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Review

Retrospect and prospect of active principles from Chinese herbs in the treatment of dementia

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Abstract

With an ageing population, dementia has become one of the world's primary health challenges. However, existing remedies offer limited benefits with certain side effects, which has prompted researchers to seek complementary and alternative therapies. China has long been known for abundant usage of various herbs. Some of these herbal decoctions are effective in stimulating blood circulation, supplementing vital energy and resisting aging, the lack of which are believed to underlie dementia. These herbs are regarded as new and promising sources of potential anti-dementia drugs. With the rapid evolution of life science and technology, numerous active components have been identified that are highly potent and multi-targeted with low toxicity, and therefore meet the requirements for dementia therapy. This review updates the research progress of Chinese herbs in the treatment of dementia, focusing on their effective principles.

Keywords: dementia; traditional Chinese medicine (TCM); active principle; neuroprotection

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Introduction

Dementia, mainly characterized by learning and memory loss, mood changes and communication problems, has been increasingly recognized as an important component of the disease spectrum in most neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). Dementia has drawn extensive attention due to its high prevalence in older people, underscored in a rapidly ageing world population.

Currently, there are no effective neurotherapeutic interventions. The widely used anti-dementia strategies are those claimed to be effective in treating AD, the most commonly encountered type of dementia. Effective drugs approved by the Food and Drug Administration of the United States include donepezil, galanthamine, rivastigmine and memantine, which have modest effects in modifying the symptoms of AD for a relatively short period of time in subsets of patients. But none of these therapies has any effect on halting the progression of AD. This inadequate effect could be due to the complicated pathological changes encountered with dementia, which include oxidative damages, mitochondrial dysfunction, inflammatory responses and apoptosis, although the underlying molecular mechanisms have not been fully elucidated. As a consequence it is very important to further investigate novel, multi-targeted and low toxicity anti-dementia drugs.

China, with an area of 9 600 000 km^2, is renowned for its abundant categories of plants. Persistent attempts and practices made in disease prevention, diagnosis and treatment have allowed the formation of an integrated theoretical system of Chinese medicine. Many herbal decoctions have claimed, in the Chinese literature (such as *A Chinese Bestiary*, *The Medical Classic of the Yellow Emperor and Compendium of Materia Medica*), to be effective for specific symptoms through stimulating blood circulation, nourishing Yin, supplementing vital energy and suppressing excess Yang. Such abundant natural resources could provide additional natural compounds for treating neurodegenerative disorders including AD. It is estimated that 25% of modern drugs directly or indirectly originated from plants. Yet most active principles from plants are not known. In recent years, scientists have isolated many novel compounds from herbs, some of which alleviate dementia with fewer side effects than conventional drugs and thus are regarded as promising anti-dementia drugs.

The current review summarizes the latest research progress on Chinese herbal medicines that show benefical effects in dementia therapy with a particular focus on active extracts

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from Chinese herbs and their possible pharmacological mechanisms.

Chinese herbs and active principles in the treatment of AD

Huperzia serrata (Thunb) Trev

Huperzia serrata (Thunb) Trev (Qian Ceng Ta) is mainly distributed in northeastern, southern and southwestern China along the Changjiang River zone. It has been traditionally used to relieve pain and as an antidote for poison, as well as for the alleviation of swelling. In the 1970s, schizophrenic patients using the extract from this herb showed signs of cholinergic stimulation, such as dizziness, nausea and vomiting, suggesting that this herb might be effective for treating cholinergic dysfunction. On the basis of the above clinical findings, novel *Lycopodium* alkaloids were isolated from *Huperzia serrata* (Thunb) Trev, which included (–)-huperzine A (Hup A), (–)-huperzine B (Hup B), *N*-methyl-Hup B, huperzinine, carinatumin A and carinatumine B. All of the aforementioned *Lycopodium* alkaloids possess anti-acetylcholinesterase (AChE) acitivity[1] (Figure 1).

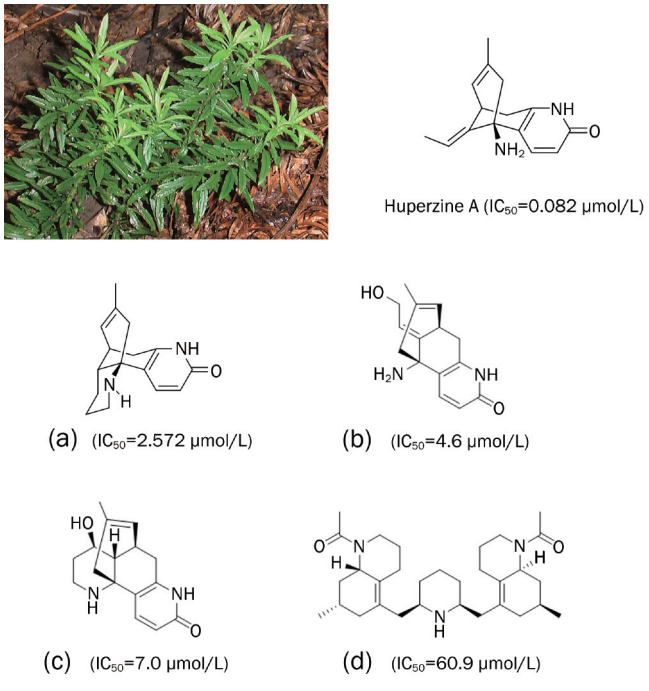

Figure 1. *Huperzia serrata* (Thunb) Trev and the representative active principles with anti-AChE activity. (a) Huperzine B; (b) Carinatumin A; (c) Carinatumin B; (d) Lycoperine A.

Hup A is the most potent acetylcholinesterase inhibitor (AChEI) among the aforementioned active principles isolated from *Huperzia serrata* (Thunb) Trev. Hup A was shown to be effective in the treatment of myasthenia gravis in previous studies[1, 2]. In the 1990s, Hup A was approved by the State Food and Drug Administration (SFDA) to treat AD. Compared with the US FDA approved AChEIs such as tacrine, donepezil, galanthamine and rivastigmine, Hup A shows the most potent AChE inhibition activity *in vivo*, better penetration through the blood–brain barrier (BBB), higher oral bioavailability, and a longer duration of anti-AChE action[3].

