via inhibition of AchE and increasing Ach levels in synaptic clefts. In addition, they are not only able to stabilize mitochondrial membrane potential, but also inhibit apoptosis partly by suppression of caspase-3 activity, which collectively results in neuronal cells vitality. The majority of these medicinal plants can also reduce amyloid-β deposition and tau hyper-phosphorylation by regulating enzymes like

GSK-3β. Besides, the augmentation of the BDNF/CREB signaling pathway was another contributing mechanism, improving synaptic plasticity and neurogenesis.[53,70] Moreover, modulation of the gut-brain axis may represent an emergent and crucial therapeutic mechanism. Medicinal plants could generate absorbable molecules through gut microbial metabolism, potentially enhancing cognitive function by rebalancing dysbiotic gut microbiota and lowering neuroinflammatory markers.[121] Altogether, these mechanisms emphasize the multi-target, synergistic neuroprotective nature of these plants in the management of cognitive decline.

The focus on selecting these plants based on their safety and accessibility clarifies why many of them are dietary spices (e.g., garlic, saffron, and cardamom) or are available as infusion teas or standardized extracts (e.g., lavender, lemon balm, ginger, and black seed). While numerous preclinical experiments have been conducted on the listed plants, only a limited number of high-quality clinical studies exist. Limitations such as insufficient robust clinical trials, lack of standardized formulations, herb-drug interactions, and study heterogeneity make it difficult to fully validate their efficacy and long-term safety. Therefore, on the basis of the clinical evidence, the selected TPM plants are able to exert positive cognitive effects in AD, mild cognitive impairment, and dementia, with *Boswellia sacra*, *Crocus sativus*, *Melissa officinalis*, *Piper nigrum*, and *Rosa damascena* improving memory, behavior, and overall cognitive function. Benefits were also observed in healthy populations as well as individuals with neurological (multiple sclerosis, opioid treatment) and metabolic disorders, where *Lavandula angustifolia*, *Allium sativum*, *Elettaria cardamomum*, *Melissa officinalis*, *Nigella sativa*, and *Zingiber officinale* enhanced memory, attention, mood, and working memory, supporting their potential as cognitive enhancers across diverse populations.

Innovative drug delivery methods, such as intranasal administration and topical oil applications used in TPM for neurological disorders, show significant potential to bypass the blood–brain barrier and improve therapeutic efficacy. The effective medicinal plants documented in this review, along with TPM's novel drug delivery systems, provide a strong foundation for developing safe, affordable, and non-toxic therapeutic agents in the form of medications,

dietary supplements, and integrative remedies for managing cognitive disorders. Importantly, these advancements not only pave the way for new therapies in cognitive health but also introduce and share Iran's rich cultural and traditional medicinal heritage with the world.

Conclusion and Future directions

Because cognitive impairment and dementia related to aging are becoming more common around the world, and because current drugs for AD are not very effective and may be associated with complications, there is a need for novel, safer, more affordable treatments.

Medicinal plants represent a promising link between TPM and current evidence-based medicine, offering accessible and cost-effective options for both preventive and adjunctive approaches to neurodegenerative disorders. Although there is promising preclinical evidence favoring their neuroprotective effects, many research gaps remain.

This includes the lack of standardized formulations and dosages, a poor understanding of pharmacokinetic and pharmacodynamic properties, and not enough translational research that links experimental findings to clinical outcomes. Furthermore, most recent researches are limited in scope, varied in methodology, and often lack comprehensive long-term follow-up data.

To address these limitations, future studies need to emphasize large-scale, multi-center, and rigorously designed randomized clinical trials to produce reliable evidence of efficacy and safety. Furthermore, efforts should concentrate on the standardization and quality assurance of bioactive components, mechanistic validation by advanced molecular and imaging techniques, and comprehensive assessments of long-term safety and any herb-drug interactions. These approaches will make the scientific basis of TPM-based medicines more reliable and facilitate their integration into standard healthcare systems.

