

# Bioactive Compounds and Traditional Herbal Medicine: Promising Approaches for the Treatment of Dementia

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**Abstract:** Dementia is a term that encompasses a group of clinical symptoms affecting memory, thinking and social abilities, characterized by progressive impairment of memory performance and cognitive functions. There are several factors involved in the pathogenesis and progression of dementia, such as old age, brain ischemia, toxin exposure, and oxidative stress. There are extensive similarities between dementia and Alzheimer's disease (AD) either in clinical manifestations or experimental animal models. AD is the most dominant form of dementia, characterized by the accumulation of beta-amyloid protein and cholinergic neurotransmission deficits in the brain. Currently available medications for the treatment of dementia, such as choline esterase inhibitors, N-methyl-D-aspartate (NMDA) antagonists (memantine), have short-term efficacy and only relieve symptoms rather than targeting the main underlying pathogenesis. Several animal studies and clinical trials are being conducted to provide a rational approach to these medicinal plants in the prevention or treatment of memory deficits. This review highlights the potential effects of medicinal plants and their derived lead molecules, and explains the related mechanisms and effects reviewed from published literature as major thrust aspects and hopeful strategies in the prevention or treatment of dementia.

**Keywords:** cognitive impairment, Alzheimer's disease, vascular dementia, dementia, medicinal plants, bioactive compounds

## Introduction

Dementia is a term that encompasses a group of clinical symptoms affecting memory, thinking and social abilities, characterized by progressive impairment of memory performance and cognitive functions. It has emerged as a major social and medical challenge that calls for urgent measures to establish its underlying pathogenesis and therapeutic interventions. There are several factors involved in the pathogenesis and progression of dementia, such as old age, brain ischemia, toxin exposure, and oxidative stress. Globally, around 50 million people are believed to be lived with dementia, with nearly 7.7 million new annual cases. The majority of them are poorly diagnosed and belong to low- and middle-income countries.<sup>1</sup> Dementia is considered one of the most common causes of death in high-income countries.<sup>2</sup> Although dementia is usually considered a disease of the elderly, the number of cases between 40 and 60 years of age rises rapidly.<sup>3</sup> In spite of the rapid progress in the development of synthetic drugs targeting memory loss, the demand for alternative or complementary medicine is also growing globally, and it should be given great attention. Herein, we review the pivotal

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role of common medicinal plants, which are widely used in various traditional systems of medicine as potential preventative or treatment strategies against dementia.

