Tzu Chi Medical Journal 2023; 35 (2): 103-110

Review Article

Anti-inflammatory and memory-enhancing properties of Chinese herbal extracts: The possible application in Alzheimer's disease

*Peeraporn Varinthra[a], Pavithra Suresh[a], Prithiviraj Chokkalingam[b], Ayooluwa Gabriel Ibiayo[a], Ingrid Y. Liu[a]**

[a]Institute of Medical Sciences, College of Medicine, Tzu Chi University, Hualien, Taiwan, [b]Department of Molecular Biology and Human Genetics, Tzu Chi University, Hualien, Taiwan

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023

Submission : 10-May-2022
Revision : 06-Jun-2022
Acceptance : 13-Jul-2022
Web Publication : 05-Sep-2022

Abstract

Alzheimer's disease (AD) is a progressive brain disease that causes cognitive impairment in seniors. The beta-amyloid (Aβ) deposition and intracellular neurofibrillary tangles are two pathological hallmarks of AD. The increase of AD hallmarks causes inflammatory response enhancement, reduction of synaptic plasticity, and impaired cognition. The percentage of the aging population is growing along with the number of AD patients; however, effective treatment of AD is still limited. Therefore, developing preventive and therapeutic drugs for AD with fewer adverse side effects is urgently needed. The crude extracts from herbs such as *Centella asiatica, Dendrobium catenatum, Litsea cubeba, Nardostachys jatamansi, Convolvulus pluricaulis, Melissa officinalis, Magnolia officinalis, Withania somnifera, and Nigella sativa* improved memory performance and reduced inflammation response in various diseases. In addition, herbal blends usually have minimum aversive effects and can be mixed into diet and served as nutritional supplements. Hence, it is promising to develop Chinese herbal extracts to prevent or treat early AD. This review article highlights the currently available treatments of AD and the therapeutic effects of a group of crude extracts from Chinese herbs that can prevent cognitive decline and reduce the excessive inflammatory response. The possible clinical use of these Chinese herbal extracts in AD is also discussed.

Keywords: *Alzheimer's disease, Anti-inflammation, Herbal medicine, Memory*

Introduction

Severity and prevalence of Alzheimer's disease

Alzheimer's disease (AD) is a disease that slowly impairs memory performance and cognitive functions. It has become the 6th leading cause of death among neurodegenerative diseases [1]. However, in-market drugs that apply to middle or late AD patients are limited and have aversive side effects. Therefore, preventive and therapeutic drugs for AD from natural products with fewer adverse side effects are necessary. More than 4.6 million new AD patients are diagnosed every year. The number is expected to double by 2030 and possibly triple by 2050 [2]. From 2002 to 2012, data showed that 3%–7% of the Europe and US population were diagnosed with AD, including France (3%), the United Kingdom (4.9%), Italy (3%), Spain (6.4%), and the USA (5%–7%) [3]. The prevalence of AD in East Asia is about 6% of the elderly population aged ≥65 years in Taiwan, 3% in Japan, 5% in China, and 9% in South Korea [4]. AD has become a severe medical issue that heavily increases the societal burden locally and worldwide. Moreover, advanced medical health care and a nursing home are required for about 43% of patients [5]. Therefore, finding a preventive treatment from nature is more practical and costs less than developing a therapeutic drug for AD.

Signs and symptoms of Alzheimer's disease

AD's signs and symptoms can be classified into three stages [6]: (1) in the early stage, the patients demonstrate disorientation, forgetfulness, and confusion with time, usually considered a typical aging process and often neglected. (2) The signs and symptoms become more apparent in the middle stage. Most patients have difficulties in personal communication, remembering the names of people and events, and exhibiting behavioral changes such as reiterating the questions and wandering that can obstruct their daily lives. (3) In the late stage, intensive medical care is necessary for AD patients because of declined awareness of recent experiences,

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_139_22

**Address for correspondence:* Prof. Ingrid Y. Liu, Institute of Medical Sciences, Tzu Chi University, 701, Zhongyang Road, Section 3, Hualien, Taiwan.
E-mail: ycliu@gms.tcu.edu.tw

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Varinthra P, Suresh P, Chokkalingam P, Ibiayo AG, Liu IY. Anti-inflammatory and memory-enhancing properties of Chinese herbal extracts: The possible application in Alzheimer's disease. Tzu Chi Med J 2023;35(2):103-10.

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023

inability to recognize familiar people, and changes in physical abilities such as difficulties in eating, swallowing, walking, sitting, and being vulnerable to infections [6]. The progression of AD is irreversible and worsens over time; therefore, the early preventive treatments of AD before the onset of the late stage are essential.

Pathology of Alzheimer's disease

Memory impairments

Several types of memory impairment are associated with AD, including working memory, episodic memory, semantic memory, procedural memory [7], and fear memory [8]. Fear response is an essential emotion for survival and is highly conserved across species [9]. Previous studies have reported that defective fear memory appears in the early stage of AD, mild cognitive impairment (MCI) patients [10]. Working memory is the brain process with limited capacity to store necessary information for responding to complicated tasks such as learning, understanding, and reasoning [11]. Reduced working memory is a common symptom in AD patients. A previous study found that theta-gamma coupling recording by electroencephalography is defective in AD patients in the N-back working memory task [12]. The functional magnetic resonance imaging examination during a visuospatial associative working memory task demonstrated working memory impairment in MCI patients [13]. Episodic memory is associated with learning, storing, and retrieval of information for specific events in daily life. Semantic memory is linked with general world knowledge such as word meaning, fact, language, math, color, and names [14]. For the early stage of AD patients, episodic and semantic memory deficits can be identified using the five-word test [15], traditional semantic memory measures, and a nonverbal test [16]. Although AD affects various types of memory, effective treatments that could prevent and reverse memory impairments in AD are still limited.

