Traditional used plants against cognitive decline and Alzheimer disease

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INTRODUCTION

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized clinically by progressive memory deficits, impaired cognitive function, and altered and inappropriate behavior (Mattson, 2004). AD represents the most common form of dementia, which places a considerable and increasing burden on patients, caregivers, and society. Aging represents the most important risk factor and dementia has become one of the major challenges in our societies due to the universal phenomenon of population aging in the world (Qiu et al., 2007). Brain regions involved in learning and memory processes, including the temporal and frontal lobes as well as the hippocampus, are reduced in size in AD patients as the result of degeneration of synapses and death of neurons (Arendt, 2009). AD is considered as a protein aggregation disorder, based on two key neuropathological hallmarks, namely the hyperphosphorylation of the tau protein resulting in the formation of neurofibrillary tangles (NFTs), and the increased formation and aggregation of amyloid-beta peptide (Aβ) derived from amyloid precursor protein (APP) (Haass and Selkoe, 2007). Although the exact underlying cause initiating the onset of AD is still unclear, an imbalance in oxidative and nitrosative stress, intimately linked to mitochondrial dysfunction, characterizes already early stages of AD pathology (Müller et al., 2010).

ALZHEIMER – A WORLDWIDE PROBLEM WITH SPECIAL IMPACT FOR DEVELOPING COUNTRIES

To understand neurodegenerative diseases is one of the major challenges of the twenty-first century. The United Nations estimate that the number of people suffering from age-related neurodegeneration, particularly from AD, will exponentially increase from 25.5 million in 2000 to an estimated 114 million in 2050 (Wimo et al., 2003). Several meta-analysis have resulted in roughly similar estimates of dementia prevalence across regions. The estimated global dementia prevalence in people aged over 60 is approximate 3.9% with regional prevalence being 1.6% in Africa, 3.9% in Eastern Europe, 4.0% in China, 4.6% in Latin America, 5.4% in Western Europe, and 6.4% in North America (Qiu et al., 2009). The global annual incidence of dementia is estimated to be around 7.5 per 1000 population (Ferri et al., 2005), with no substantial variations across continents except Africa, where incidence rates are reported to be lower than in other regions. The incidence rate of dementia increases exponentially with age and incidence rates across regions of dementia are quite similar (Qiu et al., 2007, 2009). The risk of AD grows exponentially with age, doubling approximately every 5–6 years (Ziegler-Graham et al., 2008). The largest increase in absolute numbers of old persons will occur in developing countries; it almost triples from 249 mio in 2000 to an estimated 690 mio in 2030. The developing regions’ share of the worldwide aging population will increase from 59 to 71% (Qiu et al., 2007). Most people with dementia live in developing countries (60% in 2001). Rates of increase are not uniform; numbers in developed countries are estimated to double between 2001 and 2040, but by more than 300% in India, China, and their south Asian and western Pacific neighbors (Ferri et al., 2005). Hence, the global trend in the phenomenon of population aging has dramatic consequences for public health, healthcare financing, and delivery systems in the word and, especially in developing countries (Qiu et al., 2007).

TREATMENT OF ALZHEIMER’S DISEASE – FROM MEDICAL CHEMISTRY TO PLANTS

The current standard of care for mild to moderate AD includes treatment with acetylcholine esterase inhibitors, such as donepezil or rivastigmine, to improve cognitive function. The NMDA
(N-methyl-d-aspartate) antagonist memantine has also been shown to improve cognitive function in patients with moderate to severe AD (Citron, 2010). Nimodipine, an L-type calcium current blocker or piracetam, a nootropicum, almost complete the list of non-alternative drugs to treat AD (Tsolaki et al., 2001; Evans et al., 2004). In addition, common non-cognitive neuropsychiatric symptoms, such as mood disorder, agitation, and psychosis often require the introduction of medication, even tough no existing drug is specifically indicated for their management. However, there is no approved treatment with a proven disease-modifying effect (Citron, 2010) and interventions with current drugs, if started early enough, may at best slow down the fatal pathophysiological alterations leading to manifestation of clinical AD symptoms, but are unable reverse the neurodegenerative process.

Beside synthetic drugs, a variety of AD related medicine originates from traditionally used plants. In this respect, Ginkgo biloba and galantamine represent the most famous cases.

**GINKGO BILOBA – FROM TRADITIONAL CHINESE MEDICINE TO A STANDARDIZED DRUG**

Originally, Ginkgo biloba (Coniferae) has been traditionally used for respiratory disorders in China and to improve memory loss associated with blood circulation abnormalities in Iran (Howes et al., 2003). This herb has been subjected to numerous investigations regarding its potential in cognitive disorders. Standardized extracts, particularly EGb 761, derived from the plants’ leaves are successfully used as herbal drug for the improvement of cognitive and memory impairment (for review see Kumar, 2006). EGb 761 represents a prototype of plant extracts for attenuating CNS disorders, due to the fact that both flavonoids and terpenic lactones, which are partly also present in numerous other plant extracts, have been identified as the active principles in Ginkgo extracts as well as the ample experimental evidence on EGb 761’s protective efficiency *in vitro* and *in vivo*. The potential of EGb 761 to attenuate the cytotoxic effects of Alzheimer’s related neurotoxic amyloid peptides when added to the culture medium was demonstrated not only in neuronal-like cell lines but also primary neurons, though with different efficiency (Bastianetto et al., 2000; Yao et al., 2001; Eckert et al., 2005). The impact of Ginkgo extract has been largely attributed to its antioxidant activity (Yao et al., 2001). The effects of oxidative stress were reduced in lymphocytes and brain cells derived of EGb 761-treated AD-transgenic and non-transgenic mice (Schindowski et al., 2001; Abdel-Kader et al., 2007). Recent data, however, indicate that EGb 761 also affects the production of neurotoxic beta-amyloid peptides (Aβ), for example, by up-regulating α-secretase activity both in cells and animals (Abdel-Kader et al., 2007).

In aged and/or AD transgenic mice, EGb 761 treatment resulted in improved memory compared to control animals (Stoll et al., 1996; Tang et al., 2002). The mechanisms responsible for latter observation are still a matter of debate. Whereas Luo et al. (2003) reported changes in APP load in rats treated with Ginkgo extract (100 mg/kg b.w.) for 15 days, Garcia-Alloza et al. (2006) suggested changes in the extent of oxidative stress to account for the neuroprotection in EGb 761-fed AD mice. Interestingly, the EGb 761-associated reduction in Aβ plaque-linked oxidative stress in mice brain was unaffected by plaque size or number. Similarly, Tg2576 transgenic mice benefited from repeated EGB 761 oral intake, evident by improved spatial memory, although soluble and Aβ plaque burden was unaffected (Stackman et al., 2003). Paradoxically, protein oxidation increased in Ginkgo-treated animals (Stackman et al., 2003). The authors speculated that metabolic alterations, mediated by vasodilatory and trophic effects of EGb 761, might be responsible for this finding.

