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Review article

Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function

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Abstract

In traditional practices of Ayurvedic and Chinese medicine, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer's disease (AD). An ethnopharmacological approach has provided leads to identifying potential new drugs from plant sources, including those for cognitive disorders. Many drugs currently available in Western medicine were originally isolated from plants, or are derived from templates of compounds isolated from plants. Some anticholinesterase (anti-ChE) alkaloids isolated from plants have been investigated for their potential in the treatment of AD, and are now in clinical use. Galantamine, isolated from several plants including *Lycoris radiata* Herb., which was used in traditional Chinese medicine (TCM), is licensed in the United Kingdom for the treatment of mild to moderate AD. Various other plant species have shown pharmacological activities relevant to the treatment of cognitive disorders, indicating potential for therapeutic use in disorders such as AD. This article reviews some of the plants and their active constituents that have been used in traditional Ayurvedic medicine and TCM for their reputed cognitive-enhancing or antiageing effects. Plants and their constituents with pharmacological activities that may be relevant for the treatment of cognitive disorders, including enhancement of cholinergic function in the central nervous system (CNS), anti-inflammatory and antioxidant activities, are discussed.

Keywords: Alzheimer's disease; Dementia; Acetylcholinesterase inhibitors; Anti-inflammatories; Antioxidants; Plants

1. Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disease that primarily affects the elderly population, and is estimated to account for 50–60% of dementia cases in persons over 65 years of age (Francis et al., 1999).

The main symptoms associated with AD involve cognitive dysfunction, primarily memory loss (Desgranges et al., 1998; Förstl et al., 1995; Grafman et al., 1990; Grosse et al., 1991). Other features associated with the later stages of AD include language deficits, depression, behavioural problems including agitation, mood disturbances and psychosis (Kumar et al., 1998; McGuffey, 1997; Wragg and Jeste, 1989).

The aetiology of AD remains unknown but several factors have been suggested that appear to reduce the incidence of the disease, or for which a hypothesis has been put forward based on scientific investigations. However, none of these theories have been completely accepted since they are largely based on epidemiological studies, and other factors might be responsible for the differences observed. Nevertheless, these factors have been targeted in the search for new drugs to treat AD.

The pathological features that have been identified in the central nervous system (CNS) in AD are senile plaques and neurofibrillary tangles, oxidative and inflammatory processes and neurotransmitter disturbances. A consistent neuropathological occurrence associated with memory loss is a cholinergic deficit, which has been correlated with the severity of AD (Bierer et al., 1995; Collerton, 1986; Giacobini, 1990; Perry et al., 1978; Perry, 1986; Plotkin and Jarvik, 1986; Read, 1987). Thus, attempts to restore cholinergic function have been a rational target for drugs used to treat the symptoms of AD. Approaches to enhance cholinergic function in AD have included stimulation of cholinergic receptors or prolonging the availability of acetylcholine (ACh) released into the neuronal synaptic cleft by inhibiting ACh hydrolysis by acetylcholinesterase (AChE);

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the latter may be achieved through the use of AChE inhibitors.

Some AChE inhibitors have been licensed for clinical use to treat mild to moderate AD cases, but their effect is only to alleviate symptoms and they do not achieve any permanent improvement. The synthetic drug tacrine (Cognex) was the first AChE inhibitor to be licensed, but its routine use has been restricted largely due to its hepatotoxicity (Hammel et al., 1990; Watkins et al., 1994). The use of tacrine has been eclipsed by the newer AChE inhibitors such as donepezil (Aricept, Eisai, Pfizer, UK), rivastigmine (Exelon, Novartis, UK) and galantamine (Reminyl, Shire, UK).

The use of anti-inflammatory agents has also been suggested to delay the progression of AD. Several studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of developing AD, and that patients with rheumatoid arthritis, who often use NSAIDs, have a lower incidence of AD (Breitner, 1996; Breitner et al., 1995; Jenkinson et al., 1989; McGeer et al., 1990, 1996). Thus, the use of anti-inflammatory drugs has been proposed as a therapeutic target in AD. Also implicated in the pathology of many diseases, including neurodegenerative diseases such as AD, are free radical reactions, which are reported to initiate cell injury (Maxwell, 1995; Slater, 1984; Spiteller, 1993). Consequently, the use of antioxidants has been explored in an attempt to slow AD progression and neuronal degeneration.

In traditional practices of medicine, plants have been used to enhance cognitive function and to alleviate other symptoms associated with AD. Plant constituents may not only act synergistically with other constituents from the same plant but may also enhance the activity of compounds, or counteract toxic effects of compounds, from other plant species. This approach has been used in various practices of traditional medicine, including Ayurveda and traditional Chinese medicine (TCM) where a combination of plants is frequently prescribed. An ethnopharmacological approach may be useful in providing leads to identify plants and potential new drugs that are relevant for the treatment of cognitive disorders, including AD.

This article reviews the pharmacological basis of some plants and their active constituents that have been used in traditional Ayurvedic medicine and TCM for their reputed cognitive-enhancing effects. The reputed effects for some traditional herbal drugs may not only be relevant in managing the cognitive decline that can be associated with general ageing but may also be relevant in the treatment of specific cognitive disorders such as AD. Thus, plants reputed to have ‘antiageing’ or ‘memory-enhancing’ effects could also be considered for potential efficacy in disorders now recognised to be associated with cognitive dysfunction, including conditions that feature dementia. Plants that have shown favourable effects in relation to cognitive disorders, including anticholinesterase (anti-ChE), anti-inflammatory and antioxidant activities, or other relevant pharmacological activities indicating the potential for clinical use, are discussed.

2. Plants used in traditional Ayurvedic medicine

2.1. Celastrus paniculatus Willd.

C. paniculatus (Celastraceae) seeds and seed oil have been used in Ayurvedic medicine for “stimulating intellect and sharpening the memory” (Nadkarni, 1976; Warrier et al., 1995). Most of the studies undertaken to establish any pharmacological basis for the reputed effects have focused on the seeds and seed oil. When administered orally to rats, the seed oil decreased levels of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) in the brain, which was correlated with an improvement in learning and memory processes; in addition, the oil was not shown to be neurotoxic (Nalini et al., 1995). Administration of the seed oil to rats also reversed a scopolamine-induced task deficit, but this effect was not associated with anti-ChE activity (Gattu et al., 1997). An antioxidant effect in the CNS, observed with an aqueous seed extract, may also explain the reputed benefits on memory, since this extract enhanced cognition in vivo (Kumar and Gupta, 2002a). A seed extract is also reported to increase brain phospholipid content in vivo, possibly as a consequence of increased myelination (Bidwai et al., 1987). The ‘appropriate plant part’ of *C. paniculatus*, as recommended in Ayurveda, was extracted in methanol and evaluated for *N*-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) receptor binding and nerve growth factor (NGF) effects, but did not show any response (Dev, 1997). If the correct plant part, as indicated in Ayurveda (i.e., seeds), was used in this study, then a more lipophilic solvent may have been preferred for extraction, since the seed oil reputedly and pharmacologically has been associated with the cognitive-enhancing effects. Thus, inactivity cannot be concluded until less polar extracts have also been subjected to similar investigation.