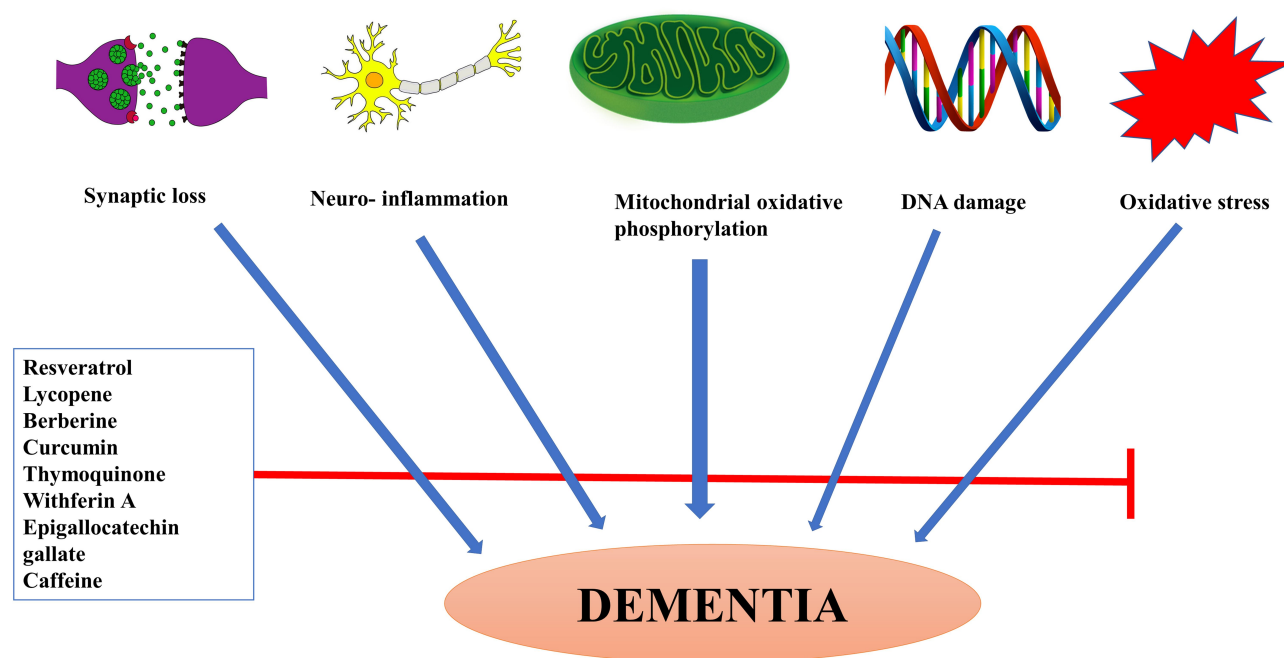
## Pathogenesis of Dementia

Substance abuse, subdural hematoma, intracranial tumors, neuro-infection, amyotrophic lateral sclerosis, and other neurodegenerative disorders are common causes of vascular dementias.<sup>4,5</sup> AD is the most dominant form of dementia, characterized by accumulation of beta-amyloid (amyloid plaques) and progressive microtubule disintegration, leading to synaptic loss, dysfunctional communication and neuronal cell apoptosis. Moreover, the  $\beta$ -amyloid plaques (insoluble proteins) accumulate between the neurons and interact with cell membranes, which trigger the oxidative stress and free calcium levels, and eventually lead to neuronal cell death. Pesticides, air pollutants and industrial toxic chemicals that easily penetrate blood-brain barriers can induce oxidative stress, neuronal damage and increase the progression of dementia.<sup>6,7</sup> Autosomal genetic mutation in the central nervous system (CNS) is an important inherent factor associated with the early onset of AD.<sup>8</sup> In the absence of definitive and effective treatment for dementia, lifestyle modification, phytopharmaceuticals, physical exercise, and practicing cognitive and social activities are considered effective means for disease treatment and prevention.<sup>9</sup> Some drugs approved by

the FDA are currently used for dementia management, but they were reported to have several adverse effects. Therefore, it is necessary to explore safer strategies from evidence-based medicine that can control dementia (Figure 1).

## Medicinal Plants and Bioactive Compounds: An Alternative Therapeutic Strategy for Dementia Treatment

Aging or cognitive diseases are characterized by amyloid protein deposition and cholinergic neurotransmission deficits in the brain. Unfortunately, currently available dementia treatments, such as choline esterase inhibitors, N-methyl-D-aspartate (NMDA) antagonists (memantine), and calcium channel blockers, have short-term efficacy, and only relieve symptoms rather than targeting the main underlying pathogenesis.<sup>10</sup> Memantine is a relatively weak NMDA receptor antagonist, approved for AD by the FDA in 2003, given to patients with moderate to severe cognitive deficits, and is known to prevent neuronal damage and synaptic loss caused by upregulation of NMDA receptors.<sup>11</sup> As conventional therapies have many side effects and fail to improve cognitive decline, natural products and non-pharmacological interventions appear to be promising and safer alternative approaches with a beneficial impact on cognitive behaviors, thus they



**Figure 1** Illustrative diagram showing the potential mechanisms of bioactive compounds against dementia.

should be central strategies in the treatment of memory impairment.

## **Ginkgo biloba (Gb) L**

*Ginkgo biloba* (Gb) is one of the most distinctive plants of the Ginkgoaceae family. Gb possesses a large genome, and it has high resistance to plant pathogens and other environmental factors, such as intense sunlight, temperature, high soil salinity, and so on.<sup>12</sup> Gb has been widely used for the treatment of various neurovascular disorders, such as vertigo, tinnitus, venous insufficiency, fatigue and age-related physical and cognitive disorders.<sup>13</sup> EGb761, is a standard Gb extract, contains a mixture of flavonoids (primarily quercetin, kaempferol, and isorhamnetin) and terpenoids (2.8–3.4% ginkgolides A, B, and C, and 2.6–3.2% bilobalide). It has been extensively studied as an effective treatment for memory impairment. Also, it has been reported as an effective therapy against a wide variety of CNS disorders, such as depression, anxiety, stroke, and cerebral insufficiency.<sup>14,15</sup> Gb extract has potential therapeutic effects on ischemic brain injury, cognitive and neurological disorders by improving cerebral perfusion and inhibiting platelet-activating factors. Flavonoids and terpene lactones like ginkgolides and bilobalides are the most isolated phytoconstituents from Gb extract. A standardized Gb extracts effectively reduced tissue damage after brain ischemia, attenuated oxidative stress, and improved cognitive dysfunction in various experimental rat models of dementia and chronic stress.<sup>16–18</sup> An in vitro study evaluated the antiplatelet activity of EGb761 and concluded that Gb extract has protective effects and functional integrity on cerebral microvascular endothelial cells.<sup>19</sup> Cell line studies showed that Gb extract protected cultured brain cells against neurotoxins like nitric oxide<sup>20</sup> and cyanide.<sup>21</sup> Oral or intraperitoneal administration of 10–100 mg/kg of Gb extract prevented neuronal damage caused by transient middle cerebral artery occlusion (MCAO) in rats.<sup>21,22</sup> In one model of vascular dementia in gerbils, EGb761 significantly improved spatial learning and memory, protected the hippocampal CA1 neurons and increased SOD activity in plasma.<sup>23</sup> Chronic administration of Gb leaf extract protected rats' brain against biochemical and degenerative changes induced by aluminum chloride through increasing endogenous antioxidant and inhibiting the formation of free radicals.<sup>24</sup> Additionally, treatment with Gb extract has been found to display antioxidant and neuroprotective activities on the prefrontal cortex and dorsal hippocampus

of middle-aged rats. The study showed that chronic treatment with Gb extract improved age-related memory impairment and increased the survival of cortical neurons.<sup>25</sup> In a randomized, placebo-controlled clinical trial, the study findings showed that daily administration of 240 mg of Gb extract was safe and effective in the treatment of patients with dementia.<sup>26</sup> Furthermore, a meta-analysis study by Wang et al proved that Gb could be an effective treatment for vascular dementia.<sup>27</sup> Another meta-analysis study explored the efficacy of EGb 761 in dementia patients treated with 120 mg or 240 mg per day when compared to placebo. The study results showed that EGb 761 was well tolerated in all trials and that 240 mg of EGb 761 was more effective in improving cognition.<sup>28</sup> In contrast, the findings of a randomized, controlled trial demonstrated that 120 mg of Gb extract twice a day is not effective in reducing either the incidence rate of dementia or AD in elderly individuals aged  $\geq 75$  years with normal cognition or those with mild cognitive impairment (MCI).<sup>29</sup>

*G. biloba* has a high cerebral bioavailability, a single dose of EGb761<sup>®</sup> (90 mg/kg) reaches its peak concentration after 1 hour and remains at measurable levels for 6 hours in rats' brain.<sup>30</sup> Despite the safety and efficacy data of Gb in improving cognition, the co-administration of Gb with antipsychotic drugs like risperidone, phenytoin, or trazodone has been resulted in serious neurological side effects.<sup>31</sup> Additional animal studies and clinical trials are required to assess the safety aspect and the potential interaction with other drugs.

