Chinese Herbs for Dementia Diseases

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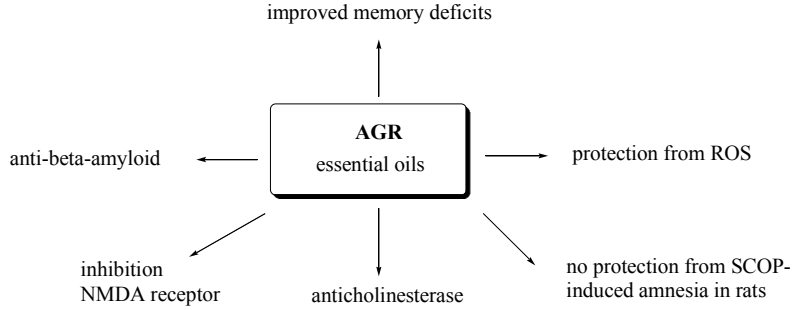
Abstract: In the last twenty years a considerable body of information has accumulated on the chemical constituents of Chinese herbs and their therapeutic potential. Our evaluation/systematic review [1, 2] of well-designed, randomized double blind controlled trials on Chinese herbal medicines beneficial for the improvement of cognitive function revealed a range of either single herbs or herbal mixtures that provided neuroprotective benefits. Oxidative stress may directly initiate neurodegeneration and herbal antioxidant neuroprotection is considered as a preventative and therapeutic approach. We encountered *Acoris gramineus rhizome* (AGR), *Panax ginseng*, *Polygala tenuifolia and Poria cocos* as the four most frequently used herbs as single/herbal mixtures that were associated with positive cognitive enhancing outcomes. This review focuses on the evidence of their medicinal effects attributed to those constituents present in relatively high concentration.

Keywords: Acoris gramineus, P. ginseng, P. tenuifolia, Poria cocos, Alzheimer disease.

INTRODUCTION

Dementia and Alzheimer's disease (AD) are aging-related incurable neurodegenerative disorders which progress through symptoms including anxiety, aggression, confusion, depression, forgetfulness, insomnia, irritability, memory loss and gradual decline in physiological function. In the elderly, dementia is a huge challenge of global proportions and a serious problem facing modern medicine. Although traditional herbal medicines have been used in China for more than 2000 years, scientific research into medicinal plants or herbs for dementia therapy is a new and emerging field. Cognitive decline is ironically the greatest cognitive challenge of the modern era. The discovery of an implantable memory chip that will support cognitive longevity into old age and that will bypass and limit the toxic effects of misfolded proteins and render their pathological effects on brain function as redundant is long awaited. In the meantime we will continue to examine the science of neuroprotective medicinal herbs, as their development relies on the understanding of the disease progression, coupled with their associated molecular modifications, pathways and targets of therapeutic application for sustainable cognitive health. Knowledge of herbal anti-dementia plant secondary metabolites integrates chemical composition/structure, molecular targets and pharmacology. To better understand how herbal medicines combat cognitive diseases, we present here the available evidence that characterizes the phytochemical basis of the therapeutic effects of these four Chinese herbs.

Monoterpene % hydrocarbons, oxygenated	Sesquiterpene % hydrocarbons, oxygenated	Phenylpropanoids % α-, β-asarone, eugenol
1.84, 1.57	19.23, 15.87	53,86



Scheme 1. An outline of the anti-dementia analysis performed on AGR.