Studies on the flowers from *C. paniculatus* have shown a methanol extract to be anti-inflammatory (Ahmad et al., 1994), which may also have some relevance in the management of neurodegenerative disorders. The studies conducted to date regarding this plant have not identified the active constituents, nor has any therapeutic potential been established for use in AD patients. Thus, further investigation is required.

2.2. Centella asiatica L.

One ancient Ayurvedic remedy is *C. asiatica* (Umbelliferae), which is reputed to restore youth, memory and longevity (Kapoor, 1990). For example, an Ayurvedic formulation composed of four herbs, including *C. asiatica*, is used to retard age and prevent dementia, and the herb combined with milk is given to improve memory (Manyam,

1999). *C. asiatica* has also been used to treat rheumatic disorders, which suggests it may have anti-inflammatory effects. In TCM, *C. asiatica* has been used for combating physical and mental exhaustion (Brinkhaus et al., 2000; Duke and Ayensu, 1985).

The essential oil (0.1% of the plant) extracted from *C. asiatica* leaf contains monoterpenes, including bornyl acetate, α-pinene, β-pinene and γ-terpinene (Asakawa et al., 1982; Brinkhaus et al., 2000), which are reported to inhibit AChE (Miyazawa et al., 1997; Perry et al., 2000a; Ryan and Byrne, 1988) (Fig. 1). However, monoterpene AChE inhibitors are weak compared to the anti-ChE alkaloid, physostigmine (Perry et al., 2000a). In view of the relatively weak anti-ChE activity of monoterpenes reported to date, it is unlikely that they would be therapeutically effective in cognitive disorders. However, analogues of active terpenoid compounds could be developed to enhance efficacy. Although alkaloids (e.g., hydrocotylin) have been identified in *C. asiatica* (Duke and Ayensu, 1985), they have yet to be evaluated for activity against AChE.

The pharmacological basis to explain the reputed anti-amnesic effects of *C. asiatica* has been explored experimentally. Studies have shown an alcoholic extract to be tranquillising in rats, an activity that was attributed to a triterpene, brahmoside (Kapoor, 1990; Sakina and Dandiya, 1990). Further studies showed the extract of *C. asiatica* leaf to be sedative, antidepressant and potentially cholinomimetic in vivo (Sakina and Dandiya, 1990). These findings suggest that *C. asiatica* may be appropriate to treat symptoms of depression and anxiety in AD, and that it may also influence cholinergic activity, and thus cognitive function. Cognitive-enhancing effects have been observed in rats following oral administration of an aqueous extract of *C. asiatica*; this effect was associated with an antioxidant mechanism in the CNS (Kumar and Gupta, 2002b).

Alterations in other neurotransmitter systems have been associated with AD pathology (Advokat and Pellegrin, 1992; Fowler et al., 1992; Nordberg, 1992; Palmer et al., 1987a,b; Reinikainen et al., 1988; Seidl et al., 2001; Storga et al., 1996; Uchihara et al., 1992). Some drugs that modulate neurotransmitter systems have shown some benefits in AD-related symptoms (e.g., trazodone improved behavioural problems associated with AD) (Lake and Grossberg, 1987; Lebert et al., 1994; Simpson and Foster, 1986). An aqueous extract of *C. asiatica* leaf modulated dopamine, 5-HT and noradrenaline systems in rat brain and improved learning and memory processes in vivo (Nalini et al., 1992).

Glutamate may induce neuronal degeneration by overstimulation of NMDA receptors. Memantine, an NMDA receptor antagonist, is licensed for the treatment of moderately severe to severe AD and it is therapeutically effective (Winblad and Poritis, 1999; Reisberg et al., 2002). The triterpene asiatic acid (found in *C. asiatica*) and its derivatives have been shown to protect cortical neurons from glutamate-induced excitotoxicity in vitro (Lee et al., 2000); thus, further research regarding the clinical potential of these compounds may be warranted.

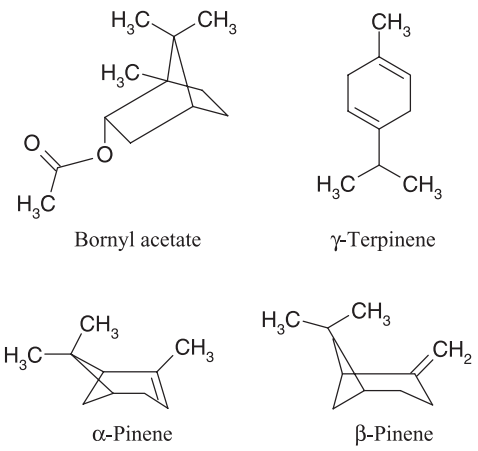

Fig. 1. Chemical structures of monoterpenoid acetylcholinesterase inhibitors.

2.3. Clitoria ternatea L.

The roots of the Indian medicinal plant *C. ternatea* (Leguminosae) have a reputation for promoting intellect (Misra, 1998; Warrier et al., 1995). This reputed effect may be related to effects on cholinergic activity in the CNS, as some studies have shown. A study investigating both the aerial parts and roots of *C. ternatea* showed alcoholic root extracts to be more effective in attenuating memory deficits in rats compared to aerial parts (Taranalli and Cheeramkuzhy, 2000). Enhanced memory retention following oral administration of *C. ternatea* root extract was associated with increased levels of ACh and choline acetyltransferase (ChAT) in rat brain, but any relationship with inhibition of AChE activity was not established, and cortical AChE activity was actually found to be increased (Taranalli and Cheeramkuzhy, 2000). An aqueous extract of the root also increased ACh levels in rat hippocampus following oral administration, and it was hypothesised that this effect may be due to an increase in ACh synthetic enzymes (Rai et al., 2002).