## **Withania somnifera (Ashwagandha)**

*Withania somnifera* or Ashwagandha or Indian Ginseng (fam. Solanaceae) is a popular Ayurvedic medicinal plant known for its adaptogenic and antistress effects. Ashwagandha is an essential ingredient in Thai traditional medicine; it is used for enhancing memory and body functions. The roots of *W. somnifera* contain several phytoconstituents such as alkaloids, withanolides, sitoindosides and flavonoids. Among these compounds, withaferin A is a molecule of interest that has shown a neuroprotective effect in various human and animal studies. The immunomodulatory and antioxidant potentials of these bioactive candidates have been explored in an experimental model of acute stress.<sup>32</sup> Some of the plausible mechanisms of action of *W. somnifera* against AD are (i) blocking  $\beta$ -amyloid (A $\beta$ ) production; (ii) inhibition of NF- $\kappa$ B pathway; (iii) reduction of neuronal death; (iv)

modulation of synaptic transmission and restoring antioxidant enzymes.<sup>33</sup> Kuboyama et al have evaluated the effect of withanoside IV on memory improvement and synaptic reconstruction in  $A\beta_{25-35}$  induced injury on cultured rat cortical neurons. The study findings revealed that oral administration of withanoside IV (10 micromole/kg/day) markedly induced neurite outgrowth, restored memory defects, and protected mice from axonal, dendritic and synaptic loss.<sup>34</sup> In a preliminary placebo-controlled trial, Chengappa et al have studied the cognitive impact of standardized *W. somnifera* extract against bipolar disease. The researchers observed that *W. somnifera* extract (500 mg/day) significantly enhanced the cognitive tests and improved auditory-verbal working memory.<sup>35</sup>

### ***Panax ginseng* C.A. Meyer (Ginseng)**

Ginseng is a slow-growing perennial herb (Family of Araliaceae; a genus of *Panax*), widely cultivated in northeastern China. In the last decade, many experimental studies have shown that this plant has a key function in preventing neurodegeneration and improving learning and memory deficits.<sup>36</sup> Ginseng is an adaptogen, protects against various biological stressors. Ginsenosides, the most valuable active constituents in *Panax ginseng* roots, are known to have a wide range of pharmacological activities including anti-inflammatory, antioxidant, immunomodulatory, anti-cancer, anti-aging, and adaptogenic activities. Zhang et al studied the neuroprotective potential of ginsenoside Rg2 on memory impairment in a vascular dementia (VD) in a rat model of cerebral ischemic reperfusion. The study results indicated that a significant improvement in cognitive abilities and neurological responses in the ginsenoside Rg2 group relative to the disease control group.<sup>37</sup> A significant reduction in  $A\beta_{40}$  and  $A\beta_{42}$  levels in the brains of transgenic mice and cultured neurons was demonstrated after treatment with ginsenoside Rg3.<sup>38</sup> Ginsenoside Rg5 has been tested and found to modulate cognitive dysfunction, neuroinflammation, and increased cholinergic activity in streptozotocin (STZ)-induced memory impairment in rats.<sup>39</sup> Hur et al patented a pharmaceutical composition containing ginsenoside Rg18, it has neuroprotective activity against  $A\beta$ -induced nerve cell death during brain inflammation.<sup>40</sup> This invention produced a significant improvement of memory and learning skills using a model of  $A\beta$  peptide to induce dementia.<sup>40</sup> Ginsenoside Rg1 modulates the neurotransmission and enhances glutamate release in the CNS through a calcium/calmodulin-dependent protein kinase II-dependent signaling pathway.<sup>41</sup> In a randomized controlled trial, recruited 61 AD patients, Mini-Mental State Examination (MMSE) and

Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) tests were used to assess the changes in cognitive and functional performance after chronic oral administration of Korean red ginseng (KRG) as an adjuvant treatment for dementia. The study results demonstrated that the ADAS and Clinical Dementia Rating Scale (CDR) were improved markedly after 24 weeks in the high-dose (9 g/day) KRG treated patients relative to those in the control group.<sup>42</sup> Briefly, the active constituents of *Panax ginseng* play a crucial role in the regulation of amyloid- $\beta$  synthesis, acetylcholine signaling and neuro-inflammatory response. Thus, they could be potential candidates in the treatment of dementia and AD.