Hup A is an effective cognition enhancer in a number of different AD/vascular dementia (VaD) animal models and patients[3]. Hup A administration enhances learning and memory in intact adult rodents, aged rodents and monkeys, as well as in rodents cognitively impaired by ischemia, scopolamine, AF64A, cycloheximide, D-galactose (D-gal), *etc*[3]. Moreover, in randomized, double-blind, placebo-controlled clinical trials, Hup A significantly improved cognitive functions [measured with the Mini-mental State Examination Scale (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)], non-cognitive functions (measured with mood and behavior-ADAS-non-Cog) and activity in daily living [measured with Activity of Daily Living Scale (ADL)][3–5]. In addition, Hup A is also effective in ameliorating neurocognitive impairments in multi-infarct dementia (MID), brain trauma, schizophrenia, and benign senescent forgetfulness (BSF)[3]. However, the precise mechanisms involved in the beneficial effects of Hup A remain unclear. Hup A exerts multiple neuroprotective effects in addition to its anti-AChE activity. Other underlying mechanisms may involve the activation of muscarinic acetylcholine receptor (mAChR)/nicotinic acetylcholine receptor (nAChR), a reduction of inflammation/apoptosis-related gene/protein expression, scavenging of reactive oxygen species (ROS)/regulating activities of antioxidative enzymes, attenuation of mitochondrial dysfunction, blocking over-stimulated N-methyl-D-aspartate acid (NMDA) receptors as well as promoting the production of neurotrophic factors[6]. These neuroprotective effects of Hup A appear to be independent of AChE inhibition. (+)-Hup A and (–)-Hup A showed similar potency towards NMDA receptors and in Aβ-induced cytotoxicity but (+)-Hup A is 50-fold less potent than (–)-Hup A in the activity of AChE inhibition *in vivo*. In the latest research, Hup A protects isolated mitochondria against Aβ-induced mitochondrial swelling, ROS and cytochrome *c* release[7], further extending the noncholinergic activitiy of Hup A. The most recent data from a clinical trial in China demonstrated that Hup A affords significant improvement in the memory of elderly people and patients with AD and VaD without noticeable side effects[8]. Moreover, a Phase II clinical trial completed in the US found dose-related improvements after Hup A administration with higher MMSE scores at higher doses and no serious side effects[4].

Hup B is another notable active principle from *Huperzia serrata* (Thunb) Trev. It is also a potent, reversible AChEI exhibiting more selective inhibition on AChE activity than galanthamine *in vitro*[9–11]. *In vivo* studies suggest improved memory retention and retrieval in both adult and aged mice treated with Hup B. The compound also reverses the disruption of memory retention induced by scopolamine, $NaNO_2$, electroconvulsive shock and cycloheximide in mice while less peripheral side effects were detected compared with galanthamine and physostigmine[11]. The antioxidant activity of

the compound may partially contribute to its neuroprotective effect[12]. Hup B also exhibits an antagonist effect on NMDA receptors in addition to its inhibitory effect on AChE[13]. Some derivatives of Hup B are potent multifunctional cholinesterase inhibitors[14]. Further clinical investigations will be required to determine the effect of Hup B on dementia.

Amaryllidaceae family

Plants of the *Amaryllidaceae* family are largely distributed in China, especially in Yunnan province. The plants have been traditionally used in China for the treatment of poisonous snake bites, acute laryngeal infection, rheumatoid arthritis, paralysis and muscle diseases brought on by infantile paralytic sequela[15]. One of the widely studied alkaloids from *Amaryllidaceae* is galanthamine, which is a tertiary alkaloid originally extracted in 1952 by a Russian scientist from the bulbs of *Galanthus woronowii*, a plant of the *Amaryllidaceae* family (Figure 2A). Since 1960, researchers in China have been isolating this compound from *Lycoris squamigera maxim*. Later, it was also isolated from many other plants of the *Amaryllidaceae* family, such as *L radiata Herb*, *L aruea Herb*, and *L squamigeric Herb*.

Considerable studies indicate that galantamine may potentiate the central cholinergic system and improve memory deficits[16, 17]. However, because the natural content of the compound in plants is low and the extraction procedure is expensive, synthetic sources are currently under development[18]. Galanthamine is a selective, reversible and competitive inhibitor of AChE; less potent than Hup A and donepezil but more potent than rivastigmine[3]. In addition, the compound is recognized as an allosteric modulator of nAChRs. Selective stimulation or modulation of nAChR subtypes improves learning and memory. Such an agonist for nAChRs could increase the synthesis of neurotrophic factors and protect neuronal cells against toxic effects of glutamate, trophic factor deprivation, hypoxia, Aβ and ischemic injury[19, 20]. Moreover, the combination of galanthamine and nicotine has a synergistic effect on the inhibition of microglia activation[21]. In addition to its actions in the regulation of cholinergic transmission, galanthamine alleviates oxidative stress[22], potentiates the NMDA response[23–25] and up-regulates anti-apoptotic protein expression[26–28]. In summary, galanthamine is a natural product with multiple molecular targets. However, the precise mechanism of its action needs further investigation.

The co-administration of galanthamine and piracetam is more effective in alleviating scopolamine-induced memory deficiency compared to treatment with either of these compounds alone, as demonstrated by our previous studies on rats subject to passive avoidance and radial maze training (unpublished data). The use of galanthamine for the treatment of mild to moderate AD has been approved by the SFDA in China and the FDA in the US. A Phase III clinical trial has been completed and has confirmed the efficacy and safety of galanthamine in the treatment of AD (http://clinicaltrials.gov/ct2/show/NCT00338117). A recent investigation indicated that the compound may also improve the cognition of patients with severe AD but it failed to improve the co-primary parameter of overall activities of daily living[29]. Patients with AD combined with cerebral vascular disease (CVD) experienced significant cognitive and functional improvement when treated with galanthamine for six months. Collectively, these findings support the effectiveness of this compound in slowing the progression of dementia.

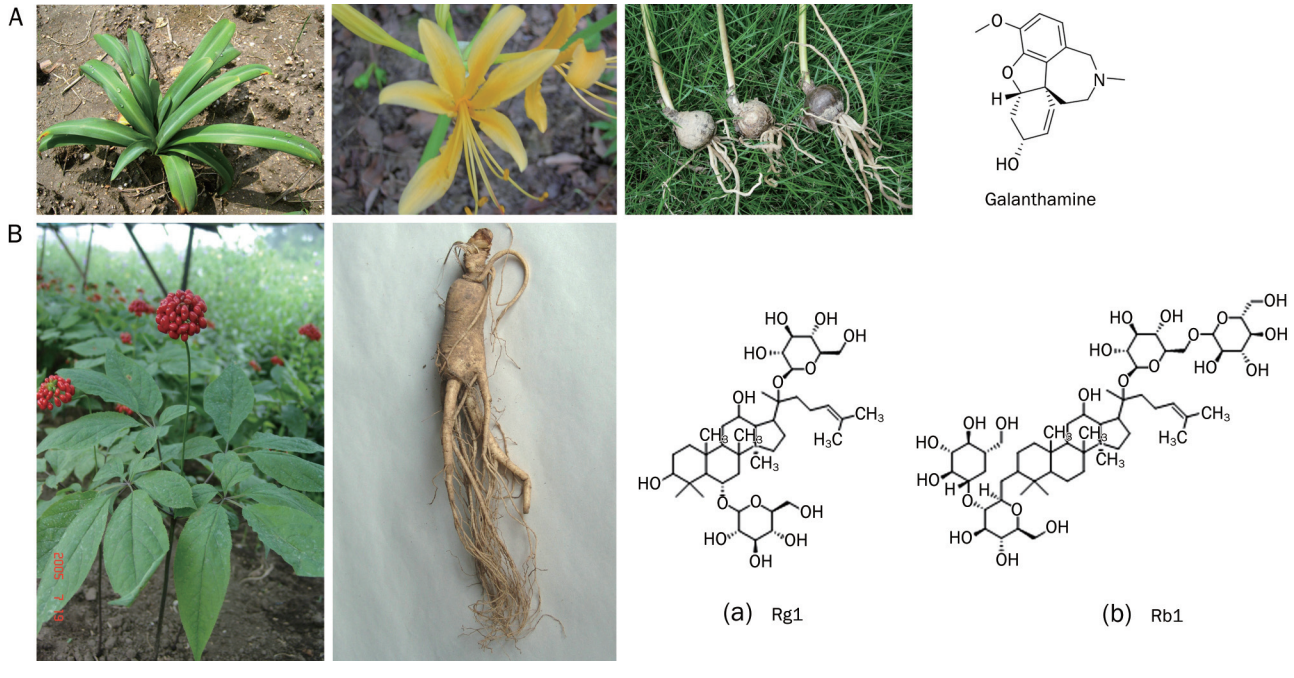

Figure 2. *Amaryllidaceae* and its extract galanthamine (Panel A); *Panax ginseng* CA Meyer and its saponins: (a) Rg1; (b) Rb1 (Panel B).