New promising targets for better understanding the molecular mode of EGb 761 action arises from microarray studies. Ginkgo supplementation (300 mg/kg diet) induced differential changes in mRNA expression in mouse hippocampus and cortex. Noteworthy, in the cortex, mRNA for neuronal tyrosine/threonine phosphatase 1 and microtubule-associated Tau were significantly enhanced. Both proteins are associated with the formation as well as breakdown of toxic, AD-typical NFTs (Watanabe et al., 2001).

Recently, the safety and effectiveness of a traditional Ginkgo fresh extract was tested clinically (Baurle et al., 2009). The tested patients suffered from age-related mild cognitive impairment of the non-Alzheimer type. About half of all patients experienced an improvement in their memory and their ability to concentrate, as well as a decrease in symptoms of forgetfulness. The holistic fresh Ginkgo extract was found to be safe and, at least, adjuvant treatment option for patients with mild cognitive impairments (Baurle et al., 2009).

In a nutshell, many placebo-controlled clinical trials proved G. biloba to be a useful herbal remedy for attenuating symptoms in dementia, with efficiency comparable to those of standard drugs in AD treatment (Le Bars, 2003). This notion has been confirmed in a recent 3-month study in comparison to donepezil (Mazza et al., 2006). Furthermore, EGb 761 has been suggested to prevent neurodegenerative pathologies (Christen, 2004). The ongoing GuidAge study, a double-blind randomized trial, will shed further light on the efficiency of EGB 761 in the prevention of AD (Andrieu et al., 2008).

**GALANTAMINE – FROM FOLK TO MODERN MEDICINE**

Galantamine is an alkaloid known form several members of the Amaryllis family (Amaryllidaceae), and the idea for developing a medical product for AD from these species seems to be based on the local use of one of these species in a remote part of Europe. It has become an important therapeutic options used to slow down the process of neurological degeneration in AD. Its development from little known observational studies in the Caucasus Mountains (Southern Russia), to the use of this drug in Eastern European countries (esp. Bulgaria) in the treatment of poliomyelitis and ultimately to the recent introduction onto Western markets in the treatment of AD (Heinrich, 2010). Galantamine was first isolated from snowdrop (Galanthus spp.) but today it is obtained from Narcissus spp. and Leucojum spp. as well as synthetically (Heinrich and Lee Teoh, 2004). According to unconfirmed reports, in the 1950s, a Bulgarian pharmacologist noticed the use of the common snowdrop growing in the wild by people who were rubbing it on their foreheads to ease nerve pain. Also, some of the earlier publications indicate the extensive use of snowdrop in Eastern Europe, such as Romania, Ukraine, the Balkan Peninsula, and in the Eastern Mediterranean countries. However, Mashkovsky and Kruglikova-Lvov (1951) published the first work that establishes the acetyl-
choline esterase inhibiting properties of galantamine isolated from Galanthus woronowii. Poliomyelitis was one of the first indications for galantamine, especially in the Eastern and Central European, since the compound enhances nerve impulse transmission at the synapse. Studies indicating blood–brain barrier penetration of the alkaloid pioneer the development of CNS-related indications. Based on the knowledge of galantamine in both the peripheral and central nervous system, many countries in Eastern Europe used it as an acknowledged treatment in Myasthenia gravis and muscular dystrophy, residual poliomyelitis paralysis symptoms, trigeminal neuralgia, and other forms of neuritis. A crucial step for the success of galantamine as a medicine against AD was based on the synthesis developed in the mid-1990s. The scientific rationale for using cholinesterase inhibitors in the management of AD is based on the cholinergic hypothesis. Impairment of the central cholinergic system represents one hallmark of AD, which is characterized by loss of cholinergic neurons in the forebrain and a marked decrease in the activity of choline acetyltransferase. Overall, galantamine represents an example for the successful ethnobotany-driven development of a natural product into a clinically important drug (Heinrich, 2010).

In the last years, focus on AD drug discovery is shifting away from AChE inhibitors and a large number of other targets are currently being explored.

However, mounting evidence obtained in vitro and in vivo suggests that various traditionally used plants significantly affect key metabolic alterations culminating in AD-typical neurodegeneration. While the impact of the aforementioned traditional used plants on AD has been reviewed comprehensively (Howes et al., 2003; Houghton and Howes, 2005; Akhondzadeh and Abbasi, 2006; Yan et al., 2007), the purpose of the present article is to bring the reader up-to-date on the most recent studies and advances describing the direct and indirect activities of plant constituents possibly relieving features of AD. Recently tested AD related drug targets include AChE activity (Oh et al., 2004; Joshi and Parle, 2006; Ren et al., 2006; Lin et al., 2008; Vasudevan and Parle, 2009), antioxidative activity (Pendry et al., 2005; Lee et al., 2007; Dhanasekaran et al., 2009), modulation of Aβ-producing secretase activities (Fujiwara et al., 2006, 2009; Dhanasekaran et al., 2009; Lv et al., 2009; Wang and Du, 2009; Zhou et al., 2009), Aβ-degradation (Lee et al., 2007; Yang et al., 2009), heavy metal chelating (Ren et al., 2006), neurotrophic factors (Yabe et al., 2003), and cell death mechanisms (Yu et al., 2005; Table 1).

The majority of recent reports on plants with traditional uses and activities relevant for AD originate from the traditional Chinese and Oriental Medicine, as well as from Campo Ayurveda and Mediterranean traditional knowledge.

**PLANTS FROM TRADITIONAL ASIAN MEDICINE**

Ginseng products are popularly referred to as “adaptogen,” which connotes that these products purportedly increase to physical, chemical, and biological stress and builds up general vitality, including physical and mental capacity for work. Panax ginseng roots are traditionally taken orally as adaptogens, aphrodisiacs, nourishing stimulants, and in the treatment of sexual dysfunction in men. The fresh root, can be directly chewed, or soaked in various wines for a period of time before drinking or chewing. Ginseng is most often available either in whole or sliced dried form. However, usually ginseng is used at subclinical doses for a short period and as such, it does not produce measurable medicinal effects (Jia et al., 2009). Panax notoginseng is widely used in traditional Chinese medicine (TCM) to improve learning and memory (Wang and Du, 2009). Moreover, protective actions against cerebral ischemia, beneficial effects on the cardiovascular system, and haemostatic, antioxidant, hypolipidemic, hepatoprotective, renoprotective, and estrogen-like activities have been described (Ng, 2006).

Ginsenoside Rgl1, a major active component of sanchi ginseng (P. notoginseng), was shown to inhibit β-secretase activity in vitro, to protect PC12 cells against Aβ25–35 (Wang and Du, 2009), and to exert neuroprotective effects (Jia et al., 2009). It has to be noted that Wang and Du (2009) treated neuronal-like cells with excessive Aβ concentrations of 50 μM for 48 h.

Ginsenoside Rg3, one of the major active components of sanchi ginseng significantly reduced the levels of Aβ1–40 and Aβ1–42 in SK–N–SH cells transfected with Swedish mutant beta-APP. Enhanced Aβ degradation is due to Ginsenoside Rg3-induced neprilysin expression (Yang et al., 2009), which represents the rate-limiting enzyme in Aβ degradation (Iwata et al., 2000).