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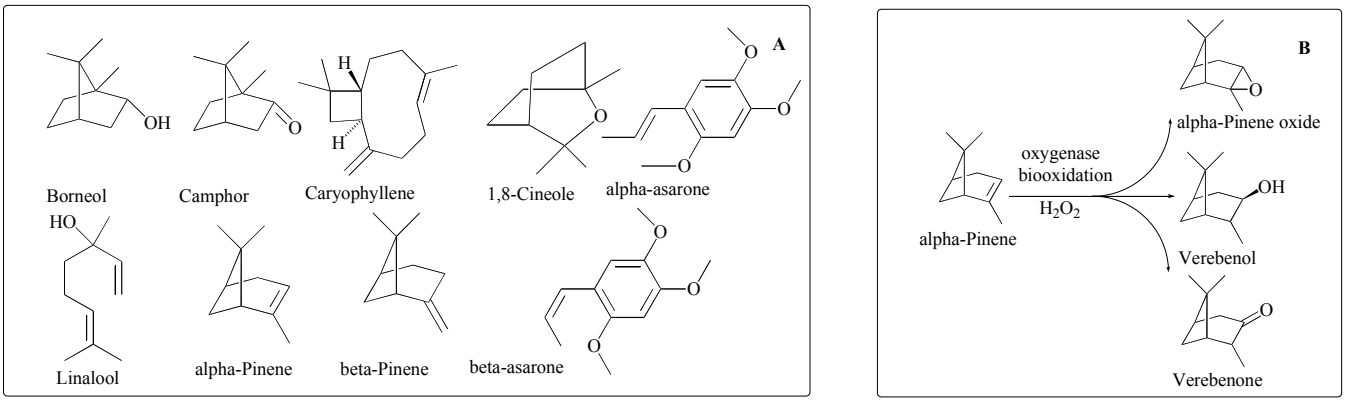


Fig. (1). A Main constituents of AGR. **B** Hydrogen peroxide oxidation products of α-pinene.

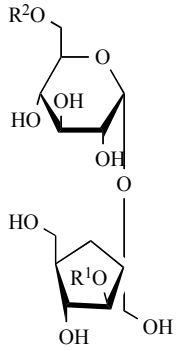
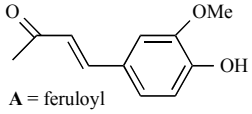
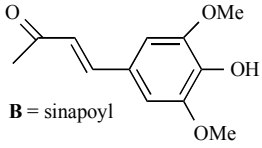
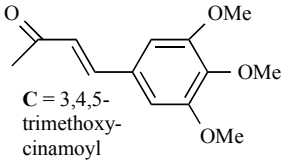
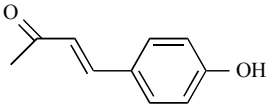
ACORIS GRAMINEUS RHIZOME [AGR]

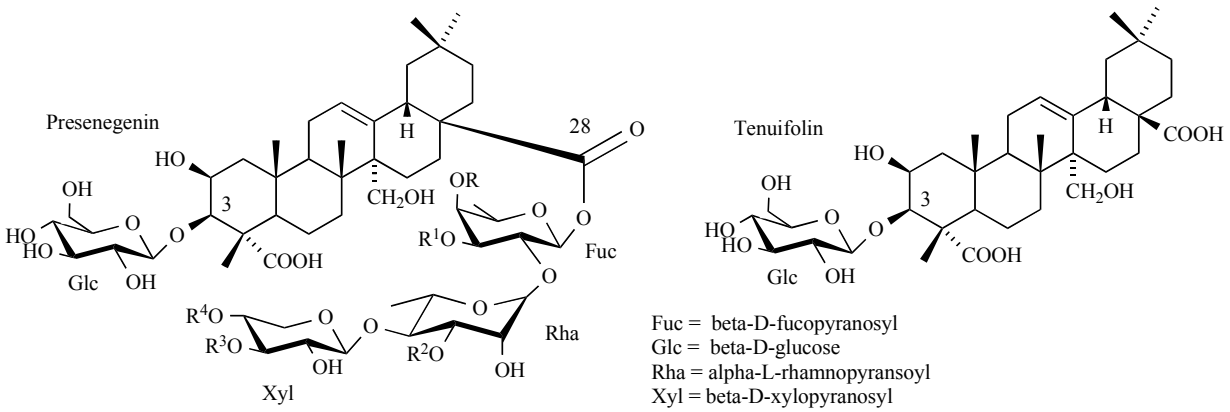
A summary of potentially beneficial molecular and cellular effects of AGR is shown in Scheme **1**. The supercritical CO_2 extraction-gas chromatography-mass spectrometry analysis of a volatile oil in commercial and cultivated AGR samples yielded 39 components with ß-asarone [phenylpropanoid] as the main constituent [3]. The SCE-GC analysis of a commercial AGR sample found the phytochemical class/peak area (%) distribution as shown in Scheme **1**.

