Brain Food for Alzheimer-Free Ageing: Focus on Herbal Medicines

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Abstract

Healthy brain aging and the problems of dementia and Alzheimer's disease (AD) are a global concern. Beyond 60 years of age, most, if not everyone, will experience a decline in cognitive skills, memory capacity and changes in brain structure. Longevity eventually leads to an accumulation of amyloid plaques and/or tau tangles, including some vascular dementia damage. Therefore, lifestyle choices are paramount to leading either a brain-derived or a brain-deprived life. The focus of this review is to critically examine the evidence, impact, influence and mechanisms of natural products as chemopreventive agents which induce therapeutic outcomes that modulate the aggregation process of beta-amyloid (Aβ), providing measureable cognitive benefits in the aging process. Plants can be considered as chemical factories that manufacture huge numbers of diverse bioactive substances, many of which have the potential to provide substantial neuroprotective benefits. Medicinal herbs and health food supplements have been widely used in Asia since over 2,000 years. The phytochemicals utilized in traditional Chinese medicine have demonstrated safety profiles for human consumption. Many herbs with anti-amyloidogenic activity, including those containing polyphenolic constituents such as green tea, turmeric, *Salvia miltiorrhiza*, and *Panax ginseng*, are presented. Also covered in this review are extracts from kitchen spices including cinnamon, ginger, rosemary, sage, salvia herbs, Chinese celery and many others some of which are commonly used in herbal combinations and represent highly

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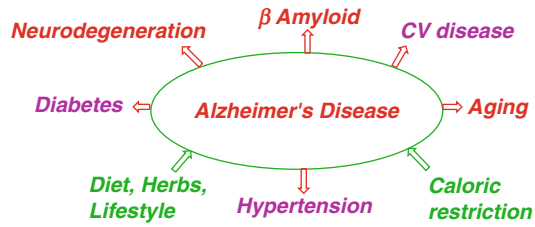
promising therapeutic natural compounds against AD. A number of clinical trials conducted on herbs to counter dementia and AD are discussed.

Keywords
Alzheimer's disease • Dementia • Amyloid-beta • Traditional Chinese medicine (TCM) • Herbal polyphenols

5.1 Beyond the Molecular Frontier – The Threats of Our Age

During the past hundred years, treatments for human diseases have helped raise life expectancy significantly. However, an aging population brings increased burdens and costs to individuals and society from age-related cognitive decline; indeed, the latter has emerged as one of the major health threats and challenges of our age. In another 36 years there will be triple the number of persons 80 years or older, with approximately 50 % of adults over 85 years afflicted with Alzheimer's disease (AD). The total number of new cases of dementia each year worldwide is nearly 7.7 million, which translates to 15 new cases every minute (International 2012). Estimates indicate that between 2 and 10 % of all cases of dementia appear before the age of 65. Advancing age is the highest risk factor for AD, with age-specific prevalence nearly doubling every 5 years beyond the age of 65. The financial estimated worldwide cost of dementia was $604 billion in 2010 (Wimo et al. 2013). Unless we act now, by 2050 the problem will be unmanageable. Recent advances in the biology of aging in model organisms, together with molecular and multidisciplinary studies of neurodegenerative and aging-related disease risks and personal practices (outlined in Scheme 5.1), are beginning to uncover these mechanisms and their potential roles in cognitive decline (Witte et al. 2009; Villeda et al. 2011)

Interrelationships between aging, apolipoprotein E (*APOE*) ε4 allele, oxidative damage, reactive oxygen species (ROS), amyloid metabolism/toxicity and neurodegenerative dysfunctions leading to dementia and AD are highly probable. Nevertheless, the precise mechanisms remain unknown. Ideally, the opportunities for making lifestyle, diet and nutritional choices to enhance human brain and body function is available and practiced by many (Gomez-Pinilla and Tyagi 2013). The theme of positive aging is to be proactive in minimizing/preventing cognitive decline and disease. Dementia and AD research priorities have also advanced from simply considering clinical symptoms. The focus is now more on early detection of the pre-symptomatic phase and the prevalence of early dementia signs, as these are considered to be potential windows of opportunity for successful therapeutic interventions and preventions. For instance, recent research supports mounting evidence implicating dysfunctional lipid metabolism in the pathophysiology of AD indicating that lipid biomarkers have the potential to predict memory impairment at a preclinical stage of AD. Changes in the blood profile of a set of ten lipids critical for proper cell membrane structure and function in elderly persons who showed no signs of cognitive problems, predicted they would go on to develop either mild memory impairment or AD within 2–3 years, with greater than 90 % accuracy (Mapstone et al. 2014).



Scheme 5.1 The interventions and disease risks related to Alzheimer's disease

Humans are able to consume a vast range of foodstuffs. However, the ready availability and low cost of food, and the freedom of being able to eat anything, does not mean that we should maximize eating practices to eat everything (Ulijaszek et al. 2012). The diet-related chronic diseases of modern society are now the single largest cause of death encompassing diabetes, cardiovascular disease, hypertension, obesity and cognitive decline (Scheme 5.1). For foods to promote the health of our aging, physical frailty and mental state, we need to reduce the consumption of processed foods and fatty diets, with negative nutritional attributes such as high-energy refined sugars, saturated fats and high sodium content, whilst increasing affinity and tendency to consume those with positive health attributes including phytochemicals and micronutrient rich foods.

5.2 Herbal Polyphenols – Modulation of Oxidative Stress, Dementia and AD

From our previous analysis of well-designed, randomized double-blind controlled trials on Chinese herbal medicines beneficial for the improvement of cognitive function, we found that neuroprotective benefits of suppression of oxidative stress as the most common feature provided by single herbs or herbal mixtures (May et al. 2009, 2012).

5.2.1 Epigallocatechin-3-Gallate

Oxidative stress may directly initiate neurodegeneration, and herbal antioxidant neuroprotection is considered as a preventative and therapeutic approach (Hugel et al. 2012). Crucially, the scientific evidence confirms that the majority of herbal polyphenolic compounds have a good safety profile, are affordable and are globally readily available to significantly reduce the burden of dementia and AD.

It has been known for at least a decade that polyphenols possess anti-amyloidogenic activity. A diverse range of herbal polyphenolic constituents including tannic acid, quercetin, kaempferol, curcumin, catechin and epicatechin are known to dose-dependently inhibit the formation of amyloid-beta (Aβ) fibrils as well as their elongation. Importantly, polyphenols can bind directly to Aβ or mature aggregates and impair their stability. Epigallocatechin-3-gallate (EGCG), a major component of green tea, significantly inhibits Aβ aggregation and has the ability to remodel large Aβ fibrils into smaller aggregates that are non-toxic (Wang et al. 2010). The gallate functionality in EGCG is critical in facilitating the reduction of Aβ and increasing APP α-proteolysis. Evidence has indicated that EGCG reduces Aβ production in both neuronal and mouse AD models in concert with activation of anti-amyloidogenic amyloid precursor protein (APP) α-processing. An extensive screening of the effect of other gallate-containing phenolic compounds on APP anti-amyloidogenic processing found that long chain gallate esters (Zhang et al. 2013b) such as octyl gallate (OG; 10 mM), a commercial food antioxidant, drastically decreased Aβ generation, in concert with increased APPα-proteolysis in murine neuron-like cells transfected with human wild-type APP or "Swedish" mutant APP. OG markedly increased production of the neuroprotective amino-terminal APP cleavage product, soluble APP-α (sAPPα). OG increases anti-amyloidogenic APPα-secretase processing by activation of ERα/PI3k/Akt signaling and ADAM10. Fish oil has been shown to have a synergistic effect in combination with EGCG, with co-treatment leading to a reduction in Aβ plaque formation and levels of Aβ(1–40) and Aβ(1–42) in AD transgenic Tg2576 mice (Giunta et al. 2010). The potential role of polyphenols in neurodegeneration and the pathogenesis of AD has expanded with discoveries that they can modulate a class of proteins called sirtuins that are involved in longevity and cell survival (Jayasena et al. 2013) (Table 5.1).

