Treating senile dementia with traditional Chinese medicine

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Abstract: Senile dementia is a syndrome in the elderly involving deficits in memory and cognition. There has been a long history of research and medical practice in dementia in China, during which the ancient Chinese people have formed a whole theory and accumulated abundant experience in the treatment of dementia. During recent decades, with new theories and technologies being digested and integrated, progress has been made in the medical and pharmacy research on senile dementia in China. In this review, we will focus on the traditional opinion, clinical practice, and recent progress in pharmacological research in China towards the treatment of dementia. We also discuss the potential trends of global convergence.

Keywords: senile dementia, Alzheimer's disease, vascular dementia, traditional Chinese medicine

The term "senile dementia" refers to a clinical syndrome seen in the elderly characterized by impairment of memory and cognition. With the dramatic improvement of average life expectancy and the fast increasing of the aged population in recent years, senile dementia has become a major problem of public health.

Alzheimer's disease (AD) is the most common type of dementia, which is a progressive neurodegenerative disease and has become the third greatest threat to elderly, inferior only to cardiovascular disease and cancer. Since 1907, when German surgeon Alois Alzheimer reported the first case of dementia that now bears his name, great efforts have been made in attempt to discover the pathology and remedy of AD. Though neither consensus concerning pathogenesis nor perfect therapy is available at present, progress has been made. Pathological hallmarks of AD include extracellular deposition of senile plaques (SP), formation of intracellular neurofibrillary tangles (NFT), and lesions of cholinergic neurons together with synaptic alterations in cerebral cortex, hippocampus, and other brain regions essential for cognitive function. It is now well accepted that multiple factors, such as apoptosis, oxidative stress, excitotoxicity, and disturbance of energy metabolism homeostasis, contribute to the progression of AD. Another common form of dementia in the elderly is vascular dementia (VD). This disorder, like AD, presents as a clinical syndrome of intellectual impairment caused by cerebrovascular elements such as stroke, infarct, and hemorrhagic brain lesion. As the common downstream pathway of neurodegenerative disease, free radical damage-induced oxidative stress and apoptosis are involved in the VD pathology.

China is well known for its long history of traditional Chinese medicine (TCM), which has endured for thousands of years. Through persistent attempts and practice for generations, Chinese people have accumulated profound experience in disease prevention, diagnosis, and treatment, and formed a whole theoretical system of medicine and therapy. We will introduce the status and progress of dementia treatment in China with TCM in this review.

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Progress in medication research

In the vast territory of China, smart and industrious Chinese people have made the best of immense natural resources for medical application. Herbal medicines of intellective and memory benefits were mentioned in some geography literature such as *Shan Hai Jing* and some medical literature like *Ben Cao Gang Mu (Compendium of Materia Medica)*.

Over the past years, quite a number of viewpoints have been put forward with the intent of explaining theories of TCM in how dementia forms and develops. In general, loss of memory was indicated to come from atrophy and empty state of brain rather than heart, and was classified according to clinical symptoms. On one hand, kidney decline as well as blood decay results in brain dystrophy. Hence, herbal medicine like ginseng, fructus lycii, polygala, angelica can be used to supplement blood and nourish kidney. On the other hand, pent-up phlegm and retarded blood circulation can induce chaos and toxicity of brain. Accordingly, such herbals as glycyrrhiza, atractylodes, rhubarb, and safflower often served as expectorants and promoters for blood circulation. Furthermore, it was suggested that normal functioning of human body not only lies on the function of every single viscus, but, more importantly, depends on the harmony and balance between each apparatus. During recent decades, a growing numbers of preclinical and clinical studies have found efficiencies of some herbal extract, some specific combinations of herbals, and herbal tea in AD treatment. In this review we will discuss the pharmacologic profiles of some representative natural products.

Huperzine A

(–)-Huperzine A (HupA) is a novel *Lycopodium* alkaloid isolated from the Chinese medicinal herb *Huperzia serrata* (Qian Ceng Ta, Figure 1A), which has been used by Chinese civilians for centuries in the treatment of such conditions as contusions, strains, swelling, and schizophrenia. As a chemically unique compound in comparison with other agents under study for AD, namely tacrine, galanthamine, donepezil, and rivastigmine, HupA is a reversible, potent, and selective acetylcholinesterase (AChE) inhibitor, and has been found to improve cognitive deficits in a broad range of animal models (Wang et al 2006a). Phase IV clinical trials conducted in China have demonstrated that HupA can significantly improve memory of elderly people and patients with AD and VD without any notable side effects (Xu et al 1995; Yang et al 2003).

