Effect of Chinese Herbal Medicine on Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is reaching epidemic proportions yet treatment strategies are limited and are restricted to providing symptomatic relief for the cognitive and behavioral and psychological symptoms of dementia (BPSD). Chinese herbal medicine (CHM) has been a valuable source of medicines for centuries and research has burgeoned in recent years to understand the scientific basis for their use. Some plants have been used in CHM for AD symptoms (e.g., *Polygala tenuifolia*), while others are CHMs for different conditions, but they show mechanistic effects relevant to AD (e.g., *Salvia miltiorrhiza*).

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Some CHMs (e.g., *Ginkgo biloba* extract, and huperzine A from *Huperzia serrata*) show pharmacological activities relevant to AD, and promising effects on cognitive functions in clinical trials. Other CHMs show effects relevant to BPSD (e.g., *Crocus sativus*). This chapter discusses available scientific evidence for CHM plants and formulae that have been used both traditionally for AD, and those that have been used traditionally but not specifically for AD symptoms, and encompasses chemical, pharmacological and clinical studies. The ethnopharmacological approach to understanding the use of CHMs for AD is also discussed.

1. INTRODUCTION

1.1 Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and is reaching epidemic proportions throughout the world. It is a major cause of disability and dependency among older people, having major physical, psychological, social and economic impact on families, caregivers, and society. Symptoms include cognitive impairments, particularly memory, attention, and executive functions, in addition to behavioral and psychological symptoms of dementia (BPSD). These include psychosis, agitation, anxiety, sleep disorders, and depression. AD pathology involves β-amyloidosis, resulting in amyloid plaques in the central nervous system (CNS) and abnormal tau, which forms neurofibrillary tangles, leading to neurodegeneration. Neurotransmitter abnormalities are characterized by cholinergic deficits, but other neurotransmitter systems, including glutamatergic and serotonergic, are also impaired in the CNS. Inflammatory mechanisms, oxidative damage, apoptosis, and attenuated neuroplasticity have also been implicated in AD pathology (Perry & Howes, 2011). Current treatment strategies are limited and only provide symptomatic relief. In Western medicine, licensed drugs include those that improve cholinergic function in the CNS to improve cognitive functions by inhibiting acetylcholinesterase (AChE) to reduce the hydrolysis of the neurotransmitter acetylcholine (ACh) by this enzyme. AChE inhibitor drugs are donepezil, galantamine, and rivastigmine, with the latter two drugs derived from natural products (Howes, 2013). Other available drugs used in AD include memantine [a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist] that targets cognitive functions, while antipsychotics, antidepressants, tranquilizers, and hypnotics are prescribed for BPSD (Perry & Howes, 2011).

1.2 Ethnopharmacology

The scientific study of traditional medicines is named "ethnopharmacology" and much research in this field has been published in recent years (Chadwick & Marsh, 1994; Heinrich, Barnes, Gibbons, & Williamson, 2012; Heinrich & Jäger, 2015; Houghton, 2009). Every human society has a traditional medicine system, with flowering plants making the biggest contribution to the materials used in every case. Traditional Chinese medicine (TCM), which includes Chinese herbal medicine (CHM), is no exception and in recent years has received much scientific attention.

Pharmaceutical interest in ethnopharmacological research has two major foci, the establishment of a scientific rationale for the traditional use of the plant material and the discovery of new leads for conventional "single-chemical entity" (SCE). SCE pharmaceuticals might consist of the "active compound" determined by the research or its derivative, or a synthetic compound based on the structure of the naturally occurring compound. CHM has yielded some important SCE drugs used worldwide, including ephedrine from Ma Huang (*Ephedra* species), but probably the most notable example is the antimalarial artemisinin from Qing Hao (*Artemisia annua* L.) herb. The Chinese scientist Youyou Tu was awarded the Nobel Prize in Physiology or Medicine in 2015 for the part she played in its discovery and development.

Although the regulatory schemes for medicines in most countries worldwide are very much biased towards the SCE model, the clinical use of plant material itself or, more commonly, extracts, is nowadays receiving much attention. It is important to note that high quality clinical trials have been carried out on only a small number of extracts, with even less being subjected to systematic clinical reviews (e.g., Cochrane studies). Such products contain a complex mixture of compounds and in many cases, thorough investigations with the aim of identifying the "active constituent" have been fruitless, and the extract appears to give a "better" result, either in terms of increased efficacy or increased safety, than any one of the compounds isolated from it. Two phenomena are given as explanations of this situation. These are synergy, where an effect given by a combination of substances is greater than would have been expected from a consideration of individual contributions; and polyvalence, where different types of constituents within the plant have different pharmacological effects, all contributing to the overall therapeutic effect observed (Houghton, Howes, Lee, & Steventon, 2007; Williamson, 2009).

With such polyvalent medicines, the treatment of AD might prove to be more useful than if a SCE drug is used, since more than one target is affected (Howes & Houghton, 2012; Li, Zhang, & Yang, 2016). However, if the plant material used has not been authenticated, or if the profile for constituents in the extract has not been defined, any investigation for activity is relatively worthless. Legislation in some parts of the world, including Europe, has sought to address issues of authenticity, quality, and chemical characterization of plant extracts used for medicinal applications, although a more coordinated and robust approach to these issues is still needed (Howes & Simmonds, 2015).

1.3 TCM and AD

One of the many difficulties in ethnopharmacological studies is identifying the disease in question from old records, either because the local culture describes the condition differently from Western medicine, or because the disease may not be common in that context. This is particularly true with AD, which was identified as a disease syndrome only about 100 years ago. Thus relevant symptoms have to be identified (e.g., age-related memory loss) and used when searching the literature or in talking with local practitioners.