EGCG has numerous health-promoting effects (Hugel and Jackson 2012) including anti-cancer, antioxidant, anti-inflammatory, anti-diabetic, anti-aging and in particular its Aβ-sheet disruption (Palhano et al. 2013) capacity

Table 5.1 Anti-amyloidogenic activity of polyphenols and herbal extracts

Polyphenol/herbal extract	Anti-amyloidogenic activity
Investigation of the ability of **EGCG** to inhibit the formation of metal-free or metal-associated Aβ(1–40) aggregates	EGCG interacted with Cu(II)- and Zn(II)-Aβ monomer, dimer species. Formed more compact peptide conformations compared to EGCG-untreated Aβ species; ternary EGCG–metal–Aβ complexes were produced. This illustrates the selective modulation of the anti-amyloidogenic reactivity of EGCG towards metal-Aβ species (Hyung et al. 2013)
Effect of the addition of **EGCG** in drinking water (1.5, 3 mg/kg for 3 weeks) intake in mice	Prevented lipopolysaccharide-induced Aβ production by the inhibition of β-secretase activity, and improved effects on memory deficiency in liposaccharide-induced AD mice models (Lee et al. 2009)
Isothermal titration calorimetry studies on the interactions between **EGCG** and Aβ	EGCG-Aβ binding was enhanced by increasing temperature, salt concentration and at pH values away from the pI of Aβ (Wang et al. 2010)
EGCG encapsulated in nanoparticles	Improved *in vivo* efficacy, doubled bioavailability; improved chemical stability and enhanced its biological activity (Li et al. 2012; Hu et al. 2013; Smith et al. 2010)
Protonation of **EGCG** at low pH	Resulted in aggregation and reduced oral bioavailability of EGCG-dispersed selenium nanoparticles (Wu et al. 2013b)
Modulation of Aβ-induced tau hyperphosphorylation by **curcumin (Cur)** in human neuroblastoma SH-SY5Y cells	Cur inhibits phosphorylation of tau at Thr231 and Ser396 by modulating the phosphatase and tensin homolog (PTEN) PTEN/Akt/GSK-3β pathway. Involves down-regulation of phosphorylation of Akt and of PTEN, a negative regulator of PIP3 induced by Aβ (Huang et al. 2014a)
Effects of **Cur** after 3-month administration to *APPswe/PS1dE9* double transgenic mice, an AD model	Reduced Aβ(1–40) and Aβ(1–42) levels, and aggregation of Aβ-derived diffusible ligands in the mouse hippocampal CA1 area; enhanced expression of γ-secretase; increased expression of β-amyloid-degrading enzymes, including insulin-degrading enzymes and neprilysin (Esatbeyoglu et al. 2012; Wang et al. 2014)
Testing of **Cur**-based fluorescence imaging probes *in vitro* and *in vivo*	Near-infrared fluorescence imaging with the Cur analogue CRANAD-58 revealed interaction with Aβ in mouse brain; CRANAD-17 was capable of inhibiting Aβ42 cross-linking induced by copper (Zhang et al. 2013c)
Targeting of endogenous neural stem cells by **Cur**-encapsulated nanoparticles	Cur nanoparticles: increase neuronal differentiation by activating the Wnt/β-catenin pathway in hippocampal neural stem cells; involved in regulation of neurogenesis; rescued learning and memory impairments in an Aβ-amyloid induced rat model of AD (Tiwari et al. 2014)
Studies on the brain accessibility of **Cur**-lipid-nanoparticles	High affinity for Aβ in post-mortem brains samples of AD patients (Mourtas et al. 2014). Cur-loaded solid lipid nanoparticles showed 30 times higher preferential distribution into the brain (Kakkar et al. 2013)
Anti-amyloidogenic effect of an ethanol extract of ***Magnolia officinalis***: 12.9 % magnolol, 16.5 % honokiol, 16.6 % 4-O–methylhonokiol, plus 42–45 % of other constituents	Administration of 10 mg/kg extract for 3 months inhibited amyloidogenesis, reduced Aβ accumulation via β-secretase 1 (BACE1) inhibition in the brain of Tg2576 mice with memory improving effects (Lee et al. 2012)
2,2′,4′-trihydroxychalcone ***Glycyrrhiza glabra***	Anti-oxidative, anti-tumor, *in vitro* inhibition of BACE1 bioactivity with IC_{50} 2.5 μM, reduced Aβ formation in mice-AD studies (Zhu et al. 2010)

(continued)

Table 5.1 (continued)

Polyphenol/herbal extract	Anti-amyloidogenic activity
Isobavachalcone, bavachinin isolated from ***Psoraleae Fructus***	Contains compounds that inhibit BACE1 (Choi et al. 2008). Isobavachalcone inhibits Aβ oligomerization and fibrillization, bavachinin transforms Aβ into non-toxic aggregates (Chen et al. 2013)
Tenuifolin, a triterpenoid saponin isolated from ***Polygala tenuifolia***	2.0 μg/mL tenuifolin significantly decreased Aβ-secretion from COS-7 cells without altering the ratio of Aβ(1–40) and Aβ(1–42) by BACE1 inhibition (Lv et al. 2009)
Effect of the ***Polygonum multiflorum***extract component 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside (TSG) on the rat Aβ model	Administration of TSG rescued Aβ(1–42) induced impairment in learning and memory, protecting synaptic structures and function; the up-regulation of Src and NR2B may be responsible for the improved learning and anti-AD properties (Zhou et al. 2012)
Effect of ethanol extract of ***Polygonum multiflorum*** in mouse neuroblastoma cells expressing Swedish APP (N2a-SweAPP)	Potent reduction in Aβ production through APP modulation, with the up-regulation of sAPPα and down-regulation of sAPPβ (Liu et al. 2012)
Salvia miltiorrhiza lipophilic constituents: Tanshinone I (TI), Tanshinone (IIA)	Molecular dynamics simulations reveal that TI and TIIA preferentially bind to a hydrophobic β-sheet groove. T1 was better than TIIA for inhibition amyloid–β aggregation; the tanshinones also affected disaggregation of amyloid fibrils, and protection of cultured cells (Wang et al. 2013)
Salvia miltiorrhiza water-soluble constituents: Danshensu and Salvianolic acid B	Protected PC-12 cells by blocking Aβ(25–35) induced Ca^{2+} intake, lactate dehydrogenase release, cell viability decrease and apoptosis (Zhou et al. 2011)
Danshen extract (danshensu 40 mg/kg, protocatechuic aldehyde 149 mg/kg, and salvianolic acid B 50 mg/kg) was administrated intragastrically in rats	From blood and brain microdialysates collected at 15 and 30 min time intervals, danshensu and protocatechuic acid (oxidative metabolite of protocatechuic aldehyde) could be detected in the blood and brain (Zhang et al. 2011)
Examination of **Salvianolic acid B** (Sal B) on human islet amyloid polypeptide (hIAPP) aggregation and phototoxicity	Sal B significantly inhibited the formation of hIAPP amyloid and disaggregated hIAPP fibrils. Cytoprotective effects by Sal B on pancreatic INS-1 cells (Cheng et al. 2013a)