Amyloid beta (Aβ) and tau

AD's two pathological hallmarks are known to be Aβ and neurofibrillary tangle (NFT) in the brain. Deposits of accumulated Aβ peptide were found within the interstitial space in the brains of AD patients. Aβ monomers can form higher-order assemblies to become dimers, trimers, tetramers, oligomers, and fibrils [17]. Accumulating Aβ can propagate excitatory synaptic alterations and loss of synaptic plasticity potential [18], which induces an inflammatory response, neurotransmission dysfunction, neuronal loss, and memory impairment [19]. Tau proteins are proteins that stabilize microtubules. They are abundant in the neurons of the central nervous system (CNS). The excessive or abnormal phosphorylation of tau results in the transformation of normal tau into NFTs. NFTs phosphorylated at S262 were found in the early pathological process of AD, which is more toxic to neurons than phosphorylation at other sites [20].

Neuroinflammation

Neuroinflammation is a significant early pathology of AD, which can be initiated by Aβ aggregation and the formation of NFTs [21]. On the other hand, increased inflammatory responses in the CNS caused by trauma, infection, and toxins can also stimulate the progressive activation of astrocytes and microglia, leading to the accumulation of Aβ and NFTs [22]. Microglia are present in the brain with different activation states according to its function and morphology, including resting, activated, and phagocytic microglia. The microglia cells protect and maintain CNS by acting on injury repair and pathogen infection. The imbalance of proinflammatory (M1)/immunosuppressive (M2) ratio is associated with neuronal dysfunction and neuronal loss in AD [23]. Aβ aggregation can stimulate microglia to acquire M1 phenotype and release interleukin-1β (IL-1β), IL-1, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), etc., to induce acute inflammation response to avoid neuronal damage. The increase of proinflammatory molecules such as IL-1β, TNF-α, and IFN-γ also interfere with the microglia's capacity to remove Aβ by suppressing microglial endocytic [24] and phagocytic activities [25]. In modulating acute inflammation to react properly, M2 microglia produces anti-inflammatory cytokines such as IL-4 and IL-10 to prevent the CNS inflammation mechanism from overreacting [23]. It suggests that suppressing neuroinflammation before the onset of AD may be a promising approach to preventing the progression of the disease.

Current treatment of Alzheimer's disease

Effective treatments to prevent and cure AD are limited. Up to date, only five medicines have been approved for AD treatment, including donepezil, galantamine, rivastigmine (cholinesterase inhibitors) [26], memantine (N-methyl-D-aspartate receptor [NMDAR] antagonist) [27], and aducanumab (anti-Aβ) [28]. These medicines only delay progressive symptoms of AD but do not prevent neuronal death. The side effects also elicit many concerns. Those patients who took cholinesterase inhibitors showed nausea, vomiting, diarrhea, abdominal cramp, and increased rates of syncope and bradycardia [29]. The side effect of NMDAR antagonist has also been reported, including dizziness, occasional restlessness/agitation, constipation, ocular effects (cataracts, conjunctivitis), nausea, dyspnea, confusion, headache, fatigue, rash, diarrhea, and urinary incontinence [30]. Moreover, the adverse effects of anti-Aβ are related to imaging abnormalities with brain effusion or hemorrhage, confusion or altered mental status, nausea, dizziness, and visual disturbances [31]. Many efforts have been invested in developing amyloid-targeting drugs, and some of them have gone through various phases of clinical trials. However, clearing beta-amyloid may be like putting out a forest fire, which is very difficult to be effective in the late stage of AD. Therefore, shifting to other approaches for AD treatments with fewer side effects, such as reducing chronic inflammation response before onset, would be hopeful.

Chinese herbal extracts

Chinese herbal extracts have been widely used for memory enhancement and inflammation alleviation in East Asian countries, and they are affordable, easy to obtain, natural, and produce fewer side effects [32]. Many Chinese herbal extracts appear to be effective in enhancing memory performance [33], preventing cognitive decline [34], and reducing inflammation

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023

response [35]. Since the chronic inflammatory response is a cause of learning and memory impairment in AD, Chinese herbal extracts with anti-inflammatory properties [Table 1] reviewed in the following paragraphs may be promising to become preventive treatments for AD.

Centella asiatica

Centella asiatica (*C. asiatica*), also known as Indian Pennywort, is a member of the plant family Apiaceae. It is well known as an enhancer of cognitive functions [90]. Several studies have demonstrated CA's effect on antidepression, anticonvulsant, neuroprotection, and anti-inflammation [90]. *In vitro* and *in vivo* studies showed that *C. asiatica* effectively improves memory impairment in AD models. *C. asiatica* extracted with water attenuated the behavioral deficit in AD mouse models [91-93]. Prolonged treatment of *C. asiatica* significantly alters Nicotinamide, glycerophospholipid, and purine metabolism associated with AD [36]. *C. asiatica*'s antioxidative property was explored in attenuating AD symptoms [37,38] and normal aging [39]. *C. asiatica* treatment lowered the lipid peroxidation [40], ROS levels, rescued mitochondrial dysfunction [41], and restored levels of antioxidative enzymes[42] in the brain. A randomized control study using *C. asiatica* on healthy elderly population showed improvement in age-related cognitive deficit and mood [43]. Similarly, another study showed improvement in MCI, depression, insomnia, and loss of appetite [44]. Recently, *C. asiatica* has been included in clinical research to find its effect on the cognitive functions of the elderly; the results are yet to be analyzed [45]. Since *C. asiatica* is edible, it can be mixed into a diet or served as a nutritional supplement for AD prevention.

Dendrobium catenatum

Dendrobium catenatum (D. catenatum), also known as *D. officinale,* is a traditional Chinese medicine and wildly distributed in many countries, including India, Japan, the US, Australia, and China [46]. *D. catenatum* appears to be safe, indicated with acute toxicity test (12.0 g/kg), genetic toxicity test (Ames test; 1000, 2000, and 4000 mg/kg), and feeding test for 90 days with 1.08, 1.67, and 5.00 g/kg in rats [46]. Previous studies reported that *D. catenatum* has anti-inflammation [47,48], anti-aging [49], and antioxidation[50] effects. *D. catenatum* treatment could also attenuate ERK, p38 MAPK, and NF-κB signaling pathways in the lung of a chronic obstructive pulmonary disease rat model [51]. In the ovariectomy mouse models, *D. catenatum* administration could improve memory deficits tested with Morris water maze and decrease Iba-1, IL-1β, and TNF-α expression via activation of Nrf2/HO-1 pathway [48]. In traditional Chinese medicine, *D. catenatum w*as used to remove arthralgia, relieve fever and pain, reinforce kidney function, attenuate irritable bowel syndrome, and build muscles [46]. These studies suggest that the effect of *D. catenatum* is a potential candidate for preventing AD.