Panax ginseng CA Meyer

Panax ginseng CA Meyer, one of the most commonly used and highly researched species of ginseng, is largely distributed in northeast China. It has been used in Chinese traditional medicine for over 2000 years as a tonic remedy for weakness, fatigue and ageing. The main active components of *Panax ginseng* CA Meyer are ginsenosides, which are triterpene saponins enriched in the stalks and leaves of the herb. Among the ginsenosides, Rb1 and Rg1 are regarded as the main compounds responsible for many of the pharmacological actions of ginseng (Figure 2B). Today, extraction, purification and analyzation procedures are optimized for large-scale production of ginsenosides[30] .

Rg1 improves learning and memory in normal, aged animals and in various model animals with impaired memory induced by anisodine, cycloheximide, alcohol, Aβ, scopolamine and ischemia[31]. Besides the significant enhancement of cholinergic function through an increase in acetylcholine (ACh) level and density of muscarinic receptors[31], the mechanism of the protective effect of Rg1 involves blockade of the inflammation cascade[32], calcium channels and cerebral nerve cell apoptosis, and regulation of neurite lengths and numbers of dopaminergic cell cultures[33], nitric oxide and its synthase, together with effects on antiperoxidation, estrogen-like action, as well as the amelioration of mitochondrial dysfunction.

Similar to Rg1, Rb1 may also improve learning and memory. The possible mechanisms could involve an enhancement of cholinergic metabolism, an increase in hippocampal synaptic density, and the maintanence of intracellular calcium homeostasis and microtubule integrity[34–36]. However, Rb1 has significant effects on both repeated and chronic stress-related changes, while Rg1 does not appear to possess an anti-stress property. Moreover, Rb1 has no effect on the decline of immune function in aged rats, which is an additional difference between Rg1 and Rb1[31]. Taken together, these studies suggest that Rb1 may rescue or protect neurons from insult and may be a potential candidate to improve the cognitive deficit of AD.

Clinical trials in China report that ginseng tonic decoction significantly improves MMSE and reduces clock drawing (CD) scores in AD patients[37]. Phase II clinical trials in China found another ginsenoside, Rd, to be of some benefit in acute ischemic stroke[38]. All the above suggest *Panax ginseng*s CA Meyer will be a promising source of principles for the treatment of dementia.

With the application of modern scientific technology, new ginsenosides such as Rg3, Rh1, Rh2, Rb3, and Re have been isolated and purified[30, 39, 40]. Many of these compounds possess bioactive effects against dementia. For example, Rg1's primary metabolite ginsenoside, Rh1, exihibted more potent actions than Rg1 in improving memory and hippocampal excitability[41]. However, more investigations are needed to determine the efficacy of these novel active principles in the therapy for dementia.

Ginkgo biloba Linn

Ginkgo biloba Linn, more than 200 million years old, is one of the best-known examples of a living fossil. It requires acidic soil with proper drainage and full sunlight at planting site. For centuries it was thought to be extinct in the wild, but it is now known to be distributed mainly in the Jiangsu, Hubei, Shandong, and Zhejiang provinces in China due to the pleasant natural conditions in those provinces. The most famous distribution district of *Ginkgo biloba* Linn might be the Tian Mu Shan Reserve in Zhejiang province, well-known for its scenic beauty and the diversity of its flora. *Ginkgo biloba* Linn extracts have long been used in China as traditional medicine for various health disorders. EGb761, the standardized extract of its leaves, contains 24% flavonoids and 6% terpene lactones[42, 43]. A mixture of many active components including ginkgolides, bilobalide, ginkgolic acids, as well as KYNA and 6-HKA (Figure 3A) may account for its various pharmacological effects, such as the alleviation of VaD, early-stage AD, peripheral claudication and tinnitus of vascular origin[44–47]. Extraction of active principles from *Ginkgo biloba* Linn has been studied for a long time in China and high production levels and purity have been achieved[48–51].

Ginkgo biloba Linn leaf preparations were marketed in France and Germany 30 years ago for the treatment of cardiovascular disease, cerebrovascular diseases and dementia. They are now classified as a food supplement in the United States and widely used in China to alleviate dementia. The protective effects of EGb761 were shown in *in vitro* injury models induced by hypoxia, hydrogen peroxide, glutamate, verapamil, Aβ and nitric oxide (NO)[52], as well as in an *in vivo* model induced by ischemia[53, 54]. The purported biological effects of EGb761 include amelioration of mitochondrial dysfunction[55], blockade of the NMDA receptor[56, 57], scavenging of free radicals, lowering of oxidative stress, reduction of neural damages, reduction of platelet aggregation, anti-inflammation[58] and anti-aging[59]. Clinically, EGb761 has been prescribed to treat central nervous system (CNS) disorders such as AD and cognitive deficits, which may be attributed to the aforementioned effects. EGb761 treatment is beneficial in patients with mild to moderate dementia compared with placebo treatment[60]. Also, several studies confirmed the equal efficacy and tolerability of EGb761 in comparison to commonly prescribed AChEIs[61, 62]. However, analytical results derived from several recent clinical trials found the predictable and clinically significant beneficial effects of *Ginkgo biloba* extracts to be inconsistent and unreliable in people with dementia or cognitive impairment[47, 63]. Further studies are needed to better understand this herbal extract.

Salvia officinalis Linn

Salvia officinalis Linn (sage) (Figure 3B), native to the Mediterranean region, grows in the Zhejiang, Anhui, Jiangsu, Jiangxi, Hubei, Fujian, Guangdong, Guangxi, and Taiwan provinces of China. It has a long-standing application in medicinal herbalism as an antibiotic, antihydrotic, astringent and antifungal. The leaves of the plant are well known for their antioxidative