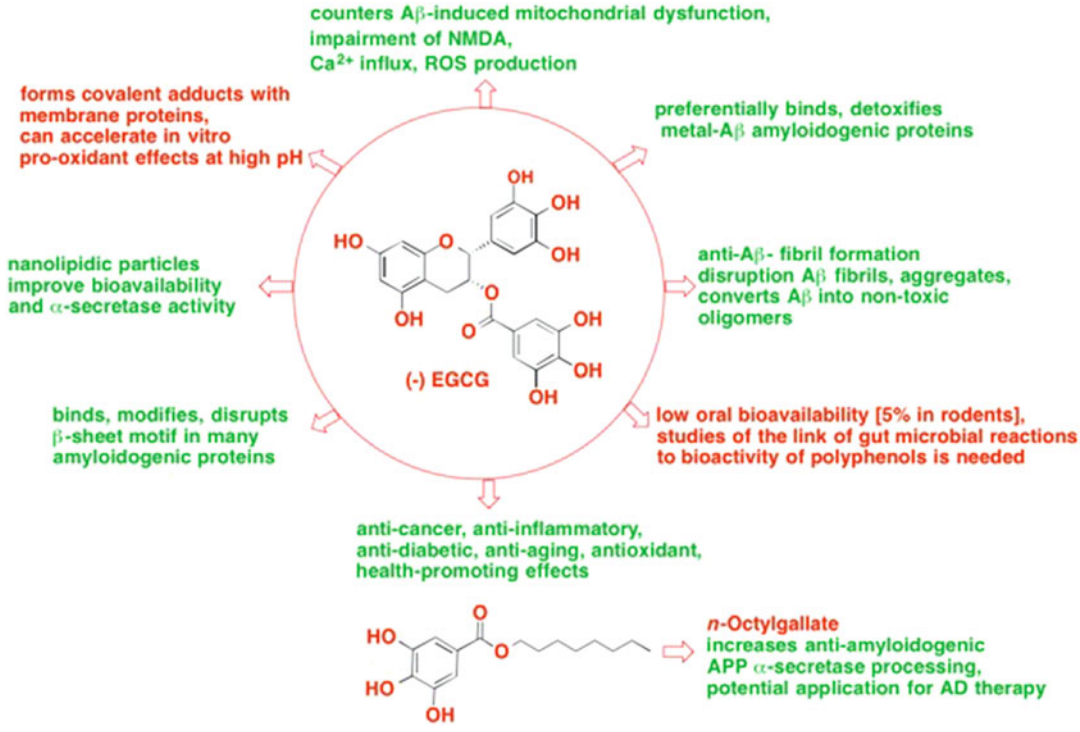
(outlined in Scheme 5.2). The major research challenge concerning the anti-amyloidogenic benefits of polyphenol-containing herbs and foods is to enhance their bioavailability and brain permeability (Schaffer and Halliwell 2012; Singh et al. 2008; Green et al. 2007; Lambert et al. 2006; Smith et al. 2010; van Duynhoven et al. 2011). Furthermore, the bioavailability of polyphenols from dietary input is highly variable between individuals and generally far too low to explain their bioactive antioxidant effects *in vivo* (Lotito and Frei 2006).

5.2.2 Curcumin

Cur is a promising neuroprotective anti-AD natural product that however has poor brain bioavailability with incompletely defined therapeutic mechanisms. Its antioxidant, anti-inflammatory properties have been extensively documented (Esatbeyoglu et al. 2012; Wang et al. 2014). Cur-nanoparticles with improved brain permeability induced adult neurogenesis through activation of the canonical Wnt/β-catenin pathway, and may provide opportunities for treating AD by enhancing a brain self repair mechanism (Zhang et al. 2013c).

5.2.3 *Magnolia officinalis*

The herbal constituents shown in Fig. 5.1 from *Magnolia officinalis* and other members of the *Magnoliaceae* family have diverse therapeutic applications (Lee et al. 2011b). The neolignan



Scheme 5.2 The multiple therapeutic applications of green tea constituent EGCG

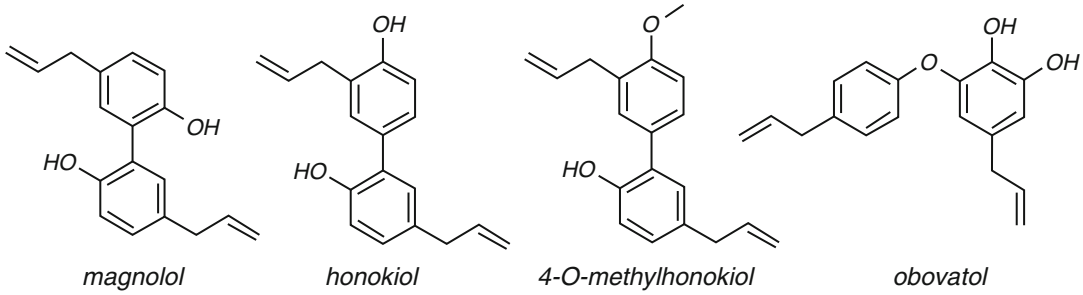
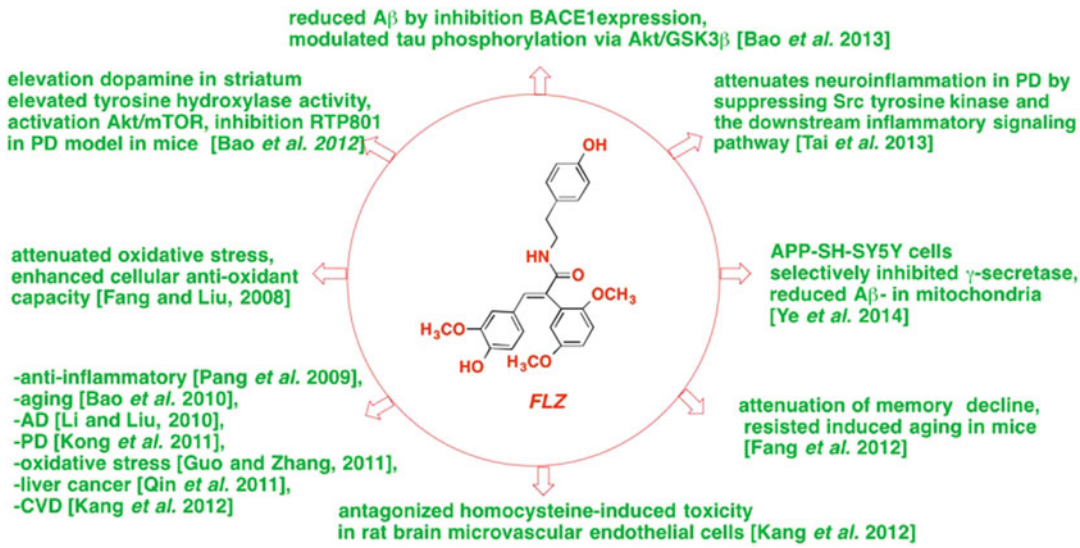


Fig. 5.1 Major bioactive constituents found in *Magnolia officinalis*

4-*O*-methylhonokiol is a potent cannabinoid receptor type-2 (CB2) ligand and has been found to attenuate memory impairment in presenilin 2 mutant mice through reduction of oxidative damage and inactivation of astrocytes and the extracellular signal-regulated kinase (ERK) pathway (Lee et al. 2011a). The various neuroprotective and anti-Alzheimer disease effects reported in rodent models (Lee et al. 2011a) may be mediated via CB2 receptors, providing evidence that the compound should be bioavailable in the brain.