CHM ethnopharmacological research has the advantage that there is a wide range of literature sources, some dating back hundreds of years, and also that CHM is still a widely practiced, with a large number of practitioners who can provide information. However, comprehension of the written and spoken language presents a problem for many non-Chinese researchers and the alignment of diagnosis and symptoms according to the traditional Chinese philosophy of medicine with that of AD as understood by modern science also poses problems.

The etiology and pathogenesis of senile dementia has long been recognized by ancient Chinese physicians, although there is no distinction between the different causes of neurodegenerative dementia (such as AD, Parkinson's disease, and vascular dementia). Treatment strategies for dementia in TCM were systematically introduced by a physician *Zhang Jing Yue* (张景岳) in his medical book *Jing Yue Quan Shu—Za Zheng Mo* (《景岳全书·杂证谟》A.D.1624) during the Ming Dynasty (Xie & Qu, 2008). The ancient TCM approach for "Tonifying the kidney essence" is the basic principle of dementia treatment. According to TCM theory, senile dementia is caused by shortage of kidney essence (精), stagnation of blood,

marrow deficiency, and it also involves weakness of the heart, liver, spleen, and lungs. The main symptoms are considered as blood stasis blocking the brain, forgetfulness, phlegm-damp (痰湿), obstruction, and rheumatism (Wang, Guo, Dou, & Wang, 2011). The associated symptoms of cognitive impairment, muscle rigidity, and movement disorders are considered to overlap with some dementia, or neurodegenerative disease, symptoms (Su et al., 2014). Thus, TCMs used for dementia are not specifically targeted at the nervous system and there is a more multifunctional approach to dementia treatment (Ho, So, & Chang, 2011).

Vast progress in TCM, particularly CHM, research has been made, particularly since the 1980s, and is discussed later. CHM has been the source of SCE drugs but also crude extracts, where synergistic and polyvalent factors can occur. Most of the plants and compounds discussed have been subjected to some in vivo as well as relevant in vitro studies, while clinical data are also discussed for those plant species and SCEs that have been evaluated in studies with humans.

2. PLANTS USED TRADITIONALLY FOR AD-LIKE SYMPTOMS

2.1 *Acorus calamus*

"Acori Calami Rhizoma" is the dried rhizome of *Acorus calamus* L. (Acoraceae), which although not indicated for AD-like symptoms in the Pharmacopeia of the People's Republic of China (CPC, 2010), is one of the most frequently reported ingredients of classical CHM formulas for memory impairment associated with aging (May et al., 2016). The rhizomes of *A. calamus* [Shi Chang Pu (石菖蒲)] are used in Far Eastern traditional medicine for memory improvement (Oh, Houghton, Whang, & Cho, 2004). Investigations arising from a similar use in Ayurvedic medicine led to the identification of β-asarone (Fig. 1) as an AChE inhibitor (Mukherjee, Kumar, Mal, & Houghton, 2007). The related α-asarone, also present in *A. calamus*, was shown to improve memory in rats injected with β-amyloid (Aβ) (Limón et al., 2009) and displays antioxidant properties in the CNS (Manikandan & Devi, 2005; Pages et al., 2010). α-Asarone enhances cognition in amnesic mice due to both cholinergic and antioxidant effects (Kumar et al., 2012), while both α- and β-asarone are sedative in vivo (Howes & Houghton, 2003), so may be useful for BPSD. Oral administration to rats of *A. calamus* suspension showed significant improvement in hyoscine-induced memory loss (Barua et al., 2015). However, β-asarone

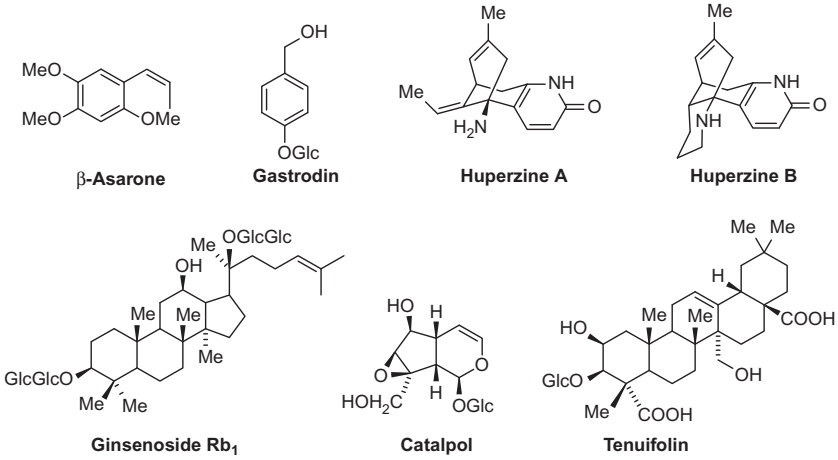

Fig. 1 Chemical structures of phytochemicals from some plants used traditionally for Alzheimer's disease-like symptoms.

has not been tested in animals, nor has the plant extract or isolated compounds been tested clinically.

It should be considered that the genotoxic and hepatocarcinogenic effects of α- and β-asarone may restrict the therapeutic use of *A. calamus* and these alkenylbenzenes for AD, and it has been recommended that their concentration in herbal medicinal products should be reduced to a minimum and diploid varieties should be preferred (HMPC, 2005) to reduce potential risks.