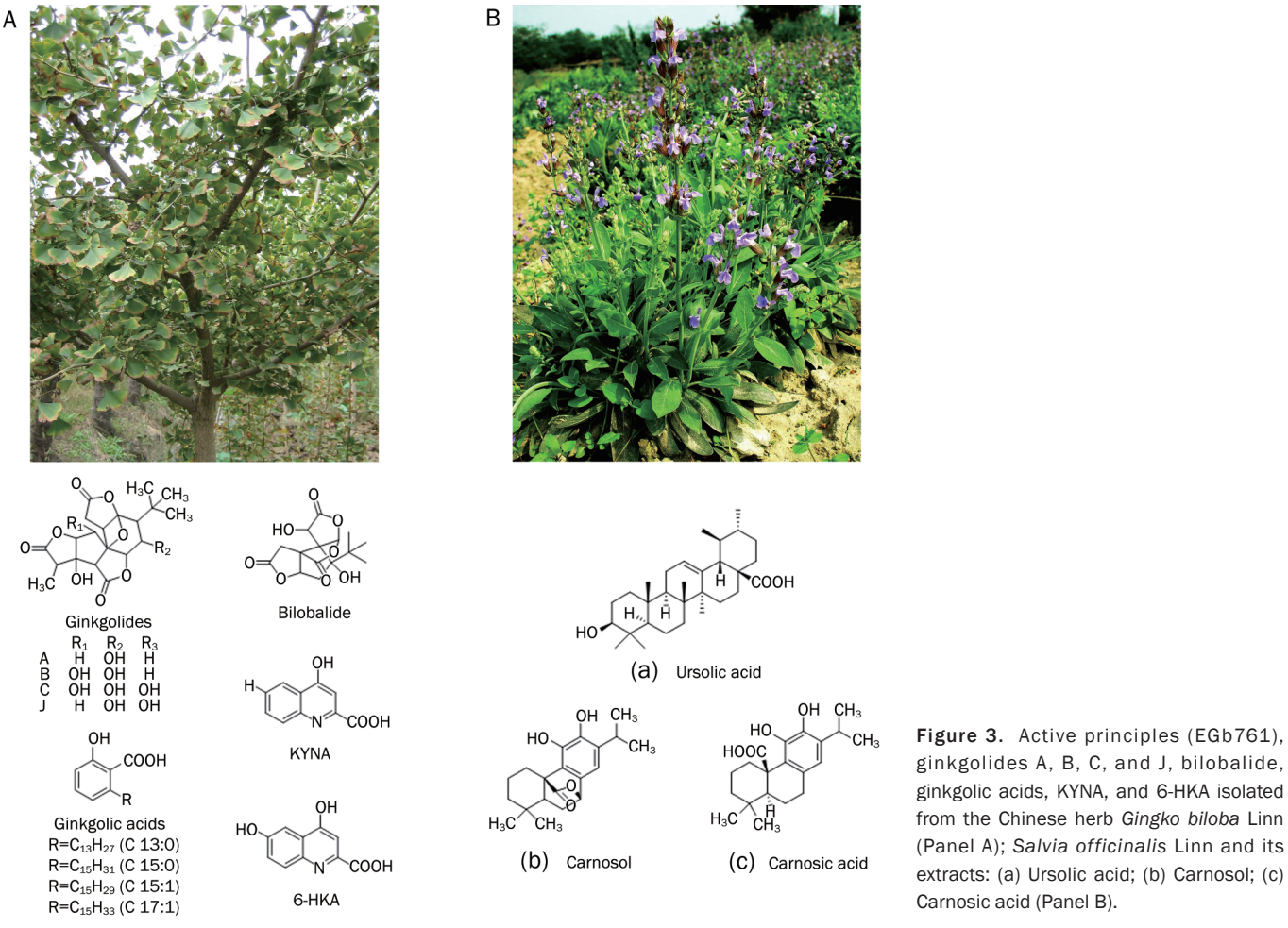

Figure 3. Active principles (EGb761), ginkgolides A, B, C, and J, bilobalide, ginkgolic acids, KYNA, and 6-HKA isolated from the Chinese herb *Gingko biloba* Linn (Panel A); *Salvia officinalis* Linn and its extracts: (a) Ursolic acid; (b) Carnosol; (c) Carnosic acid (Panel B).

properties[64]. A recent clinical trial showed that extracts of the plant are effective in treating mild to moderate AD[65]. Ursolic acid (UA), the main constituent in chloroform extracts, is a natural pentacyclic triterpenoid carboxylic acid, which could markedly reverse D-gal-induced learning and memory impairment. Increased activity of antioxidant defense enzymes together with a reduced level of lipid peroxidation were found to underlie the neuroprotective effect of UA[66]. UA is also the major component involved in anti-inflammatory activity of sage, which is two fold more potent than that of indomethacin, a reference non-steroidal anti-inflammatory drug (NSAID)[67]. Moreover, UA also effectively inhibits AChE actitivity *in vitro*[68]. Carnosol and carnosic acid, which are ethanol extracts from dried leaves of the plant, inhibit binding of t-butylbicyclophosphoro[^{35}S] thionate (TBPS) to the chloride channels of rat cerebrocortical membranes[69]. Ethanol extracts could also potentiate memory retention in rats, possibly through an interaction with the muscarinic and nicotinic cholinergic systems that are involved in the memory retention process[70]. Activation of PPAR-γ may underlie the anti-inflammatory effect of carnosol and carnosic acid[71–73]. Rosmarinic acid (RA), a naturally occurring hydroxylated compound, is present in water extracts of *Salvia officinalis* Linn. RA dose dependently inhibits the formation of Aβ fibrils from $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$, as well as their extension. In addition, RA dose dependently destabilizes preformed Aβ fibrils[74, 75]. The aforementioned activities of the *Salvia officinalis* Linn extracts predict the herb to be a promising drug for dementia.

Camellia sinensis (L) O Ktze

If there were a prize for achievement in liquid nutrition, it would have to go to green tea, which is popular among Chinese people and widely grown in China. Green tea is made from the dried leaves of *Camellia sinensis* (L) O Ktze. It is well known that green tea allows people to keep healthy, delay the onset of cardiovascular diseases, obesity and cancer, as well as slow down the process of ageing. Therefore, the effect of green tea in the prevention and alleviation of dementia has been of particular interest in recent years. As one of the oldest and healthiest beverages in the world, green tea enables people to think clearly and coherently, as indicated in a recent study on more than 1000 subjects carried out in Japan[76]. Human epidemiological and new animal data suggest that drinking green tea may decrease the incidence of dementia. The most active component of green tea involved in its therapeutic effects is (–)-epigallocatechin-3-gallate (EGCG) (Figure 4A), whose

antioxidant activity is significantly more potent than vitamin C, vitamin E, resveratrol and its counterparts (–)-epicatechin (EC), (–)-epigallocatechin (EGC) and (–)-epicatechin-3-gallate (ECG)[77–79].

EGCG exerts neuroprotective activities in a wide array of cellular and animal models of neurological disorders[80, 81]. The neuroprotective effect of EGCG could be achieved through complementary mechanisms involving the down-regulation of pro-apoptotic genes[82, 83], the influence of amyloid precursor protein (APP) processing by the elevation of α-secretase activity[84]/inhibition of β-secretase activity[85], the promotion of cell survival, defense against oxidative stress[86], anti-inflammation[87], the scavenging of ROS[88, 89] and iron chelating, as well as the stabilization of mitochondrial function[90]. The antioxidative activity of green tea has also been verified in human clinical trials[91].

Recently, numerous studies proved the beneficial effects of EGCG on learning and memory performance in various animal models, including the APP transgenic mouse model[92] and mouse models of cognitive impairment induced by Aβ[93], D-gal[94], and 3-NP[95]. The abovementioned data suggest that green tea, and in particular EGCG, could be a promising drug candidate for dementia.