In vitro and in vivo studies with respect to AChE inhibition demonstrated that AChE inhibition potency of HupA is similar or superior to those of inhibitors currently being used in AD treatment (Wang et al 1986; Wang and Tang 1998; Ogura et al 2000; Liang and Tang 2004). Studies in our laboratory showed that in cortex, hippocampus, and striatum of mammalian brain, HupA exerts preferential inhibition against G4 (10S) AChE, which is the physiologically relevant form at cholinergic synapses and is the major form for metabolizing ACh (Zhao and Tang 2002).

Changes in oxidative metabolism are thought to be involved in such neurodegenerative disease as AD and ischemia/reperfusion-induced brain injury. Accumulated damage of cellular structure and function from free radicals are thought to result in oxidative stress and be involved in events that lead to neurodegeneration. HupA has been demonstrated by recent studies in our laboratory to protect against H_2O_2- and β-amyloid (Aβ)-induced cell lesion, decrease the level of lipid peroxidation, increase antioxidant enzyme activities in rat PC12 and NG108–15 cell lines and primary cultured cortical neurons (Xiao et al 1999, 2000a, 2000b, 2002; Zhang et al 2002), and protect against serum deprivation-induced toxicity (Zhou and Tang 2002), oxygen-glucose deprivation-induced toxicity (Zhou et al 2001b, 2001c), and ischemia-induced toxicity (Zhou et al 2001d; Wang et al 2006b), which may benefit AD and VD therapy. These protective effects involve, at least in part, the abilities of HupA to regulate apoptosis-related genes (Zhou et al 2001c), upregulate NGF secretion and its down-stream signaling (Tang et al 2005a, 2005b; Wang et al 2006b), inhibit oxidative stress, and improve energy metabolism (Gao and Tang 2006). We also found that HupA can modulate the processing of amyloid precursor protein (APP) in both rats infused intracerebroventricularly with $A\beta_{1-40}$ and HEK293sw cell line, via regulating protein kinase C (PKC) (Zhang et al 2004). This effect might be beneficial for AD therapy, since it promotes the nonamyloidogenic pathway of APP metabolism and hence reduces the production of Aβ, and the nonamyloidogenic product itself, namely APPsα, is proved neuroprotective.

In the recent clinical trials carried out in China, HupA has demonstrated significant effect and safety in the treatment of neurodegenerative disease such as AD (Xu et al 1995; Yang et al 2003) and vascular dementia (Wei et al 2001; Yin et al 2001; Zhang and Fu 2001; Zhong and Liang 2004), as well as improvement of memory and cognitive deficits caused by other pathogenies, such as schizophrenia (Fang et al 2002; Ma et al 2003; Yang 2003), brain trauma (Zhou et al 2001a), and lack of iodine (Qu et al 1995). Clinical trials using HupA plus nilestriol (Wang et al 2003), or HupA plus nicergoline, aspirin as well as estrogen (Zhou et

al 2004), have shown favorable results in both AD and VD patients. Clinical investigators also found that combination with function convalescence training, daily life activities training, or a specific mental stimulation program consisting of reminiscence, reality orientation and remotivation, can promote the effects of medicine treatment.

AD is a neurodegenerative disease with complicated pathogenesis, therefore therapy with multiple drugs or drugs with polypharmacological activities will likely be the best approache to address the varied pathological aspects of the disease. Encouraging preclinical and clinical findings suggest that HupA is a promising candidate for the treatment of neurodegenerative diseases such as AD and VD, and is very likely to exert its therapeutic effects via a multi-target mechanism.

Ginkgo biloba extract

Ginkgo biloba (*Ginkgoaceae*) is an ancient Chinese tree that has been cultivated and held sacred for its health-promoting properties. There is substantial experimental evidence to support the view that the leaf extract of Ginkgo biloba (EGb) has many pharmacological effects (Sierpina et al 2003). Pharmacological studies demonstrated that EGb can reverse yohimbine-induced spatial working memory deficit in rats (Zhang and Cai 2005), improve learning performance in cerebral ischemic mice (Tadano et al 1998), reduces infarct volume and cell apoptosis in cortex of ischemic mice (Unal et al 2001), as well as reverse memory deficit and decline in choline actyltransferase activities in the hippocampus of rats infused intracerebroventricularly with $A\beta_{1-40}$ (Tang et al 2002). In vitro studies showed that EGb can protect against apoptosis induced by hydroxyl radicals (Ni et al 1996; Wei et al 2000), against cell death induced by beta-amyloid (Bastianetto et al 2000a), and against nitric oxide-induced toxicity (Bastianetto et al 2000b). Mechanisms underlying these protective effects remain unclear. As we now know, EGb is a mixture of flavonoids, terpenes, and organic acids, etc. EGb and its constituent ginkgolide B were reported to attenuate glutamate-induced neuronal damage (Zhu et al 1997). EGb's ability to decrease bax/bcl-2 ratios (Lu et al 2006), reverse ischemia-induced reductions in COX III mRNA in CA1 neurons prior to their death (Chandrasekaran et al 2001), inhibit nitric oxide synthesis (Calapai et al 2000), scavenge free radicals (Maitra et al 1995) and attenuate lipid peroxidation (Bridi et al 2001) might involve in its neuroprotective effects. A very recent study suggests that EGb has potent antioxidant activity and may play a role in the neuroprotective process by attenuating the ischemia/reperfusion-induced oxidative protein modification and lipoperoxidation (Urikova et al 2006).

