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Review Article

# Traditional Chinese medicines and Alzheimer's disease

Tzong Yuan Wu [a,b,c], Chih Ping Chen [d,e,f,g,h,i], Tzyy-Rong Jinn [g,*]

[a] Department of Bioscience Technology, Chung Yuan Christian University, Chung Li, Taiwan
[b] Center for Nanotechnology, Chung Yuan Christian University, Chung Li, Taiwan
[c] R&D Center of Membrane Technology, Chung Yuan Christian University, Chung Li, Taiwan
[d] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
[e] Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan
[f] Department of Biotechnology, Asia University, Taichung, Taiwan
[g] School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[h] Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
[i] Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan

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## Abstract

Traditional Chinese medicines have been widely investigated for the treatment of Alzheimer's disease (AD) because none of the current therapies—either the cholinesterase inhibitors or antagonist of *N*-methyl-D-aspartate receptors—has profound effects on halting the progression of AD. In recent years, scientists have isolated many active compounds from herbs, which can alleviate dementia and neurodegenerative syndrome with fewer side effects than conventional drugs and, thus, are regarded as promising drug candidates for AD therapy. In this review, we summarize the latest research progress on six herbs for AD therapy—*Huperzia serrata*, Amaryllidaceae family, *Ginkgo biloba*, *Uncaria rhynchophylla*, *Polygala tenuifolia*, and *Salvia officinalis*—and focus on the analysis of their active components and possible mechanisms of pharmacological actions on AD.


*Keywords:* Alzheimer's disease; Acetylcholinesterase; Cognitive impairment; Dementia; Neuroprotection; Traditional Chinese medicine

## Introduction

With the rapid increase in the aged population in recent years, senile dementia has become one of the world's important public health issues. Alzheimer's disease (AD) is the most common type of senile dementia, a neurodegenerative disease characterized by progressive memory loss and cognitive impairment in the elderly [1]. Pathological characterization of AD includes extracellular deposition of senile plaques; formation of intracellular neurofibrillary tangles; and lesions of cholinergic neurons together with synaptic alterations in cerebral cortex, hippocampus, and other brain regions [2]. At present, it is well accepted that multiple factors involved in the progress of AD are apoptosis, oxidative stress, mitochondrial dysfunction, inflammatory responses, and disturbance of energy metabolism homeostasis. However, the severe loss of function of the cholinergic neurons correlating with dementia in AD is still not clearly understood [3]. Current clinical drugs administered to slow down the progress of the deterioration in AD patients include cholinesterase inhibitors and agonists of *N*-methyl-D-aspartate receptors (NMDA) [4], but none of these therapies has profound effects on halting the advancement of AD. As a consequence, it is very important to identify novel and pharmacotherapeutic drugs for AD.

Traditional Chinese medicine (TCM) is practiced in the Chinese health care system for more than 2,000 years. Many active pharmacological compounds from Chinese herbal medicines have been identified for the treatment of various diseases, including diabetes, microbial infections, allergy,

* Corresponding author. Graduate Institute of Chinese Medical Science, China Medical University, Taichung, Taiwan.
*E-mail address:* jinn@mail.cmu.edu.tw (T.-R. Jinn).

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inflammation, and cancer. In addition, many Chinese herbs have been claimed to enhance human health by stimulating blood circulation and by supplementing vital energy. Thus, Chinese herbs provide a good source of drugs for screening that may be beneficial for AD patients. In recent years, scientists have isolated many novel compounds from herbs, some of which improve dementia with fewer side effects than conventional drugs and are regarded as promising anti-AD drugs. In this review, we summarize the latest research progress on Chinese herbal medicines showing their possible pharmacological actions in alleviating dementia and AD.