Cho and coworkers [4] have discovered that α- and β-asarone in AGR oil exhibited neuroprotective activity against NMDA or Glu-induced cytotoxicity *via* blockade of NMDA receptor function. The aqueous-AGR extract in mice showed a sedative effect as the pentobarbital induced sleeping time was increased [5]. The major mono- and sesquiterpenes found in the essential oil extracted from aerial parts of *Salvia officinalis* and *S. lavandulaefolia* were attributed with the *in vitro* anticholesterase activity [6,7] in both human erythrocytes and brain tissues (post mortem). The volatile essential oils found in these herbs shown in Fig. (**1A**) are also present in AGR and may be predicted to also inhibit the acetylcholinesterase enzyme. However the relatively weak anti-cholinesterase activity of terpenoids, precludes their therapeutic application for cognitive disorders. To improve efficacy analogues of active terpenes may be developed.

The protective effects of α-pinene and α-humulene, essential oil components of *Salvia fruticosa* on cultured primary brain astrocytes from H_2O_2-induced death have

Table 1. Chemical Constituents of *Polygala tenuifolia* Sucrose Esters

Polygala tenuifolia Sucrose esters	Phenol glycosides	R^1	R^2	Cinnamic acid derivatives
	Sibiricose A_5	A	H	 **A** = feruloyl
	Sibiricose A_6	B	H	 **B** = sinapoyl
	Glomeratose A	C	H	 **C** = 3,4,5-trimethoxy-cinamoyl
	3′, 6-di-O-Sinapoyl-sucrose	B	B	
	Tenuifoliside A	C	D	 **D** = *p*-hydroxybenzoyl
	Tenuifoliside B	B	D	
	Glomeratose	C	C	

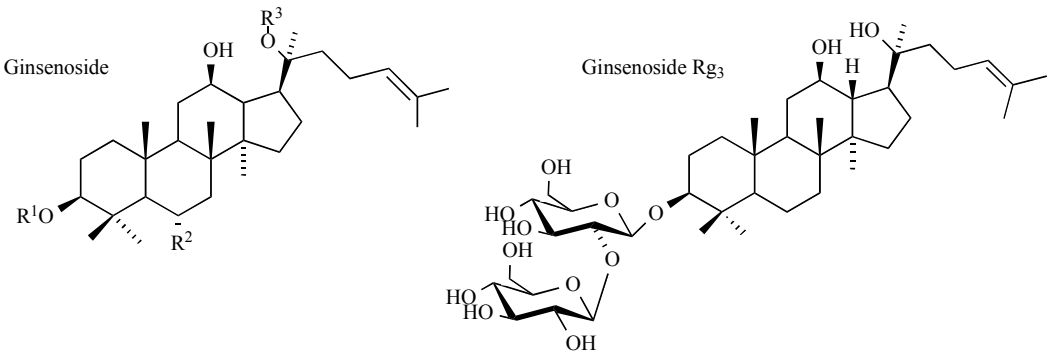


Onjisaponins	R	R^1	R^2	R^3	R^4
A	4-methoxycinnamoyl-	Rha-	Api-	H	Gal-
B	4-methoxycinnamoyl-	Rha-	H	H	Gal-
E	3,4,5-trimethoxycinnamoyl-	H	H	H	Gal-
F	3,4,5-trimethoxycinnamoyl-	H	Api-	Ara-	H
G	3,4,5-trimethoxycinnamoyl-	H	Api-	H	H