Litsea cubeba

Litsea cubeba (L. cubeba) or Lauraceae is a medicinal plant widely distributed in India, Southeast Asia, southern China, Taiwan, and Japan [94]. It is called "Shan Cang Zi or shan jiao ji" in China and "makauy" in Taiwan. The indigenous people in Taiwan used the essential oil of *L. cubeba* to cure headaches, inflammation, intoxication, bronchitis, and dyspepsia [52]. The effect of *L. cubeba* essential oil has been studied in Aβ-induced AD mice and revealed decreasing oxidative stress, brain atrophy, and Aβ plaques. Besides, oral administration of *L. cubeba* (30.2 mg/day) for 8 weeks could improve spatial and working learning and memory deficit in Aβ-induced AD mice [52]. The *L. cubeba* essential oil also displayed its effect on anxiolytic and analgesic activities and prolonged sleeping in ICR mice [53]. Furthermore, the study on healthy female subjects demonstrated that *L. cubeba* essential oil has a sedative effect by decreasing alpha and beta wave powers [54]. In addition, *L. cubeba* essential oil can improve mood disorders and reduce confusion accompanied with decreased cortisol levels in the saliva of healthy subjects [55]. These studies suggest that *L. cubeba* essential oil is effective on CNS functions, including anti-inflammatory, antioxidant, memory enhancement, and attention improvement. Therefore, *L. cubeba* essential oil may be hopeful for AD prevention.

Nardostachys jatamansi

Nardostachys jatamansi (*N. jatamansi*) belongs to the plant family of Caprifoliaceae. *N. jatamansi* is widely used in Asian countries as herbal medicine, and its protective effects against neurotoxicity, sleep deprivation, and inflammation[95] have been well studied. *N. jatamansi* can improve memory performance in diazepam-induced amnesia mice. NJ can also increase the lifespan of drosophila and protect cells from Aβ-42 protein-induced neurotoxicity [56-58]. Besides, methanolic extract of *N. jatamansi* reverses the cognitive deficit caused by sleep deprivation [59]. Studies on primary insomnia patients showed that NJ with milk can significantly improve the duration and disturbed sleep [60]. *N. jatamansi* is known to benefit patients suffering from cognitive disturbances and depression with only one dose [61]. Since sleep deprivation and depression are common symptoms of AD, *N. jatamansi* can become a possible therapeutic candidate for treating AD.

Convolvulus pluricaulis

Convolvulus pluricaulis (*C. pluricaulis*) is commonly used for memory improvement in Ayurvedic Medhya Rasayana. Old mice (18–20 months) treated with *C. pluricaulis* extract showed significantly increased memory retention in elevated plus maze compared to the group treated with the marketed drug "piracetam" [62]. The active compound of the *C. pluricaulis* extract, kaempferol, has anti-inflammatory activity and rejuvenates cerebral infarction in ischemic mice [63,64]. *C. pluricaulis* extract reduced the anxiety-like and depression-like behavior of the CUMS rats in the open field and forced swimming tests[65] and enhanced memory in contextual fear conditioning and novel object recognition test [66]. It also enhances the long-term potentiation in the hippocampi of rats [67]. *C. pluricaulis* can also improve survival latency, locomotor activity of human tau-expressing drosophila, by decreasing the tau protein levels, increasing antioxidant enzymes, and acetylcholine neurotransmitters [68]. Administration of herbal mixture with *C. pluricaulis* as a