Akebia saponin B was found to antagonize Aβ25–35 toxicity in PC12 cells (Zhou et al., 2009). Akebia saponin B belongs to the saponin fraction of a water extract from Dipsacus Asper Wall. This plant is a well-known TCM for enhancing kidney activity and the rational to test this pant for AD originates form the idea that according to TCM, the etiopathogenesis of AD lies in kidney deficiency during aging (Zhou et al., 2009).

Penta-O-galloyl-beta-d-glucopyranoside (PGG), a major component of the traditional herb Paonia suffructosa Andrews (Moutan Cortex), inhibits Aβ fibril formation and destabilizes preformed Aβ fibrils in a concentration dependent manner (Fujiwara et al., 2009). Moreover, the herb improved long-term memory impairment in an AD mouse model and inhibited Aβ accumulation in brains of treated mice (Fujiwara et al., 2009). The traditional Chinese herb Moutan Cortex is commonly used to treat inflammatory and pyretic disorders (Hsieh et al., 2006) and possess potent antioxidant, antimutagenic, and antiproliferative effects (Choi et al., 2002). It was earlier reported that PGG could protect neuronal cells from oxidative stress by induction of HO-1 gene expression (Choi et al., 2002).

Tenuifolin, a crude extract derived from Polygala tenuifolia Willd (Polygalaceae) (PTW) was found to decrease Aβ secretion from transfected cells, probably due to inhibition of the beta-site APP cleaving enzyme (Lv et al., 2009). Treatment of rat cortical neurons with PTW enhanced axonal length density-dependently after Aβ25–35 induced axonal atrophy. However, dendritic atrophy and synaptic loss induced by Aβ25–35 were not recovered after treatment with PTW extract. In contrast, Aβ25–35-induced cell damage was completely inhibited by PTW extract (Naito and Tohda, 2006). PTW is classically mentioned as an anti-dementia drug in Chinese and Japanese traditional medicine (Naito and Tohda, 2006). It has been shown that PFW can improve hippocampus-dependent learning and memory, possibly through improvement of synaptic transmission, activation of the MAP kinase cascade, and enhancement BDNF levels (Xue et al., 2009). Accordingly, PTW up-regulated the expression of BDNF and TrkB mRNA to promote the recovery
| Plant name | Active ingredient | Traditional use | AD drug target | References |
|------------|-------------------|-----------------|----------------|------------|
| *Panax notoginseng* | Ginsenoside Rg1 | TCM; improve learning and memory function | Secretase activity | Wang and Du (2009) |
| *P. notoginseng* | Ginsenoside | TCM; improve learning and memory function | Neprilysin | Yang et al. (2009) |
| *Ginkgo biloba* | Fresh plant extract | TCM; for respiratory disorders, improve memory loss | DemTec cognition score | Baurle et al. (2009) |
| *Dipsacus asper Wall* | Akebia saponin D | TCM; enhancing kidney function | Aβ toxicity | Zhou et al. (2009) |
| *Paonia suffruticosa Andrews* | 1,2,3,4,6-penta-O-galloyl-eta-d-glucopyranose | TCM; to treat inflammatory and pyretic disorders | Aβ fibril formation, stabilization; *in vivo* long-term memory impairment | Fujiwara et al. (2009) |
| *Polygala tenuifolia Willd* | Tenuifolin (extract) | TCM; to improve memory loss | Secretase activity; *in vivo* long-term memory impairment | Lv et al. (2009), Naito and Tohda (2006) |
| *Radix salviae miltiorrhizae* (Dashen) | Triterpenoids; Tanshinone | TCM; to treat heard conditions and stroke | AChE activity; Aβ toxicity *in vivo* and *in vitro*; NOS | Lin et al. (2008), Yin et al. (2008), Liu et al. (2010b) |
| *Danggui-Shaoyao-San* | Extract | TCM, TJM, enhancement of women’s health | Apoptosis *in vitro* | Qian et al. (2008), Hu et al. (2010) |
| *Toki-shakuyaku-san* | JD-30 | TCM; enhancement of blood flow | Learning and memory | Lee et al. (2007, 2010) |
| *Fungi Monascus purpureus* | *Monascus* fermented red rice | TCM; enhancement of blood flow | AChE activity, antioxidant; secretase activity | Lee et al. (2007, 2010) |
| *Uncaria rhynchophylla* | Triterpene esters and uncarinic acids | TCM, oriental medicine; improvement of cardiovascular and nervous system | Aβ aggregation and fibril stabilization | Fujiwara et al. (2006) |
| *Kami-kihi-to* | Composition of 12 crude drug herbs | Kampo; to treat neurosis, amnesia, anemia | Aβ toxicity in vivo: neuritic, synaptic and myelin losses | Tohda et al. (2008) |
| *Yokukansan* | Composition of four crude drug herbs | Kampo; to treat restless leg syndrome and agitation in children | Aβ toxicity in vivo: decrease in the anxiety, increase in locomotor activity in Tg2576 AD mice | Tabuchi et al. (2009), Sekiguchi et al. (2009) |
| *Zokumei-to* | Composition of different crude drug herbs | Kampo; to treat postapoplectic sequelae | Aβ toxicity in vivo; increase in synaptophysin levels, abolishes neuronal loss | Tohda et al. (2003) |
| *Bacopa monnieri* | Bogenines, Steroids, Triterpene | Ayurvedic medicine, improve intelligence and memory | Ameliorates ACh deficits *in vivo* | Uabundit et al. (2010) |
| *Salvia officinalis* | Essential oils, containing cineole, thujone and others | Mediterranean, anti-inflammatory agent | Clinical trial | Akhondzadeh et al. (2003b) |
| *Crocus sativus* | Carotenoids and others | Mediterranean, Asia; to treat treatment for all varieties of gastrointestinal ailments | Clinical trial | Akhondzadeh et al. (2010) |
| *Melissa officinalis* | Terpenes, tannins, Eugenol, Rosmarinic acid | Mediterranean, used as anxiolytic or mild sedative agent | Clinical trial; AChE inhibition *in vitro* | Akhondzadeh et al. (2003a), Dastmalchi et al. (2009) |
| *Murraya koenigii* | Carbazole alkaloids, Scoponin | Indian flavor | Antiamnestic, reduced cholinesterase activity | Vasudevan and Parle (2009) |
| *Cassia obtusifolia* | Obtusifolin | Eastern medicine, used as a topical analgesic and anti-inflammatory natural medicine | AChE inhibition | Kim et al. (2009), Drever et al. (2008) |

(Continued)
of the neurons from chronic stress-induced damages (Sun et al., 2009). The methanol fraction of an ethanolic extract from PTW showed antagonistic action on neurotoxicity induced by glutamate and serum deficiency in PC12 cells (Li et al., 2008a). Some of the active ingredients of PTW are oligosaccharide esters, which provide a high in vivo antioxidant activity in senescence-accelerated mice (Liu et al., 2010a).