2.2 *Gastrodia elata*

The CHM "Rhizoma Gastrodiae" [Tian Ma (天麻)] is from the tuber of *Gastrodia elata* Blume (Orchidaceae). It is traditionally used to "stop endogenous wind" (antispasmodic), to "expel wind" (to relieve rheumatic pain), and to "dredge the meridians." It is indicated for convulsions, tetanus, headaches, epilepsy, dizziness, numbness, rheumatism, and paralysis (CPC, 2015). It is usually combined with other CHMs as a compound prescription (Tang & Xun, 2003) and is a component of traditional formulas for dementia (May et al., 2016).

Studies in vivo demonstrated that *G. elata* could significantly improve spatial memory in animal models of AD, associated with raised choline acetyltransferase (ChAT) expression and AChE inhibition in the brain (Huang et al., 2013). Further evidence that *G. elata* improves cholinergic

function to mediate cognitive effects was revealed in a study which concluded that prolonged intake (6 weeks) of *G. elata* extract improved learning and memory capabilities in scopolamine-treated rats (Park et al., 2015). *G. elata* tuber extract also increased superoxide dismutase activity and reduced tau protein expression in the brains of experimental dementia rats (Huang, Luo, & Yu, 2007).

Studies in vitro concluded that tuber extracts were neuroprotective against fragments of amyloid precursor protein (APP) (Kim, Kim, Lyu, Lee, & Kang, 2006) and against Aβ, possibly via regulation of protein-folding mechanisms, with the tuber constituents gastrodin (Fig. 1) and 4-hydroxybenzylalcohol associated with these effects (Lee, Kim, Han, Bhandary, et al., 2012). Thus, modulation of amyloid appears to be a promising target for *G. elata* and its constituents. Other studies have revealed that a tuber extract enhances α-secretase-mediated processing of APP and this action may contribute to the neuroprotective and cognitive-enhancing effects of *G. elata* (Mishra et al., 2011).

In addition to gastrodin and 4-hydroxybenzylalcohol, other tuber constituents, including 4-hydroxybenzaldehyde, vanillin, and vanillyl alcohol, are also considered as active components with antioxidant, antiinflammatory, and neuroprotective effects (Jang et al., 2015). Gastrodin in particular appears to be an important constituent for mediating the cognitive-enhancing effects of *G. elata*. This phenolic glucoside improved learning and memory in animal models of brain ischemia (Li & Zhang, 2015) and AD, with the latter observation associated with neuroprotection via antiinflammatory and anti-amyloidogenic effects (Hu, Li, & Shen, 2014). Furthermore, gastrodin attenuated apoptosis in neural progenitor cells in vitro and improved hippocampal neurogenesis in mice injected with Aβ (Li & Qian, 2016), while it also suppressed β-site APP-cleaving enzyme 1 (BACE1) expression to alleviate memory deficits in vivo (Zhang, Zhou, et al., 2016). *G. elata* and its constituents have not been evaluated in randomized-controlled trials (RCTs) to evaluate potential efficacy in AD.

It is important to consider that overharvesting of plant material in the wild has resulted in the decline of populations of *G. elata*, such that this species is described in the International Union for Conservation of Nature and Natural Resources (IUCN) Red List as vulnerable (IUCN, 2016), while trade is regulated under the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES, 2016). Therefore further evaluation of the medicinal properties of *G. elata* must also respect conservation strategies for this species to protect it from extinction.

2.3 *Huperzia serrata*

Qian Ceng Ta (千层塔) is prepared from *Huperzia serrata* (Thunb.) Trevis. (Lycopodiaceae), which has been used in CHM to alleviate memory loss, to promote circulation and to counteract fever and inflammation (Howes & Houghton, 2009a). Huperzine A (Fig. 1), a major quinolizidine-related alkaloid present, reversibly inhibits AChE in vitro and in vivo (Williams, Sorribas, & Howes, 2011) and it may also favorably affect other neurotransmitter systems to improve memory, so has potential in treating AD symptoms (Howes, 2013). Huperzine B (Fig. 1) also inhibits AChE, although is less potent than huperzine A (Houghton, Ren, & Howes, 2006).

Huperzine A is neuroprotective against Aβ (Xiao, Zhang, & Tang, 2002), oxygen-free radicals (Xiao, Yang, & Tang, 1999), and glutamate (Ved, Koenig, Dave, & Doctor, 1997), and recent reviews highlight this varied protective effect and its mechanisms relevant to AD (Howes, 2013; Howes & Houghton, 2009a, 2009b; Williams et al., 2011). Additional activities include antagonism at NMDA receptors in the cerebral cortex (Wang, Zhang, Yang, & Hu, 1999) and a reduction in brain iron levels (Huang et al., 2014). Huperzine A improved memory retention processes in vivo (Howes & Houghton, 2009b); while RCTs have been conducted, e.g., a multicenter, double-blind trial showed that huperzine A significantly improved memory and behavior in AD patients, being more selective for AChE than butylcholinesterase and less toxic than donepezil and tacrine (Shu, 1998; Small et al., 1997).

Huperzine A is used clinically in China for AD (Ban et al., 2016) and several RCTs have been carried out with AD patients. However, different meta-analyses have concluded that the published trial data were of poor quality (Rafii et al., 2011; Yang, Wang, Tian, & Liu, 2013; Yue et al., 2012) and toxicity data are considered as inadequate (Ha, Wong, & Zhang, 2011). However, a more recent meta-analysis concluded that eight trials studied were of sufficient quality to be valid and that huperzine A was significantly beneficial in several aspects of AD and was well tolerated (Xing, Zhu, Zhang, & An, 2014). In another recent clinical study with AD patients, when cholinesterase inhibitors (ChEIs) were added to memantine, it was shown that huperzine A gave the best results (Shao, 2015).