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Figure 1. Captured images of selected medicinal plants.

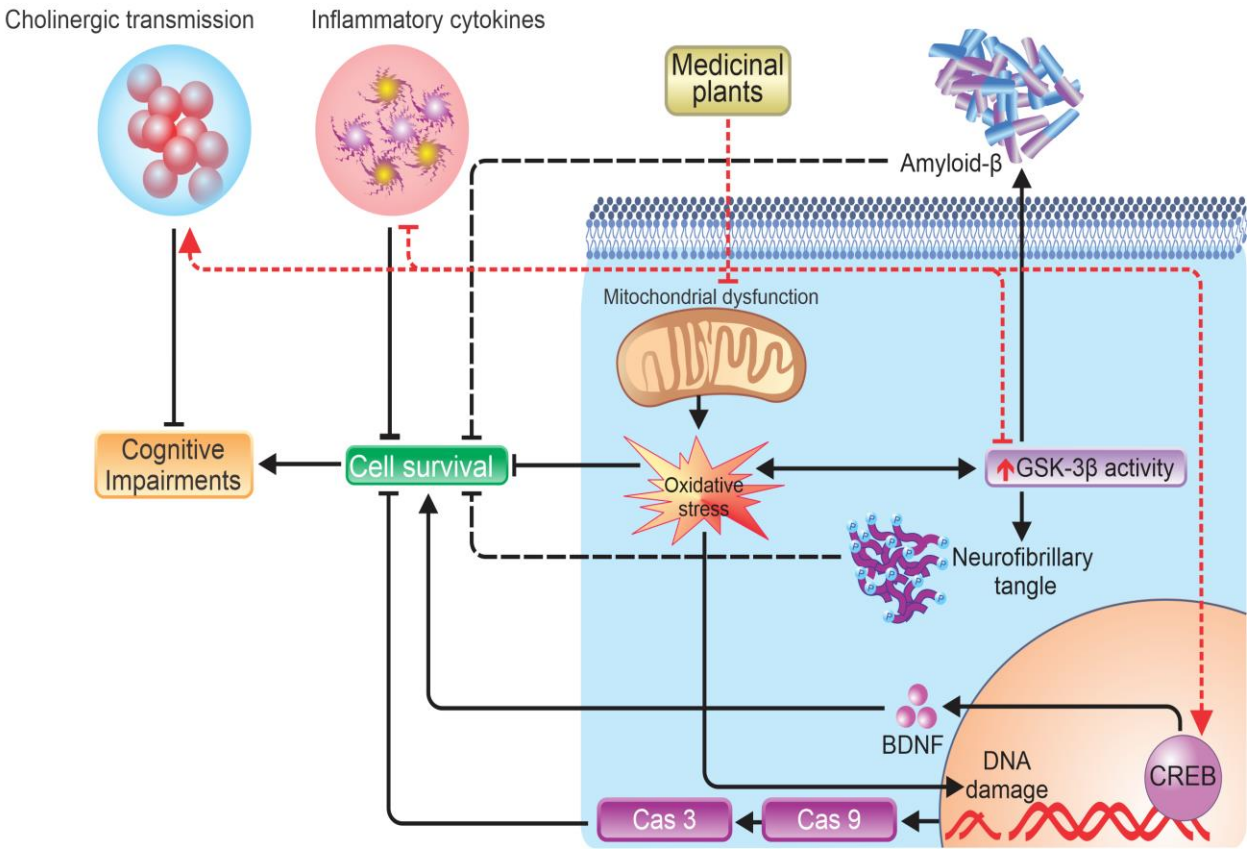

Figure 2. Summarized mechanisms contributing to the neuroprotective effects of TPM medicinal plants. Note: Amyloid-β: Amyloid beta, BDNF: Brain Derived Neurotrophic Factor, Cas 3 & 9: Caspase-3 & 9, CREB: cAMP-response element binding protein, GSK-3β: Glycogen synthase kinase-3 beta.