Fig. (2). The chemical structures of major onjisaponins and tenuifolin found in *Polygala tenuifolia.*

P. tenuifolia **cognitive effects**	**Bioactivity**
Short-term memory improvement by scopolamine-induced memory impairment [23-25]	Sinapinic acid, tenuifolin, saponins
Aqueous extract had memory repairing effect & behavioral disorders produced by lesioning of the NBM in rats [26]	Enhanced ChAT activity, AChE inhibition
Induction of NGF synthesis in astrocytes [18]	Onjisaponins A,B,E,F,G
Antipsychotic activity [27]	Onjisaponins
Inhibition of TNF-α by inhibition of IL-1 secretion, anti-inflammatory activity on CNS [28]	Attributed to aqueous extract [70^0C, 5 h] of *P.*t,
PAP 9704 [*P.*t, *A.g*, *P.*g] sedative action, Adenosine A_{2A} receptor stimulant [29]	Methamphetamine hyperlocomotion inhibition
DX 9386 [*P.*t, *A.g*, *P.*g P.*c*] promotes long-term potentiation in the dentate gyrus of rats [30]	*A.g*, *P.*g individually promote LTP
Anti-neurodegenerative effect for $A\beta_{25-35}$ treated cortical neurons [31]	Activity attributed to onjisaponins
Ethanol & butanol *P.*t, fractions attenuation of brain damage during ischemia & reprefusion [32]	Activity attributed to onjisaponins
Cognitive improving & cerebral protective effect [33]	Tenuifoliside B
Decreased secretion Aβ by inhibition of BACE-1 [34]	Tenuifolin
NMDA inhibition [35]	Methanolic plant extract
Activity against diabetic cognitive dysfunction [36]	Tenuigenin, onjisaponins

recently been reported [8] and suggested as therapy in the treatment of neurodegenerative diseases. The unsaturated mono- and sesquiterpenes are most likely catalytically biooxidized by H_2O_2 as illustrated for α-pinene in Fig. (**1B**). The oxidation of natural terpenes [9] has been observed *in vitro*. Hydroxyl radicals [10] have been found to react with biogenic terpenes. Similarly, the previously hard to explain [11] potent antioxidant activity of pine needles *Pinus sylvestris* against H_2O_2-induced cytotoxicity can be rationalized by the H_2O_2 oxidation of the high concentration of unsaturated terpenoids found in pine needle extracts. We are currently investigating the oxidation of natural terpenoids in the elimination of ROS in dementia. Which of the chemical constituents of AGR are responsible for its neuroprotective effect against Aß insult is controversial and have not been identified. It has been reported [12] that commercial eugenol and β-asarone protected PC-12 cells from $A\beta_{1-40}$ toxicity whilst others found a methanol extract of the herb exhibited neuronal protection with an ED_{50} value of 11.6 μg/mL but further tests on the isolated eugenol and