An alcoholic extract, obtained from the stem, flowers, leaves and fruits of *C. ternatea*, was sedative in mice (Kulkarni et al., 1988), but this study does not distinguish which plant part was responsible for the observed effects, and roots were excluded; thus, information regarding potential sedative effects of *C. ternatea* is lacking. Further studies are necessary to establish the mechanism of action to explain the observed effects of the root extract on the CNS and to identify the compounds responsible for activity.

2.4. Curcuma longa L.

Regarded as a ‘rasayana’ herb in Ayurveda (to counteract ageing processes), *C. longa* (Zingiberaceae), known in English as ‘turmeric,’ has also been used for culinary

purposes. Much research has focused on curcumin, a curcuminoid from *C. longa* rhizomes. In particular, studies have shown that some curcuminoids are associated with antioxidant and anti-inflammatory activities, but studies with particular attention to cognitive disorders and any clinical effects are lacking. In addition, further evaluation of potentially active compounds from *C. longa*, other than the curcuminoids, may contribute to the understanding of the traditional uses of this herb.

The antioxidant activity of curcumin is well documented (Das and Das, 2002; Miquel et al., 2002; Priyadarsini, 1997; Scartezzini and Speroni, 2000). Curcumin was shown to be neuroprotective against ethanol-induced brain injury in vivo following oral administration; an effect that was related to a reduction in lipid peroxide levels and enhancement of glutathione in rat brain (Rajakrishnan et al., 1999). Some compounds from *C. longa*, including curcumin, demethoxycurcumin, bisdemethoxycurcumin and calebin-A (and some of its synthetic analogues) (Fig. 2), were shown to protect PC12 cells from β-amyloid insult in vitro (Kim and Kim, 2001; Park and Kim, 2002); this activity was also suggested to be due to an antioxidant effect (Kim et al., 2001).

Curcumin is also reported to be anti-inflammatory (Miquel et al., 2002) and has been suggested to modulate eicosanoid biosynthesis and to inhibit cyclooxygenase (COX)-1, COX-2 and lipoxygenase (LOX) (Ramsewak et al., 2000; Skrzypczak-Jankun et al., 2000; Srivastava et al., 1995). Another activity that is perhaps relevant to the management of symptoms of cognitive-related disorders is antidepressant activity. An aqueous extract of *C. longa* demonstrated antidepressant activity in mice following oral administration, which was associated with inhibition of brain monoamine oxidase (MAO) A (Yu et al., 2002).

2.5. Other plants used in traditional Ayurvedic medicine

In Ayurveda, herbal medicines with rasayana effects are believed be restorative, to attain longevity, intelligence and freedom from age-related disorders. *Acorus calamus* (Araceae) root is regarded in Ayurvedic medicine as promoting rasayana effects (Manyam, 1999) and has been used to treat

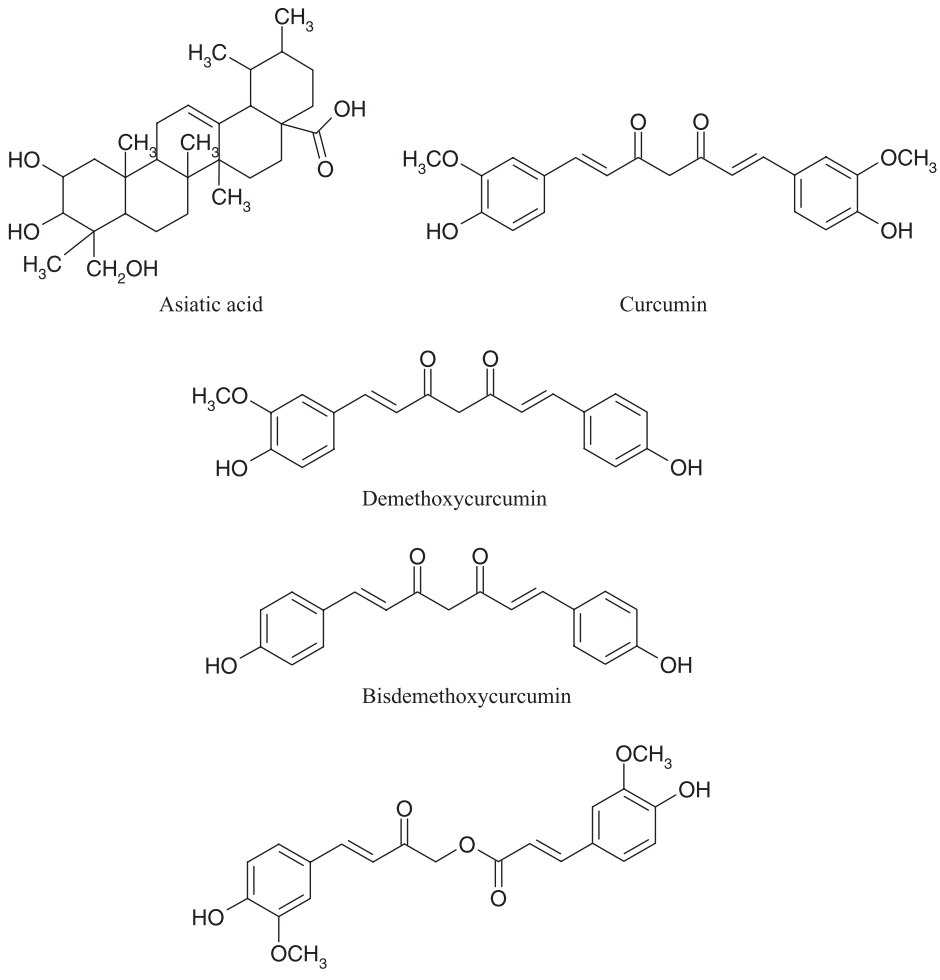

Fig. 2. Chemical structures of compounds, isolated from plants used in traditional Ayurvedic medicine, with activities relevant to the treatment of cognitive disorders.

memory loss. An ethanolic *A. calamus* root extract and α- and β-asarone, isolated from the essential oil, are reported to exert sedative effects and potentiate hypnosis in vivo (Vohora et al., 1990; Zanoli et al., 1998). The root has also shown antioxidant activity in vitro (Acuna et al., 2002). More specifically, in relation to the reputed effects in traditional medicine, *A. calamus* root extract protected rats against acrylamide-induced neurotoxicity and reduced the incidence of paralysis (Shukla et al., 2002).