### ***Curcuma longa* (Turmeric)**

*Curcuma longa* L. is a tuberous herbaceous perennial plant with yellow flowers and wide leaves, belongs to the *Zingiberaceae* family, and grows in the tropical climate. Curcumin (diferuloylmethane) and curcuminoid analogs such as demethoxycurcumin and bisdemethoxycurcumin are the main bioactive components in the rhizome of *Curcuma longa*, and commonly used as natural coloring agents in food. In traditional Indian medicine, turmeric is widely used for the treatment of many pathological conditions, such as asthma, epilepsy, gallstone and diabetic.<sup>43</sup> As previously described, neuroinflammation is one of the key causes of cognitive decline. Significant evidence from preclinical and clinical studies elucidated the key role of curcumin in attenuating the neuroinflammatory cytokines, such as monocyte chemoattractant protein 1 (MCP-), TNF- $\alpha$ , IL-6 and TGF- $\beta$ .<sup>44</sup> A cell line study conducted by Park et al to assess the neuroprotective mechanisms of curcumin against  $A\beta_{25-35}$  induced neurotoxicity in PC12 cells. The study findings have shown that curcumin exposure inhibited hyperphosphorylation of microtubule-associated tau proteins, reduced oxidative stress and intracellular calcium influx.<sup>45</sup> Fluorescence and confocal microscopy were used to measure the  $A\beta$  uptake by the macrophages of AD patients and control individuals. The results showed a significant increase of  $A\beta$  uptake by the macrophages of AD patients compared to curcuminoids-treated and control groups.<sup>46</sup> Curcumin has been found to enhance glutathione expression, antioxidant enzyme and heme oxygenase in dementia and AD patients.<sup>47</sup> Agrawal et al studied the effect of curcumin on memory functions, brain insulin receptors (IRs), and acetylcholinesterase (AChE) activity in dementia model in rats. The researchers demonstrated that curcumin could significantly enhance cholinergic activity, attenuate oxidative damage and improve memory deficits in the (STZ)-treated rats compared to controls.<sup>48</sup> Ganguli et al have noticed

lower AD incidence in the Indian population consuming a curcumin-rich diet compared to the US population.<sup>49</sup> This neuroprotective potential was likely due to attenuation of oxidative stress and reduction of A $\beta$  deposition, which are the main causes of mitochondrial damage in the brain. Due to the poor oral bioavailability of curcumin, 2000 or 4000 mg/day orally administered curcumin C3 complex (70–80% curcumin) has shown a non-significant difference in the clinical efficacy between treatment groups.<sup>50</sup>

## Glycyrrhiza Genus

*Glycyrrhiza* or liquorice is a perennial herb growing in the Mediterranean region, Asia, Southern Russia, and Iran. *Glycyrrhiza* is derived from ancient Greek, glykys means “sweet,” and rhiza is “root.”<sup>51</sup> Glycyrrhizin is the main active component in liquorice, commonly used as a natural sweetener. In Ayurvedic and Unani medicine, liquorice is extensively used for various medical conditions, such as inflammation of respiratory airways and gastrointestinal tract disorders. Glycyrrhizic acid (GA), a triterpenoid saponin glycoside, has demonstrated its anti-inflammatory and neuroprotective effects in many experimental studies. Isoflavonoid derivatives, including glabrone, lico-isoflavone A and B, glabridine and galbrene, are also essential bio-active components isolated from liquorice extract. Liquiritigenin from *Glycyrrhizae radix* is a selective estrogen receptor- $\beta$  (ER $\beta$ ) agonist, these receptors are distributed in the brain centers of learning and memory.<sup>52</sup> Liquiritigenin has shown a good cerebral bioavailability with neuroprotective and anti-inflammatory effects on A $\beta$ <sub>25–35</sub>-induced neurotoxicity on rat hippocampal neurons.<sup>53</sup> The neuroprotective effects of glycyrrhizin against neurotoxin 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>) have been tested by Soo et al. They demonstrated that glycyrrhizin has neuroprotective potential via prevention of mitochondrial damage, attenuation of oxidative stress, and restoration of glutathione depletion in differentiated PC12 cells.<sup>54</sup> Isoliquiritigenin is another component identified in *Glycyrrhiza* species that can suppress the caspase-3 proapoptotic activity, and produce potential effectiveness against dementia similar to memantine.<sup>55</sup>

## Tea (*Camellia sinensis*)

Worldwide, green tea, black tea, and oolong tea are popular stimulant drinks. In traditional Indian and Chinese systems of medicine, green tea is also used for the treatment of obesity, diabetes mellitus, and neuroinflammation.<sup>56</sup> Here, we searched evidence from animal and human studies showing the crucial role of green tea-

related compounds on cognitive functions and memory impairment. (–)-epigallocatechin-3-O-gallate (EGCG), is a natural compound contained in green tea extract has anti-atherogenic and anti-inflammatory properties, and plays a key role in the prevention and treatment of neurodegenerative diseases.<sup>57</sup> In Wistar rat model of dementia, 10 mg/kg/day oral administration of EGCG for 4 weeks significantly reversed the cognitive deficit, reduced oxidative and nitrosative stress, and modulated AChE activity in STZ treated rats.<sup>58</sup> Lee et al conducted a preclinical study on ICR mice to investigate the effect of EGCG on the systemic neuroinflammation and memory impairment. The study results showed that chronic oral administration of 1.5 and 3 mg/kg EGCG could inhibit lipopolysaccharide (LPS) induced cytokine release and amyloidogenesis, as well as prevent memory impairment, apoptotic neuronal cell death, and microglia activation.<sup>59</sup>