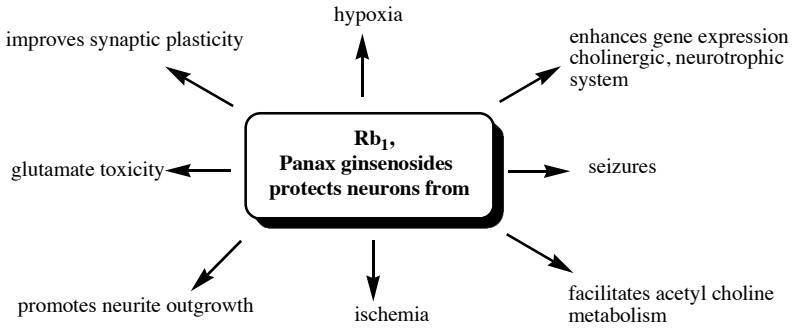


Ginsenoside	R^1	R^2	R^3	Bioactive molecules
Protopanaxtriol				
Rg_1	H	*-O-glc*	*glc*	Rh_1
Rg_2	H	*-O-glc(2-1)rha*	H	
Re	H	*-O-glc(2-1)rha*	*glc*	Rh_1
Rf	H	*-O-glc(2-1)glc*	H	
Rh_1	H	*-O-glc*	H	
F1	H	-OH	*glc*	
Protopanaxdiol				
Rb_1	*glc(2-1)glc*	H	*glc(6-1)glc*	Compound K
Rb_2	*glc(2-1)glc*	H	*glc(6-1)ara(p)*	
Rg_3	*glc(2-1)glc*	H	H	Rh_2
Rh_2	*glc*	H	H	
Rc	*glc(2-1)glc*	H	*glc(6-1)ara(f)*	
Rd	*glc(2-1)glc*	H	*glc*	
Ra	*glc(2-1)glc*	H	*glc(6-1)glc*	
F2	*glc*	H	*glc*	
Compound Y	H	H	*glc(6-1)ara(p)*	
Compound K	H	H	*glc*	
Compound O	*glc*	H	*glc(6-1)ara(p)*	
Compound Me	*glc*	H	*glc(6-1)ara(f)*	

Fig. (3). Chemical structures of the most abundant ginsenosides in *Panax ginseng*.

Panax ginseng **cognitive effects**	**Bioactivity**
Rg_3 caused a reduction in $A\beta_{40}$ (19.65%), $A\beta_{42}$ (23.61%) [42]	Rg_3 enhanced neprilysin (NEP, rate limiting enzyme in Aβ degradation) gene expression
Rg_3 neuroprotective effects [43]	Fermented red ginseng→Rh_2 inhibited ischemia reprefusion brain injury
Rg_3 neuroprotective effects [39]	Reductions in levels of the $A\beta_{42}$ after oral administration of ginsenosides Re, Rg_1, Rg_3
Rg_3 neuroprotective effects [44]	Rb_1 and Rg_3 protect cultured rat cortical cells from glutamate-induced neurodegeneration

Rg_3 anti-stress effects [45]	20(S)-Rg_3 and Rc may inhibit the i.c.v. injection stress-induced hypothalamo-pituitary-adrenal response by inducing NO production in the brain
Rg_3 anti-stress effects [46]	The metabolism of the brain neurosteroids in linked to psychological stress, and Rb1 attenuates the stress-induced increase in neurosteroids
Rg_3 anti-stress effects [47]	Rg_3 and Rb_1 may play a neuroprotective role in the immobilization-stressed brain
Rb_1, Rg_3 attenuate glucocorticoid-induced neurotoxicity [48]	Rb_1, Rg_3 completely blocked DEX-mediated up-regulation of *bax* expression
Protects neurons from ischemia [49]	Rb_1 neuromodulatory effects
Protects neurons from hypoxia [50]	Rb_1 neuromodulatory effects
Protects neurons from seizures 51]	Rb_1 neuromodulatory effects
Enhances the expression of genes-cholinergic and neurotrophic systems [52]	Rb_1 neuromodulatory effects
Active against scopolamine-induced neuronal & cognitive impairment in rats [53]	Wild ginseng neuromodulatory effects



Scheme 2. An outline of the reported neuroprotective activities of *Panax* ginsenosides.

β-asarone were negative [13]. ß-Asarone has been shown to reduce Aß-induced JNK activation as well as down-regulation of Bcl-w and Bcl-xL family proteins in a JNK-dependent manner [14].

POLYGALA TENUIFOLIA

The chemical analysis of *Polygala tenuifolia* indicated that phenol, xanthone glycosides, and complex saponins are the predominant components and these have been investigated for a wide range of medicinal uses including anti-anxiolytic, sedative-hypnotic activities [15], anti-depression, anti-psychotic behaviour [16, 17], cognitive improvement, anti-dementia [18] and memory failure. Chromatographic HPLC analysis of the roots of *Polygala tenuifolia* quantified nine glycosides [19]. Of the seven sucrose esters shown in Table **1**, 3′,6-di-O-sinapoylsucrose was the most abundant polysaccharide ester found in 17 sourced samples ranging from 2.70 to 8.41 mg/g.