5.2.4 *Annona glabrais* – Squamosamide Derivative (FLZ Compound)

Traditional Chinese medicine makes use of several constituents from the leaves and roots of *Annona glabrais,* including a natural squamosamide. Importantly, the squamosamide derivative FLZ showed enhanced antioxidant activity; in APP-SH-SY5Y expressing cells it selectively inhibited γ-secretase activity without



Scheme 5.3 Anti-amyloidogenic properties of compound FLZ, a squamoside analogue of a constituent from *Annona glabrais*

modulating the Notch pathway (Ye et al. 2014). The many positive anti-amyloidogenic studies suggest FLZ may have therapeutic potential for the treatment of AD (illustrated in Scheme 5.3) (Fang et al. 2012; Kang and Zhang 2012; Pang et al. 2009; Li and Liu 2010; Kong et al. 2011; Qin et al. 2011; Fang and Liu 2008; Bao et al. 2012, 2013; Tai et al. 2013)

5.2.5 *Ginseng*

The available types of ginseng, all belonging to the *Araliaceae* family, are Asian ginseng (*Panax ginseng*), American ginseng (*P. quinquefolus*) and Siberian ginseng (*Eleutherococcus senticosus*). Water extracts of the dried roots and leaves of *Panax ginseng* have been used as a stimulant/tonic, diuretic and digestive aid in traditional Chinese medicine for over 2,000 years. Ginseng phytomedicines are sold as ergogenic supplements to enhance mental and physical performance – reflective of Chinese medicine where body and mind are inseparable – to provide resistance to stress, and to prevent 'exhaustion' and disease. The major active principles of *P. ginseng extracts* are ginsenosides, which are glycosylated derivatives of the triterpene dammarane such as for instance Rg_1. Rg_3 is one of the major constituents of ginseng. The ginsenosides that reduce Aβ levels in animal models and other *in vitro* studies are summarized in Table 5.2.

The diverse constituents and multiple actions of ginseng constituents in the CNS reviewed recently (Kim et al. 2013a) will not be elaborated here. The *in silco* analysis of 12 ginsenosides (see Table 5.2) revealed those with potential interactions with the BACE1 receptor active site essential for enzyme inhibition (Karpagam et al. 2013). Further studies included ADMET screening to find the drug-like ginsenosides with a specific ability to cross blood brain barrier (BBB), and to determine safety/toxicity. Also the BACE1-ginsenosides complexes were further subjected to a molecular dynamics simulation to study their stability and hydrogen bond interactions. Of the 12 ginsenosides, CK, F_1, Rh_1, and Rh_2 were predicted to pass the BBB and ADMET analysis predicted toxic effects for ginsenosides Ro and ginsenoside Rg_1, while Rf showed low oral absorption in human gastrointestinal tract. These results suggest that of the seven ginsenosides demonstrating BACE1

Table 5.2 The anti-AD bioactivities of *P. ginseng* constituents

Panax ginseng AD cognitive effects	Anti-Aβ bioactivities
	Ginsenoside Rg_3 inhibited γ-secretase activity in mouse model AD
	Aβ lowering by modulation/reduction of lipid kinase PI4KIIα activity (Kang et al. 2013)
	Rg_3 enhanced neprilysin (NEP, rate-limiting enzyme in Aβ degradation) gene expression. Caused a reduction in Aβ(1–40) and Aβ(1–42). (Yang et al. 2009)
Fermented red ginseng – ginsenoside Rh_2 neuroprotective effects. Inhibited ischemia reperfusion brain injury in rats (Bae et al. 2004)	
	P. notoginseng modulates protein, gene expression related to α- and β-secretases. Reductions in levels of β-secretase resulting in decline of Aβ generation (Huang et al. 2014b)
Fermented ginseng (FG) ameliorated memory impairment in transgenic mouse model of AD	Brain soluble Aβ(1–42) levels measured from the cerebral cortex of transgenic mice were significantly reduced by the FG extract treatment (Kim et al. 2013b)
	Commercially-available preparations of **ginseng Rg_1**, **Rg_3**, and **RE**, resulted in significant reductions in the amount of Aβ(1–42) detected in the brains of animals after single oral doses of these agents (Chen et al. 2006)
Oral administration of **ginsenoside Rb_1** to mice stressed with acute immobilization; Rb_1 modulated stress effects by attenuating the stress-induced increase in neurosteroids (Lee et al. 2006a)	
Oral administration of **Rg_3** and **Rb_1** to mice stressed with acute immobilization; both lowered levels of the stress-marker putrescine (Lee et al. 2006b)	
Ginsenoside Rg_1 improved learning & memory in rat model of AD (Quan et al. 2013)	**Rg_1** inhibits the transcription and translation of BACE1, suppresses the activity of BACE1, and ultimately attenuates Aβ generation (Chen et al. 2012)
	Rg_1 promoted α-secretase cleavage of APP via estrogenic activity, indicating that it may be useful in the prevention of AD, in particular in postmenopausal females (Shi et al. 2013)
Rg_1, applied to primary cultured cortical neurons, rescued Aβ-mediated mitochondrial dysfunction	May attenuate Aβ-induced neuronal death through the suppression of intracellular mitochondrial oxidative stress (Huang et al. 2012)
Rd attenuated β-amyloid-induced pathological tau phosphorylation	Enhanced the activity of protein phosphatase 2A (PP-2A) involved in tau dephosphorylation (Li et al. 2013a)
In silico approach for discovery of BACE1 inhibitors from ***Panax ginsenosides*** included Rb_1, Rd, Rf, Re, Rg_1, Rg_2, Rg_3, Ro, Rh_1, Rh_2, CK, and F1	Rh_1, Rh_2, CK, F1 passed the criteria of: molecular docking-evaluated interaction with BACE1 receptor proteins, complex stability, H-bond interactions, ADMET for BBB permeability, having no toxicity (Karpagam et al. 2013)
Ginsenoside Rg_5 effect on cognition and beta-amyloid deposition in STZ-induced memory impaired rats	Rg_5 (5, 10 and 20 mg/kg) improved cognitive dysfunction in rats which was related to attenuating neuro-inflammatory responses with decreased brain levels of inflammatory cytokines TNF-α, IL-1β; Congo Red staining and Western blot analysis showed decreased Aβ deposits (Chu et al. 2014)

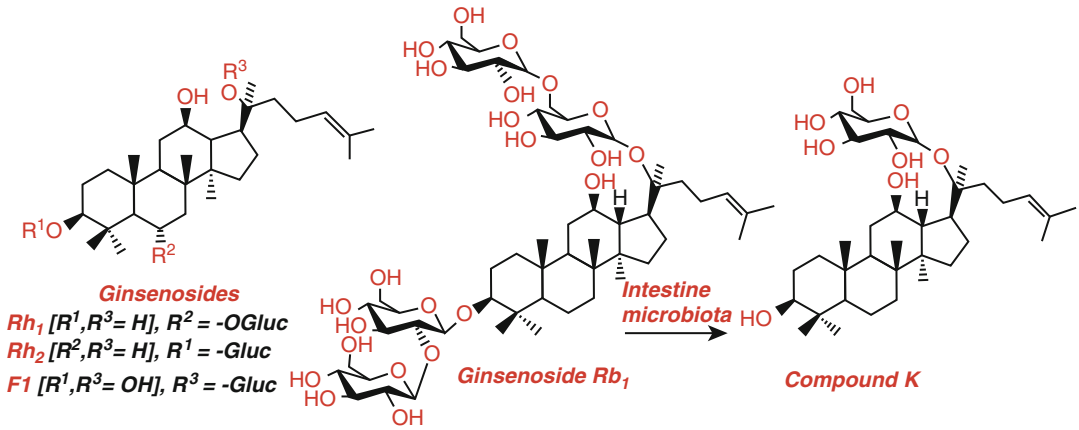


Fig. 5.2 The structures of ginsenosides Rb_1 and its metabolic transformation product K, and those of Rh_1, Rh_2, F_1