Recently there has been considerable interest in huprines, synthetic compounds combining structural features of both huperzine A and tacrine, the first ChEI to be used clinically. Huprine X showed AChE inhibitory effects in vitro (Camps et al., 2000) and displayed beneficial effects in

reducing amyloidogenic processes and increasing synaptophysin levels (Hedberg et al., 2010), but no clinical studies using this compound have yet been reported.

2.4 *Panax ginseng*

"Ginseng Radix et Rhizoma" [Ren Shen (人参)] is the dried root of *Panax ginseng* C.A.Mey (Araliaceae) and it is indicated for conditions such as frailty caused by long-term illness, and is considered to tranquilize the mind and replenish wisdom (CPC, 2010). It has also been an ingredient of multiple CHM formulas indicated for memory impairment in the context of aging (May et al., 2016). The chemistry of *P. ginseng* has been extensively studied and the major constituents are the triterpene saponins, designated as ginsenosides (e.g., Re, Rg_2, Rf) (Court, 2000; Kite, Howes, Leon, & Simmonds, 2003).

In RCTs with normal young volunteers, ginseng improved memory (Kennedy, Haskell, Wesnes, & Scholey, 2004), however, frequent use for extended periods ($\leq$2 years) by healthy subjects did not improve memory (Radad, Gille, Liu, & Rausch, 2006). The majority of other RCTs with AD subjects and those with mild cognitive impairment (MCI) concluded ginseng could improve cognitive functions, although trials were mainly open-label or single-blind and could have been more methodologically robust (Howes & Perry, 2011; Perry & Howes, 2011).

Mechanistically, ginsensosides show a range of biological activities relevant to AD pathology, including antioxidant, inhibition of glutamate- and Aβ-induced cytotoxicity (Rb_1, Rh_2, Rg_2, Rg_3), and Aβ-induced tau phosphorylation (Rb_1; Fig. 1), they are neuroprotective (Rg_3), antagonize NMDA receptors (Rg_3, Rh_2), modulate ACh release, and increase ChAT (Rb_1, Rg_1); they also decrease Aβ in transgenic AD mice (Re, Rg_1, Rg_3) and improve cognition in vivo (Howes & Perry, 2011).

2.5 *Polygala* Species

"Polygalae Radix" [Yuan Zhi (远志)] is the dried root of *Polygala tenuifolia* Willd. or *P. sibirica* L. (Polygalaceae) and its indications in CHM include insomnia, dream-disturbed sleep and forgetfulness (CPC, 2010). *P. tenuiflora* root has also been an ingredient of multiple CHM formulas indicated for memory impairment in the context of aging (May et al., 2016).

P. tenuifolia root constituents have been associated with a range of mechanistic effects relevant to AD in vitro and in vivo, suggesting extracts from

this species may act via polyvalency. For example, tenuigenin is anti-apoptotic and inhibits Aβ secretion, while tenuifolin (Fig. 1) displays the latter effect and it modulates neurotransmitter systems to improve learning and memory in vivo (Howes & Houghton, 2012). Onjisaponins increase nerve growth factor (NGF) synthesis and are neuroprotective against Aβ, while onjisaponin B also reduces Aβ production and improves memory; and polygalasaponins are anxiolytic and sedative in vivo, with one such compound (XXXII) also improving learning abilities (Howes & Houghton, 2012; Li, Cui, et al., 2016). However, more studies on the bioavailability and pharmacokinetics of *Polygala* constituents are needed, with consideration of the potential for saponin components to be hydrolyzed in the gastrointestinal (GI) tract, prior to absorption into the systemic circulation. In this context, one of the main triterpene aglycones produced following hydrolysis of *Polygala* saponins is polygalacic acid, which modulates cholinergic function and neuroinflammation in vivo to mediate a neuroprotective effect against cognitive impairment (Guo, Shen, Meng, Yang, & Li, 2016).

Extracts from this species also improve memory and behavioral disorders are neuroprotective and promote stem cell proliferation in vivo (Chen, Hsieh, Wu, & Lin, 2004; Park et al., 2002, 2008). Standardized extracts have not been investigated for efficacy in AD patients, although two RCTs in normal and elderly subjects concluded that *P. tenuifolia* extract (BT-11) could improve cognitive functions (Lee et al., 2009; Shin et al., 2009).

2.6 *Rehmannia glutinosa*

"Rehmanniae Radix" [Di Huang (地黄)] is the root tuber of *Rehmannia glutinosa* (Gaertn.) DC. (Plantaginaceae) and although it is not indicated in the current Pharmacopeia for symptoms associated with AD (CPC, 2010), it is one the most frequently reported ingredients of multiple CHM formulas indicated for memory impairment associated with aging (May et al., 2016). Root extracts improve memory in vivo and also increase expression of NGF in hippocampal neurons (Lin et al., 2012), while in a fly (*Drosophila*) model of AD, *R. glutinosa* extract was protective against Aβ neurotoxicity (Liu, Lee, et al., 2015).

Iridoids, catalpol (Fig. 1) in particular, isolated from the root of *R. glutinosa* have shown mechanistic effects that appear to contribute to the actions of root extracts in studies relevant to AD. Catalpol attenuates Aβ-induced neurotoxicity in vitro (Jiang, Du, Liu, Bao, & An, 2008) and

improves memory in vivo, possibly via favorable effects on the cholinergic system (Xia, Zhang, Wu, Xia, & Hu, 2012). Other studies revealed catalpol has antioxidant, antiinflammatory, neurotrophic, and antiapoptotic effects (Lin et al., 2012), so may mediate a range of actions. Catalpol is also neuroprotective in vivo (Zhang et al., 2008), while a different root constituent, 5-hydroxymethyl furfural, was neuroprotective in vitro (Zhang, Jin, Zhang, Gong, & Gu, 2014). Although root extracts and constituents have shown some promising mechanistic effects that are potentially useful in AD, there is a lack of RCTs investigating their efficacy in humans, particularly in AD. However, *R. glutinosa* has been explored for its effects on cognitive functions as a component of CHM formulae (see later), although the specific contribution of this species to clinical outcomes, and any polyvalent or synergistic effects, remain to be evaluated.