The ripe fruit of *Terminalia chebula* (Combretaceae) is regarded as a promoter of intellect and memory, and is believed to prolong life (Manyam, 1999; Misra, 1998). The ripe fruit (unripe fruit is reported to produce different effects) is reputed to retard the ageing process and to improve cognitive processes (Manyam, 1999), thus suggesting apparent benefits in AD. There is a general lack of research substantiating the reputed effects in Ayurveda, and only a limited number of studies provide some explanation for the reputed effects. A methanol extract is reported to bind to NMDA and GABA receptors, but did not show anti-ChE activity (Dev, 1997); however, this study only provides limited data and further investigation should be conducted to gain more conclusive information regarding any pharmacological basis of activity. Another study showed an aqueous extract of *T. chebula* to be antioxidant (Naik et al., 2002).

3. Plants used in TCM

3.1. Ginkgo biloba L.

The use of *G. biloba* (Coniferae) in circulatory disorders dates back to the 1960s, but it has also been used in TCM for respiratory disorders (Kenner and Requena, 1996). *G. biloba* has also been used traditionally in Iran to improve memory loss associated with blood circulation abnormalities (Ross, 2001). Numerous investigations have been conducted regarding the potential of *G. biloba* in cognitive disorders. The *G. biloba* extract EGb 761 has shown biological activities relevant to the treatment of cognitive dysfunction. There is some evidence (electroencephalographic data) to suggest that *G. biloba* extract EGb 761 has a local effect in the CNS (Maurer et al., 1997); in addition, this extract has shown various biological activities relevant to the treatment of cognitive dysfunction. Favourable effects have been observed on cerebral circulation and neuronal cell metabolism (Heiss and Zeiler, 1978; Loffler et al., 2001; Tea et al., 1987), on the muscarinic cholinergic system (Kristofiková et al., 1992), and the extract showed antioxidant activity (Barth et al., 1991; Marcocci et al., 1994; Topic et al., 2002). EGb 761 was also neuroprotective against β-amyloid- and nitric oxide (NO)-induced toxicity in vitro (Bastianetto et al., 2000a,b), and could reduce apoptosis both in vitro and in vivo (Schindowski et al., 2001; Yao et al., 2001). EGb 761, and a terpene lactone isolated from it (bilobalide), were protective against ischaemia-induced neuronal death and reductions in mitochondrial gene expression in vivo (Chandrasekaran et al., 2001).

G. biloba extracts have also been evaluated for their influence on cognitive function. Treatment with *G. biloba* extracts attenuated scopolamine-induced amnesia in rats (Chopin and Briley, 1992), enhanced memory retention in both young and old rats (Petkov et al., 1993) and improved short-term memory in mice (Stoll et al., 1996).

Further studies have demonstrated the clinical efficacy of *G. biloba*. Extracts, including EGb 761, have been associated with modest improvements in cognitive function following administration to both AD and non-AD patients in various studies, including randomised, double-blind, placebo-controlled, multicentre trials (Hofferberth, 1994; Kanowski et al., 1997; Le Bars et al., 1997, 2000, 2002; Oken et al., 1998; Rai et al., 1991; Rigney et al., 1999). However, a number of the studies assessing the clinical efficacy of *G. biloba* base the results on self-assessment questionnaires; thus, the reliability of the results may require confirmation through the use of more objective methods of analysis. However, the numerous investigations in vitro and in vivo that do show *G. biloba* to display numerous pharmacological activities in relation to AD treatment apparently support the results of clinical studies.

The compounds responsible for these pharmacological and clinical observations require further investigation, but activity is perhaps due to vasodilatory flavonoids (Kuboto et al., 2001), although other mechanisms of action may also be responsible for the favourable effects observed. For example, ginkgolide B from *G. biloba* is a platelet-activating factor (PAF) antagonist (Braquet et al., 1994), which indicates activity against inflammatory processes.

With reference to the numerous studies conducted, it is apparent that *G. biloba* may be useful in the treatment of AD symptoms, but further research is necessary to identify appropriate dosing regimens, potential effects of long-term use, interactions with other medicines, and standardisation of extracts must also be a consideration.

3.2. Huperzia serrata Thunb.

The prescription Qian Ceng Ta has been used in TCM to alleviate problems of memory loss (Foster, 1989; Skolnick, 1997) and *H. serrata* (from which Qian Ceng Ta is prepared) is used in TCM for promoting circulation, for fever and for inflammation. Huperzine A, isolated from *H. serrata* (Lycopodiaceae), is a lycopodium alkaloid related to the quinolizidines and it reversibly inhibits AChE in vitro and in vivo (Ashani et al., 1992; Laganière et al., 1991; McKinney et al., 1991; Wang et al., 1986); it may also favourably affect other neurotransmitter systems to improve memory (Ou et al., 2001).

Huperzine A improved memory retention processes in cognitively impaired aged and adult rats (Lu et al., 1988). This alkaloid also attenuated cognitive deficits in chron-

ically hypoperfused rats (Wang et al., 2000), and in gerbils following ischaemia (Zhou et al., 2001a). These observations suggest huperzine A has clinical potential in cerebrovascular disorders as well as in AD. In a multicentre, double-blind trial, huperzine A significantly improved memory and behaviour in AD patients, and was reported to be more selective for AChE than butylcholinesterase (BuChE) and was less toxic than the synthetic AChE inhibitors donepezil and tacrine (Shu, 1998; Small et al., 1997).

AChE inhibition may not be the only explanation for the clinical effects observed with huperzine A, as it has also been shown to be neuroprotective. Huperzine A was neuroprotective against β-amyloid peptide fragment 25–53 (Xiao et al., 2002), oxygen-glucose deprivation (Zhou et al., 2001b), free-radical-induced cytotoxicity (Xiao et al., 1999) and glutamate (Ved et al., 1997); huperzine A is also reported to act as an NMDA receptor antagonist in the cerebral cortex (Wang et al., 1999). A mechanism has been proposed to explain the action of huperzine A against apoptosis. Zhou and Tang (2002) reported that huperzine A attenuates apoptosis by inhibiting the mitochondria-capase pathway, thus inhibiting apoptosis.

3.3. *Lycoris radiata* Herb.