Apium graveolens Linn

Apium graveolens Linn, a herb from Europe and temperate parts of Asia, is a species in the family of *Apiaceae*. It was believed in Chinese folklore that *Apium graveolens* Linn alleviates hypertension, vertigo, headache, redness of the face and eyes, swelling and pain. L-3-*n*-butylphthalide (L-NBP) (Figure 4B) is the active component of the essential oil extracted from the seeds of *Apium graveolens*[96].

L-NBP is a potential new agent for the treatment of neurodegenerative diseases through multiple targets. L-NBP treatment could significantly reverse Aβ-induced cytotoxicity, probably through an inhibition of tau protein hyperphosphorylation[97]. L-NBP significantly attenuates cerebral hypoperfusion-induced learning dysfunction and brain damage in rats[98]. Moreover, recent results indicate that long-term treatment with L-NBP may prevent age-associated cognitive dysfunction in rats[99]. In addition to the inhibition of β-amyloid cleaving enzyme (BACE) expression and tau hyperphosphorylation reported in the present research, increase in cerebral blood flow, enhancement of energy metabolism, improvement of mitochondrial function, inhibition of neuronal apoptosis and reduction of oxidative stress may be related to the neuroprotective effects of L-NBP. Therefore, the compound may emerge as a new drug candidate for the long-term treatment of dementia[99]. To this end, the compound has been recently approved for Phase I clinic trials by the SFDA.

DL-3-*n*-butylphthalide (DL-NBP) has been synthesized and shown to be effective in multiple ischemia models. The underlying mechanism may involve improvement of microvessel potency and increasing of newly developed microvessels[100, 101], enhancing the activity of antioxidative enzymes, improving mitochondrial function, inhibiting lipid peroxidation[102], blocking platelet aggregation[103], increasing regional cerebral blood flow[104], as well as reducing ischemia ipsilateral cortical calcineurin and calpain activities[105]. These would collectively result in an elevated survival rate of neurons and a smaller infarct volume of the brain, thus protecting rats from severe ischemic injury[106]. The compound was approved by the SFDA of China for clinical use in stroke patients in 2002.

Tripterygium wilfordii Hook F

Tripterygium wilfordii Hook F (Figure 4C), widely known as Lei Gong Teng in China, is mainly distributed in the Zhejiang, Fujian, Jiangxi, Hunan, Hubei, Guangdong, and Taiwan provinces of China. It has long been used for the treatment of rheumatoid arthritis due to its anti-inflammatory and immunosuppressive properties. With the progress of neuroimmunological research on neurodegenerative diseases such as AD and PD, the neuroprotective capabilities of *Tripterygium wilfordii* Hook F to rescue neurons from immunological injury are currently being explored.

The most abundant and active component is triptolide (Figure 4C), which was shown to be promising for the treatment of PD. Accumulating evidence has shown that triptolide can promote neuronal survival and neurite outgrowth, facilitate brain functional recovery through an inhibition of neuroinflammatory toxicity of activated microglia, reduce oxidative stress, stimulate the expression and release of nerve growth factor (NGF) and inhibit nuclear factor kappa B (NF-κB) activation[107]. An *in vivo* study demonstrated that triptolide significantly inhibited microglial activation, partially prevented dopaminergic cells from death and improved behavioral performances in MPP^+-induced hemiparkinsonian rats[108]. The beneficial activities of triptolide on dopaminergic neurons were further comfirmed in an inflammatory PD model by injection of LPS into the substantia nigra[109]. *In vivo* administration of the compound significantly attenuated the rotational behavior challenged by D-amphetamine in rats subject to transection of the medial forebrain bundle. Increased survival rate of dopaminergic neurons in the substantia nigra pars compacta (SNpc) area together with elevated levels of dopamine in the striatum were found in rats treated with tripchlorolide after axotomy[110].

Although research regarding the action of *Tripterygium wilfordii* Hook F extracts on CNS dysfunction were mainly carried out in PD models[111], the abovementioned neuroprotective effects predict that these extracts may be promising anti-dementia drugs, because neuronal death in AD models is related to the overwhelming inflammatory response.

Carthamus tinctorius Linn

Carthamus tinctorius Linn (safflower) (Figure 5A), originating in Egypt, is widely cultivated in the Henan, Hebei, Zhejiang, and Sichuan provinces of China. Safflower is an important crude drug in traditional Chinese medicine for promoting blood circulation, restoring menstrual flow and removing obstruction in the channels and collaterals. It has long been used in the prevention and treatment of cardiovascular dis-

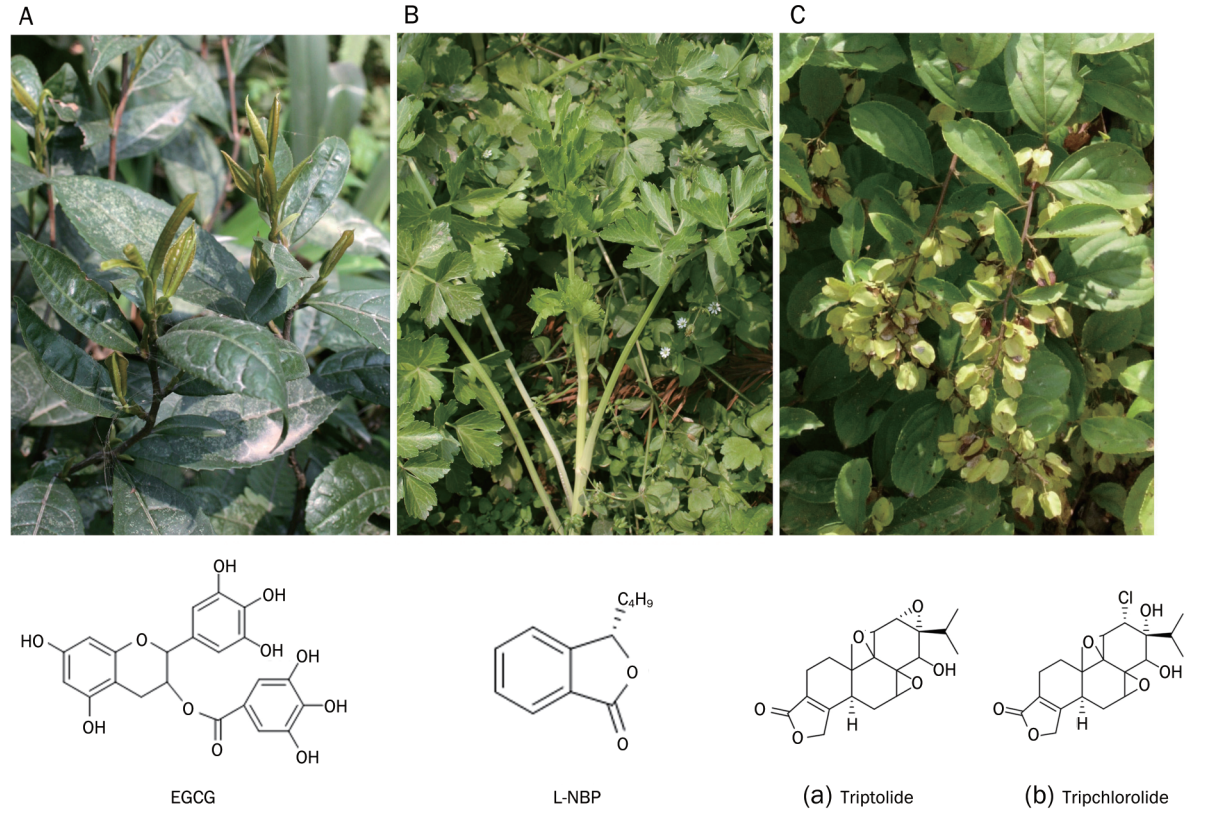

Figure 4. *Camellia sinensis* (L) O Ktze and its extract EGCG (Panel A); *Apium graveolens* Linn and its extract l-3-*n*-butylphthalide (Panel B); *Tripterygium wilfordii* Hook F and its extracts: (a) Triptolide; (b) Tripchlorolide (Panel C).