A prospective cohort study by Tomato et al assessed the cognitive-enhancing action of green tea among Japanese dementia patients aged  $\geq 65$  years. The results have shown that more frequent intake of green tea could reduce dementia's incidence rate by 8.7% over 5.7 years of intake.<sup>60</sup> L-theanine extracted from the leaves of green tea could protect memory deficits and hippocampal cell death by attenuating the neuronal oxidative damage and blocking NF- $\kappa$ B signaling pathway induced by A $\beta$ <sub>42</sub>.<sup>61</sup> Several findings from animal and human studies have demonstrated the neuroprotective potential of tea polyphenols, catechins and epicatechin, in improving cognitive decline and neuronal signaling. The potential mechanisms behind that are due to improving the endogenous antioxidant activities, regulation of apoptosis, reduction of A $\beta$  synthesis, and modulation of mitochondrial function and neural growth factors.<sup>62–64</sup>

## Brahmi (*Bacopa monnieri*)

*Bacopa monnieri* (L.) also known as Brahmi, belongs to *Scrophulariaceae* family, it is a creeping, succulent, herb cultivated in the wetlands of the Indian subcontinent.<sup>65</sup> Brahmi herbs have long been used in Indian Ayurvedic medicine to improve cognitive deficits related to brain aging. It has been demonstrated that Brahmi extract contains bacoside A, which has anti-inflammatory, analgesic, antistress, and antiepileptic actions.<sup>66</sup> The bacoside metabolites of Brahmi can cross the BBB easily and improve cognition by increasing blood flow, not necessarily due to direct interactions with neural cells. Holcomb et al evaluated the effect of the Brahmi extract on amyloid  $\beta$ -induced AD in PSAPP mice. The study findings revealed that Brahmi extract is



able to reduce amyloid plaque in mice cortex, and reverse Y-maze performance and open field hyperlocomotion behavior.<sup>67</sup> Another study by Limpeanchob et al evaluated the protective effect of Brahmi on A $\beta$ -induced cell death in primary cortical neurons. The study confirmed that the neuroprotective effect is being due to the suppression of neuronal oxidative stress and enhancing cholinergic activity.<sup>68</sup> Khan et al found that oral administration of Brahmi extract at 30mg/kg for 14 days significantly improved memory and learning capability, and ameliorated the morphological changes due to oxidative damage induced by intracerebroventricular-streptozotocin (ICV-STZ) in the brain tissue of rats. This neuroprotective effect of Brahmi was attributable to the upregulated expression of hippocampal antioxidant enzymes.<sup>69</sup> In a mouse model of trimethyltin (TMT)-induced neurodegeneration and cognition dysfunction, administration of 50 mg/kg/day of Brahmi extract significantly protected hippocampal neurons, enhanced neurogenesis, and improved cognitive performance in mice.<sup>70</sup> Uabundit et al explored beneficial cognitive effects of Brahmi extract against ethyl choline aziridinium ion mediated cognitive decline and neurodegenerative in rats. They observed a decline in both the number and density of cholinergic neurons and improvement in spatial learning and memory.<sup>71</sup> Bacoside treatment attenuated neurotoxics (scopolamine, sodium nitrite, and platelet-activating factor antagonist)-induced amnesia, increased cholinergic activity, and reduced latency escape period in mice.<sup>72</sup> Brahmi has positive effects on the treatment of attention deficit hyperactivity disorder (ADHD) in children and can improve cognitive functions in stroke and epileptic patients.<sup>73</sup> Among the plausible mechanisms behind the neuroprotective effect of *Brahmi* are increasing glutathione expression and enhancing cerebral blood supply.<sup>72,74</sup> Oral administration 300 mg/day of standardized Brahmi extract in healthy elderly participants for 12 weeks significantly enhanced the cognitive tasks, Rey Auditory Verbal Learning Test (AVLT), Stroop test, and depression scores, confirming its safety and memory-enhancing effects.<sup>75</sup> A randomized placebo-controlled trial has been conducted in India and enrolled 60 medical students to assess the impact of *Bacopa monnieri* on improving cognition among medical students. 150 mg of standardized Brahmi extract (Bacognize®) twice daily for six weeks substantially improved auditory and visual neuropsychological tests and increased serum calcium compared to the control group.<sup>76</sup> A study performed by Thakkar et al to enhance the poor solubility of Bacognize®. Inclusion complex containing 16% bacosides and  $\beta$ -cyclodextrin at a molar ratio of 1:4 by

co-precipitation method improved solubility and stability of Bacognize® by three times.<sup>77</sup> Poor learning and ADHD are very common childhood disorders in the Western world. Administration of 10 g Brahmi to 40 rural Indian school children aged 6–8 years for 3 months significantly enhanced memory and response performance.<sup>78</sup> Meta-analyses of randomized, double-blind, controlled trials demonstrated the beneficial effects of Brahmi on cognitive performance, particularly attention speed.<sup>79</sup> In contrast, a study reported that supplementation of Brahmi extract and multiple micronutrients twice daily for 4 months did not show a significant impact in improving short-term memory in Indian school children.<sup>80</sup> Despite the safety of Brahmi in animal studies and human trials, no studies regarding its safety in pregnancy, so it should not be used.<sup>81,82</sup>