Galantamine is an Amaryllidaceae alkaloid isolated from the Chinese medicinal herb *L. radiata* Herb. (and also from the European *Galanthus nivalis* L. and *Narcissus* spp.) (Bores et al., 1996). It is reported to be more selective for AChE than BuChE, and provides complete oral bioavailability (Bickel et al., 1991; Fulton and Benfield, 1996; Harvey, 1995). Galantamine is licensed in Europe for AD treatment and was well tolerated and significantly improved cognitive function when administered to AD patients, in multicentre randomised controlled trials (Wilcock et al., 2000; Wilkinson and Murray, 2001). Galantamine is also reported to stimulate nicotinic receptors (Pearson, 2001; Woodruff-Pak et al., 2001), which may also enhance cholinergic function and memory. This additional activity suggests galantamine may have therapeutic advantages over other AChE inhibitors. Clinical studies have also shown galantamine to improve symptoms in hemiplagia due to cerebral haemorrhage (Chang and But, 2001). Another alkaloid isolated from *L. radiata*, lycoramine, is also reported to have anti-ChE activity (Irwin and Smith, 1960), but it has not been subjected to the vigorous pharmacological and clinical testing to which galantamine has been subjected. However, it is evident that members of the Amaryllidaceae may be a source of other anti-ChE alkaloids that show promise for clinical use.

3.4. *Magnolia officinalis* Rehder & Wilson

The bark of the root and stem of *M. officinalis* (Magnoliaceae) has been used in TCM to treat anxiety and nervous disturbances. Extracts of *M. officinalis* and its isolated compounds have been evaluated in numerous studies to substantiate the reputed activities. Particular attention has been paid to the biphenolic lignans isolated from *M. officinalis*, honokiol and magnolol. One study investigated a traditional Chinese prescription (Banxia Houpu), consisting of *Pinellia ternata*, *Poria cocos*, *M. officinalis*, *Perilla frutescens* and *Zinziber officinale*, which was shown to be antidepressant in vivo (Luo et al., 2000).

Typically, as with other 'antidementia' drugs, activities relevant to cholinergic function have been explored in an attempt to explain the reputed effects of *M. officinalis*. Honokiol and magnolol increased ChAT activity and inhibited AChE activity in vitro, and increased hippocampal ACh release in vivo (Hou et al., 2000). Other activities relevant to AD pathology have also been identified. The anxiolytic effects of honokiol (Kuribara et al., 1999; Kuribara et al., 2000) and magnolol (which are perhaps relevant in the symptomatic management of AD) have been attributed to their ability to potentiate GABAergic neurotransmission (Squires et al., 1999). *M. officinalis* extracts (Zhou and Xu, 1992) magnolol (Chen et al., 2001; Kong et al., 2000; Lo et al., 1994) and honokiol (Chiu et al., 1997; Lo et al., 1994) are also reported to have antioxidant activity, and magnolol was neuroprotective against chemical hypoxic damage and necrotic cell death in cortical neuron-astrocyte cultures in vitro (Lee et al., 1998). In addition, magnolol showed anti-inflammatory activity in vitro and in vivo, perhaps via inhibition of COX and 5-LOX (Wang et al., 1992, 1995). *M. officinalis*, particularly honokiol and magnolol, apparently have multiple actions appropriate for AD therapy. Further research to evaluate the therapeutic potential of this plant is a justifiable aim in the search for effective drugs for AD.

3.5. *Polygala tenuifolia Willd.*

P. tenuifolia (Polygalaceae) root is used in TCM as a cardiotonic and cerebrotonic, as a sedative and tranquilliser, and for amnesia, neuritis and insomnia (Chang and But, 2001; Duke and Ayensu, 1985). According to the *Chinese Materia Medica*, the root is supposed to have a special effect upon the will and mental powers, improving understanding and strengthening the memory.

There have been numerous studies regarding the reputed memory-enhancing potential of *P. tenuifolia* root, many of which have focused on the traditional Chinese prescription DX-9386. DX-9368 is composed of four herbs (*Panax ginseng*, *P. tenuifolia*, *Acorus gramineus* and *P. cocos*) and it has shown favourable effects in relation to AD symptoms in several animal models. DX-9386 improved motor activity, reduced lipid peroxidation, ameliorated memory impairment and prolonged the life span of senescence-accelerated mice and, ameliorated the ethanol- and scopolamine-induced memory impairment in mice (Nishiyama et al., 1994a,b,c; Zhang et al., 1994b). Further investigations are required to clarify the contribution of

each of the four herbs in DX-9386 to the observed pharmacological activities.

P. tenuifolia has also been used in traditional Japanese medicine and is a component of Kami-utan-to (KUT), a prescription that contains 12 other herbs, which is used for the treatment of psychoneurological diseases. KUT dose-dependently up-regulated ChAT activity and increased NGF secretion in vitro, it improved passive avoidance behaviour and induced ChAT activity in the cerebral cortex of aged rats and in scopolamine-induced memory-impaired rats (Yabe et al., 1997; Yamada and Yabe, 1997). The effects on ChAT activity and NGF secretion in vitro were not as pronounced when treated with KUT in the absence of *P. tenuifolia* root, but *P. tenuifolia* root extract alone did up-regulate ChAT activity and increase NGF secretion in vitro (Yabe et al., 1997; Yamada and Yabe, 1997). The cinnamic acid derivative sinapinic acid, from *P. tenuifolia* root, increased ChAT activity in the frontal cortex in brain-lesioned rats (Yabe et al., 1997). These results suggest that *P. tenuifolia* root, particularly the cinnamic acid derivatives, significantly contribute to the pharmacological activities of KUT, and may explain the reputed beneficial effects of *P. tenuifolia* in both TCM and traditional Japanese medicine. A clinical study showed KUT treatment in AD patients to improve memory-related behaviour (Yamada and Yabe, 1997).

P. tenuifolia root extract alone has been shown to reverse scopolamine-induced cognitive impairment in rats, it was neuroprotective against glutamate and toxic metabolites of amyloid precursor protein (APP) in vitro, and it dose-dependently inhibited AChE activity in vitro (Park et al., 1996, 2002). Polygalasaponins from *P. tenuifolia* are reported to have dopamine and 5-HT receptor antagonist properties, and thus have been suggested for treatment of psychosis (Chung et al., 2002), perhaps relevant in patients with other CNS disorders such as AD.

The reputed favourable effects of *P. tenuifolia* root in CNS disorders may also involve anti-inflammatory activity. An aqueous extract of *P. tenuifolia* root inhibited interleukin-1 (IL-1)-mediated tumour necrosis factor (TNF) secretion by astrocytes in vitro (Kim et al., 1998) and also dose-dependently inhibited ethanol-induced IL-1 secretion in vitro (Koo et al., 2000). *P. tenuifolia* may have potential as a tranquilliser, as an aqueous extract is reported to prolong hexobarbital sleeping time in mice (due to onjisaponin F) (Chang and But, 2001; Huang, 1993; Tang and Eisenbrand, 1992).