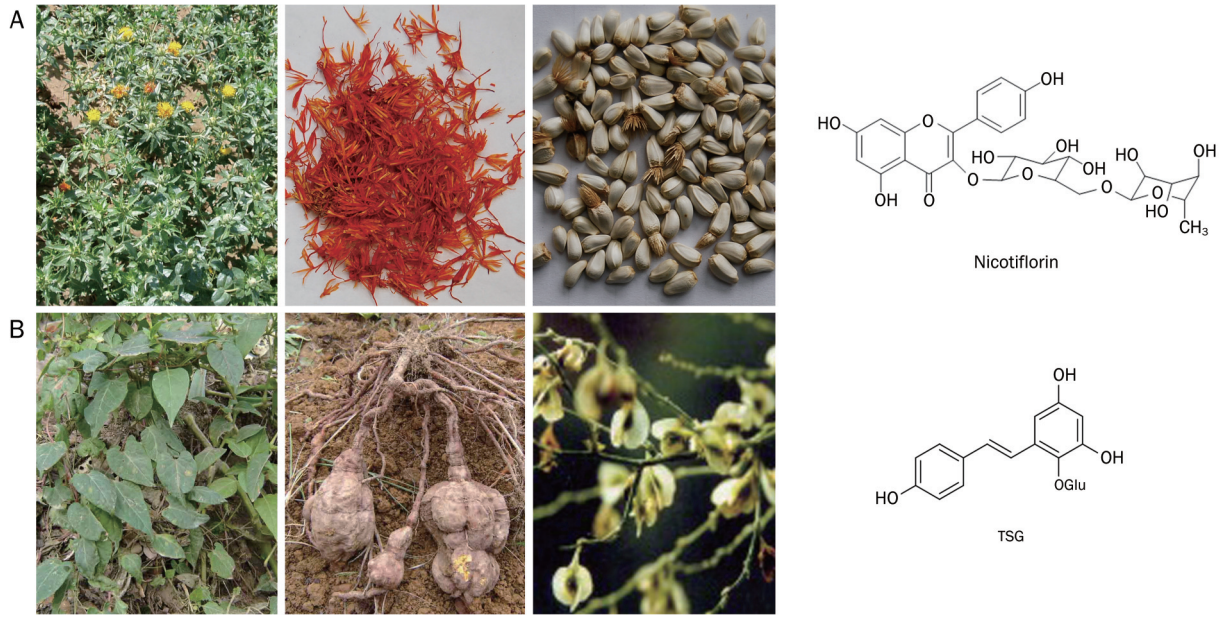

Figure 5. *Carthamus tinctorius* Linn (safflower) and its extract nicotiflorin (Panel A); *Polygonum multiflorum* Thunb and its extract TSG (Panel B).

eases and thrombosis in Chinese people.

The major component of the safflower are flavonoids, which have been intensively studied in China[112]. Nicotiflorin (Figure 5A), a flavonoid extracted from the dried and powdered corona of the safflower, appears to be a kind of yellow amorphous powder soluble in acetoacetate, ethyl alcohol and

methyl alcohol. In a permanent model of focal brain ischemia, nicotiflorin administration reduced the size of the infarction and ameliorated the neurological deficits[113]. Moreover, nicotiflorin also enhances learning and memory performance in a multi-infarct ischemia rat model. Such improvement could be attributed to its potency in protecting energy metabolism and alleviating oxidative stress [114]. Furthermore, safflower oil extracts, N-(p-coumaroyl)serotonin and N-feruroylserotonin, which are two serotonin derivatives, could prevent the guinea pig Langendorff heart from injury caused by ischemia-reperfusion, probably through direct quenching of the activity of active radicals[115].

Recent clinical experiences from many hospitals in China have shown that safflower extracts have good efficacy in the treatment of stroke-induced brain damage and diabetic peripheral nervous system lesions. Accumulating evidence suggests that stroke and diabetes both have a close relationship with the incidence of dementia, especially VaD, which is thought to be caused by blood stasis and phlegm deposits according to Chinese traditional medicine. Interestingly, as demonstrated by Liu Junfeng, decoction of safflower with herbals like *Angelica sinesis*, *Rhizoma Chuanxiong*, *Semen Persicae*, *Salvia Miltrorrhiza*, *Radix Platycodi*, and others available to specific patients could significantly improve cognition, memory and behavior in more than 90% of the patients in clinical trials by promoting circulation, expelling phlegm, and cultivating healthy mentality. Based on the promising effect of safflower on the cardiovascular system, it is worthwhile to put more effort into investigating its novel active principles in the treatment of dementia, especially VaD.

Polygonum multiflorum Thunb

Polygonum multiflorum (PM) (Figure 5B), the dry root of *Polygonum multiflorum* Thunb, rejuvenates the body and has been used in China since ancient times to prevent ageing. Wild PM mainly grows in the Guangxi, Henan, and Guizhou provinces, with some growth scattered throughout the Yunnan, Guangdong, Hubei, Henan, and Jiangsu provinces. PM is traditionally used for the treatment of hyperlipemia, neurasthenia, premature white hair, nerve injury and constipation. Recent pharmacological studies suggest that PM has various functions, which include anti-ageing, improvement of the immune system, lowering of serum cholesterol, reversal of hardening of the arteries, improvement of bowel movements, stimulation of the adrenal cortex, regulation of epinephrine, norepenephrine and blood sugar, and others[116]. A great deal of effort has gone into clarifying the nature of the active principles in PM. PM contains a number of active principles such as stilbene glycosides, anthraquinone and phospholipids. One of the consitutents effective in dementia is 2,3,5,4′-tetrahydroxy stilbene-2-O-β-D-glucoside (TSG), which could be obtained through heating and reflux in 50% alcohol[117].

TSG significantly decreases amyloid plaque formation and improves learning and memory abilities in APP transgenic mice[118] and rats subject to chronic ischemia[119], ibotenic acid or Aβ injection[120, 121]. Multi-target pharmacological mechanisms contribute to the cognitive enhancement of TSG, which may involve calcium channel blockade, antioxidation, anticholinesterase activity and anti-apoptotic activity.

VaD patients administered PM extractum tablets showed a dramatic improvement in scores of MMSE, ADL, Blessed–Roth Scale, and Clinical Global Impression (CGI) without their vital signs being affected and laboratory indices influenced[122]. These effects allow the active components of PM such as TSG to be of considerable value in treating dementia.