Recently, Lin et al. (2008) have tested the anti-acetylcholinesterase activities of aqueous and ethanolic extracts of various TCM. Ethanolic extracts from Caulis spatholobi, Radix paeoniae alba, and Radix salviae miltiorrhiza were found to have the strongest AChE inhibitory activity as indicated by IC50 values lower than 10 μg/mL. The most active extract from Radix salviae miltiorrhiza was further fractionated and found that AChE inhibition is due to the presence of two triterpenoids (Lin et al., 2008) confirming earlier data (Ren et al., 2004). Yin et al. (2008) tested 10 μg/ml extract. The most active extract from the cells with Tanshinone prior to Aβ demonstrated in cortical neurons (Liu et al., 2010b). Pretreatment of the neurons from chronic stress-induced damages (Sun et al., 2009). The methanol fraction of an ethanolic extract from PTW showed antagonistic action on neurotoxicity induced by glutamate and serum deficiency in PC12 cells (Li et al., 2008a). Some of the active ingredients of PTW are oligosaccharide esters, which provide a high in vivo antioxidant activity in senescence-accelerated mice (Liu et al., 2010a).

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Danggui-Shaoyao-San (DSS; Tangkuei or Peony Powder) (Toki-Shakuyaku-San, TSS in Japanese), used as TCM and TJM for centuries for the enhancement of women’s health, e.g., for gynecological and obstetrical purposes (Qian et al., 2008). In early studies it was shown that a powdered extract of DSS ameliorates dysfunction of the central cholinergic nervous system and scopolamine-induced decrease in ACh levels in mouse brain (Itoh et al., 1996). In another study the effects of aqueous extract of Danggui-Shaoyao-San on naturally aged mice were examined to investigate the pharmacological basis for its therapeutic efficacy on senile dementia. In agreement with earlier data (Komatsu et al., 1999) the results showed that DSS improves impaired cognitive function of aged mice. Results indicated that DSS ameliorates age-related memory dysfunction, modulates metabolism of monoamine neurotransmitters, and protects ultra structure of the cortex (Kou et al., 2005). These findings suggest that DSS may be a useful therapeutic agent for senile dementia, especially AD (Kou et al., 2005). Accordingly, in a recent in vitro study, DSS exhibits anti-apoptotic effects after challenging PC12 cells with hydrogen peroxide: the compound counteracts the down regulation of anti-apoptotic BCl-2 protein, the upregulation of pro-apoptotic Bax protein, the release of mitochondrial cytochrome c, and sequential activation of caspases (Qian et al., 2008). Moreover, DSS significantly reduced the Aβ25–35-induced neuronal death and the lipid peroxidation in vivo (Egashira et al., 2005). Accordingly, the DSS extract JD-30 ameliorated Aβ25–35-induced impairment of spatial learning and memory in mice, as well as inhibition of long-term potentiation (LTP) in the hippocampus (Hu et al., 2010).

The seeds of Cassia obtusifolia (Fabaceae) have long been used in traditional eastern medicine and more recently the ethanolic fraction of the seeds has been shown to attenuate memory in mice (Kim et al., 2009). Cassia obtusifolia extract (COE) attenuated calcium dysregulation and promoted mitochondrial protection in mouse primary hippocampal cultures. However, COE had no effect on cell death induced by incubation with oligomeric Aβ (Drever et al., 2008). Gluco-obtusifolin, isolated from the seeds of C. obtusifolia, and its aglycone, obtusifolin, was found to inhibit acetylcholinesterase activity in vitro and ex vivo (Kim et al., 2009). However, a recent study reported C. obtusifolia related hepatotoxicity in chronic hepatitis B patients (Yuen et al., 2006).

Lycium barbarum (Solanaeae; Wolfberry) is a fruit that is known for its eye-protective and anti-aging properties in Asian countries (Ho et al., 2010). Recent in vitro investigations evaluated that pretreatment of rat cortical neurons with an extract isolated from L. barbarum significantly reduced the release of lactate dehydrogenase (LDH). In addition, it attenuated Aβ peptide-activated caspases-3-like activity by reduced phosphorylation of JNK-1 and its substrates c-Jun (Yu et al., 2005). Recently, polysaccharides were identified as active ingredient of L. barbarum that provides protective properties against Aβ and homocysteine (Ho et al., 2010).

Uncaria rhynchophylla (Rubiacaeae) has been used as a TCM for cardiovascular and neurological diseases (Chou et al., 2009) and for convulsive disorders in Oriental medicine (Lee et al., 2003). Triterpene esters and uncarinic acids C and D were identified as

Table 1 | Continued

| Plant name | Active ingredient | Traditional use | AD drug target | References |
|------------|------------------|----------------|----------------|------------|
| Centella asiatica | Triterpen glycosides, saponins | Ayurveda, anxiolytic agent and cerebral tonic | Reducing Aβ in vivo | Dhanasekaran et al. (2009) |
| Fungus Ganoderma lucidum | Ganoderic acid (Triterpen glycoside) | TCM, as anti-tumor, immunomodulatory and immunotherapeutic agent | Preserving synaptic density; preserving Aβ-induced apoptosis | Lai et al. (2008) |
| Desmodium gangeticum | Aminogluconsyl-glycerolipids, cerebrosides | Ayurveda, treatment of neurological disorders | Reserved amnesia, AChE inhibition | Joshi and Parle (2006) |
| Lycium barbarum | Polysaccharides | TCM; used as anti-tumor, immunomodulatory, anti-hypertension agent | Reverses Aβ and homocysteine induced apoptosis | Yu et al. (2005), Ho et al. (2010) |
active components of *U. rhynchophylla* (Shi et al., 2003; Lee et al., 2008; Umeayama et al., 2010). The alkaloids of *U. rhynchophylla* mainly act on the cardiovascular and central nervous system including hypertension, brachycardia, antiarrhythmia, and protection of cerebral ischemia and sedation. The active mechanisms were related to blocking of calcium channels, opening of potassium channels, and regulating of nerve transmitters transport and metabolism (Shi et al., 2003) as well as suppression of c-Jun N-terminal kinase (JNK) phosphorylation (Hsieh et al., 2009). *U. rhynchophylla* significantly inhibited NMDA receptor-activated ion currents in acutely dissociated hippocampal CA1 neurons in cultured brain slices (Lee et al., 2003). Moreover, anxiolytic effects of the aqueous extract of *U. rhynchophylla* were reported (Jung et al., 2006). In view to AD, *U. rhynchophylla* intensively inhibited Aβ aggregation and significantly destabilized preformed Aβ_{40} and Aβ_{42} fibrils (Fujiwara et al., 2006).

*Kami-kihi-to* is a TCM (Jia-Wei-Gui-Pi-Tang), which is composed of 12 crude herbs also used in Japanese kampo tradition. It has been used to treat neurosis, amnesia, anemia, and some other diseases (Nishizawa et al., 1994). Kampo uses fixed combinations of herbs in standardized proportions according to the classical literature of Chinese medicine. Today in Japan, Kampo is integrated into the Japanese health care system (Dharmananda, 2004). Clinically, Kihi-to may improve chronic immune thrombocytopenic purpura (Yamaguchi et al., 1993). However, possible adverse effects on glycaemia were reported (Kawasaki et al., 2000). Recently, effects of Kihi-to on memory deficits and losses of neuritis and synapses were examined using AD mice. Short time administration of Kihi-to resulted in marked improvements of Aβ_{25-35} induced impairments in memory in mice. Kihi-to was shown to attenuate neutritic, synaptic, and myelin losses in brain of cranial Aβ injected mice (Tohda et al., 2008). An aqueous extract of *Ganoderma lucidum* (Ganodermateaeae; Lingzhi mushroom; GLE), a medicinal fungus used clinically in many Asian countries to promote health and longevity was also shown to attenuate Aβ-induced synaptotoxicity by preserving the synaptic density protein, synaptophysin (Lai et al., 2008). In addition, GLE antagonized Aβ(1-40)-triggered apoptotic caspase cleavage and attenuated c-JNK phosphorylation (Lai et al., 2008).