3. PLANTS USED TRADITIONALLY BUT NOT FOR AD-LIKE SYMPTOMS: EVIDENCE FOR RELEVANT ACTIVITY

3.1 *Crocus sativus*

"Croci Stigma" [Xi Hong Hua (西红花)] is the dried stigma of *Crocus sativus* L. (Iridaceae), often described by the vernacular name "saffron" and in CHM it is used to treat depression, fear, confusion, menstrual difficulties, abdominal pain, and to activate blood circulation. Long-term use is considered to relieve anxiety and create feelings of joy (Zhao, Dai, & Chen, 2006); in CHM, it is also indicated for conditions that include psychosis and is considered to tranquilize the mind and to relieve depression (CPC, 2010); thus, some traditional uses appear to suggest some relevance to BPSD (although not used traditionally for dementia).

Clinical studies concluded that saffron extracts (30 mg daily for 6 weeks) improve mild-to-moderate depression in patients compared to placebo, and were as effective as the antidepressant drugs imipramine and fluoxetine (Akhondzadeh, Fallah-Pour, Afkham, Jamshidi, & Khalighi-Cigaroudi, 2004, Akhondzadeh et al., 2005; Noorbala, Akhondzadeh, Tahmacebi-Pour, & Jamshidi, 2005; Nourbala, Tahmasebipour, Akhoundzadeh, Khani, & Jamshidi, 2004). Further evidence for potential usefulness in BPSD was suggested as the component safranal was anxiolytic and hypnotic in vivo (Hosseinzadeh & Noraei, 2009). RCTs also indicate saffron extracts (30 mg daily for 16 or 22 weeks) can improve cognitive functions in AD patients when compared to the AChE inhibitor drug donepezil, and caused fewer adverse effects (Akhondzadeh et al., 2010a, 2010b). Another RCT

concluded the same dose of saffron taken for 1 year was comparable to memantine in reducing cognitive decline in AD patients (Farokhnia et al., 2014).

Although the extracts investigated in these clinical studies were not chemically characterized, mechanistic studies suggest the crocin constituents (a series of different sugar esters of the dicarboxylic acid crocetin) may contribute to the observed effects. Crocin is antiapoptotic, neuroprotective, and antioxidant in vitro, and improves memory in vivo; crocetin (Fig. 2) and crocin are antiinflammatory in microglia, while

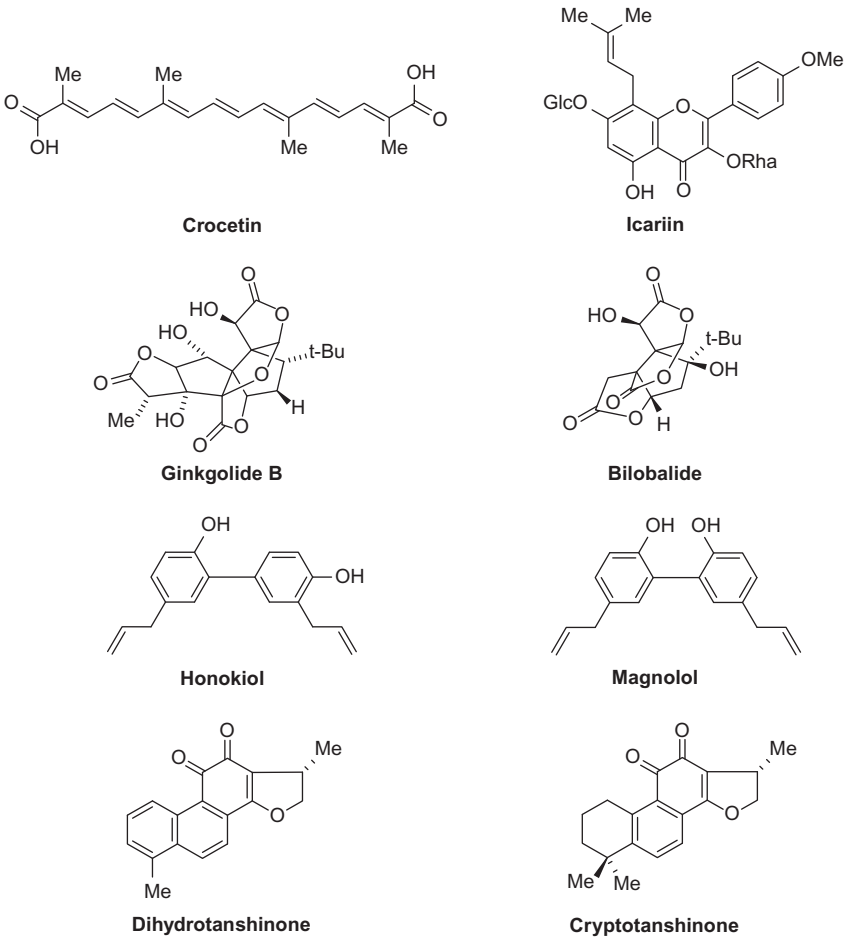

Fig. 2 Chemical structures of phytochemicals from some plants used traditionally but not for Alzheimer's disease-like symptoms.

trans-crocin-4 inhibits Aβ fibrillogenesis (Howes & Houghton, 2012; Howes & Perry, 2011). Further studies are needed to characterize the "active" constituents of saffron and their modes of action relevant to AD, particularly as the crocins show poor intestinal absorption in vivo and are hydrolyzed to crocetin in the GI tract (Lechtenberg et al., 2008).