It is apparent that further research is necessary to fully elucidate the pharmacological mechanisms and active compounds, to explain the activities observed with *P. tenuifolia* extracts and traditional prescriptions. Thus, an evaluation of the clinical potential of this herb and isolated compounds in neurodegenerative disorders may be a valuable pursuit.

3.6. Salvia miltiorrhiza Bung.

Throughout history, *S. miltiorrhiza* (Labiatae) has been used for the treatment of various medical conditions. The dried root of *S. miltiorrhiza* is red in colour, and was therefore used in folk medicine for the management of blood disorders. It is prescribed in TCM to stabilise the heart and calm nerves (Huang, 1993). Official indications for the root include treatment of blood circulation disorders, insomnia, neurasthenia and alleviation of inflammation (Tang and Eisenbrand, 1992).

S. miltiorrhiza, or Chinese sage, has been the subject of thorough investigation, and consequently, numerous pharmacological activities that may be relevant in CNS disorders, including AD, have been identified. *S. miltiorrhiza* has been employed for the treatment of cerebral vascular disease (and has shown benefits in some patients (Chang and But, 2001)), and there are several studies to investigate possible mechanisms for the protective effect of *S. miltiorrhiza* against cerebral ischaemia.

S. miltiorrhiza root has been implicated in attenuating dysfunction of vasoactive intestinal peptide (VIP), a neuropeptide distributed within the gastrointestinal tract and CNS, which may participate in the changes that occur in cerebral ischaemia (Kuang et al., 1989). Distribution abnormalities of the neuropeptide substance P have also been associated with some CNS disorders, including AD. Decreased levels of substance P are reported in the AD brain (Quigley and Kowall, 1991) and have been suggested as a consequence of neuronal damage following cerebral ischaemia; *S. miltiorrhiza* root has been implicated in protecting neurons from ischaemia (Kuang et al., 1991), and so may actively protect against cerebral ischaemia and perhaps other CNS disorders via this mechanism.

S. miltiorrhiza root may inhibit neuronal cell death by inhibition of presynaptic glutamate release (Kuang and Xiang, 1994); modulation of glutamatergic activity is now recognised as a therapeutic target in AD. It has been suggested that inhibition of NO formation could also explain the CNS protective effects observed with *S. miltiorrhiza* root (Kuang et al., 1996a). It should also be considered that the biological function of NO has been suggested to involve the effects of excitatory amino acids, including their effects on brain development, learning and memory (Moncada et al., 1991). This physiological role may aid the explanation of the effects of *S. miltiorrhiza* root on the CNS. Further investigations indicate *S. miltiorrhiza* root may modify ischaemic cell changes by modulating somatostatin (Kuang et al., 1993), a CNS neuropeptide that has been implicated in learning and memory (Dutar et al., 2002; Lamirault et al., 2001).

S. miltiorrhiza root may offer an additional therapeutic approach to management of stroke and ischaemia. Reperfusion to aid recovery of ischaemia can cause further brain damage. During reperfusion, metabolism of free fatty acids from the breakdown of lipid membranes during ischaemia has been proposed to generate oxygen free radicals leading to further brain injury (Traystman et al., 1991). *S. miltiorrhiza* root has been shown to offer protection against this process by reducing lipid peroxidation (Kuang et al.,

1996b; Liu et al., 1992; Peigen et al., 1996; Zhao et al., 1996).

In view of the potential relevance of antioxidants in cerebrovascular disease and AD, numerous compounds responsible for the antioxidant effects of *S. miltiorrhiza* have been identified. Several quinones isolated from *S. miltiorrhiza* root have demonstrated an antioxidant effect in lard, with dihydrotanshinone, tanshinone I, methylene tanshinquinone and cryptotanshinone providing significant antioxidant activity; tanshinone IIa has shown no antioxidant activity (Weng and Gordon, 1992; Zhang et al., 1990). Other components of *S. miltiorrhiza* root have displayed antioxidant effects including salvianolic acids A and B (compounds found to protect against memory impairment induced by cerebral ischaemia in mice (Du et al., 2000; Guanhua and Juntian, 1997)), rosmariquinone (also known as miltirone) and several other phenolic compounds (Huang and Zhang, 1992; Kang et al., 1997; Liu et al., 1992; Weng and Gordon, 1992).

'*Salvia* compositus' is a herbal mixture of the Chinese herbs *S. miltiorrhiza* and *Dalbergia odorifera*, which has been used traditionally for management of coronary heart disease (Fan et al., 1979). Investigations suggest this herbal remedy has a potential role in antioxidation of lipids (Zhang et al., 1994a), and in amelioration of cerebral oedema (Kuang et al., 1995). *Salvia* compositus has also shown effects on electrical activities of the cerebral cortex, showing a CNS depressant action (Fan et al., 1979). There are also reports of *S. miltiorrhiza* root being analgesic and sedative. A reduction in the spontaneous activity of mice and increased duration of the hypnotic action induced by chloral hydrate and barbiturates in the presence of *S. miltiorrhiza* root have been observed (Huang, 1993; Chang and But, 2001). Further investigation has established a structure–activity relationship for rosmariquinone, a quinone isolated from *S. miltiorrhiza* root, as an active central benzodiazepine receptor ligand (Chang et al., 1991). Rosmariquinone and perhaps other quinones from *S. miltiorrhiza* may explain the tranquillising effects observed, and could be developed as anxiolytic agents for managing the behavioural disturbances often observed in AD patients.

Tanshinones isolated from *S. miltiorrhiza* root have demonstrated anti-inflammatory activity in mice and were active against 5-LOX in porcine leukocytes but were not as active as the crude extracts (Chang and But, 2001; Paulus and Bauer, 2000). Tanshinone I was anti-inflammatory in vivo, it inhibited type IIA recombinant phospholipase A_2 and it inhibited prostaglandin (PG) E_2 formation in vitro but did not affect COX-2 activity or expression (Kim et al., 2002). The tanshinones are also reported to show weak oestrogenic activity (Chang and But, 2001). These activities require further investigation for confirmation, but may be of some relevance in AD prevention or therapy. However, it must be considered that the majority of studies that suggest anti-inflammatory drugs prevent or delay the onset of AD, are associated with the use of the COX inhibiting NSAIDs (Breitner, 1996; Breitner et al., 1995; Jenkinson et al., 1989; McGeer et al., 1990, 1996). Thus, any contribution of *S. miltiorrhiza* (which may not affect COX-2 activity (Kim et al., 2002)) in the prevention or delay of AD symptoms via anti-inflammatory activity remains questionable until further investigations have been conducted. Further assessment of the relevance of *Salvia* species in CNS disorders is discussed by Perry et al. (2000b).