Along with the progress in pharmacological research, quite a few preparations of EGb have been developed and put into home and overseas market during recent years. At present EGb is used clinically for improving peripheral vascular diseases in France and Germany and is ingested widely as an herbal medicine in some countries. Double-blinded randomized controlled clinical trial has demonstrated the efficacy of EGb 761, the standardized preparation of EGb, in treatment for mild to moderate AD (Maurer et al 1997). A 24-week, multicenter, double-blind, placebo-controlled, randomized trial confirmed that EGb 761 improves cognitive function in a clinically relevant manner in patients suffering from dementia (Kanowski and Hoerr 2003). Moreover, a very recent randomized placebo-controlled double-blind study showed that EGb 761 (160 mg/d) had a comparable efficacy with donepezil (5 mg/d) in treating mild to moderate AD, and also suggested the efficacy and tolerability of the Ginkgo biloba special extract (Flavogin) in the dementia of the Alzheimer type with special respect to moderately severe stages (Mazza et al 2006). Results from clinical trials in China demonstrated that treatment with EGb can significantly improve the cognitive function and living ability of patients with VD (Li 2003; Zhang and Li 2003; Shi et al 2006), multi-infarct dementia (Wu et al 2001), and cerebral infarction dementia (Wu 2003). Moreover, the active component of EGb, such as ginkgo flavone glycoside, was also reported to be efficient and safe for VD treatment (Li et al 2004a).

Radix ginseng

As a well known invigorant, there has been a long history of ginseng (Figure 1B) application in China. Its active compounds, including total ginsenosides, ginsenoside Rg1, and panaxynol, were found to possess central cholinomimetic and catecholaminomimetic activity, and can modulate the balance of stimulating and inhibiting process in central nervous system as well as promote neuronal plasticity and neurogenesis. Researchers found that ginsenosides Rb1 and Rg3 exerted significant neuroprotective effects on cultured cortical cells against glutamate-induced neurodegeneration (Kim et al 1998), indicating it may be efficacious in protecting neurons from oxidative damage produced by exposure to excess glutamate. Furthermore, protopanaxadiol-type saponins were reported to enhance axonal and dendritic formation activity (Tohda et al 2002). Pharmacological studies have demonstrated that saponins can improve learning and memory in animals impaired with scopolamine (Ni et al 2000; Zhao et al

2000; Chen and Zhu 2005) and transient global ischemia (Shen and Zhang 2004), as well as protect brain function and postpone brain aging by decreasing free radicals damage and increasing activities of GSH-Px and SOD (Zhang et al 2003). The ability of ginsenoside to enhance TrkB expression might also be involved in its protective effect (Lai et al 2006). Using 3H-(-)nicotine displacement assay, Panax ginseng was found to have affinity for both the nicotinic receptor, and to a lesser extent the muscarinic receptor (IC50 2.12 mg/mL and 5.25 mg/mL respectively), and the activity of the plant extracts was excluded as resulting from choline (Lewis et al 1999), and the demonstrated nicotinic activity of ginseng warrants further investigation with reference to therapeutic activity in age-related conditions such as dementia.

Rhizoma anemarrhenae (Zhimu)

Rhizoma anemarrhenae (Figure 1C) is a commonly used medicinal material for nourishment. The main active constituents include sarsasapogenin, smilagenin, neogitogenin, and markosapogenin. Pharmacological studies demonstrated that it can protect from learning and memory impairment induced by D-galactose (Chen et al 2000; Ma et al 2004), scopolamine, $AlCl_3$ (Ma et al 2005), β-amyloid peptide (Chen et al 2001a; Ouyang et al 2005), ibotenic acid (Sun et al 2004), cholesteremia and ischemic brain injury (Deng et al 2005), and enhance memory of normal aged animals (Hu et al 2003). These effects are very likely related with its activity of improving the synthetic speed of acetylcholine (ACh) and density of M-type ACh receptors (Chen et al 2001b, 2004; Hu et al 2001), scavenging free radicals (Chen et al 2000), upregulating brain-derived neurotrophic factor (BDNF) (Hu et al 2003), as well as antioxidation (Ouyang et al 2005).