Table 1: The Chinese herbal extract's effects on memory and anti-inflammation

Herbal extracts	Experimental models *In vivo*	Properties		Clinical use in TAM	References
		Anti-inflammation	Memory		
Centella asiatica	Laca mice (2-3-month-old) CB6F1 mice (20-month-old) 5xFAD (7.6±0.6-month-old) STZ induced rat model Tg2576 (20-month-old)	(↓) COX2, IL-6, IL-1β, IRAK1-TAK1, TNF- α, NF-κB, iNOS (↑) Nrf2	(+) memory in MWM and Y-maze (+) memory retention in EPM, NOR, OLM, ODRL, fear memory in CFC	Sedative effect Improved age-related cognitive deficit and mood disturbance Anti-depressant	[36-45]
Dendrobium catenatum	Ovariectomy mice COPD rat model	(↓) Iba-1, TNF-α, IL-1β, IL-6, TLR4, NLRP3, Caspase-1 (↓) ICAM-1 mRNA, VCAM-1 mRNA (↑) Nrf2/OH-1	(+) memory in MWM, neuronal damage	Relieve pain and fever Remove arthralgia Building muscles Reinforce kidney and stomach	[46-51]
Litsea cubeba	Aβ-induced AD mice ICR mice (4-week-old)	(↓) TNF-α, IL-1β, IL-6, IL-8, IL-17A (↑) IL-10 (↓) oxidative stress, brain atrophy, Aβ plaques	(+) memory in MWM and T-maze (↔) locomotor in OFT (↓) memory retention in EPM	Sedative effect Anti-depressant Aromatherapy	[52-55]
Nardostachys jatamansi	Scopolamine and diazepam induced Swiss mice (3, 7-month-old) Oregon K fly LPS induced C57BL/6 mice Swiss albino mice	(↓) glia activation, NO, NF-κB, iNOS, COX2, PGE2, IL-1β, IL-6 and TNF-α	(+) memory retention in PAT, EPM, Y-maze, MWM, NOR learning by olfactory conditioning assay	Sedative effect Anti-depressant Improve cognitive deficit	[56-61]
Convolvulus pluricaulis	Male laka mice (18-20-month-old and young) Transgenic *Drosophila* taupathy model Adult male Wistar rats	(↓) IL-1β, IL-6, TNF-α (↓) IL-8, MCP-1 and ICAM-1	(+) memory retention in EPM (+) memory in CFC and NOR (↑) Locomotor activity, life span, and LTP	Herbal mixture - Mood regulator Memory enhancer	[62-69]
Magnolia officinalis	Tg2576 mice (12-month-old) $A\beta_{1-42}$ infused Slc: ICR mice STZ induced BALB/c mice TgCRND8	(↓) TNF-α, IL-6, IL-1*β*, Iba-1, GFAP (↑) IL-10	(+) memory retention in PAT and EPM, RAM (+) spatial memory in MWM, NOR	Anti-stress Anti-depressant	[70-74]
Melissa officinalis	Carrageenan-induced paw edema rat model Diabetic rats Wistar rats (6-week-old)	(↓) IL-1β, TNF-α and IL-6 (↓) edema (↓) COX-2, PGE2, BDNF (↑) Nrf2 and HO-1	(+) memory in MWM, Y-maze, and NOR (+) memory retention in PAT	Aromatherapy Anti-anxiety Anti-depressant Anti-inflammatory	[75-80]
Withania sommifera	Sprague Dawley rats Swiss albino mice (6-week-old) Wistar albino rats	(↑) Bcl-xL (↓) TNF-α, IL-1β, IL-6, MAPK, NF-κB	(+) memory in MWM and Y-maze (↑) memory in MCI patients	Anti-aging Anti-depressant Anti-anxiety Anti-inflammatory Memory enhancer Fertility Growth promotor in children	[81-84]
Nigella sativa	Amyloid beta-induced U87 (human astrocytoma cell line) LPS-induced Wistar rats (8-week-old) Pentylenetetrazole-induced repeated seizures in Wistar rats (8-week-old)	(↓) TNF-α, NO (↑) SOD, CAT (↓) Caspase 3	(+) memory and learning (↑) spatial memory and memory retention	Improved cognition and mood Memory enhancer Anti-anxiety	[85-89]

(+) Improved, (↑) Increase, (↓) Decrease, (↔) No change. LPS: Lipopolysaccharide, AD: Alzheimer's disease, ICR: Institute of Cancer Research, STZ: Streptozotocin, COPD: Chronic obstructive pulmonary disease, MWM: Morris water maze, EPM: Elevated plus maze, CFC: Contextual fear conditioning, NOR: Novel object recognition, PAT: Passive avoidance test, MCI: Mild cognitive impairment, LTP: Long-term memory, OFT: Open field test, TAM: Traditional Asia medicine, OLM: Object location memory, ODRL: Object discrimination reversal learning, RAM: Radial arm maze

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023

primary ingredient for 6 weeks improved sleep and energy level in 91% of patients who were undergone treatment [69]. *C. pluricaulis* extract can effectively enhance learning and memory in various animal models, including mice, rats, and drosophila, making it a promising candidate for treating early-stage AD symptoms.

Magnolia officinalis

Magnolia officinalis (MO) is a commonly used herb in Chinese, Japanese, and Korean medicine, added to food or applied to cosmetic products. The bark and flower of MO have been used widely in Chinese medicine for their low toxicity [96]. Several studies have found that MO could improve cognitive deficit and synaptic dysfunction [70,71]. MO treatment also exerts the anti-inflammation effect and helps the activation of phagocytosis of Aβ [72,73]. MO as a dietary supplement for healthy adults reduces daily stress and weekly depression [74]. Thus, MO can be a potential therapeutic target for AD.

Melissa officinalis

Melissa officinalis (M. officinalis) is one of the oldest aromatic plants with an aroma of lemon, which is still used in treating dementia and amnesia [97]. The extract of *M. officinalis* ameliorates the learning and memory deficits in scopolamine-injected rats by increasing the time spent in the target quadrant of the Morris water maze test [75]. *M. officinalis* can improve long-term memory in the passive avoidance test along with decreased acetylcholinesterase enzyme activity[76] and increased alterations in the Y-maze test of diabetic rats [76]. In the carrageenan-induced paw edema model, the inflammation response was decreased significantly in rats treated with *M. officinalis* leaf extract compared with the drug "indomethacin" [77]. Pilocarpine-induced neural death is rescued by the administration of *M. officinalis* leaf extract. It reduces inflammation by suppressing the proinflammatory cytokines and exhibiting antioxidative activity [78]. The administration of *M. officinalis* extracts to patients with mild-moderate AD for 4 months significantly improved memory [79]. In addition, *M. officinalis* extract is an excellent calming agent and is effective for patients disturbed with stress and agitation [80]. Combining *M. officinalis* extract with other treatments would be a promising preventive approach for AD.

Withania somnifera

Withania somnifera (*W. somnifera*) has been used in ayurvedic medicine to enhance memory and cognitive functions. The leaf extract of *W. somnifera* improved the locomotor activity and memory in rats receiving low-fat or high-fat diets [81]. Pretreatment with *W. somnifera* root extract enhanced thioacetamide-induced memory deficit and reduced inflammation in rats. Patients with mild-cognitive impairment receiving root extract of *W. somnifera* for 8 weeks showed a significant improvement in cognitive functions measured with Wechsler Memory Scale [82]. Uptake of *W. somnifera* root extract for 90 days can improve sleep quality, attention, and memory performance, on the other hand, reducing stress levels in human subjects [83]. The human trials treated with *W. somnifera* extract showed a significant memory improvement [82-84], making it a promising candidate for AD prevention.