*Yokukansan* (Yi-ga-san), a remedy composed of four herbs, traditionally used for restlessness and agitation in children (Tsuyoshi and Jun, 2009), has in recent times attracted attention as drug to treat dementia including AD (Maruyama et al., 2006; de Caires and Subramanian, 2007; Birari et al., 2010). The results of a recent pilot study indicated that Yokukansan can alleviate the behavioral symptoms of frontotemporal dementia (Kimura et al., 2010). An open-label study suggested that Yokukansan might be effective in the treatment of behavioral and psychological symptoms of dementia (Hayashi et al., 2010). Evidences for a possible mode of action comes from two recent preclinical studies: Yokukansan reduces aggressiveness without suppressing physical activity in mice injected intracerebroventricular with Aβ_{25-35} (Sekiguchi et al., 2009). Using an AD mouse model Tabuchi et al. (2009) demonstrated that Yokukansan ameliorates learning deficits and non-cognitive defects including a decrease in the anxiety and an increase in locomotor activity observed in Tg2576 mice. Only few studies of *Zokumei-to* used as Kampo in Japanese medicine for postapoplectic sequelae have been carried out (Tohda et al., 2003). Kamatsu and coworkers generated pre-clinical evidence for *Zokumei-to* as possible drug for AD (Tamura et al., 2002). Treatment of mice intracerebroventricularly injected with Aβ_{25-35} showed beneficial effects on memory impairment and synaptic loss after Zokumei-to treatment (Tohda et al., 2003).

*Monascus*-fermented red mold rice (RMR), a TCM and health food, include monacolins and multifunctional metabolites. RMR is traditionally used for improvement of blood circulation (Ma et al., 2000). Preparation of RMR following ancient methods by fermenting the fungal strain *Monascus purpureus* Went on moist and sterile rice indicated the presence of a group of metabolites belonging to the monacolin family of polyketides, together with fatty acids, and trace elements. The presence of these compounds may explain in part the cholesterol-lowering ability associated with this traditional Chinese food (Ma et al., 2000). Monacolins, like statins, affect lipid homeostasis by inhibition HMG-CoA reductase the rate-limiting enzyme in cholesterol biosynthesis (Wang and Lin, 2007; Barrios-Gonzalez and Miranda, 2010). Accordingly, oral administration of *Monascus* powder in hyperlipidemic hamsters proved to decrease TC, TG, and LDL-C levels (Lee et al., 2006). In *vitro* studies indicated that ethanolic RMR extract provides stronger neuroprotection in rescuing cell viability as well as repressing inflammatory response and oxidative stress. RMR administration to mice potently reverses the memory deficit in the memory task. Moreover, *in vivo* RMR potentely reversed Aβ_{1-40} infusion induced acetylcholinesterase activity, reactive oxygen species, and lipid peroxidation and increases total antioxidant status and superoxide dismutase activity in brain. Compared to lovastatin the protective activities of RMR was more significant (Lee et al., 2007). A recent study showed that RMR provided neuroprotection by reduction of Aβ_{1-40} formation and deposition due to suppressing the cholesteral-raised beta-secretase activity and apolipoprotein E expression. Moreover, RMR mediated the proteolytic process of APP toward neuroprotective sAPPα secretion in hippocampus (Lee et al., 2010).

**PLANTS FROM TRADITIONAL ORIENTAL MEDICINE**

*Bacopa monnieri* (Scrophulariaceae) has been used in the traditional system of Ayurvedic medicine to improve intelligence and memory (Uabundit et al., 2010). A randomized, double-blind, placebo-controlled trial provides further evidence that *B. monnieri* has potential for safely enhancing cognitive performance in the aging (Calabrese et al., 2008). Recent *in vivo* studies identified neuroprotective effects in a rat model of AD: escape latency time in Morris water maze test was improved and the reduction of neurons was mitigated after *B. monnieri* treatment (Uabundit et al., 2010).

*Murraya koenigii* (Rutaceae) leaves commonly known as curry patta are added routinely to Indian gravy and vegetable dishes as favorite condiment (Vasudevan and Parle, 2009). The leaves of *M. koenigii* are also used as Ayurvedic medicine as antimicrobial, anti-inflammatory, hepatoprotective, anti-hypercholesterolemic, or anti-inflammatory remedy (Xie et al., 2006; Arulselvan and Subramanian, 2007; Birari et al., 2010). Diets composed of *M. koenigii* leaves significantly improved memory scores and reduced amnesia induced by scopolamine and diazepam in young...
and aged mice in a dose dependent manner (Vasudevan and Parle, 2009). Moreover, brain cholinesterase activity and total cholesterol were reduced.

Centella asiatica (Gotu Kola; Mackinlayaceae) is used as leafy green in Sri Lankan cuisine and besides others used medicinally as anxiolytic agent and as cerebral tonic (Bradwejn et al., 2000). Earlier findings indicated that an aqueous extract of C. asiatica is effective in preventing the cognitive deficits, as well as the oxidative stress, caused by intracerebroventricular injection of streptozotocin in rats (Veerendra Kumar and Gupta, 2003). Subsequent studies in neuroblastoma cells expressing Aβ identified the ERK/RSK signaling pathway to be involved in a possible molecular mechanism for memory enhancing property of Gotu Kola extract (Xu et al., 2008). Recently, C. asiatica extract was found to selectively decrease hippocampal Aβ levels in AD mouse model expressing the Swedish’ APP and the M146L presenilin 1 mutations (Dhanasekaran et al., 2009).

Desmodium gangeticum (Fabaceae) commonly known as Salparni, is widely used in ayurveda for the treatment of neurological disorders (Joshi and Parle, 2006). An aqueous extract of Desmodium gangeticum (DGE) was shown to significantly improve learning and memory in mice and reversed the amnesia induced by both, scopolamine and natural aging. DGE also decreased whole brain acetylcholinesterase activity (Joshi and Parle, 2006).

PLANTS WITH TRADITIONAL EUROPEAN USE

Salvia officinalis (Sage; Lamiaceae) traditionally used, e.g., in tea preparations as anti-inflammatory agent, recently attract attention as beneficial in dementia (Akhondzadeh et al., 2003b; Abdel-Kader, R., Hauptmann, S., Keil, U., references). Recently, A. Djebali et al. (2009) identified the ERK/RSK signaling pathway to be involved in a possible molecular mechanism for memory enhancing property of Gotu Kola extract (DGE) and Aβ levels in AD mouse model expressing the Swedish’ APP and the M146L presenilin 1 mutations (Dhanasekaran et al., 2009).