## *Huperzia serrata* (Qian Ceng Ta)

*Huperzia serrata* has been traditionally used to relieve pain and as an antidote for poisoning as well as for the treatment of contusions, strains, swelling, and schizophrenia. It has been found that active compounds—the *Lycopodium* alkaloids—from *H. serrata* include huperzine A (Hup A, Fig. 1); huperzine B (Hup B); *N*-methyl-Hup B; huperzinine; carinatumin A; and carinatumine B [5], and among these, Hup A is considered the most potent acetylcholinesterase (AchE) inhibitor. Hup A had been approved by the Food and Drug Administration to treat AD in the 1990s. Compared with other approved drugs, such as tacrine, donepezil, galanthamine, and rivastigmine, Hup A not only exhibits the most powerful activity as an anti-AchE agent, it also acts better in penetrating the blood–brain barrier. Besides, it also shows higher oral bioavailability and has longer duration of anti-AchE activity [6]. More interestingly, Hup A is also found to be an effective cognition enhancer. It has been demonstrated that Hup A exerts multiple neuroprotective effects, in which the mechanisms may involve the activation of both muscarinic and nicotinic acetylcholine receptors; enhancement of the production of neurotrophic factors; as well as blocking of overstimulated NMDA receptors. It has also been known to regulate the activity of antioxidative enzymes, to attenuate mitochondrial dysfunction, and to scavenge reactive oxygen species [7]. Therefore, Hup A is effective in improving cognitive impairments in multi-infarct dementia, brain trauma, schizophrenia, and benign senescent forgetfulness [6]. These neuroprotective effects may be the result of the upregulation of c-jun and bax as well as the downregulation of bcl-2 [8,9]; the upregulation of nerve growth factor secretion and its downstream signaling; the inhibition of oxidative stress; and the improvement in energy metabolism [10]. More importantly, Hup A can modulate the processing of amyloid precursor protein (APP) by the regulation of protein kinase C [11] and the promotion of the nonamyloidogenic pathway of APP metabolism and reduction in the production of Aβ amyloid. Clinical studies have demonstrated that Hup A can significantly improve the memory of elderly people and AD patients without any notable side effects [12]. In summary, all the advantageous effects of Hup A may be attributed to its potent, reversible, and selective inhibition of AchE [13,14]. Its potency in AchE inhibition is adequate to treat AD and other relevant cognitive impairments.

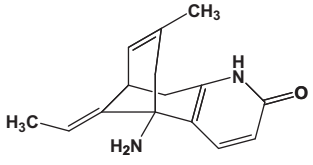


Fig. 1. The chemical structure of huperzine A isolate from the club moss *Huperzia Serrata*, known as Qian Ceng Ta. The club moss is usually found in deep-shaded forests. Traditional Chinese medicine has used this plant in tea for centuries to heal a variety of illnesses, including seizures, brain swelling, fevers, and inflammation.

## Amaryllidaceae family

Plants belonging to the Amaryllidaceae family have been traditionally used in China for the treatment of poisonous snakebites, acute laryngeal infection, rheumatoid arthritis, paralysis, and muscle diseases brought about by infantile paralytic sequela [15]. One of the well-studied alkaloids from Amaryllidaceae is galanthamine (Fig. 2), which is a tertiary alkaloid originally extracted from the bulbs of *Galanthus woronowii*. Galanthamine was also isolated from other herbs of the Amaryllidaceae family, such as *Lycoris radiate*, *Lycoris aruea*, and *Lycoris squamigeric* [16]. It acts as a selective, reversible, and competitive inhibitor of AchE. Previous studies have indicated that galanthamine may potentiate memory deficits [16,17]. Furthermore, the compound has the ability to selectively stimulate or/and modulate neuronal nicotinic acetylcholine receptor, which could facilitate an increase in the synthesis of neurotrophic factors and protect neuronal cells against hazardous effects of oxidative stress and injury [18,19]. Moreover, the combination of galanthamine and nicotine works synergistically in inhibiting microglia activation [20]. A clinical trial has confirmed the efficacy and safety of galanthamine in the treatment of AD [21]. Thus, the use of galanthamine for the treatment of mild to moderate AD has been approved by the State Food and Drug Administration in China and the Food and Drug Administration in the United States. Generally, galanthamine is a natural product with multiple molecular targets as it acts in the regulation of cholinergic transmission and in easing oxidative stress [22];

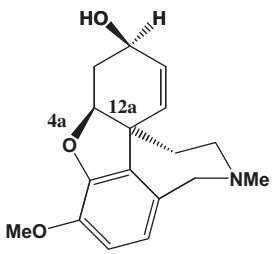


Fig. 2. The chemical structure of galanthamine extract from the bulbs of *Galanthus woronowii*, plants of the Amaryllidaceae family, which have been customarily used in Traditional Chinese medicine for the treatment of poisonous snakebites, acute laryngeal infection, rheumatoid arthritis, paralysis, and muscle diseases brought on by infantile paralytic sequela.