Integripetal rhodiola herb (Rhodiola rosea L.)

Integripetal rhodiola herb (Figure 1D) is a perennial plant of Rhodiola family with succulent rhizome. The essential component, rhodosin, is well known for protection against hypoxia and external injury. Recent studies have found that rhodosin or the crude extract can protect from learning and memory impairment induced by D-galactose (Xie et al 2003), scopolamine (Wu et al 2004b), β-amyloid peptide (Xie et al 2004), hypoxia (Liu et al 2003), and cerebral ischemia-reperfusion (Song et al 2005). Rhodosin can also enhance memory of normal-aged rats (Jiang et al 2001). Its ability to increase ACh content and reduce cholinesterase activity in the brain (Wu et al 2004b) and antioxidation activity (Jiang et al 2001) might contribute to preventing neurodegenerative changes.

Danshen root (Salvia miltiorrhiza Bunge.)

Danshen root (Figure 1E) is a kind of medical material with activity of blood flow promotion and blood-stasis elimination, which has been frequently used for cardiovascular and hematological disorders in China. One of its constituent, namely tanshinone, can improve cholinergic functions in central nervous system (Li et al 2004b) and inhibit inflammatory reaction by inhibiting the expression of pro-inflammatory cytokines (Hu et al 2006) and inducible nitrogen oxidase (iNOS) (Li et al 2004b). Salvianolic acid, another essential component, is an antioxidant (Huang and Zhang 1992) found to protect from ischemic brain injury (Wu et al 2000).

Radix puerariae (Pueraria lobata [Willd.] Ohwi)

Various medical properties of Radix puerariae (Figure 1F) have been documented over 2000 years. Flavone extracted from its radix and leaves are found to be of multiple health benefits. The active component, puerarin, proved to widen coronary artery and cerebral artery and help lower blood pressure. Recent studies revealed that puerarin can protect from learning and memory impairment induced by D-galactose (Xu and Zhao 2002), scopolamine (Hsieh et al 2002), β-amyloid peptide (Yang et al 2005), ischemic brain injury (Wu et al 2004a), and chronic alcoholism (Sun 2005).

Green tea

The history of cultivating and drinking green tea in China is centuries old. Green tea is a popular beverage and is now widely believed to promote blood flow, lower blood fat, and help weight-loss. Recently, dietary components with antioxidant activity have attracted particular attention for their potential role in modulating oxidative stress associated with aging and chronic conditions. Consistent with epidemiological studies, recent research indicates that the antioxidant properties of polyphenols, the active components enriched in green tea, may contribute to reducing the risk of cardiovascular disease, cancer, and dementia (Yan and Wu 2001; Li et al 2006), which are the leading causes of morbidity and mortality among the elderly (Meydani 2001). The in vitro anti-beta-secretase and dual anticholinesterase activities of green tea was reported recently, indicating that tea contains active agents, which may function synergistically, to retard