REFERENCES

Abdel-Kader, R., Hauptmann, S., Keil, U., Scherping, L., Leuner, K., Eckert, A., and Müller, W.E. (2007). Stabilization of mitochondrial function by Ginkgo biloba extract (EGb 761). Pharmacol. Res. 56, 493–502.

Akhondzadeh, S., and Abbasi, S. H. (2006). A randomized, double-blind, placebo-controlled, multi-center trial in Iran (Akhondzadeh et al., 2003b; Ahkondzadeh and Abbasi, 2006). At 4 months, S. officinalis extract produced a significant better outcome on cognitive functions than placebo (Akhondzadeh et al., 2003b). Using comparable clinical settings Ahkondzadeh et al. (2003a) also reported beneficial effects for the traditional used remedies Crocus sativus (Iridaceae), traditionally used to treat all varieties of gastrointestinal ailments and Melissa officinalis (Lamiaceae) traditionally used, e.g., as an anxiolytic or mild sedative agent (Akhondzadeh et al., 2010). Recent screening assays identified rosmarinic acid from M. officinalis extracts to potently inhibit AChE (Dastmalchi et al., 2009).

CONCLUSION

Although advances have been made in unraveling AD neuropathology, only few treatment options currently exist. Various potential therapeutic or preventive compounds have been tested in clinical trials, yet most have failed to show a clear therapeutic benefit. The lack of effective therapies in connection with the predicted dramatic increase in AD cases in the coming decades evoke the demand on new drug candidates. Numerous direct and indirect activities of traditional used plants and its constituents that relieve features of AD have been reported recently. Although pre-clinical investigations identified promising drug candidates for AD, clinical evidences are still pending and it can be doubted that the track record of Galantamin or G. biloba extract will be repeated in the near future.
Citron, M. (2010). Alzheimer’s disease: strategies for disease modification. Nat. Rev. Drug Discov. 9, 387–398.

Dastmalchi, K., Ollilainen, V., Lackman, P., Boije af Gennas, G., Dormann, H. J., Jarvinen, P. P., Yli-Kauhaluoma, J., and Hiltunen, R. (2009). Acetylcholinesterase inhibitor guided fractionation of Melissa officinalis L. Biog. Med. Chem. 17, 867–871.

de Caires, S., and Steenkamp, V. (2010). Use of Yokukansan (T-54) in the treatment of neurological disorders: a review. Phytother. Res. 24, 1265–1270.

Dhanasekaran, M., Holcomb, L. A., Citron, M. (2010). Alzheimer’s disease: Chinese medicinal herb, has potent anti-aggregation effects on Alzheimer’s beta-amyloid proteins. J. Neurosci. Res. 84, 427–433.

Fujihara, H., Tabuchi, M., Yamaguchi, T., Iwasaki, K., Furukawa, K., Sekiguchi, K., Ikashiri, Y., Kudo, Y., Higuchi, M., Saito, T. C., Maeda, S., Takashima, A., Hara, M., Yaegashi, N., Kase, Y., and Arai, H. (2009). A traditional medici-
nal herb Paonia suffruticosa and its active constituent 1,2,3,4,6-penta-O-
galloyl-beta-D-glucopyranose have potent anti-aggregation effects on Alzheimer’s amyloid beta proteins in vitro and in vivo. J. Neurochem. 109, 1648–1657.

Garcia-Alloza, M., Dodwell, S. A., Meyer-Luehmann, M., Hyman, B. T., and Bacsaki, B. J. (2006). Plaque-derived oxidative stress mediates distorted neurite trajectories in the Alzheimer mouse model. J. Neuropathol. Exp. Neuropath. 65, 1082–1089.

Haass, C., and Selkoe, D.J. (2007). Soluble protein oligomers in neurodegenera-
tion: lessons from the Alzheimer’s amyloid beta-peptide. Nat. Rev. Mol. Cell Biol. 8, 101–112.

Hayashi, Y., Ishida, Y., Inoue, T., Udagawa, M., Takeuchi, K., Yoshimura, H., Kuie, K., Ninomiya, Y., Kawa, I., Sameshima, T., Kawa, T., Goto, I., Shiado, K., Kurayama, S., Nakamura, J., Ohakara, K., and Mitsuayma, Y. (2010). Treatment of behavioral and psycho-
logical symptoms of Alzheimer-type dementia with Yokukansan in clinical practice. Prog. Neuropsychopharmacol. Biol. Psychiatry 34, 541–545.

Heinrich, M. (2010). Galanthamine from Galanthus and other Amaryllidaceae-chemistry and bio-
ology based on traditional use. Alkaloids Chem. Biol. 68, 157–165.

Heinrich, M., and Lee Troh, H. (2004). Galanthamine from snowdrop – the development of a modern drug against Alzheimer’s disease from local Caucasian knowledge. J. Ethnopharmacol. 92, 147–162.

Ho, Y. S., Yu, M. S., Yang, X. F., So, K. F., Yuen, W. H., and Chang, R. C. (2010). Neuroprotective effects of polysaccha-
rides from wolfberry, the fruits of Lycium barbary, against homocysteine-in-
duced toxicity in rat cortical neurons. J. Alzheimers Dis. 19, 813–827.

Houghton, P. J., and Howes, M. J. (2005). Natural products and derivatives affecting neurotransmission relevant to Alzheimer’s and Parkinson’s disease. Neurosciences 14, 6–22.

Howes, M. J., Perry, N. S., and Houghton, P. J. (2003). Plants with traditional uses and activities, relevant to the manage-
ment of Alzheimer’s disease and other cognitive disorders. Phytother. Res. 17, 1–8.

Hsieh, C. L., Cheng, C. Y., Tsai, T. H., Lin, I. H., Liu, C. H., Chiang, S. Y., Lin, Y. G., Liao, C. J., and Tang, N. Y. (2006). Paenol reduced cerebral infarction involving the superoxide anion and microglia activation in ischemia-reperfusion injured rats. J. Ethnopharmacol. 106, 208–215.

Hsieh, C. L., Ho, T.Y., Su, S.Y., Lo, W.Y., Liu, C. H., and Tang, N.Y. (2009). Uncaria rhynchophylla and Rhynchophylline inhibit c-Jun N-terminal kinase phosphorylation and nuclear factor-
kappaB activity in kainic acid-treated rats. Am. J. Chin. Med. 37, 351–360.

Hu, Z. Y., Liu, G., Yuan, H., Yang, S., Zhou, W. X., Zhang, Y. X., and Qiao, S. Y. (2010). Danggui-Shaoyao-San and its active fraction JD-30 improve Abeta-induced spatial recognition deficits in mice. J. Ethnopharmacol. 126, 358–372.

Ito, T., Sako, Y., Murai, S., Saito, H., Ninomura, K., Itsukaichi, O., Fujihara, H., and Okubo, N. (1996). Regulatory effect of Danggui-Shaoyao-San on central cholinergic nervous system dysfunction in mice. Am. J. Chin. Med. 24, 205–217.