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potentiates the NMDA response [23–25]; and upregulates the antiapoptotic protein expression [26–28].

### *Ginkgo biloba*

*Ginkgo biloba* L. has customarily been used in China as a medicine to promote vitality in humans. It is well known that many active components exist in *G. biloba* L.; a few of them are ginkgolides, bilobalide, ginkgolic acids, and ginkgo flavone glycoside (Fig. 3) [29]. It is noteworthy to cite that the leaf extract of *G. biloba* (EGb), labeled EGb761, possesses the capacity to treat a variety of neurological disorders, including AD and age-related dementia [30]. EGb761 is a mixture of flavonoids, terpenes, and organic acids. It was reported that the antioxidant activity of EGb761 may play a substantial role in neuroprotection by decreasing bax/bcl-2 ratios [31], reversal of ischemia-induced reductions of cycloxygenase III mRNA in hippocampal CA1 neurons, inhibition of nitric oxide synthesis, scavenging of free radicals, and attenuation of lipid peroxidation [32,33]. Consistent with the aforementioned findings, many experimental evidences have demonstrated that EGb761 has many pharmacological effects, including amelioration of mitochondrial dysfunction, blockade of the NMDA receptor, scavenging of free radicals, lowering of oxidative stress, reduction of neural damages, reduction of platelet aggregation, anti-inflammation, and anti-aging [34,35].

### *Uncaria rhynchophylla*

*Uncaria rhynchophylla* Havil is a medicinal plant that has been used to alleviate neuropsychiatric symptoms, such as headache, dizziness, vertigo, and tinnitus. The extracts of this herb contains several different compounds, such as corynoxeine, rhynchophylline, isorhynchophylline, isocorynoxeine, geissoschizine methyl ether, hirsuteine, and hirsutine. Some of these mentioned alkaloids have been regarded as neuroprotective compounds [37]. Because one of the etiologies of AD is progressive deposition of insoluble highly neurotoxic Aβ proteins in the form of senile plaques in the central nervous system [38], attractive therapeutic strategies for the treatment of AD would be the following: inhibition of Aβ generation, prevention of Aβ fibril formation, or destabilization of preformed Aβ fibrils. It was reported that the extracts from *U. rhynchophylla* have significant inhibitory and destabilizing effects on Aβ fibril than other Chinese medical herbs [39]. Hence, *U. rhynchophylla* could have the potential to be a novel therapeutic agent for AD prevention in the future.

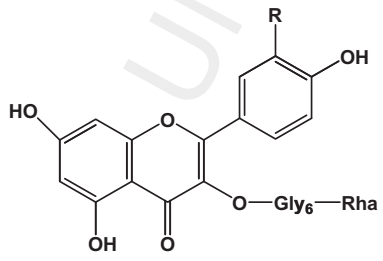


Fig. 3. The chemical structure of ginkgo flavone glycoside, including kaempferol, quercetin (rutin), and isorhamnetin, extracts from *Ginkgo biloba* L. *Ginkgo biloba* L. has long been used in China as a traditional medicine to promote the vital energy of humans. R=O: kaempferol-3-*O*-rutinoside; R=OH: quercetin-3-*O*-*O*-rutinoside (rutin); R=$OCH_3$: isorhamnetin-3-*O*-rutinoside.