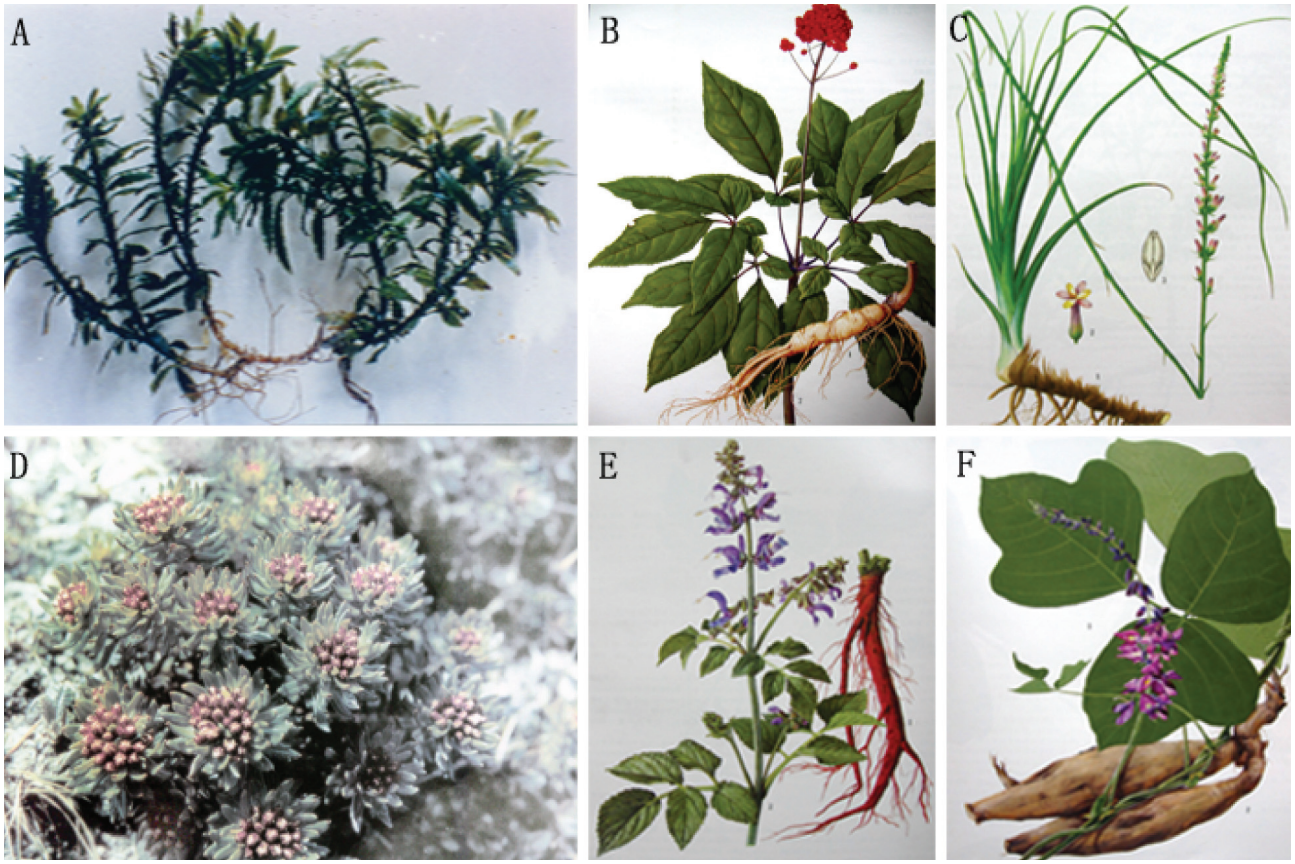

Figure 1 Pictures of Chinese herbs and the parts effective in treating dementia. A: *Huperzia serrata* (Qian Ceng Ta); B: *Panax ginseng* C.A. Mey. (Ginseng), drawn by Zeng Li Li; C: *Anemarrhena asphodeloides* Bunge. (Zhimu), drawn by Chun Quan Xu; D: *Rhodiola saccharinensis* A. Bor. (Integripetal rhodiola herb); E: *Salvia miltiorrhiza* Bunge. (Danshen), drawn by Zeng Li Li; F: *Pueraria lobata* (Willd.) Ohwi (Radix Puerariae), drawn by Zeng Li Li. Panels B, C, E, and F are from (Lou and Xiao 1995). Panel D is from (Zhu 1999).

progression of the diseases, assuming that these agents, yet to be identified, reach the brain (Okello et al 2004).

Clinical studies

Though the term "senile dementia" did not appear in the traditional Chinese medical literature, ancient medics were conscious of the phenomena and depicted elaborately its clinic exhibitions in medical books, including memory letdown, vacant face expression, lack of responsiveness and decline of intellectual ability such as comprehension and judgment, as well as emotional abnormity. Over 2000 years before, there were remarks of dementia and forgetfulness in the oldest medical book in China, *Huang Di's Canon of Internal Medicine*. With the development of modern medicine, people are more acquainted with dementia. More and more new therapeutic programs are put forward and tested during the course of clinical practice, such as combination therapy using drugs of different pharmacological profiles, or using drugs in combination with mental training.

Assisting therapy and prevention

Most patients with dementia are looked after by family in China. Therefore lifestyle can influence the efficacy of clinical therapy to a certain degree, and access to social guidance, consultants, and assistance can be of a large beneft to the dementia patient. More people are beginning to realize the importance of a regular and disciplined healthy lifestyle. The daily diet is acquiring accumulating attention for its potential influence on health condition. With the development of imageology and neuropsychology, diagnosis and classification of dementia are becoming easier and more accurate. Patients with dementia now have access to more reasonable and scientific diagnosis, treatment, and nursing.

Summary

Chinese people have studied and fought with dementia for a long period of time. An immense experience and systematic theory of treating dementia has been accumulated during the long history of development of TCM. Nowadays part of the experience is still relevant. With the global application

of modern science and technology, more and more natural resources and products from TCM are being studied and recognized. The resources and experience of TCM will continue to play an important role in the fight against aging and dementia.

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