3.2 *Epimedium* Species

Leaves from *Epimedium brevicornum* Maxim. (accepted name: *E. brevicornu* Maxim.), *E. sagittatum* (Siebold & Zucc.) Maxim., *E. pubescens* Maxim., and *E. koreanum* Nakai (Berberidaceae) are indicated in CHM as "Epimedii Folium" [Yin Yang Huo (淫羊藿)] for debilitation of kidney yang, impotence, sinew and bone disorders, "painful impediment caused by wind-dampness," numbness, and spasms (CPC, 2010). Various species of *Epimedium*, a genus of small herbaceous plants, have been used in Far Eastern medicine, and it is of interest that *E. koreanum* is a traditional remedy for forgetfulness in Korea (Ma et al., 2011).

Much interest has been shown in the flavonoid glycosides present in *Epimedium* species, particularly icariin (Fig. 2). Icariin protects PC-12 cells from apoptosis induced by Aβ (Wang, Zhang, Wang, Qi, & Lou, 2007; Zhang, Wang, et al., 2015) and shows a dose-dependent protective effect at low concentrations on neurons damaged by ischemia/reperfusion, while in vivo, it improved learning and memory, possibly via some antioxidant effect (Li, Zhou, & Shi, 2005; Xu et al., 2009). Another in vivo study using the 5xFAD mouse, considered to be a better model for AD, showed markedly less damage in axons and dendrites caused by Aβ in the groups treated with icariin (Urano & Tohda, 2010). The related compound icariside II has recently been shown to improve cognition in rats treated with streptozocin, which has a deleterious effect in the hippocampus (Yin et al., 2016). A possible extra contributing factor to the usefulness of *Epimedium* species in treating AD symptoms is the fact that the aporphine alkaloid epimediphine, present in *E. koreanum*, has AChE inhibitory activities (Zhang et al., 2013).

A clinical trial of a CHM formula comprising six herbs, including *Epimedium*, showed that the herbal mixture was better than donepezil at improving scores for mild AD (Zhang, Lin, et al., 2015), but studies with *Epimedium* alone or with icariin are needed to establish clinical efficacy of this herb and its constituents.

3.3 *Ginkgo biloba*

"Ginkgo Folium" [Yin Xing Ye (银杏叶)] is the dried leaf of *Ginkgo biloba* L. (Ginkgoaceae), which is indicated in CHM for a range of conditions, including those associated with respiratory disorders and for "heart pain" (CPC, 2010). In recent years, leaf extracts have become very popular worldwide to alleviate conditions associated with reduced microvascular flow, especially in the CNS (Heinrich et al., 2012). *G. biloba* leaves contain a mixture of phytochemical classes, each of which displays several activities which could be relevant to alleviating AD symptoms, so *G. biloba* extract is an excellent example of an herb displaying polyvalence. Antiinflammatory flavonoids are present, e.g., ginkgetin, but these are also antioxidant and may also be vasodilatory (Kubota et al., 2001); and the flavonol quercetin inhibits Aβ-induced cell death (Shi et al., 2009) and stimulates neurite outgrowth (Tchantchou et al., 2009). The diterpene ginkgolides, e.g., ginkgolide B (Fig. 2), are unique to this species and are potent platelet aggregation factor (PAF) antagonists (Braquet, Hosford, & Koltai, 1994) as well as being antioxidant scavengers of reactive oxygen species. More recently they have been shown to inhibit Aβ-induced cell death (Bate, Tayebi, & Williams, 2008). The related sesquiterpene bilobalide (Fig. 2) also has strong antioxidant activity, promotes expression of growth factors, leading to neural outgrowth (Tchantchou et al., 2009) and reduces levels of proinflammatory nuclear factor (NF)-κB (Li et al., 2008).

Studies on *G. biloba* extracts in animals and healthy elderly humans gave encouraging results which demonstrated significant improvement in markers of cognitive function; e.g., a meta-analysis in 2002 covered eight RCTs, each showing significant improvement in memory tests, anxiety, dizziness, headaches, and tinnitus, with no serious adverse effects (Canter & Ernst, 2001). These findings stimulated interest in *G. biloba* for possible prevention, or alleviation of symptoms, of AD. The first double-blind RCT study reported encouraging results with patients given *G. biloba* extract showing stabilization and, in some cases improvement in cognitive performance and social functioning with no adverse effects observed (Le Bars et al., 1997). However, other RCTs were more equivocal about any improvements and the conclusions of meta-analyses about the value of *G. biloba* for treating AD have become increasingly negative (Birks & Grimley Evans, 2002, 2009), with the latter review stating that "There is no convincing evidence that *G. biloba* is efficacious for dementia and cognitive impairment." However some reported RCTs still show a

positive outcome (e.g., Hashiguchi, Ohta, Shimizu, Maruyama, & Mochizuki, 2015; Wang et al., 2010; Yang, Wang, Sun, Zhang, & Liu, 2016), although another RCT showing some positive effects in AD concluded that the ChEI rivastigmine gave a better outcome than *G. biloba* (Nasab, Bahrammi, Nikpour, Rahim, & Naghibi, 2012). Thus, *G. biloba* does appear to have more potential than some other plant species in having clinical usefulness for AD. Most published trials note that it displays fewer adverse effects than other agents used clinically, although it has been associated with anticoagulant effects (Howes & Houghton, 2009a), so might interact with medication such as warfarin, causing excessive bleeding.