### *Polygala tenuifolia*

Herbal medicines have long been used for improving cognitive functions and for the treatment of memory loss. Of these, *P. tenuifolia* Willdenow is one of the most frequently used medicinal herbs for memory loss in TCM. In addition, *P. tenuifolia* has been known to have therapeutic effects, such as expectorant, sedative, antipsychotic, and anti-inflammatory [40]. The polygalasaponins in the dried root of *P. tenuifolia* plant can inhibit cAMP activity [41]. In addition to this, it was accounted that an effective compound from the dried root of *P. tenuifolia*, tenuifolin, could inhibit AchE activity or could enhance cholinergic neurotransmission [42]. It had also been reported that tenuifolin could penetrate the blood–brain barrier and improve cognitive impairment through elevation of the cholinergic system by blocking acetylcholine hydrolysis [42]. Moreover, a decrease in the secretion of $A\beta_{1-40}$ and $A\beta_{1-42}$ by tenuifolin was also reported [43]. These important findings will facilitate the development of tenuifolin or its derivatives as pharmaceuticals in the treatment and management of AD.

### *Salvia officinalis*

*Salvia officinalis* L. is a multifunctional Chinese medicine herb. It has a longstanding application as an antibiotic, antihydrotic, astringent, and antifungal agent. The plant, *S. officinalis*, is well known for its antioxidative properties [44] for the reason that its leaf extract has its main constituent, ursolic acid (Fig. 4), a pentacyclic triterpenoid carboxylic acid, which can effectively reduce the level of lipid peroxidation and efficiently reverse D-galactose-induced learning and memory impairment [45]. Because oxidative stress is linked with damage and progressive cell death occurring in neurodegenerative disorders, such as Parkinson's disease and AD [46], a recent clinical trial had demonstrated that the extracts of *S. officinalis* are effective in treating mild to moderate AD [47]. Moreover, ursolic acid also efficaciously inhibits AchE activity *in vitro* [48]. These results implied that the extracts of *S. officinalis* can be beneficial to AD patients through

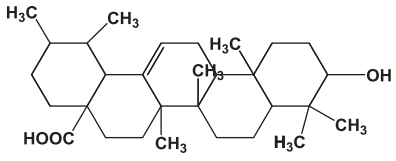


Fig. 4. The chemical structure of ursolic acid, a pentacyclic triterpenoid carboxylic acid, which can effectively reduce the level of lipid peroxidation and efficiently reverse D-galactose-induced learning and memory impairment.



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protection of neurons by reducing oxidative stress and boosting memory through inhibitions of AchE activity. Likewise, rosmarinic acid, a phenolic derivative of caffeic acid, is also found in water extracts of *S officinalis*, which exhibits a dose-dependent stalling of the Aβ fibril formation from $A\beta_{1-40}$ and $A\beta_{1-42}$ as well as Aβ fibril aggregation, and it can also destabilize the integrity of Aβ fibrils [49,50]. Thus, the *S officinalis* L. extract could be a promising drug candidate for dementia and AD therapy.

## Conclusion

The treatment of AD remains a challenge in the modern day medicine because of the incomplete understanding of its pathogenesis, and still, none of the current therapeutic modalities can successfully halt the progression of AD at an early stage. Thus, perpetual extensive studies to search for new active extracts or components derived from various plants for the treatment of AD are carried out. Indeed, some active extracts or components from herbs are highly potent and multitargeted with low toxicity for the treatment of AD, although the underlying molecular mechanisms have not been fully elucidated. These herbs are regarded as new and promising sources of potential anti-AD drugs. Generally, these encouraging preclinical and clinical trials suggest that TCM is a promising candidate for the treatment of neurodegenerative diseases, such as dementia and AD. This "conventional" TCM also provides a new direction in drug development to obtain advanced therapeutic agents that possess both high efficacy and safety for the treatment of AD other than the conventional "western" medicine. Interestingly, recent studies have implicated memantine, an analog of amantadine, which can inhibit the internal ribosome entry site (IRES) of piconavirus-mediated translation [51] and can also prevent the expression of APP and tau through the inhibition of a translation initiation mechanism that is mediated by the IRES [52,53]. The IRES of tau and APP could be new targets to screen the TCM that can act as potential therapeutic drugs for AD.

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