Nigella sativa

Nigella sativa (*N. sativa*), identified as black cumin or black seeds, is one of the most commonly used herbal medicinal plants which belong to the Ranunculaceae family. It grows annually in the Mediterranean region, Europe, and Asia [98,99]. It is used for treating various diseases for its antibacterial, anticancer, antioxidative, antidiabetic, neuroprotective, gastroprotective, immunomodulatory, antihistaminic, and anti-inflammatory activities. In a placebo-controlled clinical trial, 40 healthy elderly volunteers were administered NS seed capsule twice a day for 9 weeks and showed improvement in cognition, memory, and attention [85]. Another study reported similar results in 48 healthy adolescent males treated with *N. sativa* capsules once per day for 4 weeks showed mood stability and decreased anxiety [86]. Thymoquinone bioactive constituent of *N. sativa*, elevated SOD, CAT levels and decreased caspase 3 level in amyloid beta-induced U87, a human astrocytoma cell line, thus protecting against oxidative stress and cellular death [87]. Hydroalcoholic extract of *N. sativa* (100, 200, or 400 mg/kg) decreased TNF-alpha and NO expression levels and improved spatial memory performance and retention in LPS-treated rats [88]. In a pentylenetetrazole-induced seizure rat model, 400 mg/kg treatment with *N. sativa* increased spatial memory and memory retention [89]. Taken together, *N. sativa* may be a promising therapeutic candidate for AD prevention.

Conclusion

The excessive inflammatory response is an initiation factor of AD, which can induce later disease pathologies, including Aβ aggregation, NFTs, synaptic dysfunction, neuronal loss, and cognitive impairment. Unfortunately, the current AD treatments have limited success in preventing or curing the disease and caused many side effects. However, as studies reviewed in this paper, several Chinese herbal medicines may be promising in preventing AD. Many Chinese herbal extracts effectively decrease inflammation response, enhance memory performance, and prevent cognitive impairment *in vitro, in vivo*, and in human studies. Therefore, taking Chinese herbal medicines that are natural, affordable, and produce fewer side effects may become a promising therapeutic approach to preventing AD.

Financial support and sponsorship

This review article is supported by the Buddhist Tzu Chi Medical Foundation "TCMF-SP 108-04".

Conflicts of interest

Prof. Ingrid Y. Liu, an editorial board member at *Tzu Chi Med J*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Alzheimer's Association. 2019-Alzheimer's disease facts and figures. Alzheimers Dement 2019;15:321-87.
2. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement 2013;9:63-75.e2.

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023

3. Takizawa C, Thompson PL, van Walsem A, Faure C, Maier WC. Epidemiological and economic burden of Alzheimer's disease: A systematic literature review of data across Europe and the United States of America. J Alzheimers Dis 2015;43:1271-84.
4. Wu YT, Brayne C, Matthews FE. Prevalence of dementia in East Asia: A synthetic review of time trends. Int J Geriatr Psychiatry 2015;30:793-801.
5. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007;3:186-91.
6. WHO. Dementia: A Public Health Priority. Switzerland: WHO Press; 2012.
7. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011;1:a006189.
8. Varinthra P, Ganesan K, Huang SP, Chompoopong S, Eurtivong C, Suresh P, et al. The 4-(Phenylsulfanyl) butan-2-one improves impaired fear memory retrieval and reduces excessive inflammatory response in triple transgenic Alzheimer's disease mice. Front Aging Neurosci 2021;13:615079.
9. Wotjak CT, Pape HC. Neuronal circuits of fear memory and fear extinction. E-Neuroforum 2013;4:47-56.
10. Nasrouei S, Rattel JA, Liedlgruber M, Marksteiner J, Wilhelm FH. Fear acquisition and extinction deficits in amnestic mild cognitive impairment and early Alzheimer's disease. Neurobiol Aging 2020;87:26-34.
11. Camina E, Güell F. The neuroanatomical, neurophysiological and psychological basis of memory: Current models and their origins. Front Pharmacol 2017;8:438.
12. Goodman MS, Kumar S, Zomorrodi R, Ghazala Z, Cheam AS, Barr MS, et al. Theta-gamma coupling and working memory in Alzheimer's dementia and mild cognitive impairment. Front Aging Neurosci 2018;10:101.
13. Kochan NA, Breakspear M, Slavin MJ, Valenzuela M, McCraw S, Brodaty H, et al. Functional alterations in brain activation and deactivation in mild cognitive impairment in response to a graded working memory challenge. Dement Geriatr Cogn Disord 2010;30:553-68.
14. Renoult L, Rugg MD. An historical perspective on Endel Tulving's episodic-semantic distinction. Neuropsychologia 2020;139:107366.