inhibition, only the four monoglucosylated ginsenosides CK, Rh_1, Rh_2, and F_1 pass the BBB and possess satisfactory drug-like properties. BACE1 and ginseng inhibitor complex crystal structural data to describe their binding modes would provide an accurate picture of the number and length of hydrophobic and hydrogen bond ginsenoside-enzyme interactions. These two descriptors have reliably predicted the activity of synthetic BACE1 inhibitors (Nastase and Boyd 2012). The wider implications of this research are that the brain-permeation/bioactivity of di- and multi-glycosylated ginsenosides is questionable. Intestinal microbial metabolism (Zhang et al. 2013d) similar to that of Rb_1 shown in Fig. 5.2 may be a pre-requisite for their neuroprotective activity.

5.2.6 Herbal Foods, Formulations and Supplements

L-3-*n*-Butylphthalide (Fig. 5.3) was first extracted from Chinese celery (*Apium graveolens* var. *secalinum*). The chemically prepared compound is used as an anti-hypertensive herbal medicine for the treatment of ischemic stroke, and has therapeutic application for the prevention of vascular dementia by up-regulation of Akt expression in the hippocampus (Huai et al. 2013; Peng et al. 2008, 2012). Potassium 2-(1-hydroxypentyl)-benzoate (dl-PHPB), a precursor to *n*-butylphthalide, has neuroprotective effects on cerebral ischemic, vascular dementia and Aβ-induced animal models by inhibiting oxidative injury, neuronal apoptosis and glial activation. Further research has suggested that dl-PHPB could be an attractive multi-target neuronal protective agent for the treatment of AD (Zhao et al. 2013; Peng et al. 2014). *Z*-ligustilide found in *R. angelica sinensis* promotes the activities of superoxide dismutase and thereby reduces oxidative stress in brain tissues; protects against Aβ-induced neurotoxicity and is a potential therapeutic against vascular dementia (Huang et al. 2008; Kuang et al. 2006; Feng et al. 2012; Xin et al. 2013). An appreciation of the amount of *Z*-ligustilide, the bioactive component in 10 g of herb is detailed in Fig. 5.3. The pharmacokinetics and bioavailability of Z-ligustilide were determined by the systematic investigation in Sprague–Dawley rats. With an extraction efficiency of 62.3 %, 0.93 g *Z*-ligustilide was isolated from 100 g of *R. angelica sinensis*. Therefore, based on animal pharmacokinetic data, with the absolute bioavailability at a 50 mg/kg dose of 75.44 %, a single medicinal use of 10 g of the herb may deliver 43.7 mg of *Z*-ligustilide.

Studies on 27 herbs revealed that some lesser known herbs such as *Curcuma aromatica* and *Zingiber officinale* (ginger) extracts effectively protected cells from Aβ insult, followed by Ginkgo biloba (ginkgo), Polygonatum

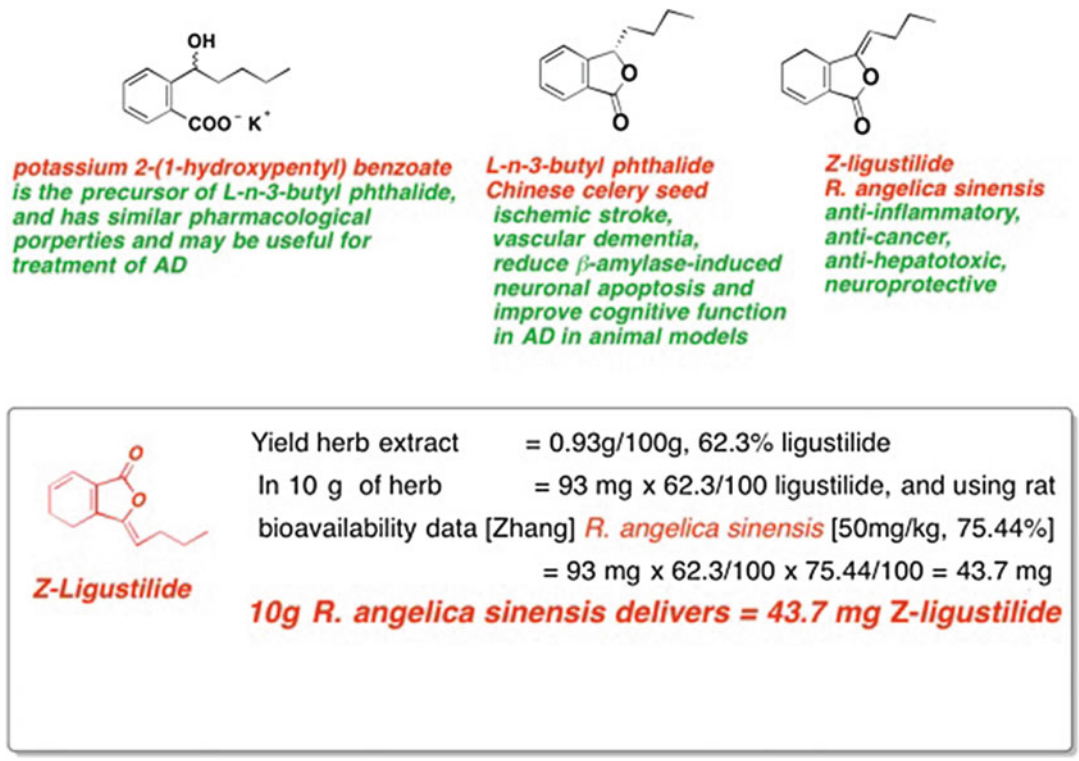


Fig. 5.3 Herbal bioactive compounds and *Z-ligustilide* bioavailability calculations (Zhang et al. 2014)

sp., *Cinnamum cassia* (Chinese cinnamon), *Rheum coreanum* (Korean rhubarb), *Gastrodia elata* (gastrodia), and *Scutellaria baicalensis* (skullcap) (Kim et al. 2007). With regards to herbs, spices and food products that disrupt, destabilize or reverse amyloid aggregation, these have been investigated for their ability: (i) to detour the generation of toxic amyloid precursors (off-pathway); (ii) to prevent the assembly of amyloid oligomers into fibrils; (iii) to inhibit fibril growth and deposition; (iv) to disassemble preformed fibrils; and (v) to promote Aβ clearance. The structures of the active anti-dementia constituents in Chinese herbs most widely used and investigated as potential amyloid inhibitors are presented in Fig. 5.4.