Iwunse, T., De Filippis, D., Esposito, G., D’Amico, A., and Izzo, A. A. (2003). The spic pace and its active ingredi-
ents rosmarinic acid protect PC12 cells from amyloid-beta peptide-induced neurotoxicity. J. Pharmacol. Exp. Ther. 317, 1143–1149.

Iwata, N., Tsubuki, S., Takaki, Y., Watanabe, K., Sekiguchi, M., Hosoki, E., Kawashima-Morishima, M., Lee, H. J., Hama, E., Sekine-Aizawa, T., and Saito, T. C. (2000). Identification of the major Abeta1-42-degrading cata-
bolic pathway in brain parenchyma: cationic emanated from traditional
Chinese medicine. J. Ethnopharmacol. 85, 3171–3182.

Kato, M., Ueda, Y., and Hiramatsu, M. (1999). Different changes in concen-
trations of monoamines and their metabolites and amino acids in various brain regions by the herbal medicine/ Todi- Shakuyaku-San between female and male senescence-accelerated mice (SAMP8) [In Process Citation]. Neurochem. Res. 24, 825–831.

Kou, J., Zhu, D., and Yan, Y. (2005). Neuroprotective effects of the aque-
ous extract of the Chinese medicine Danggui-Shaoyao-san on aged mice. J. Ethnopharmacol. 97, 313–318.

Kumar, V. (2006). Potential medicinal plants for CNS disorders: an overview. Phytother. Res. 20, 1023–1035.

Lai, C. S., Yu, M. S., Yuen, W. H., So, K. F., Zee, S. Y., and Chang, R. C. (2008). Antagonizing beta-amyloid peptide neurotoxicity of the anti-aging fun-
gus Ganoderma lucidum. Brain Res. 1190, 215–224.

Le Bars, P. L. (2003). Magnitude of effect and special approach to Ginkgo biloba extract EGB 761 in cognitive disor-
ders. Pharmacopsychiatry 36(Suppl. 1), S44–S49.

Lee, C. L., Kuo, T. F., Wang, J. I., and Pan, T. M. (2007). Red mold rice ameliorates impairment of memory and learn-
ing ability in intracerebroventricular amyloid beta-infused rat by repress-
ing amyloid beta accumulation. J. Neurosci. Res. 85, 3171–3182.

Lee, C. L., Kuo, T. F., Wu, C. L., Wang, J. I., and Pan, T. M. (2010). Red mold rice promotes neuroprotective SAPPalp ache secretion instead of Alzheimer’s risk factors and amyloid beta expression in hyperlipidemic Abeta40-infused rats. J. Agric. Food Chem. 58, 2230–2238.

Lee, C. L., Tai, T. Y., Wang, J. I., and Pan, T. M. (2006). In vivo hypolipidemic effects and safety of low dosage Monascus powder in a hamster model
of hyperlipidemia. Appl. Microbiol. Biotechnol. 70, 533–540.

Lee, J. Y., Jang, J., Lee, P., Kim, D. K., Shin, M. C., Jang, M. H., Kim, C. J., Kim, Y. S., Kim, S. Y., and Kim, H. (2003). Protective effect of methanol extract of Uncaria rhynchophylla against excitotoxicity induced by N-methyl-D-aspartate in rat hippocampus. J. Pharmacol. Sci. 92, 70–73.

Lee, J. S., Yoo, H., Suh, Y. G., Jung, J. K., and Kim, J. (2008). Structure-activity relationship of pentacyclic triterpene esters from Uncaria rhynchophylla as inhibitors of phospholipase C-gammaII. Planta Med. 74, 1481–1487.

Li, C., Yang, J., Yu, S., Chen, N., Xue, W., Hu, J., and Zhang, D. (2008a). Triterpenoid saponins with neuroprotective effects from the roots of Polygala tenuifolia. Planta Med. 74, 133–141.

Li, M. H., Chen, J. M., Peng, Y., Wu, Q., and Gao, P. (2008b). Investigation of Danshen and related medicinal plants in China. J. Ethnopharmacol. 120, 419–426.

Lin, H. Q., Ho, M. T., Lau, L. S., Wong, K. K., Shaw, P. C., and Wan, D. C. (2008). Anti-acetylcholinesterase activities of traditional Chinese medicine for treating Alzheimer’s disease. Chem. Biol. Interact. 175, 352–354.

Liu, P., Hu, Y., Guo, D. H., Lu, B. R., Rahman, K., Mu, L. H., and Wang, D. X. (2010a). Antioxidant activity of oligosaccharide ester extracted from Polygala tenuifolia roots in senescence-accelerated mice. Pharm. Biol. 48, 828–833.

Liu, T., Jin, H., Sun, Q. R., Xu, J. H., and Hu, H. T. (2010b). The neuroprotective effects of Tanshinone IIA from Danshen and related medicinal plants. Neuropharmacology 59, 594–604.

Luo, C., Wu, Q., Huang, X. N., Sun, A. S., and Shi, J. S. (2003). Ginseng biloba leaf extract enhances levels of caspase-3 and amyloid precursor protein in normal rat hippocampus. Acta Pharmacol. Sin. 24, 152–156.

Lv, J., Jia, H., Jiang, Y., Ruan, Y., Liu, Z., Yue, W., Beyreuther, K., Tu, P., and Zhang, D. (2009). Tenuifolin, an extract derived from tenuigenin, inhibits amyloid-beta secretion in vitro. Acta Physiol. (Oxf.) 196, 419–425.

Ma, J., Li, Y., Ye, Q., Li, J., Liu, Y., Yu, D., Zhang, D., Cooper, R., and Chang, M. (2000). Constituents of red yeast rice, a traditional Chinese food and medicine. J. Agric. Food Chem. 48, 5220–5225.

Maruyama, M., Tomita, N., Iwasaki, K., Ootsuki, M., Matsui, T., Nenomoto, M., Okamura, N., Higuchi, M., Tsutsui, M., Suzuki, T., Seki, T., Kaneta, T., Furukawa, K., and Ariai, H. (2006). Benefits of combining donepezil plus traditional Japanese herbal medicine on cognition and brain perfusion in Alzheimer’s disease: a 12-week observer-blind, donepezil mono-therapy controlled trial. J. Am. Geriatr. Soc. 54, 869–871.

Maslowski, M. D., and Kruglikova-Lyov, R. P. (1951). On the pharmacology of the new alkalioid galantamine. Farmakol. Toxicol. (Moscow) 14, 27–30.

Mattson, M. P. (2004). Pathways towards and away from Alzheimer’s disease. Nature 430, 631–639.

Mazza, M., Capuano, A., Bria, P., and Mazza, S. (2006). Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer’s dementia in a randomized placebo-controlled double-blind study. Eur. J. Neurol. 13, 981–985.

Maurice, W. E., Eckert, A., Kurz, C., Eckert, G. P., and Leuner, K. (2010). Mitochondrial dysfunction: common final pathway in brain aging and Alzheimer’s disease—therapeutic aspects. Mol. Neurobiol. 41, 159–171.

Naito, R., and Tohda, C. (2006). Characterization of anti-neurodegenerative effects of Polygala tenuifolia in Abeta(25–35)-treated cortical neurons. Biol. Pharm. Bull. 29, 1892–1896.