Curcuma longa Linn

There are about 16 different *Curcuma* L plants growing mainly in the southeastern and the western parts of China. One of the most widely used herbs in traditional Chinese medicine is *Curcuma longa* Linn (Figure 6A), which is mainly distributed in the Guangdong, Guangxi, and Taiwan provinces. It was traditionally used to relieve pain, pressure, edema and hematoma and to improve the symptoms of depression.

Curcumin, a potent polyphenol extract of *Curcuma* longa root, is the major component of this herb (Figure 6A). The extraction of the compound has been widely studied in China[123, 124]. Recently, its effect in the prevention and alleviation of dementia has been of particular interest. A large number of studies indicate that curcumin is effective on multiple pathological targets, such as inhibiting lipid peroxidation, scavenging ROS and reactive nitrogen species (RNS)[125], elevating γ-glutamyl-cysteinal synthetase and glutathione (GSH)-linked detoxifying enzymes[126], inhibiting NF-κB activation[127], and suppressing inflammation[128]. The activity of curcumin to increase heme oxygenase-1 (HO-1) in astrocytes and vascular endothelial cells may partially explain its antioxidant property[129, 130]. Interestingly, curcumin could also significantly interfere with Aβ-associated pathogenesis through decreasing cholesterol level, inhibiting aggregation of proteins in non-native conformation via binding to α-helical intermediate and amyloid forms of prion protein[131], together with increasing microglia adjacent to plaques, which may stimulate microglial phagocytosis of amyloid[125, 128].

Studies in animal models suggested that curcumin is beneficial to improving learning and memory deficiency caused by $AlCl_3$, D-gal[132], and streptozotocin[133]. Human clinical trials in patients with mild to moderate AD were performed at the University of California, Los Angeles (UCLA)[134].

Angelica sinensis (Oliv) Diels

Angelica sinensis (Oliv) Diels (AS) (Figure 6B) is a kind of herb from the Apiaceae family indigenous to China. It is distributed in provinces like Gansu, Yunnan, Sichuan, Qianghai, Shaanxi, Hunan, Hubei, and Guizhou. Its dry root, commonly known as *Radix Angelicae Sinensis*, or Chinese angelica, is widely used in China to treat amnesia, mild anemia, gynecological ailments and hypertension. Non-aromatic fractions, such as ferulic acid (FA) (Figure 6B), and polysaccharides are found in the aqueous phase of AS extracts. Although the traditional water extraction procedure has been optimized to allow for a high yield of FA, the semi-bionic extraction is a

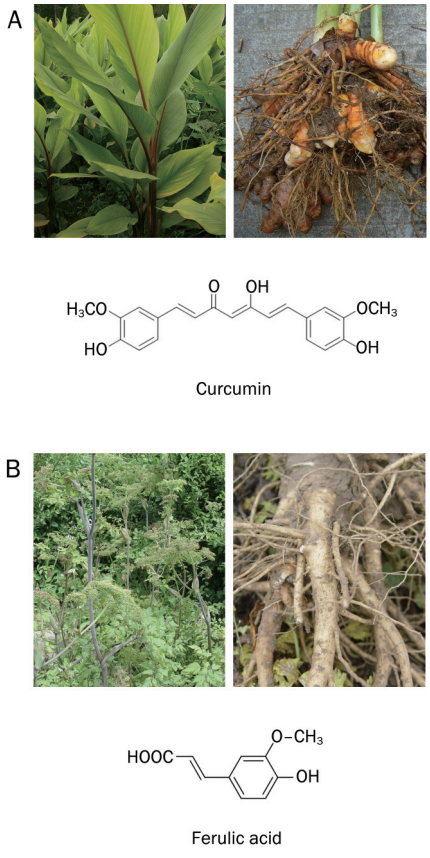

Figure 6. *Curcuma Longa* Linn and its extract curcumin (Panel A); *Angelica sinensis* (Oliv) Diels and its extract ferulic acid (Panel B).

more suitable procedure[135].

FA has various pharmacological activities involving anti-tumor, anti-virus and anti-bacteria actions, as well as heart protection and inhibition of cholesterol synthesis and the release of TXA_2. A considerable number of studies has demonstrated that FA can significantly reduce inflammation, oxidative stress and apoptosis *in vivo*[136, 137]. FA treatment significantly alleviated middle cerebral artery occlusion (MCAO)-induced injury, which is mediated through the down-regulation of ICAM-1 transcription, reducing the number of activated microglia[137]. FA prevents cognitive dysfunction caused by trimethyltinas[138] and buthionine-sulfoximine[139]. Although clinical trials in China have found that Danggui Shaoyao San, a mixture made from the decoction of AS with other herbs, could improve the MMSE and AIM scores for AD patients while reducing the level of blood superoxide dismutase (SOD) and lipid peroxidase (LPO)[140], clinical trials will be needed for the evaluation of the anti-dementia effect of FA.

Clausena lansium (Lour) Skeels

Clausena lansium (Lour) Skeels (Figure 7A), native to southern China, is in the family *Rutaceae*. It was mainly used for cough and indigestion in ancient Chinese times. Recent studies indicate that clausenamide, one of the major components isolated from the aqueous extract of the leaves of *Clausena lansium* (Lour) Skeels, may be a promising candidate for the treatment of dementia.

Compared with piracetam, a nootropic drug developed in Europe, clausenamide is more favorable in learning and memory improvement[141]. Its neuroprotective effect has been

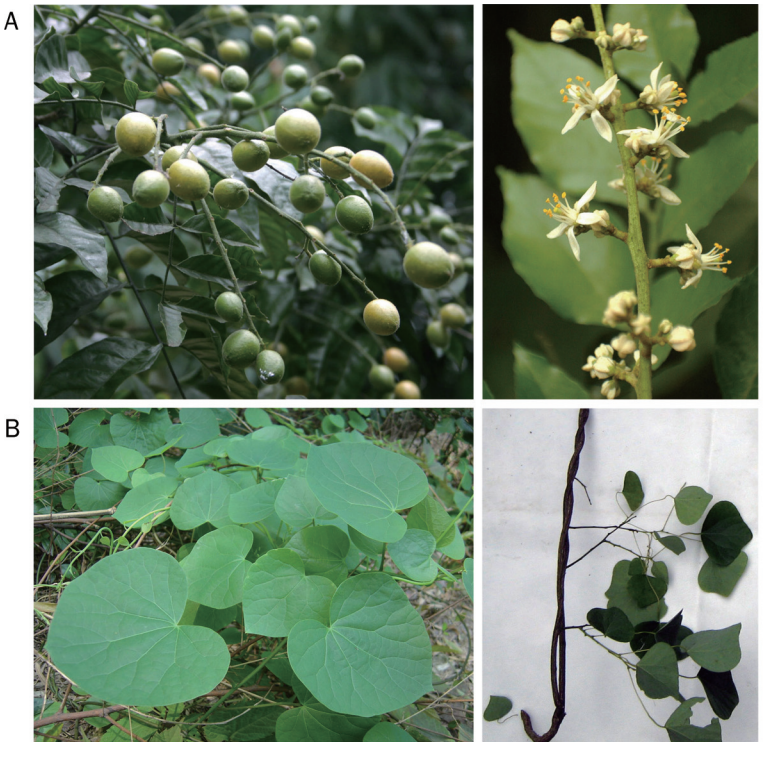

Figure 7. *Clausena lansium* (Lour) Skeels and its extract clausenamide (Panel A); *Sinomenium acutum* (Thunb) Rehd EtWils and its principle extract sinomenine (Panel B).

recognized in multiple models. In addition to prolonging survival time of mice subject to acute brain ischemia, clausenamide inhibits lipid peroxidation caused by alcohol, probably by increasing GSH peroxidase activity. It also increases blood flow in the brain by inhibiting basilar artery contraction induced by 5-HT, PGF2α, and arachidonic acid[142]. Clausenamide could also protect nerve cells against apoptosis induced by ischemia-reperfusion in renovascular hypertensive rats by elevating Bcl-2 expression[143].