3.4 *Magnolia officinalis*

"Magnoliae Officinalis Cortex" [Hou Po (厚朴)] is the dried stem bark, root bark, or branch bark of *Magnolia officinalis* Rehder & E.H.Wilson or *M. officinalis* var. *biloba* Rehder & E.H.Wilson (Magnoliaceae) and it is indicated in CHM for conditions that include vomiting and diarrhea, abdominal disorders, and cough (CPC, 2010). Extracts of *M. officinalis*, and its isolated compounds, particularly the biphenolic lignans honokiol and magnolol (Fig. 2), have been evaluated for activities relevant to AD, although RCTs are lacking.

Studies have shown that honokiol and magnolol increased ChAT activity, inhibited AChE activity in vitro, and increased hippocampal ACh release in vivo (Hou, Chao, & Chen, 2000). Other activities relevant to AD pathology have also been identified. Antioxidant effects have been shown for *M. officinalis* extract (Zhou & Xu, 1992), magnolol (Chen et al., 2001), and honokiol (Lo, Teng, Chen, Chen, & Hong, 1994). Magnolol showed neuroprotective properties in cortical neuron-astrocyte cultures (Lee, Hseih, Kuo, Yeh, & Huang, 1998), while both magnolol and honokiol protect against Aβ damage (Hoi, Ho, Baum, & Chow, 2010; Xian, Ip, Mao, & Lin, 2016). Honokiol also promoted neurite outgrowth in cultured PC-12 cells (Fukuyama et al., 2002), while magnolol showed antiinflammatory activity perhaps via inhibition of cyclooxygenase and 5-lipoxygenase (Wang, Ho, Chang, & Chen, 1995). Thus, the extract of *M. officinalis*, and honokiol and magnolol, apparently display polyvalence, having multiple actions relevant to AD therapy.

The promise for amelioration of symptoms associated with AD held out by such in vitro studies has been fulfilled by several in vivo experiments, using the extract of the bark (Lee, Choi, Han, Kim, et al., 2012), magnolol

(Li et al., 2013) and honokiol (Hu et al., 2013; Xian et al., 2015) when improved memory, reduced accumulation and toxicity of Aβ, and reduced oxidative damage were noted. Another constituent, 4-*O*-methylhonokiol, has also shown similar activities in vivo (Jung, Lee, Choi, & Hong, 2014; Lee, Choi, Choi, et al., 2012; Lee, Choi, Lee, et al., 2012). With respect to BPSD, honokiol and magnolol have also shown anxiolytic effects, associated with modulation of GABAergic neurotransmission; and when combined in a prescription with other CHM herbs (Banxia Houpu), *M. officinalis* was antidepressant in vivo (Howes, Perry, & Houghton, 2003).

3.5 *Salvia miltiorrhiza*

"Salviae Miltiorrhizae Radix et Rhizoma" [Dan Shen (丹参)] is the dried root and rhizome of *Salvia miltiorrhiza* Bunge (Lamiaceae) and its main uses in CHM include for cardiovascular and bleeding disorders (CPC, 2010). Root extracts have shown a range of mechanistic effects in the CNS, with many studies showing some promising effects relevant to vascular and ischemic disorders in particular (Houghton & Howes, 2005; Perry, Howes, Houghton, & Perry, 2000). More recently, root extracts have shown neuroprotection against Aβ in vitro (Yu et al., 2014) and could improve learning and memory in an animal model of AD (Liu, Guo, et al., 2015), although RCTs in AD patients are lacking. It is also important to consider that *S. miltiorrhiza* preparations may interact with other medicines, such as anticoagulant drugs (Zhou, Chan, & Yeung, 2012).

There has been much research on the chemical constituents of *S. miltiorrhiza* root and their modes of action. Salvianolic acid constituents protect against ischemia-induced memory impairment in vivo, with salvianolic acids A and B also protecting against Aβ-induced neurotoxicity in vitro via antioxidant effects (Cao et al., 2013; Howes & Houghton, 2012), and they inhibit aggregation of Aβ in vitro (Zhang, Qian, Zhang, & Wang, 2016). Salvianolic acid B also improves memory in animal models of cholinergic impairment and Aβ-induced cognitive deficits (Bonaccini, Karioti, Bergonzi, & Bilia, 2015). Recent studies suggest root extracts and salvianolic acids A and B may enhance neural stem cell proliferation and differentiation (Zhang, Qian, et al., 2016), although more research on potential applications in vivo is needed.

Other antioxidant components of the root include the diterpene constituents (tanshinones), which are also considered to explain some of the antiinflammatory mechanisms of root extracts (Howes & Houghton, 2009a),

including inhibition of eicosanoid generation (Howes, Houghton, & Hoult, 2000), inhibition of other inflammatory mediators, including interleukin (IL)-8, IL-10, and tumor necrosis factor (TNF)-α (Liang et al., 2013), and modulation of the NF-κB pathway (Akaberi, Iranshahi, & Mehri, 2016). Both antioxidant and antiinflammatory mechanisms are suggested as important to mediate the observed neuroprotective effects of the tanshinones (Bonaccini et al., 2015).