Many herbs are considered to be responsible for multiple beneficial effects such as improving vascular dementia, energy homeostasis, improving mitochondrial antioxidant capacity, and anti-inflammatory neuroprotection. The many and varied constituents in herbs can also enhance the bioavailability and bio-effectiveness of the active constituents and thus have more therapeutic value than individual compounds. Preliminary animal model studies suggest that antioxidants in spearmint and rosemary might be useful in modulating age-associated cognitive decline. Furthermore, rosemary improves local blood circulation, relieves pain, has anticancer activity, and controls blood lipid and anti lipid peroxidation. Carnosic acid, one of the major phenolic constituents of rosemary, is a pro-electrophile specifically activated by the oxidative stress pathological state resulting in its conversion from the hydroquinone to the oxidized quinone form, before it activates the Keap1/Nrf2 pathway leading to gene induction of the antioxidant response element (ARE) and gene products that protect against oxidative stress. A survey of Chinese herbs and herbal formulas that improve cognition in dementia rated the following as the top 10 herbs for improving memory: *Poria cocos*, *Radix et*

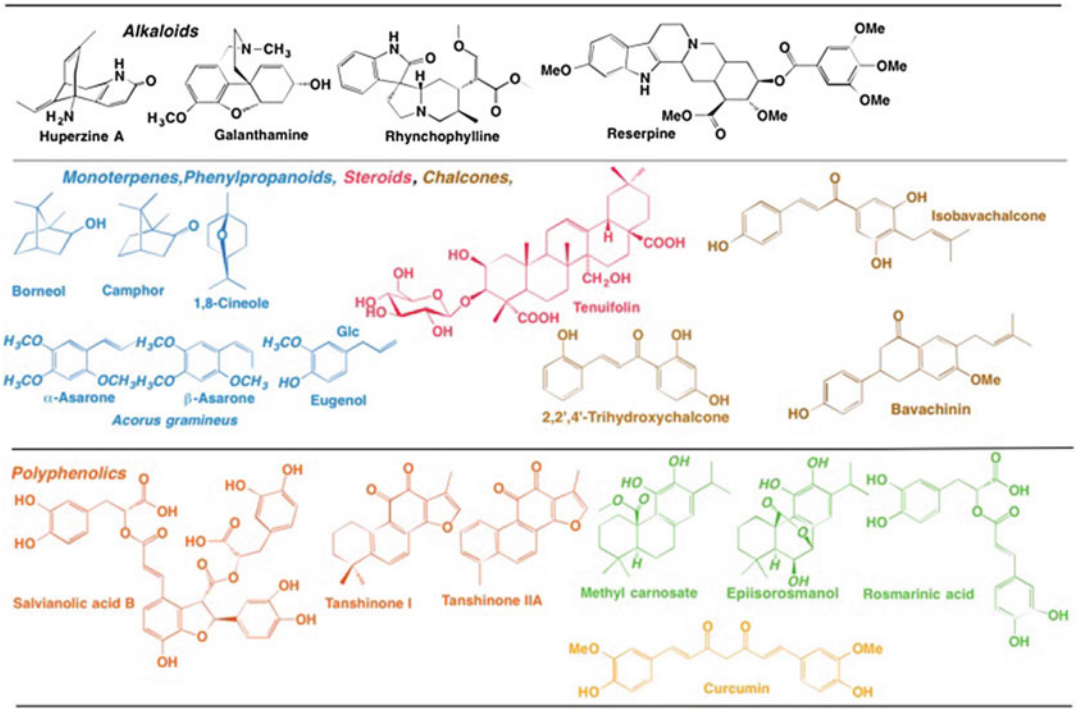


Fig. 5.4 Structures of the major chemical families of active constituents found in Chinese herbs having anti-dementia and β-amyloid anti-aggregation activities

rhizome ginseng, Radix polygalae, Radix et rhizome glycyrrhizae, Radix Angelica sinensis, Rhizoma acori tatarinowii, Semen ziziphi spinosae, Radix rehmanniae, Radix ophiopogonis and Rhizoma zingiberis (Lin et al. 2012; Shen and Chen 2013). The anti-Aβ bioactivity and neuroprotective mechanisms of many of these herbs are outlined in Table 5.3. In Schemes 5.4 and 5.5, the focus is on the particular herbs and spices that can effectively protect against amyloid disease. Their Aβ disaggregation properties and inhibition of tau protein hyperphosphorylation are highlighted (Yoshida et al. 2014; Xian et al. 2012; Fujiwara et al. 2006; Frydman-Marom et al. 2011; Kumaraswamy et al. 2013; Airoldi et al. 2013; Zeng et al. 2013).

5.2.7 Chinese Herbal Formulae for Anti-dementia Protection

Baicalin, jasminoidin, and cholic acid structures (Fig. 5.5) are the main active components of Qingkailing (QKL, Scheme 5.6). QKL is one of the most well-known Chinese herbs and is an aqueous preparation containing extracts of 7 herbs (Cheng et al. 2012). Baicalin is a strong antioxidant; jasminoidin elicits a protective effect on neurons under a broad range of stresses and cholic acid strongly promotes the expression of growth factors in the brain. Upon further investigation of the therapeutic effects and molecular mechanisms of a combination of the three components baicalin, jasminoidin and cholic acid (CBJC) in a rat dementia model, it was found that they significantly up-regulated genes in the forebrain related to neurogenesis and antioxidant neuroprotection (Zhang et al. 2013a).

Kai-xin-san (KXS), a Chinese herbal decoction contains *Ginseng Radix rhizoma*, *R. Polygalae radix*, *R. Acori Tatarinowii*, and *Poria*. KXS has been used in China to treat stress-related psychiatric diseases with the symptoms of depression and forgetfulness. A chemically-standardized water extract of KXS applied to astrocytes significantly stimulated the

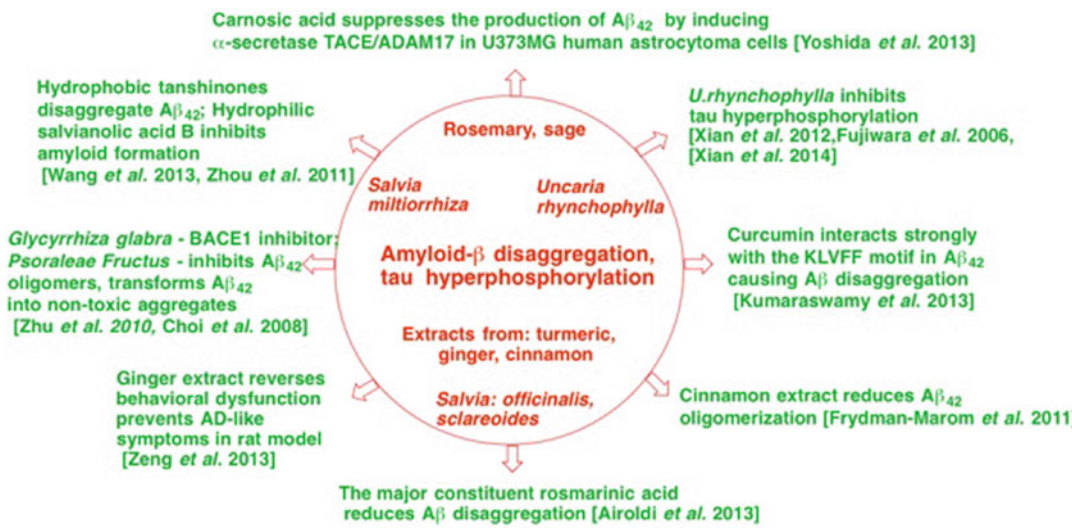
Table 5.3 The top Chinese herbs for improving memory, their major constituents, anti-dementia and neuroprotective actions