15. Mormont E, Jamart J, Robaye L. Validity of the five-word test for the evaluation of verbal episodic memory and dementia in a memory clinic setting. J Geriatr Psychiatry Neurol 2012;25:78-84.
16. Shi Y, Huang W, Wang Y, Zhang R, Hou L, Xu J, et al. Bis (9)-(-)-Meptazinol, a novel dual-binding AChE inhibitor, rescues cognitive deficits and pathological changes in APP/PS1 transgenic mice. Transl Neurodegener 2018;7:21.
17. Murphy MP, LeVine H 3rd. Alzheimer's disease and the amyloid-beta peptide. J Alzheimers Dis 2010;19:311-23.
18. Rolland M, Powell R, Jacquier-Sarlin M, Boisseau S, Reynaud-Dulaurier R, Martinez-Hernandez J, et al. Effect of Aβ oligomers on neuronal APP triggers a vicious cycle leading to the propagation of synaptic plasticity alterations to healthy neurons. J Neurosci 2020;40:5161-76.
19. Cline EN, Bicca MA, Viola KL, Klein WL. The amyloid-β oligomer hypothesis: Beginning of the third decade. J Alzheimers Dis 2018;64:S567-610.
20. Alonso AD, Di Clerico J, Li B, Corbo CP, Alaniz ME, Grundke-Iqbal I, et al. Phosphorylation of tau at Thr212, Thr231, and Ser262 combined causes neurodegeneration. J Biol Chem 2010;285:30851-60.
21. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21:383-421.
22. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: Where do we go from here? Nat Rev Neurol 2021;17:157-72.
23. Tang Y, Le W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. Mol Neurobiol 2016;53:1181-94.
24. Solé-Domènech S, Cruz DL, Capetillo-Zarate E, Maxfield FR. The endocytic pathway in microglia during health, aging and Alzheimer's disease. Ageing Res Rev 2016;32:89-103.
25. Koenigsknecht-Talboo J, Landreth GE. Microglial phagocytosis induced by fibrillar beta-amyloid and IgGs are differentially regulated by proinflammatory cytokines. J Neurosci 2005;25:8240-9.
26. Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord 2013;6:19-33.
27. Emre M, Mecocci P, Stender K. Pooled analyses on cognitive effects of memantine in patients with moderate to severe Alzheimer's disease. J Alzheimers Dis 2008;14:193-9.
28. Walsh S, Merrick R, Milne R, Brayne C. Aducanumab for Alzheimer's disease? BMJ 2021;374:n1682.
29. Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand SL, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: A population-based cohort study. Arch Intern Med 2009;169:867-73.
30. Olivares D, Deshpande VK, Shi Y, Lahiri DK, Greig NH, Rogers JT, et al. N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. Curr Alzheimer Res 2012;9:746-58.
31. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate use recommendations. J Prev Alzheimers Dis 2021;8:398-410.
32. Abdel-Aziz SM, Aeron A, Kahil TA. Health Benefits and Possible Risks of Herbal Medicine. Cham: Springer; 2016.
33. Halder S, Anand U, Nandy S, Oleksak P, Qusti S, Alshammari EM, et al. Herbal drugs and natural bioactive products as potential therapeutics: A review on pro-cognitives and brain boosters perspectives. Saudi Pharm J 2021;29:879-907.
34. Choi Y, Kim AR, Lee JY, Kim HS, Yang C, Kim JK, et al. Herbal medicine for patients with cognitive impairment: An observational study. Neuropsychiatr Dis Treat 2021;17:3183-94.
35. Ghasemian M, Owlia S, Owlia MB. Review of anti-inflammatory herbal medicines. Adv Pharmacol Sci 2016;2016:9130979.
36. Speers AB, García-Jaramillo M, Feryn A, Matthews DG, Lichtenberg T, Caruso M, et al. *Centella asiatica* alters metabolic pathways associated with Alzheimer's disease in the 5xFAD mouse model of ß-amyloid accumulation. Front Pharmacol 2021;12:788312.
37. Chen CL, Tsai WH, Chen CJ, Pan TM. *Centella asiatica* extract protects against amyloid β(1-40)-induced neurotoxicity in neuronal cells by activating the antioxidative defence system. J Tradit Complement Med 2016;6:362-9.
38. Gray NE, Zweig JA, Caruso M, Martin MD, Zhu JY, Quinn JF, et al. *Centella asiatica* increases hippocampal synaptic density and improves memory and executive function in aged mice. Brain Behav 2018;8:e01024.
39. Doknark S, Mingmalairak S, Vattanajun A, Tantisira B, Tantisira MH. Study of ameliorating effects of ethanolic extract of *Centella asiatica* on learning and memory deficit in animal models. J Med Assoc Thai 2014;97(Suppl 2):S68-76.
40. Shinomol GK, Muralidhara. Prophylactic neuroprotective property of *Centella asiatica* against 3-nitropropionic acid induced oxidative stress and mitochondrial dysfunctions in brain regions of prepubertal mice. Neurotoxicology 2008;29:948-57.
41. Kumar A, Prakash A, Dogra S. *Centella asiatica* attenuates D-galactose-induced cognitive impairment, oxidative and mitochondrial dysfunction in mice. Int J Alzheimers Dis 2011;2011:347569.
42. Haleagrahara N, Ponnusamy K. Neuroprotective effect of *Centella asiatica* extract (CAE) on experimentally induced parkinsonism in aged Sprague-Dawley rats. J Toxicol Sci 2010;35:41-7.