3.7. Other plants used in TCM

Nicotine is reported to up-regulate nicotinic receptors and to increase ACh release (Balfour and Fagerström, 1996; Flores et al., 1992; Whitehouse and Kalaria, 1995). Thus, nicotinic agonists (particularly those which are not associated with the adverse effects of nicotine, e.g., vascular disorders) may enhance cholinergic neurotransmission in AD. A crude alcoholic extract of *Angelica archangelica* (Umbelliferae), which has been used in TCM for cerebral diseases (Ross, 2001), displaced nicotine binding to nicotine receptors in a concentration-dependent manner (Perry et al., 1996), but it is unknown if this effect was due to agonistic or antagonistic binding. *A. archangelica* also inhibited AChE activity in vitro (Park et al., 1996) and is reported to enhance cerebral blood flow (Ross, 2001).

Biota orientalis (Coniferae) is used in TCM for insomnia and amnesia. An herbal prescription (S-113m) composed of *B. orientalis*, *P. ginseng* and *Schisandra chinensis* preferentially improved memory registration and consolidation (rather than memory retrieval) in mice (Nishiyama et al., 1995b). The seed extract of *B. orientalis* ameliorated the memory-acquisition disorders induced by amygdala and also basal forebrain lesions in mice (Nishiyama et al., 1992, 1995a).

In TCM, *Codonopsis pilosula* (Campanulaceae) root is used for various disorders including amnesia, and is believed to promote blood circulation and enhance vitality (Duke and Ayensu, 1985). *C. pilosula* extract reduced the impairment of memory acquisition in vivo (Wang et al., 1998) and has shown nootropic effects (Zhang and Liu, 1990).

Coptis chinensis (Ranunculaceae) has been used in TCM for several conditions. A methanol extract fraction of *C. chinensis*, jatrorrhizine and berberine are MAO inhibitors (Kong et al., 2001), indicating potential antidepressant activity, and *C. chinensis* and some alkaloids isolated from this plant (berberine, coptisine and palmatine) are reported to be anti-ChE (Huang, 1993; Park et al., 1996; Shigeta et al., 2002). *C. chinensis* has also shown anti-inflammatory (Cuéllar et al., 2001) and antioxidant activities (Liu and Ng, 2000; Schinella et al., 2002; Song et al., 1992) and it improved a scopolamine-induced learning and memory deficit in rats (Hsieh et al., 2000). As well as inhibiting AChE, the alkaloids coptisine, palmatine and berberine in particular, also showed NGF-enhancing activity in PC12 cells (Shigeta et al., 2002) (Fig. 3).

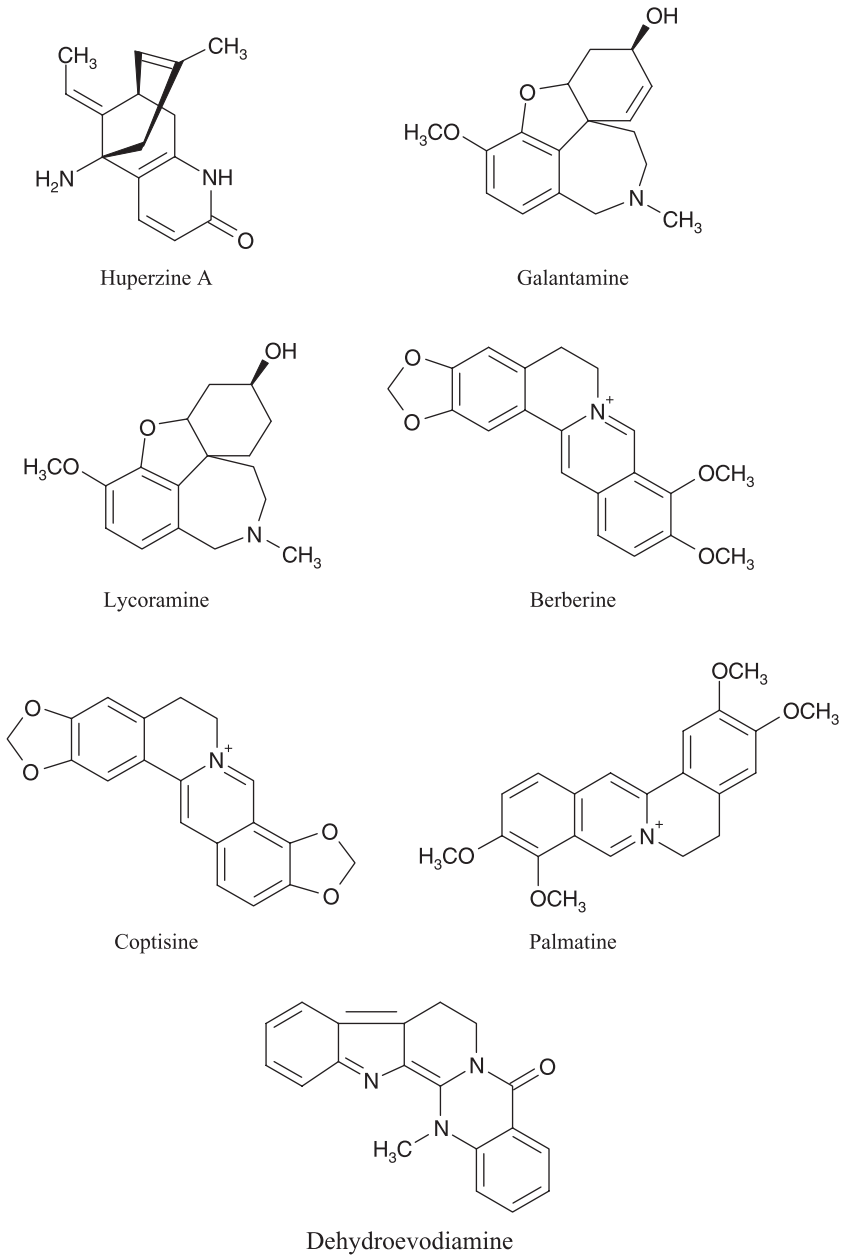

Fig. 3. Chemical structures of alkaloid acetylcholinesterase inhibitors.