Chinese herbs and constituents	Therapeutic and anti-dementia bioactivities
P. cocos (a medicinal mushroom) triterpenes, pachymic acid, dehydropachymic acid.	Antioxidant; water extract enhanced hippocampal long-term potentiation, improved scopolamine-induced spatial memory impairment in rats (Cheng et al. 2013b; Hatip-Al-Khatib et al. 2004; Smriga et al. 1995)
Radix ginseng	Refer to Table 5.2
Radix polygalae (RP) oligosaccharide multi-esters, sucrose esters, triterpene onjisaponins, xanthone and xanthone C-glycosides	Sedative, antipsychotic, cognitive-improving, neuroprotective, with anti-inflammatory therapeutic effects on the central nervous system. Onjisaponin B was able to induce autophagy and accelerate both the removal of mutant huntingtin and A53T α-synuclein, associated with Huntington's and Parkinson's diseases (Ling et al. 2013; Wu et al. 2013a)
Radix Glycyrrhizae (RG) and the active constituent isoliquiritigenin	RG antioxidant activity related to flavonoids and total phenolics (Li et al. 2013b). Prevented Aβ(25–35)-induced neuronal apoptotic death by interfering with the increases of intracellular Ca^{2+} and ROS, and RG potential therapeutic for preventing the progression of AD (Lee et al. 2012)
Radix glycyrrhizae glabra	Administration of 150 and 225 mg/kg improved learning and memory via antioxidant, anti-inflammatory effects in rat model studies. Glycyrrhiza (60–200 μg/mL) contributed to the suppression of Aβ oligomer-induced neuronal damage, DNA fragmentation, and caspase-3 activation (Chakravarthi and Avadhani 2013; Kanno et al. 2013)
R. angelica sinensis (RAS); *Z*-Ligustilide (Lig) (Fig. 5.3) is the major constituent of the lipophilic extract of RAS	Decreased Aβ content and deposition in SAMP8 mice (Huang et al. 2008; Kuang et al. 2006; Hu et al. 2012b)
Semen ziziphi spinosae Jujuboside A (JuA) a major hypnotic-sedative	JuA has shown notable neuroprotective activities via anti-oxidative and anti-inflammatory effects in dementia animals and has potential utilization for the therapeutic treatment of AD (Liu et al. 2014)
Radix Rhemanniae Catalpol, iridoid glycoside	Catalpol reversed brain damage and memory deficits in mice; antioxidant, anti-inflammatory, neurogenetic, antiapoptotic, neuroprotective activities (Liang et al. 2009)
Rhizoma zingiberis ginger root extract (GRE)	GRE reverses behavioral dysfunction and prevents AD-like symptoms in rat model. Ginger has been shown to possess free radical scavenging, antioxidant inhibition of lipid peroxidation, dementia and multiple other therapeutic applications (Zeng et al. 2013; Haniadka et al. 2013)

expression and secretion of neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), in a dose-dependent manner: the stimulation was both in mRNA and protein expression (Zhu et al. 2013; Man et al. 2012). *Rhizoma Acori Tatarinowii* (grassleaf or sweet-flag rhizome), the rhizome of *Acorus tatarinowii Schott,* is used in TCM as an anti-convulsant; it can prevent convulsions as well as convulsion-related GABAergic neuron damage in the brain (Liao et al. 2005).

From the analysis of 1,232 traditional Chinese medicine formulae for anti-dementia (Kong et al. 2009) it was suggested that the most commonly used herbal formulation (Fig. 5.5) was *Rhizoma Chuanxiong, Radix Salviae Miltiorrhizae, Radix Polygalae Tenuifoliae and Rhizoma Acori Tatarinowii.* Their major chemical constituents and anti-AD activities are summarized in Table 5.4.

Yukukansan (Yigan San) is a classical TCM formula used for dementia (Iwasaki et al. 2005b) composed of seven herbs, *Angelica acutiloba*, *Atractylodes lancea*, *Bupleurum falcatum*, *Poria cocos*, *Cnidium officinale*, *Uncaria rhynchophylla* and *Glycyrrhiza uralensis*, in a ratio of 3:4:2:4:3:3:1.5. Clinical randomized controlled trials (RCTs) revealed that Yigan San improved behavioral and psychological symptoms of dementia that include aggression,



Scheme 5.4 Anti β-amyloid effects of food spices and herbs

Scheme 5.5 Chinese herbs most commonly used against dementia and AD

agitation, screaming, wandering, hallucinations and delusions. Yigan San reduces cholinesterase inhibitor-resistant visual hallucinations in dementia patients (Iwasaki et al. 2005a). Yigan San improved psychiatric symptoms and sleep structure in dementia patients (Shinno et al. 2008). The mechanisms of action are related to regulating multiple signal pathways, such as the glutamatergic neurotransmitter system, the serotonin receptor and excitotoxicity (Ho et al. 2011).

A key challenge in validating and translating fundamental science of herbal medicines into better anti-dementia outcomes is to evaluate and scrutinize clinical trial outcomes using scientific research methodologies. Some animal and clinical research performed on herbs leading to improved cognitive health providing options for dementia management and prevention is presented in Table 5.5.

5.3 Summary and Future Outlook

The individual-based interventionist approach against dementia and AD for extending healthy life — better diet and regular exercise — is effective, however it needs much greater promotion, acceptance and adoption early on in life. Alkaloids, monoterpenes, diterpenes, triterpenes, flavonoids, and polyphenolic compounds represent the most prevalent classes of herbal constituents with anti-AD bioactivity. It is unclear to what extent many of these bioactive phytochemicals utilized in single or herbal formulae doses can reach the brain in sufficient concentrations, and in a biologically active form, to exert their beneficial neuroprotective effects. The majority of herbs are consumed as aqueous extracts

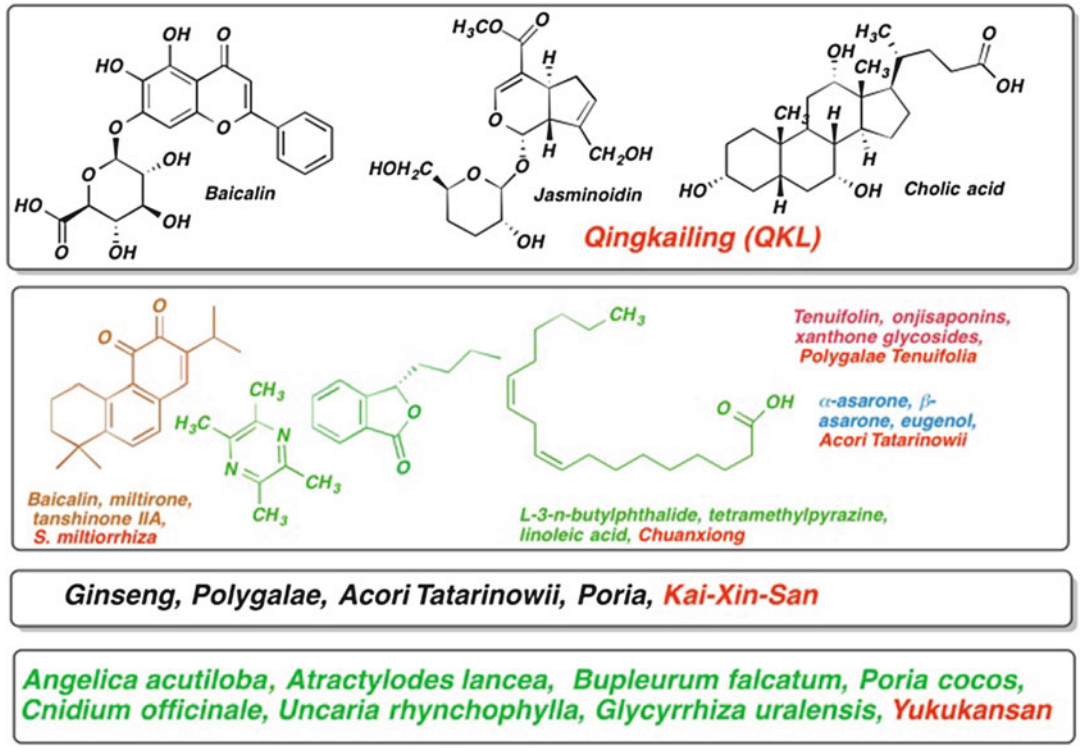
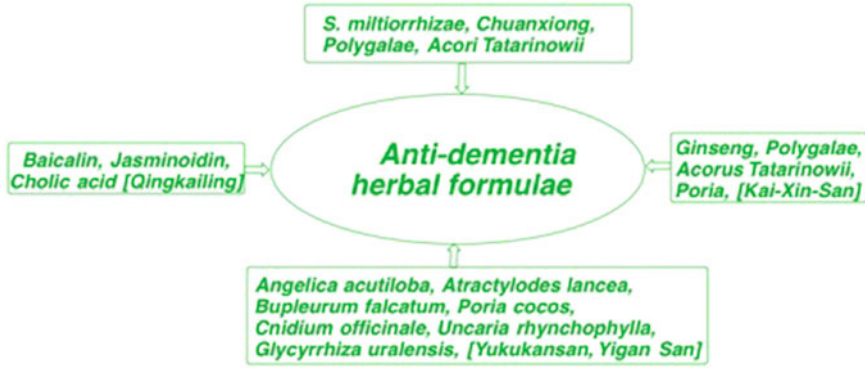