## Nigella sativa

*Nigella sativa* is a small black seed that belongs to the *Ranunculaceae* family, native to Southern Europe, North Africa, and Asia Minor, and it is also cultivated in Pakistan and India. *N. sativa* has long been used in traditional medicine as astringent, diuretic, anthelmintic, and for the treatment of intermittent fever and skin disease.<sup>83</sup> Moreover, the therapeutic value of *N. sativa* was mentioned in many chapters of the Prophetic medicine book. *N. sativa* contains a variety of constituents, including proteins, alkaloid, alpha-hederin, saponin, vitamins, minerals, volatile and fixed oils. Unsaturated fatty acids represent up to 26.6% to 38% of the total oil content.<sup>84</sup> Thymoquinone is the molecule of interest attributed to the pharmacological activities of the *N. sativa*.<sup>85</sup> Thymol and carvacrol attenuated the disruption of cholinergic function and memory deficits induced by A $\beta$ - and scopolamine in rats.<sup>86</sup> Emerging evidence confirms that flavonoids of *N. sativa* are able to modulate specific changes in hippocampal protein expression involved in the learning and memory process.<sup>87</sup> A preclinical study was conducted by Hosseini et al to explore the protective mechanism of *N. sativa* hydroalcoholic extract in scopolamine-induced spatial memory impairment in male Wistar rats. The study results explored that *N. Sativa* purified oils enhanced memory performance, cholinergic activity, and reduced oxidative stress in rat brain tissues.<sup>88</sup> Similarly, a study performed by Khan et al to evaluate the neuroprotective effect of thymoquinone (3mg/kg body weight) for 15 days against streptozotocin-induced cognitive impairment in rats. The study findings revealed that thymoquinone reduced the levels of

oxidative stress markers, and significantly decreased the latency time and the path length in the Morris Water Maze (MWM) test.<sup>89</sup> Thymoquinone (1.642 mg) ameliorated A $\beta$ <sub>1–42</sub> induced neurotoxicity in rat hippocampal and cortical cultured neurons, and prevented the mitochondrial membrane potential depolarization.<sup>90</sup> A clinical study by Bin Sayeed et al has investigated the effect of *N. sativa* on anxiety and cognitive decline. The study findings reported that oral intake of *N. sativa* 500 mg/day over four weeks as a nutritional supplement was found to stabilize mood, decrease anxiety and modulate cognition on adolescent human male participants.<sup>91</sup> Taken together, these collective evidences put thymoquinone in the top list of phytopharmaceuticals as a promising candidate for the treatment of dementia and AD.

## Phytochemicals

Resveratrol (3,5,4'- trihydroxystilbene) belongs to a family of polyphenolic compounds known as stilbenes. Peanuts, pistachios, berries, and grapes are essential sources of resveratrol.<sup>92</sup> The trans-isomer of resveratrol in the skin of most grape species is more effective and more stable than Cis-isomer. Resveratrol has been shown to exhibit anti-cancer, anti-inflammatory, anti-aging, cardioprotective and anti-oxidant properties.<sup>93,94</sup> Also, it has anti-amyloidogenic effects and could inhibit the formation and extension of neurotoxic A $\beta$  fibrils.<sup>95</sup> A cell line study by Vingtdeux et al studied the potential effect of resveratrol in AD. The investigators observed that resveratrol was able to inhibit the extracellular A $\beta$  accumulation by facilitating its proteolytic clearance in neuronal cells, and activation of AMP-activated protein kinase in the cerebral cortex of transgenic mice.<sup>96</sup> In order to enhance the cerebral bioavailability of resveratrol, the development of novel formulations for brain targeting is highly recommended.

Lycopene is an aliphatic hydrocarbon carotenoid extracted from tomatoes, watermelons, and papayas. It is a strong anti-oxidant, anti-inflammatory, and anti-proliferative agent. Lycopene is well known for its beneficial effects against solid tumors and non-alcoholic fatty liver.<sup>97,98</sup> Improvement of prostate cancer after a long period of tomato sauce consumption and the prospective association between reduction of plasma glucose level and chronic lycopene intake have been reported in independent clinical studies.<sup>99,100</sup> The underlying mechanism of lycopene in the treatment of memory deficits is not fully

understood. Long-term lycopene intake has been found to inhibit the oxidative stress and reduce infarct volume and neuronal apoptosis in cerebral ischemia/reperfusion in high-fat diet-induced cognitive impairment in rats.<sup>101</sup> 50 mg/kg of lycopene supplementation for 60 days significantly reduced the levels of inflammatory cytokines, prevented neuronal degeneration and nucleus shrinkage in the brains of aged CD-1 mice.<sup>101</sup> Zhu et al conducted a study on a rat model of bilateral carotid artery occlusion induced VD to evaluate the protective effect of lycopene on memory impairment. The study results indicated that chronic administration of lycopene could effectively inhibit oxidative stress and reduce the expression of neuron-restrictive silencer factor (*NRSF*) in rats' brains.<sup>102</sup>

Berberine is an isoquinoline alkaloid extracted from barberry, it has wide medicinal uses in the treatment of bacterial diarrhea, hypercholesterolemia, type 2 diabetes, cardiac disease, and cancer.<sup>103</sup> Despite many experimental studies elucidating the neuroprotective effects of berberine, its definite mechanism of enhancing memory functions is not fully understood. An in vitro study by Asai et al explored that 10  $\mu\text{mol L}^{-1}$  berberine could reduce amyloid  $\beta$  levels to 30% via modulation of the amyloid precursor protein (APP) pathway in human neuroglioma H4 cells.<sup>104</sup> Another in vitro study investigated the potential effect of berberine on A $\beta$ -induced mitochondrial dysfunction in primary cultured hippocampal neurons. The study findings confirmed that berberine may preserve mitochondrial membrane potential, improve mitochondrial motility and prevent synaptic loss.<sup>105</sup>