Tanshinone diterpene constituents display a range of other biological activities that appear to provide further scientific evidence for the potential usefulness of root extracts in AD. Tanshinones inhibit AChE, with the dihydrofurans dihydrotanshinone and cryptotanshinone (Fig. 2) being more potent ChEIs than the furans, tanshinones I and IIa (Ren, Houghton, Hider, & Howes, 2004). Cryptotanshinone also ameliorates cognitive impairments in vivo, induced by scopolamine (Wong et al., 2010) and by Aβ, while also reducing plaque deposition of the latter (Zhang, Qian, et al., 2016). These findings suggest this diterpene can cross the blood–brain barrier to mediate cognitive effects via the cholinergic system and via anti-amyloidosis. Other studies revealed tanshinone IIa is neuroprotective against cerebral ischemia/reperfusion injury in vivo via an antiapoptotic action (Chen et al., 2012), and against Aβ-induced neurotoxicity in vitro (Qian, Xiao, & Xu, 2012), while tanshinone I enhances neurogenesis in the mouse hippocampus (Chen et al., 2016).

4. CHM FORMULAS RELEVANT TO AD

CHM formulas are often composed of complex mixtures of different herbal and other substances, which introduces challenges for their quality control and for understanding their mechanistic and clinical effects, in the context of the role of polyvalency and synergy. The plant species discussed earlier are also included in CHM formulas, with some of these (and others) evaluated in pharmacological and clinical studies. Examples include "DX-9386," which is composed of *Polygala tenuifolia*, *Panax ginseng*, *Acorus gramineus*, and *Poria cocos* (1:1:25:50), and it improves learning and memory in different animal models (Howes & Houghton, 2003; Howes et al., 2003); and "ZiBuPiYin" [滋补脾阴], which is a modification of the "Zicheng decoction" [资成汤], traditionally used for memory loss and composed of 12 components (including roots from red ginseng, white peony, and Dan Shen) that has been suggested to prevent diabetes-related cognitive decline in vivo (Chen et al., 2014). *Panax ginseng* is also a component of "Yizhi capsule" [益智胶囊], in addition to

Polygala tenuifolia and other components, which has been investigated for efficacy in vascular dementia, although RCT outcomes to date are inconclusive with regard to efficacy (Howes & Perry, 2011).

The genus *Acorus* appears to be particularly important in CHM formulas for dementia. In a recent data-mining study, 104 CHM formulas were analyzed, including 147 CHMs for senile dementia, and the results enabled the medication rules on the CHM inheritance auxiliary system to be summarized. It was concluded that CHM prescriptions for senile dementia are mainly composed of a combination of three types of herbs: tonifying, activating blood circulation, and resuscitating, to reflect the TCM theory for senile dementia. The most frequently used herbs, accounting for 28% of all the relevant formulas, were *Ligusticum striatum* DC. rhizome ["Chuanxiong Rhizoma," Chuan Xong (川芎)] and *Acorus calamus* var. *angustatus* Besser ["Acori Tatarinowii," Shi Chang Pu (石菖蒲)] (Zong, Ji, Wei, & Shi, 2014).

The formula "Sailuotong" [塞络通] has been systematically studied in the laboratory and in RCTs. This formula is composed of *Panax ginseng*, *Ginkgo biloba*, and *Crocus sativus* and produced small improvements in working memory when taken by healthy adults for one week in a small RCT (Steiner et al., 2016), and it improved the cognitive and memory impairments associated with vascular dementia (Steiner et al., 2015). Other formulas investigated in small RCTs include "Liuweidihuang-tang" [六味地黄汤], consisting of six components including *Rehmannia* Radix, which enhanced cognitive ability in normal young adults (Park et al., 2005) and "Ba wei di huang wan" [八味地黄丸] which has muscarinic receptor effects, improves memory in vivo, and cognitive functions in patients with mild-to-severe dementia (Howes & Perry, 2011). Also of potential relevance for use in AD is the formula "Jia wei wu zi yan zong ke li" [加味五子衍宗颗粒], composed of six CHMs, including *Epimedium grandiflorum* C.Morren herb, since when a granule preparation was taken for 3 months by volunteers with MCI, it was concluded as superior to the placebo in improving cognitive functions (May et al., 2009).

5. CONCLUSION

There has been much research to investigate the scientific basis to understand the traditional uses of CHMs for dementia. Other research has associated plant species not used traditionally for dementia with mechanistic effects suggesting potential relevance for use in AD. For plant species

investigated in both circumstances, there is considerable variation in the extent of the research performed. Available data range from extensive pharmacological and clinical studies on plant extracts, including those standardized to contain specific levels of constituents (e.g., *Ginkgo biloba*), and on SCEs (e.g., huperzine A), to studies that are limited to pharmacological tests with such species not adequately evaluated for safety and efficacy in robust RCTs (e.g., *Acorus calamus*). In addition to the need for more extensive pharmacological studies and RCTs to investigate efficacy of promising CHMs for dementia, evaluation of their safety is also needed.

Other challenges for the investigation of CHMs for their potential relevance in AD include their standardization to known active constituents. Relatively few plants that modify cognitive functions, or those with relevance to BPSD, have been extensively studied to determine the compounds responsible to mediate such effects. More research is needed on their modes of action, and on whether they are therapeutically active and bioavailable at appropriate clinical doses. Other complexities include understanding polyvalent and synergistic effects, which is particularly difficult to elucidate for CHM formulae composed of a mixture of different species. Other factors to consider are the effects of traditional processing methods on the chemical and pharmacological profiles of CHMs and how this may impact on their potential for therapeutic use in AD. It is under these circumstances that the appropriate qualitative and quantitative chemical profiles of specific CHMs must be investigated to determine their safety and efficacy.

In conclusion, CHMs provide a vast resource for biologically active constituents that may be therapeutically useful in AD, either in the form of standardized extracts or as SCEs. Further research on the role of CHMs in AD therapy is important to explore further, and should encompass respect for TCM theory and traditions, while also involving robust chemical and pharmacological tests, reliable RCTs, and consideration of the conservation of biodiversity and the sustainable uses of plants.

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