Fig. 5.5 Neuroprotective constituents of Chinese herbal formulae against dementia



Scheme 5.6 Herbal combinations and formulations used for dementia treatment

so their formulation has to provide increased bioavailability and BBB permeability (Hugel and Jackson 2014). An overview of the metabolism and strategies for enhancing polyphenol bioavailability (Lewandowska et al. 2013) include encapsulation of phospholipid-polyphenol complexes; formation of inclusion complexes with cyclodextrins or dendrimers; use of bioactive analogues; derivatisation (e.g., amidation); use of adjuvants (e.g. piperine) as absorption enhancers; and transdermal delivery systems.

It is imperative that herbs and herbal constituents are consumed regularly and in sufficient quantities in the diet. Indeed, for *in vivo* and clinical studies, producing active compounds and extracts in large quantities is an important

Table 5.4 Neuroprotective effects of the four herb TCM formulae commonly used for dementia treatment

The constituents of a four herb anti-dementia TCM formula	Anti-AD activities
Rhizoma Chuanxiong Tetramethylpyrazine ligustrazine	Improved hippocampal cholinergic system function, antioxidant, enhanced learning and memory in AD mice model (Zhao et al. 2008; Shi et al. 2012)
L-3-*n*-butylphthalide (86,89) 9-*cis*, 12-*cis*-linoleic acid (CLA)	*L*-3-n-butylphthalide has been shown to reduce β-amylase-induced neuronal apoptosis, improve cognitive function, blood flow in AD animal models
	CLA as a μ-calpain-specific inhibitor. CLA showed neuroprotective effects against neurotoxins such as H_2O_2 and Aβ(1–42) in SH-SY5Y cells; inhibited Aβ oligomerization and fibrillation. CLA decreased the levels of pro-apoptotic proteins (Lee et al. 2013)
Radix Salviae Miltiorrhizae Baicalin, polyphenolic acids, tanshinones	Antioxidants, anti-inflammatory, neuroprotection; inhibition of Aβ aggregation, oligomerization, and fibril formation (Wang et al. 2013; Zhou et al. 2011; Mei et al. 2009)
Radix Polygalae Tenuifoliae 3,6′-di-O-sinapoyl-sucrose (DISS) tenuifolin, onjisaponins, xanthone glycosides	DISS exerts neuroprotective effects against glutamate toxicity. Reinforces cognitive performance in aged and dysmnesia mice, elevating levels of dopamine, norepinephrine. Onjisaponins indicated cytoprotective activity in PC12 cells, exposed to serum deficiency or glutamate; improved memory in rats by enhancing cholinergic function, inhibiting Aβ secretion (Hu et al. 2009, 2012a; Lin et al. 2012)
Rhizoma Acori Tatarinowii Eugenol, α-asarone, β-asarone	Eugenol derived from *Rhizoma Acori Tatarinowii* increased BDNF mRNA expression level in hippocampus of mice. Modified Wen-Dan-Tang decoction containing *Acori Tatarinowii* attenuated the neurotoxicity of Aβ(25–35) and rescued neurons via suppressing apoptotic process (Liu et al. 2009)

Table 5.5 Clinical trials with herbs to counteract dementia and AD

Natural product	Animal studies; bioactivity mechanisms	Clinical trials
EGCG		300 mg/day of EGCG for 12 weeks had no adverse effect on liver function; did not enhance energy-restricted diet-induced adiposity reductions; did not improve weight-loss-induced changes in cardio-metabolic risk factors in obese Caucasian women (Mielgo-Ayuso et al. 2014)
Huperzine A (alkaloid shown in Fig. 5.3)	APPswe/PS1dE9 transgenic mice reduced Aβ fibrils, oligomers; inhibition of BACE1, regulating APP metabolism (Smriga et al. 1995). EGCG addition to huperzine A, significantly enhanced and prolonged the AChEI effects of huperzine A (Wang et al. 2012; Xiao et al. 2008)	Commonly used in China. USA clinical data (Ha et al. 2011) suggests 0.4 mg doses are required. Further non-Chinese clinical trials are necessary before the implementation of huperzine A for dementia and AD treatment (Yue et al. 2012)
		Systematic review and meta-analysis of 20 RCTs of Huperzine A for AD. Huperzine A appears to have beneficial effects on improvement of cognitive function, daily living activity, and global clinical assessment in participants with AD. The quality of some of the trials was an issue (Yang et al. 2013)

(continued)

Table 5.5 (continued)

Natural product	Animal studies; bioactivity mechanisms	Clinical trials
Curcumin	Curcumin *in vitro* inhibits: Aβ aggregation, Aβ-induced inflammation; the activity of β-secretase; AChE. In *in vivo* studies: oral curcumin inhibition of Aβ deposition, oligomerization, tau phosphorylation in AD animal models. Improvement in behavioral impairment in animal models (Hamaguchi et al. 2010)	Safe to use at dosage of 8 g/day for 3 months
		RCT study on 34 AD patients found no cognitive improvement, increase in anti-oxidant activity and vitamin E levels (Baum et al. 2008)
		Two CTs performed in China and USA have reported no significant differences in changes in cognitive function between placebo and curcumin groups (Gupta et al. 2013)
Korean red ginseng (KRG)		Used for adjuvant treatment for cognitive impairment in AD patients. High-dose KRG (9 g/day, $n = 15$) patients showed significant improvement on the AD Assessment and Clinical Dementia Rating Scale after 12 weeks of KRG therapy (Heo et al. 2008)
Rosemary (*Rosmarinus officinalis L.*; carnosic and rosmarinic acids)		Cognition improving effects of dried rosemary leaf powder on 28 adults (mean age 75 years). Only the lowest dose (750 mg) of rosemary had a statistically significant beneficial effect compared with placebo. Requires further work on effects of low doses over the longer term (Pengelly et al. 2012)

challenge for the utilization of natural products as therapeutic agents. Generally speaking, herbal products offer a wide range of brain-targets, nutritional benefits, safe dosage, long-term applications and efficacious treatment of AD pathology. The focus on engagement of sustainable optimal biochemical performance through diet and factors influencing it, including lifestyle choices, are key to a better mental health.

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