(–)-Clausenamide, the first chiral nootropic agent developed in China, increased the magnitude of long-term potentiation (LTP) and potentiated synaptic transmission in rats by interfering with calcineurin, calpain and voltage-dependent calcium channels[144]. (–)-Clausenamide was again confirmed to protect hippocampus neurons from apoptosis caused by sodium nitroprusside through the up-regulation of anti-apoptotic proteins and the down-regulation of pro-apoptotic proteins. In okadaic acid-treated *in vitro* models and $A\beta_{25-35}$-injected ovariectomized (OVX) rats, (–)-clausenamide promoted cell survival and ameliorated learning and memory in a step-through test[142]. (–)-Clausenamide was approved by the SFDA in Jan 2007 and a Phase I clinical trial is underway.

Sinomenium acutum (Thunb) Rehd EtWils

Sinomenium acutum (Thunb) Rehd EtWils (Figure 7B) is mainly distributed in the Anhui, Jiangsu, Zhejiang, Fujian, Hubei, Sichuan and Guizhou provinces of China. It is clinically used for the treatment of rheumatoid arthritis due to its anti-inflammatory and analgesic activities. One of the active components of *Sinomenium acutum* (Thunb) Rehd EtWils is sinomenine, which is a kind of NSAID with multiple neuroprotective effects and few side effects.

A number of studies demonstrated that sinomenine could protect aganist cerebral ischemia/reperfusion injury through resisting inflammatory responses[145] and regulating apoptotic gene expression[146]. Based on the promising effects of NSAIDs in the treatment of dementia, sinomenine may also be beneficial for alleviating pathological changes that occur in AD and VaD, although further studies are needed to test this hypothesis. Interestingly, our studies showed that S52, a derivative of sinomenine[147] isolated from *Sinomenium acutum* (Thunb) Rehd EtWils, exerted neuroprotective effects in multiple *in vitro* and *in vivo* models (unpublished data). This synthetic alkaloid could elevate cortical ACh levels with no anti-AChE activity. S52 was effective in various cytotoxicities induced by H_2O_2, glutamate, rotenone or $A\beta_{25-35}$. *In vivo* studies also showed that S52 ameliorated scopolamine- or ischemia-induced deficiency in spatial performance and cognition in mice. The underlying mechanisms may involve resisting oxidative stress, anti-apoptosis, and attenuating mitochondrial dysfunction.

Other Chinese herbs potential for anti-dementia drug development

In addition to the aforementioned herbs, there are others shown to be active in alleviating dementia. Some of them have been extensively studied with the chemical structures and pharmacology of the active principles elucidated and the extraction procedures optimized. Yet there are many other plants which have only their crude extractions studied and deserve further research, such as *Radix puerariae*, *Rhizoma Chuanxiong*, *Salvia miltiorrhiza*, and others (Table 1).

Summary

Elderly people are particularly prone to affliction by certain debilitating diseases such as dementia, which bring endless anguish to the patients and their families. The pathology of dementia is such a complex process that for years the mechanisms have not been fully elucidated. Over-production of ROS, decreased levels of antioxidants and neurotrophic factors, glutamate toxicity, activation of apoptosis signaling pathways, aggregation of misfolded proteins and dysfunction of blood circulation are believed to speed up the progression of the disease. Today, the majority of approved drugs for dementia are single-targeted, whose therapeutic effects are not ideal. In recent years, a multi-target strategy has been attracting more attention. China has long been known for its numerous species of herbs and the long-standing practice of traditional Chinese medicine. It has a long history and rich experience in treating amnesia, tremor and rigidity, most of which are symptoms of progressive CNS debilitation. Although the philosophy of traditional Chinese medicine differs from that of occidental medicine, sound therapeutic effects promote more scientists, domestic and abroad, to study extracts from herbal medicines. Today, a great number of compounds from herb extracts have proven to be multi-targeted, low toxicity and potent in alleviating dementia. In light of the complex organization of the CNS, currently available Western remedies may not be suitable for the treatment of dementia because of their side effects. The wide distribution of herbs in China, their multiple active principles and low toxicity, together with progress in isolation procedures would render traditional Chinese medicine particularly suitable for the long-term treatment of dementia.

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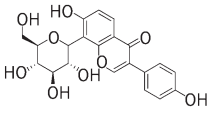
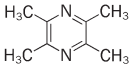
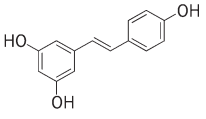
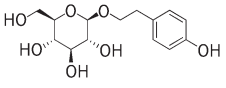
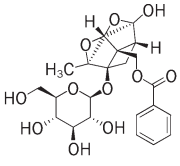
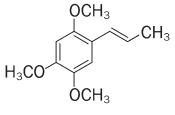
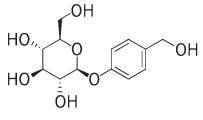
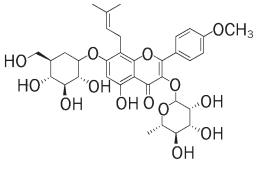
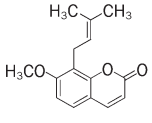
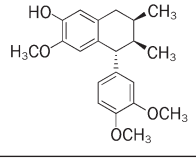
Table 1. Potential herbal extracts for dementia therapy.

Active components (Herb)	Molecular structure	Improvement on learning and memory impairment induced by Aβ	Scopolamine	Ischemia	Others
Puerarin [*Pueraria lobata* (Willd) Ohwi]		[148, 149]		[150]	SAMP8[151]
Ligustrazine (*Ligusticum wallichii* Franch)				[152]	$NaNO_2/AlCl_3$[153]
Resveratrol (*Polygonum cuspidatum* sieb et zucc)					Colchicine[154]; STZ[155]; TBI[156]
Rhodosin (*Rhodiola Rosae* Linn)		[157]	[158]		
Paeoniflorin (*Paconia lactiflora* Pall)			[159]	[160]	$NaNO_2$/Ethanol[161]
Asarone (*Acorus gramineus* Soland)					$AlCl_3$[162]
Gastrodine (*Gastrodia elata* Bl)				[163, 164]	
Icariin (*Epimedium brevicornum* Maxim)				[165]	$AlCl_3$[166]
Osthol (*C monnieri* (L) Cusson)			[167]		$AlCl_3$[168]; $NaNO_2$[169]
Schisandrone (*S sphenanthera Rehd et Wils*)		[170]			

113: 15-34.

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