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023

43. Wattanathorn J, Mator L, Muchimapura S, Tongun T, Pasuriwong O, Piyawatkul N, et al. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of *Centella asiatica*. J Ethnopharmacol 2008;116:325-32.
44. Tiwari S, Singh S, Patwardhan K, Gehlot S, Gambhir I. Effect of *Centella asiatica* on mild cognitive impairment (MCI) and other common age-related clinical problems. Dig J Nanomater Bios 2008;3:215-20.
45. Wright KM, Bollen M, David J, Speers AB, Brandes MS, Gray NE, et al. Pharmacokinetics and pharmacodynamics of key components of a standardized *Centella asiatica* product in cognitively impaired older adults: A phase 1, double-blind, randomized clinical trial. Antioxidants (Basel) 2022;11:215.
46. Chen W, Lu J, Zhang J, Wu J, Yu L, Qin L, et al. Traditional uses, phytochemistry, pharmacology, and quality control of *Dendrobium officinale* Kimura et. Migo. Front Pharmacol 2021;12:726528.
47. Han J, Dong J, Zhang R, Zhang X, Chen M, Fan X, et al. *Dendrobium catenatum Lindl.* Water extracts attenuate atherosclerosis. Mediators Inflamm 2021;2021:9951946.
48. Liang J, Wu Y, Yuan H, Yang Y, Xiong Q, Liang C, et al. *Dendrobium officinale* polysaccharides attenuate learning and memory disabilities via anti-oxidant and anti-inflammatory actions. Int J Biol Macromol 2019;126:414-26.
49. Liang CY, Liang YM, Liu HZ, Zhu DM, Hou SZ, Wu YY, et al. Effect of *Dendrobium officinale* on D-galactose-induced aging mice. Chin J Integr Med 2017. [doi: 10.1007/s11655-016-2631-x].
50. Luo QL, Tang ZH, Zhang XF, Zhong YH, Yao SZ, Wang LS, et al. Chemical properties and antioxidant activity of a water-soluble polysaccharide from *Dendrobium officinale*. Int J Biol Macromol 2016;89:219-27.
51. Liang Y, Du R, Chen R, Chu PH, Ip MSM, Zhang KYB, et al. Therapeutic potential and mechanism of *Dendrobium officinale* polysaccharides on cigarette smoke-induced airway inflammation in rat. Biomed Pharmacother 2021;143:112101.
52. Lee KT, Chu CY, Chiang SS. Ameliorating effect on Aβ-Induced Alzheimer's mice by *Litsea cubeba* Persoon Powder. Molecules 2021;26:5709.
53. Chen CJ, Tseng YH, Chu FH, Wen TY, Cheng WW, Chen YT, et al. Neuropharmacological activities of fruit essential oil from *Litsea cubeba* Persoon. J Wood Sci 2012;58:538-43.
54. Sattayakhom A, Songsamoe S, Yusakul G, Kalarat K, Matan N, Koomhin P. Effects of Thai local ingredient odorants, *Litsea cubeba* and garlic essential oils, on brainwaves and moods. Molecules 2021;26:2939.
55. Chaiyasut C, Sivamaruthi BS, Wongwan J, Thiwan K, Rungseevijitprapa W, Klunklin A, et al. Effects of *Litsea cubeba* (Lour.) persoon essential oil aromatherapy on mood states and salivary cortisol levels in healthy volunteers. Evid Based Complement Alternat Med 2020;2020:4389239.
56. Anupama KP, Shilpa O, Antony A, Raghu SV, Gurushankara HP. Jatamansinol from *Nardostachys jatamansi* (D.Don) DC. Protects $A\beta_{42}$-induced neurotoxicity in Alzheimer's disease drosophila model. Neurotoxicology 2022;90:62-78.
57. Liu QF, Jeon Y, Sung YW, Lee JH, Jeong H, Kim YM, et al. *Nardostachys jatamansi* ethanol extract ameliorates Aβ42 cytotoxicity. Biol Pharm Bull 2018;41:470-7.
58. Anupama KP, Shilpa O, Antony A, Gurushankara HP. Jatamansinol from *Nardostachys jatamansi*: A multi-targeted neuroprotective agent for Alzheimer's disease. J Biomol Struct and Dyn 2021;1-21. Available from: https://www.tandfonline.com/doi/full/10.1080/07391102.2021.2005681.
59. Rahman H, Muralidharan P. *Nardostacys jatamansi* DC protects from the loss of memory and cognition deficits in sleep deprived Alzheimer's disease (AD) mice model. Int J Pharm Sci Rev Res 2010;5:160-7.
60. Toolika E, Bhat NP, Shetty SK. A comparative clinical study on the effect of Tagara (*Valeriana wallichii* DC.) and Jatamansi (*Nardostachys jatamansi* DC.) in the management of Anidra (primary insomnia). Ayu 2015;36:46-9.
61. Mamta S, Garima S, Shveta A. Evaluation of anti stress effects of *Nardostachys jatamansi* Dc root extract on clinical patients: A psycological estimation. ESSENCE Int J Env Rehab Conser 2017;2:54-61.
62. Sharma K, Bhatnagar M, Kulkarni SK. Effect of *Convolvulus pluricaulis* Choisy and *Asparagus racemosus* Willd on learning and memory in young and old mice: A comparative evaluation. Indian J Exp Biol 2010;48:479-85.
63. Shalavadi MH, Chandrashekhar VM, Muchchandi IS. Neuroprotective effect of *Convolvulus pluricaulis* Choisy in oxidative stress model of cerebral ischemia reperfusion injury and assessment of MAP2 in rats. J Ethnopharmacol 2020;249:112393.
64. Balkrishna A, Thakur P, Varshney A. Phytochemical profile, pharmacological attributes and medicinal properties of *Convolvulus prostratus*-A cognitive enhancer herb for the management of neurodegenerative etiologies. Front Pharmacol 2020;11:171.
65. Gupta GL, Fernandes J. Protective effect of *Convolvulus pluricaulis* against neuroinflammation associated depressive behavior induced by chronic unpredictable mild stress in rat. Biomed Pharmacother 2019;109:1698-708.
66. Nahata A, Patil UK, Dixit VK. Effect of *Convulvulus pluricaulis* Choisy. on learning behaviour and memory enhancement activity in rodents. Nat Prod Res 2008;22:1472-82.
67. Das R, Sengupta T, Roy S, Chattarji S, Ray J. *Convolvulus pluricaulis* extract can modulate synaptic plasticity in rat brain hippocampus. Neuroreport 2020;31:597-604.
68. Kizhakke PA, Olakkaran S, Antony A, Tilagul KS, Hunasanahally PG. *Convolvulus pluricaulis* (Shankhapushpi) ameliorates human microtubule-associated protein tau (hMAPτ) induced neurotoxicity in Alzheimer's disease Drosophila model. J Chem Neuroanat 2019;95:115-22.
69. Kumar V. Potential medicinal plants for CNS disorders: An overview. Phytother Res 2006;20:1023-35.
70. Xian YF, Qu C, Liu Y, Ip SP, Yuan QJ, Yang W, et al. Magnolol ameliorates behavioral impairments and neuropathology in a transgenic mouse model of Alzheimer's disease. Oxid Med Cell Longev 2020;2020:5920476.
71. Hoi CP, Ho YP, Baum L, Chow AH. Neuroprotective effect of honokiol and magnolol, compounds from *Magnolia officinalis*, on beta-amyloid-induced toxicity in PC12 cells. Phytother Res 2010;24:1538-42.
72. Xie Z, Zhao J, Wang H, Jiang Y, Yang Q, Fu Y, et al. Magnolol alleviates Alzheimer's disease-like pathology in transgenic *C. elegans* by promoting microglia phagocytosis and the degradation of beta-amyloid through activation of PPAR-γ. Biomed Pharmacother 2020;124:109886.
73. Chen T, Shou L, Guo X, Wei M, Zheng H, Tao T. Magnolol attenuates the locomotor impairment, cognitive deficit, and neuroinflammation in Alzheimer's disease mice with brain insulin resistance via up-regulating miR-200c. Bioengineered 2022;13:531-43.
74. Nelson E, Knowles S, Jadhav S, Walsh A, Palombo E. Assessing the beneficial effects of a magnolia extract supplemented with phosphatidylserine: A randomised, double-blind, placebo-controlled clinical trial. In: Gupta VK, editor. 3. New Delhi, India: M/S Daya Publishing House; 2014. p. 143-52.
75. Soodi M, Naghdi N, Hajimehdipoor H, Choopani S, Sahraei E. Memory-improving activity of *Melissa officinalis* extract in naïve and scopolamine-treated rats. Res Pharm Sci 2014;9:107-14.
76. Naseri M, Arabi Mianroodi R, Pakzad Z, Falahati P, Borbor M, Azizi H, et al. The effect of *Melissa officinalis* L. extract on learning and memory: Involvement of hippocampal expression of nitric oxide synthase and brain-derived neurotrophic factor in diabetic rats. J Ethnopharmacol 2021;276:114210.
77. Bounihi A, Hajjaj G, Alnamer R, Cherrah Y, Zellou A. *In vivo* potential