Caffeine is a naturally occurring CNS stimulant found in coffee, tea, and other plants. It has been used for medicinal purposes in many systems of traditional medicine for over thousands of years. Coffee is the main source of caffeine, and it contains phenolics and other bioactive compounds that may have either positive or negative effects on health. Different coffee preparations contain varying levels of caffeine, such as 0.6–3.3 mg/mL in espresso, 0.7–1.1 mg/mL in boiled or filtered coffee, and 0.2–0.6 mg/mL in instant coffee.<sup>106</sup> Caffeine is absorbed from the gastrointestinal tract rapidly; 99% is absorbed in about 45 min after ingestion.<sup>107</sup> Caffeine binds with A1 and A2A adenosine receptors. It has positive effects on attention, arousal, mood and vigilance. In high amounts, caffeine can induce anxiety, restlessness, insomnia and psychomotor agitation.<sup>108</sup> Crude caffeine has higher levels of hydrophilic and lipophilic antioxidant activity than pure caffeine. Caffeine when given in high doses has been

reported to inhibit phosphorylation of esterase enzyme which in turn leads to the induction of calcium release from the sarcoplasmic reticulum, thus activating protein kinase A. This cascade of signaling pathways is in the phosphorylation of enzymes involved in glucose and lipid metabolism. Caffeine intake minimizes the risk of cognitive impairment in neurological conditions, including sleep deprivation, alcohol consumption, diabetes, Parkinson's disease, and AD.<sup>109,110</sup> Several in vitro and in vivo studies reported that caffeine exhibits neuroprotective effects as it protects cortical neurons against A $\beta$  toxicity as well as prevents A $\beta$ -induced memory deficits in mice.<sup>111</sup> A long-term study in mice has supported that as well, showing that caffeine intakes can prevent the memory decline related to age which is associated with changes in neurotrophic factor (BDNF).<sup>112</sup> It has been reported that caffeine treatment at 40 mg/kg significantly enhances A $\beta$  clearance (20%) in the brain endothelial cells of C57BL/6 mice.<sup>113</sup> In another related study, it is found out that caffeine (0.6 mg/d) increases hippocampal mitochondrial respiration (25%) and ATP levels (46%) in the APPSw mice. Caffeine increases hippocampal mitochondrial membrane potential (78%) and decreases ROS production (100%) in Alzheimer's mice.<sup>114</sup> Caffeine decreased the cholesterol-induced increase in A $\beta$ , phosphorylated tau, and oxidative stress levels in rabbits' hippocampus and reversed the cholesterol-induced decrease in adenosine A1 receptors (A1R) levels when given in the drinking water at 0.5 and 30 mg/day.<sup>115</sup> Many randomized controlled trials support the potential role of caffeine in improving cognition. A 21-year follow-up study (875 women and 534 men, age 50 years) concluded that moderate consumption (3–5 cups) of coffee substantially reduced the risk of AD (62–64%) and dementia (65–70%) later in life, compared with low coffee consumers (0–2 cups).<sup>116</sup> The consumption of caffeine is linked to faster processing of new information and improved simple reaction time.<sup>117</sup> In a large prospective cohort study of 2475 females over 65 years old with vascular diseases, the relation between habitual caffeine uses and long-term cognitive decline was examined over five years. As a result, coffee consumption was linked to a slower rate of cognitive decline, especially in women with stable diets.<sup>118</sup> In another prospective study conducted by the Canadian Study of Health and Aging (CSHA) for five years, daily coffee consumption reduced the risk of AD by 31%.<sup>119</sup> However, at autopsy, patients who consumed more than 277.5 mg of caffeine a day had a decreased probability of presenting AD-related lesions, or other ischemic lesions.<sup>120</sup> Caffeine has been found

to reduce the risk of developing AD in patients with apolipoprotein E (ApoE  $\epsilon$ 4) allele.<sup>121</sup> In contrast, a recent study from the Honolulu-Asian Aging Study failed to establish a significant correlation between caffeine consumption and dementia risk.<sup>36</sup> Similarly, a longitudinal study in the Netherlands reported that no significant correlation between caffeine intake and a reduced risk of cognitive decline.<sup>122</sup>