Crocus sativus (Iridaceae) was used in TCM to treat disorders of the nervous system. *C. sativus* extract and crocin improved ethanol-induced impairment of learning behaviour in mice (Abe and Saito, 2000; Sugiura et al., 1995a), an effect that may be related to an antagonistic effect on ethanol-induced impairment of hippocampal synaptic plasticity (Sugiura et al., 1995a,b). In addition, crocin suppressed TNF-α-induced apoptosis of neuronally differentiated PC12 cells in vitro (Soeda et al., 2001) (Fig. 4).

Evodia rutaecarpa (Rutaceae) is used in TCM for cardiotonic, restorative and analgesic effects. Pharmacological activities relevant to AD have been identified with the herb extract and with some alkaloids isolated from this plant. Rutaecarpine inhibited COX-2 activity in vitro, and rutaecarpine and limonin were anti-inflammatory in vivo (Matsuda et al., 1998; Moon et al., 1999). *E. rutaecarpa* and dehydroevodiamine inhibited AChE in vitro and reversed scopolamine-induced memory impairment in rats (Park et al., 1996), and dehydroevodiamine increased cerebral blood flow in vivo (Haji et al., 1994). Numerous TCM prescriptions used for CNS disorders have also been investigated for the pharmacological basis of their activities. For example, the decoction Banxia Houpu (composed of five herbs including *M. officinalis*) was antidepressant in vivo (Luo et al., 2000) and a TCM prescription, Oren-gedoku-to (Huang-Lian-Jie-Du-Tang: composed of four herbs includ-

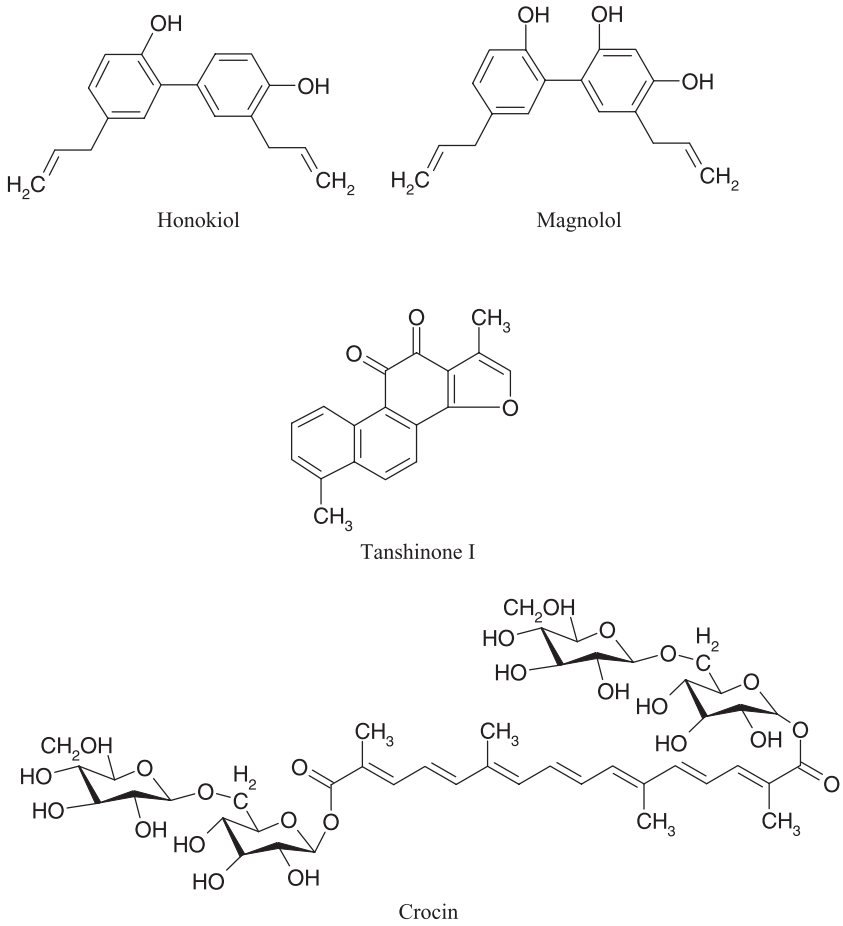

Fig. 4. Chemical structures of compounds, isolated from plants used in TCM, with activities relevant to the treatment of cognitive disorders.

ing *C. chinensis*), has shown numerous effects suggesting it is an advantageous treatment in cognitive disorders. Antioxidant (Fushitani et al., 1995; Hayashi et al., 2001; Ohta et al., 1997) and anti-inflammatory (including via inhibition of COX-2) activities (Dai et al., 2000; Fukutake et al., 2000; Wang and Mineshita, 1996), neuroprotection (including in the cholinergic system) against ischaemia (Kabuto et al., 1997; Kondo et al., 2000) and a protective action against impairment of learning and memory following ischaemia are some of the activities that have been observed with Oren-gedoku-to. However, some TCM prescriptions that claimed to prevent memory disorders have not been shown to be effective. The TCM preparation NaO Li Su (composed of bee pollen and five herbs including *Polygonum multiflorum* and *S. miltiorrhiza*) did not improve cognitive function in a double-blind placebo-controlled crossover trial (Iversen et al., 1997).

4. Conclusion

It is apparent that a variety of plants show, or have the potential to show, numerous activities that may be relevant to the treatment of cognitive disorders such as AD. The majority of studies have focused on enhancement of cholinergic function, with particular attention being paid to the anti-ChE alkaloids, such as galantamine. This is perhaps a reflection of the relative success of the use of AChE inhibitors in AD patients, and a lack of understanding of the pathological mechanisms that occur in AD and the subsequent targets for treatment. However, numerous studies have shown that a diverse array of compounds, and not just the anti-ChE alkaloids, may have potential for efficacy in cognitive disorders.

Although some plants, such as *G. biloba*, have shown beneficial effects on cognitive function, further studies regarding the compounds responsible for activity are necessary to identify which compounds are responsible for the pharmacological activities observed, or if compounds act synergistically to enhance activity. For many of the plants and compounds that have shown activities relevant to AD therapy, clinical data are very limited. Clinical efficacy and potential toxicity of active plants and compounds in larger trials require further assessment before recommendations regarding their use can be established.

In conclusion, it is apparent that the pharmacological activities of plants often appear to reflect their uses in traditional practices of medicine. The ethnopharmacological approach for selecting plants to investigate for the treatment of a particular disease is a relatively successful method to identify plants and compounds that may be exploited, for use therapeutically in neurodegenerative and other cognitive disorders.

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