anti-inflammatory activity of *Melissa officinalis* L. essential oil. Adv Pharmacol Sci 2013;2013:101759.

78. Abd Allah HN, Abdul-Hamid M, Mahmoud AM, Abdel-Reheim ES. *Melissa officinalis* L. ameliorates oxidative stress and inflammation and upregulates Nrf2/HO-1 signaling in the hippocampus of pilocarpine-induced rats. Environ Sci Pollut Res Int 2022;29:2214-26.
79. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry 2003;74:863-6.
80. Kennedy DO, Scholey AB, Tildesley NT, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). Pharmacol Biochem Behav 2002;72:953-64.
81. Manchanda S, Kaur G. *Withania somnifera* leaf alleviates cognitive dysfunction by enhancing hippocampal plasticity in high fat diet induced obesity model. BMC Complement Altern Med 2017;17:136.
82. Choudhary D, Bhattacharyya S, Bose S. Efficacy and safety of ashwagandha (*Withania somnifera* (L.) Dunal) root extract in improving memory and cognitive functions. J Diet Suppl 2017;14:599-612.
83. Gopukumar K, Thanawala S, Somepalli V, Rao TS, Thamatam VB, Chauhan S. Efficacy and safety of ashwagandha root extract on cognitive functions in healthy, stressed adults: A randomized, double-blind, placebo-controlled study. Evid Based Complement Alternat Med 2021;2021:8254344.
84. Singh RH, Narsimhamurthy K, Singh G. Neuronutrient impact of Ayurvedic Rasayana therapy in brain aging. Biogerontology 2008;9:369-74.
85. Bin Sayeed MS, Asaduzzaman M, Morshed H, Hossain MM, Kadir MF, Rahman MR. The effect of *Nigella sativa* Linn. seed on memory, attention and cognition in healthy human volunteers. J Ethnopharmacol 2013;148:780-6.
86. Bin Sayeed MS, Shams T, Fahim Hossain S, Rahman MR, Mostofa A, Fahim Kadir M, et al. *Nigella sativa* L. seeds modulate mood, anxiety and cognition in healthy adolescent males. J Ethnopharmacol 2014;152:156-62.
87. Ozbolat G, Alizade A. Investigation of the protective effect of thymoquinone of U87 cells induced by beta-amyloid. Bratisl Lek Listy 2021;122:748-52.
88. Norouzi F, Hosseini M, Abareshi A, Beheshti F, Khazaei M, Shafei MN, et al. Memory enhancing effect of *Nigella sativa* hydro-alcoholic extract on lipopolysaccharide-induced memory impairment in rats. Drug Chem Toxicol 2019;42:270-9.
89. Vafaee F, Hosseini M, Hassanzadeh Z, Edalatmanesh MA, Sadeghnia HR, Seghatoleslam M, et al. The effects of *Nigella sativa* hydro-alcoholic extract on memory and brain tissues oxidative damage after repeated seizures in rats. Iran J Pharm Res 2015;14:547-57.
90. Gray NE, Alcazar Magana A, Lak P, Wright KM, Quinn J, Stevens JF, et al. *Centella asiatica*-Phytochemistry and mechanisms of neuroprotection and cognitive enhancement. Phytochem Rev 2018;17:161-94.
91. Kumar A, Dogra S, Prakash A. Neuroprotective effects of *Centella asiatica* against intracerebroventricular colchicine-induced cognitive impairment and oxidative stress. Int J Alzheimers Dis 2009;2009:972178.
92. Matthews DG, Caruso M, Murchison CF, Zhu JY, Wright KM, Harris CJ, et al. *Centella asiatica* improves memory and promotes antioxidative signaling in 5XFAD mice. Antioxidants (Basel) 2019;8:630.
93. Soumyanath A, Zhong YP, Henson E, Wadsworth T, Bishop J, Gold BG, et al. *Centella asiatica* extract improves behavioral deficits in a mouse model of Alzheimer's disease: Investigation of a possible mechanism of action. Int J Alzheimers Dis 2012;2012:381974.
94. Kamle M, Mahato DK, Lee KE, Bajpai VK, Gajurel PR, Gu KS, et al. Ethnopharmacological properties and medicinal uses of *Litsea cubeba*. Plants (Basel) 2019;8:150.
95. Joshi H, Parle M. *Nardostachys jatamansi* improves learning and memory in mice. J Med Food 2006;9:113-8.
96. Sarrica A, Kirika N, Romeo M, Salmona M, Diomede L. Safety and toxicology of magnolol and honokiol. Planta Med 2018;84:1151-64.
97. Shakeri A, Sahebkar A, Javadi B. *Melissa officinalis* L.-A review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol 2016;188:204-28.
98. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, et al. A review on therapeutic potential of *Nigella sativa*: A miracle herb. Asian Pac J Trop Biomed 2013;3:337-52.
99. Dalli M, Bekkouch O, Azizi SE, Azghar A, Gseyra N, Kim B. *Nigella sativa* L. phytochemistry and pharmacological activities: A review (2019-2021). Biomolecules 2021;12:20.

Downloaded from http://journals.lww.com/tcmj by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdgGj2MwlZLeI= on 04/13/2023