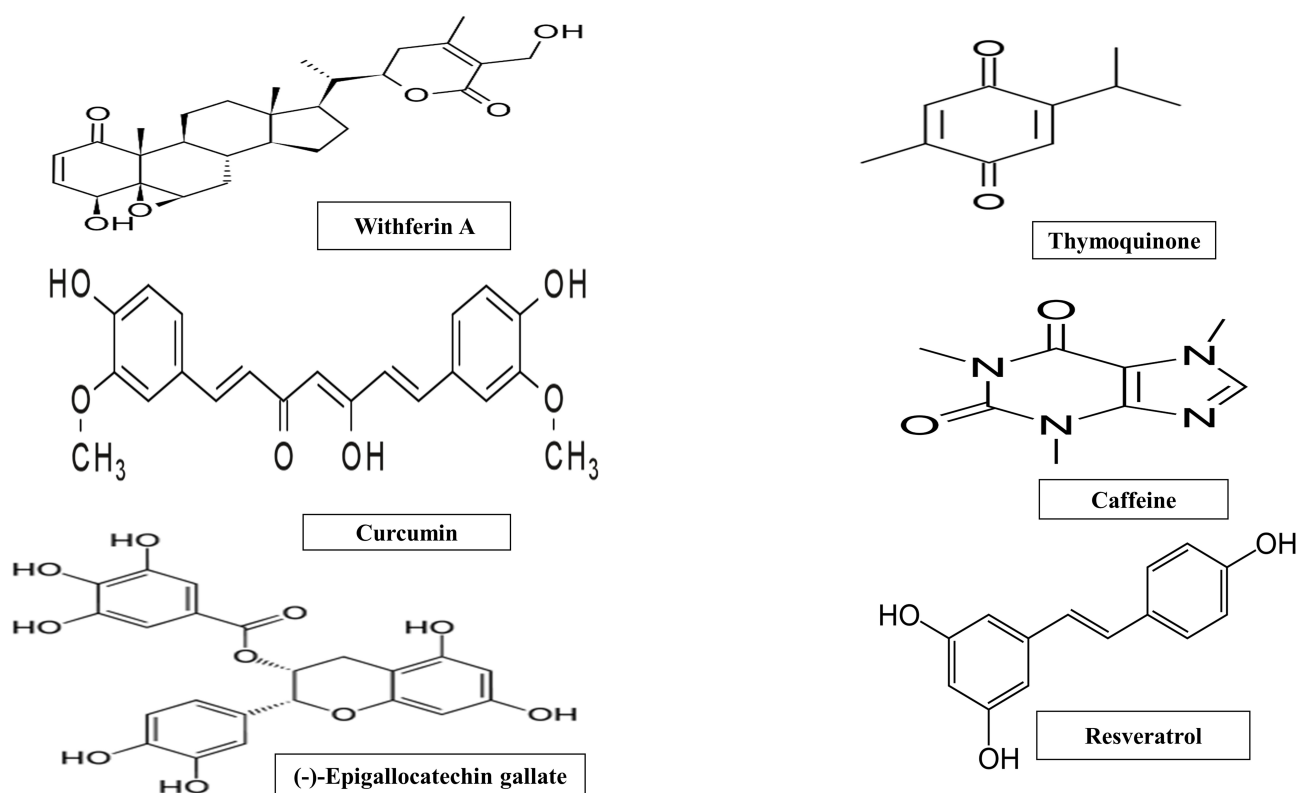
In addition to the aforementioned medicinal plants and bioactive candidates (Figure 2), several marketed herbal formulations are currently used for dementia treatment. Yukmijihwang-tang is a common herbal product in Korea, China and Japan used to enhance memory. It has been found to inhibit apoptosis by enhancing the expression of the neuron-specific proteins transthyretin and PEP-19 in the brains of rats exposed to neurotoxicant.<sup>123</sup> Another cognitive enhancer herbal formulation is a Chinese Naoweikang, containing *Ginkgo biloba* and *Panax ginseng*. It has been tested and found to modulate the cholinergic pathway against A $\beta$ <sub>1–40</sub> induced neurotoxicity in the brain of Sprague Dawley rats.<sup>124</sup> ESP-2, a standardized Korean combined extract of *Angelica gigas*, *Saururus chinensis* and *Schizandra chinensis* effectively inhibited AChE activity and reversed scopolamine-induced memory impairment in ICR mice.<sup>125</sup>

## Future Prospective

Dementias and Alzheimer's disease are closely intertwined multifactorial diseases caused by a cascade of genetic and environmental risk factors developing over a period of time. The heterogeneous nature of factors causing the disease has made it very difficult to find the right treatment as one drug will not be sufficient to make a difference in all related dementias. Therefore, there has not been any substantial progress in the development of a successful line of dementia treatment. The reason behind the multiple failures of clinical trials of drugs targeting memory loss could be attributed to delay in the starting of therapies in the disease progression, ineffective drug doses, incorrect target of the treatment, and most importantly an incomplete understanding of the pathophysiology of memory loss, as well as the progression of neuro-degeneration.

It is the need of the hour to identify the underlying cause of the disease and to develop alternative approaches targeting multiple pathways of dementia and AD. Herbal drugs could be used as an alternative medicine for the treatment of neurodegenerative disorders and could also help in alleviating the sufferings of the patients. Herbal





**Figure 2** Chemical structure of bioactive molecules with potential anti-dementia activity.

drugs are less toxic as compared to their synthetic counterparts, bioavailable, have multiple synergistic effects and enhance cognition. However, the variable constituents in medicinal plants and variable preparations based on genetic, cultural and environmental factors are the biggest impediment in the amalgamation of herbal medicines into modern medicines.

To ensure efficient and ethical care in dementia, psychoeducation, advanced planning for future care needs as well as appropriate pharmaceutical treatment along with environmental and behavioral techniques are instrumental. Several studies are ongoing in full swing for assessment of the benefits of an Alzheimer's vaccine (having component of an antigenic amyloid protein, amyloid enzyme inhibitors and nerve growth factor therapies). These approaches may prove to be promising, however, extensive research needs to be done. It becomes imperative to develop a standardized approach for treating patients individually with the help of detailed research which should focus on identifying the active ingredients of plants and investigating their mechanism of action.

## Conclusions

Herein, we reviewed the most medicinal plants which are being used in various traditional systems of medicine, and explain the related mechanisms and effects against dementia. All these collective evidences gathered from clinical trials and animal studies support the treasured value of medicinal plants as an alternative strategy for the prevention or treatment of dementia. Herbal plants and phytoactive compounds are superior in terms of safety when compared with synthetic drugs such as donepezil, and considered as promising alternative strategies for improving memory deficits. Animal models of dementia are not sufficient to understand the plausible explanation of these herbal candidates, thus further clinical studies with a larger sample size are required for developing evidence-based medicines for the treatment of dementia and AD.

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