Ng, T. B. (2006). Pharmacological activity of the new alkaloid galantamine. Jpn. J. Pharmacol. 92, 70–73.

Nguyen, X. D. (2008). Aqueous extract of the roots of Polygala tenuifolia Wild YZ-50 on the mRNA expression of brain-derived neurotrophic factor and its receptor TrkB in rats with chronic stress depression. Nan Fang Y. Ke Da Xue Xue Bao 29, 1199–1203.

Tabuchi, M., Yamaguchi, T., Ikarashi, Y., and Kase, Y. (2009). Effects of yokukansan, a traditional Japanese medicine, on aggressiveness induced by intracerebroventricular injection of amyloid beta protein into mice. Phytother. Res. 23, 1175–1181.

Shi, J. S., Yu, J. X., Chen, X. P., and Xu, R. X. (2003). Pharmacological actions of Uncaria alkaloids, Rhynchophylline and Isorychnophylline. Acta Pharm. Sin. 24, 97–101.

Stuckman, R. W., Eckenstein, F., Frei, B., Kulhanek, D., Nowlin, J., and Quinn, J. F. (2003). Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer’s disease by chronic Ginkgo biloba treatment. Exp. Neurol. 184, 510–520.

Stoll, S., Scheuer, K., Pohl, O., and Muller, W. E. (1996). Ginkgo biloba extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse. Pharmacochemistry 29, 144–149.

Sun, Y., Xie, T. T., Wang, D. X., and Liu, P. (2009). Effect of Polygala tenuifolia Wild YZ-50 on the mRNA expression of brain-derived neurotrophic factor and its receptor TrkB in rats with chronic stress depression. Nan Fang Yi Ke Da Xue Xue Bao 29, 1199–1203.

Tang, W. Y., and Du, G. H. (2009). Ginsenoside Rg1 inhibits beta-secretase activity in vitro and protects against Abeta-induced cytotoxicity in PC12 cells. J. Asian. Nat. Prod. Res. 11, 604–612.

Wang, T. H., and Lin, T. F. (2007). Monascus rice products. Adv. Food Nutr. Res. 53, 123–159.

Wang, Y., and Du, G. H. (2009). Hinsenoside Rg1 inhibits beta-secretase activity in vitro and protects against Abeta-induced cytotoxicity in PC12 cells. J. Asian. Nat. Prod. Res. 11, 604–612.

Yamaguchi, T., Ikarashi, Y., and Kase, Y. (2009). Ameliorative effects of yokukansan, a traditional Japanese medicine, on learning and non-cognitive disturbances in the Tg2576 mouse model of Alzheimer’s disease. J. Ethnopharmacol. 122, 157–162.

Yamada, M., and Seki, T. (2008). Protective effect of methanol extract of Uncaria rhynchophylla on cerebral ischemia-hypoxia in rats. Brain Res. 1275, 138–144.

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The in vivo neuromodulatory effects of the herbal medicine *Ginkgo biloba*. *Proc. Natl. Acad. Sci. U.S.A.* 98, 6577–6580.

Wimo, A., Winblad, B., Aguero-Torres, H., and von Strauss, E. (2003). The magnitude of dementia occurrence in the world. *Alzheimer Dis. Assoc. Disord.* 17, 63–67.

Xie, J. T., Chang, W. T., Wang, C. Z., Mehdendale, S. R., Li, J., Ambhaipahar, R., Ambhaipahar, U., Fong, H. H., and Yuan, C. S. (2006). Curry leaf (*Murraya koenigii* Spreng,) reduces blood cholesterol and glucose levels in ob/ob mice. *Am. J. Chin. Med.* 34, 279–284.

Xu, Y., Cao, Z., Khan, I., and Luo, Y. (2008). Gotu Kola (*Centella asiatica*) extract enhances phosphorylation of cyclic AMP response element binding protein in neuroblastoma cells expressing amyloid beta peptide. *J. Alzheimer Dis.* 13, 341–349.

Xue, W., Hu, J. F., Yuan, Y. H., Sun, J. D., Li, B. Y., Zhang, D. M., Li, C. J., and Chen, N. H. (2009). Polygalasaponin XXXII from *Polygala tenuifolia* root improves hippocampal-dependent learning and memory. *Acta Pharmacol. Sin.* 30, 1211–1219.

Yabe, T., Tuchida, H., Kiyohara, H., Takeda, T., and Yamada, H. (2003). Induction of NGF synthesis in astrocytes by onjisaponins of *Polygala tenuifolia*, constituents of kampo (Japanese herbal) medicine, Ninjin-yoei-to. *Phytomedicine* 10, 106–114.

Yamaguchi, K., Kido, H., Kawakatsu, T., Fukuroi, T., Suzuki, M., Yanabu, M., Nomura, S., Kokawa, T., and Yasunaga, K. (1993). Effects of kami-kihi-to (*jia-wei-gi-pi-tang*) on autoantibodies in patients with chronic immune thrombocytopenic purpura. *Am. J. Chin. Med.* 21, 251–255.

Yan, H., Li, L., and Tang, X. C. (2007). Treating senile dementia with traditional Chinese medicine. *Clin Interv Aging* 2, 201–208.

Yang, L., Hao, J., Zhang, J., Xia, W., Dong, X., Hu, X., Kong, F., and Cui, X. (2009). Ginsenoside Rg3 promotes beta-amyloid peptide degradation by enhancing gene expression of neprilysin. *J. Pharm. Pharmacol.* 61, 375–380.

Yao, Z. X., Drieu, K., and Papadopoulos, V. (2001). The *Ginkgo biloba* extract EGB 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands. *Brain Res.* 889, 181–190.

Yin, Y., Huang, L., Liu, Y., Huang, S., Zhuang, J., Chen, X., Zhang, L., Wu, H., Shao, E., and Zhao, Z. (2008). Effect of tanshinone on the levels of nitric oxide synthase and acetylcholinesterase in the brain of Alzheimer’s disease rat model. *Clin. Invest. Med.* 31, E248–E257.

Yu, M. S., Leung, S. K., Lai, S. W., Che, C. M., Zee, S. Y., So, K. F., Yuen, W. H., and Chang, R. C. (2005). Neuroprotective effects of anti-aging oriental medicine *Lycium barbarum* against beta-amyloid peptide neurotoxicity. *Exp. Gerontol.* 40, 716–727.

Yuen, M. F., Tam, S., Fung, J., Wong, D. K., Wang, B. C., and Lai, C. L. (2006). Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study. *Aliment. Pharmacol. Ther.* 24, 1179–1186.

Zhou, Y. Q., Yang, Z. L., Xu, L., Li, P., and Hu, Y. Z. (2009). Akebia saponin D, a saponin component from *Dipsacus asper* Wall, protects PC12 cells against amyloid-beta induced cytotoxicity. *Cell Biol. Int.* 33, 1102–1110.

Ziegler-Graham, K., Brookmeyer, R., Johnson, E., and Arrighi, H. M. (2008). Worldwide variation in the doubling time of Alzheimer’s disease incidence rates. *Alzheimers Dement.* 4, 316–323.

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