The neuroprotective effects and potential antidepressant properties of an ethanol extract of radix *Polygala tenuifolia* containing 3′,6-di-O-sinapoylsucrose and tenuifoliside A were shown to prevent corticosterone-induced injury [20] in human neuroblastoma SH-SY5Y cells and increased cell neuronal survival. Other researchers have isolated polygalatenosides [21] (oligosaccharide derivatives) from the roots of *Polygala tenuifolia* which were found to block norepinephrine transport, thereby acting as norepinephrine reuptake inhibitors and antidepressant agents.

The chemical structure of eighteen triterpenoid saponins found in *Polygala tenuifolia* have been structurally characterized [22]. They consist of a triterpene presenegenin aglycone substituted at C-3 with a mono- or bi-glucosyl saccharide and at C-28 with a complex oligosaccharide which includes various saccharide substituents that may be elaborated with cinnamoyl or acetyl groups. The onjisaponins have molecular weights in the range 1542 to 1936 and the major compounds are presented in Fig. (**2**).

PANAX GINSENG

Panax ginseng (*Renshen, Chinese ginseng, Pg*) is commonly used either by itself or with multiple ingredients as a major herb in Chinese medicine. This medicinal herb has been universally advocated/used for many years as an invigorant to combat memory lapses/loss by improving blood and oxygen flow to the brain. *Pg* is considered to stimulate mental activity and acts as a tonic (energy boosting). *Pg* exhibits multiple pharmacological actions summarized in Scheme **2**. Its bioactive constituents are a

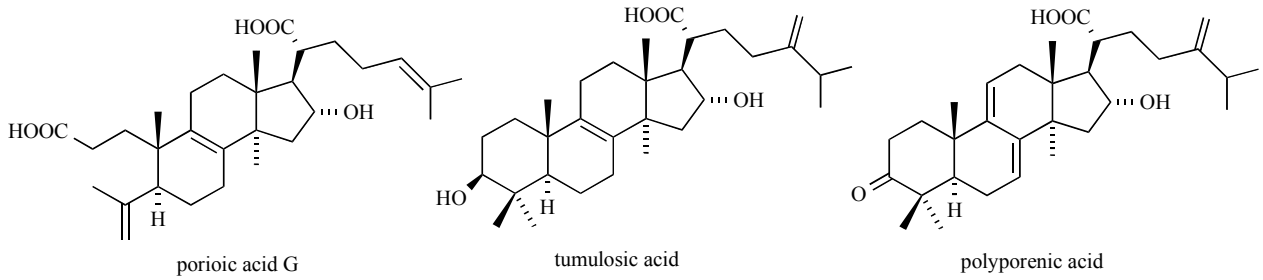


Fig. (4). Representative chemical structures of triterpenic acids from *Poria cocos.*

family of ginsenosides [37] shown in Fig. (**3**), are a class of steroid glycosides, and triterpene saponins, found exclusively in the plant genus *Panax* (ginseng). The Aβ lowering capacity of a family of ginseng extracts has been provided in a patent [38]. The influence of feeding single doses of the ginsenosides Re, Rg_1, Rg_3 at 50μM in a CHO 2*B7* cells resulted in a reduction of 32.2%, 19.4%, 69.3% respectively of $Aβ_{1-42}$ after 3 h of treatment [39] and for Rg_3 the apparent IC_{50} was under 25 μM. This was supported by further evidence from the administration of 25 mg/kg of the ginsenosides which resulted in 20 to 30% reduction in $Aβ_{1-42}$ *in vivo* studies in a Tg2576 mouse model after 18 h.

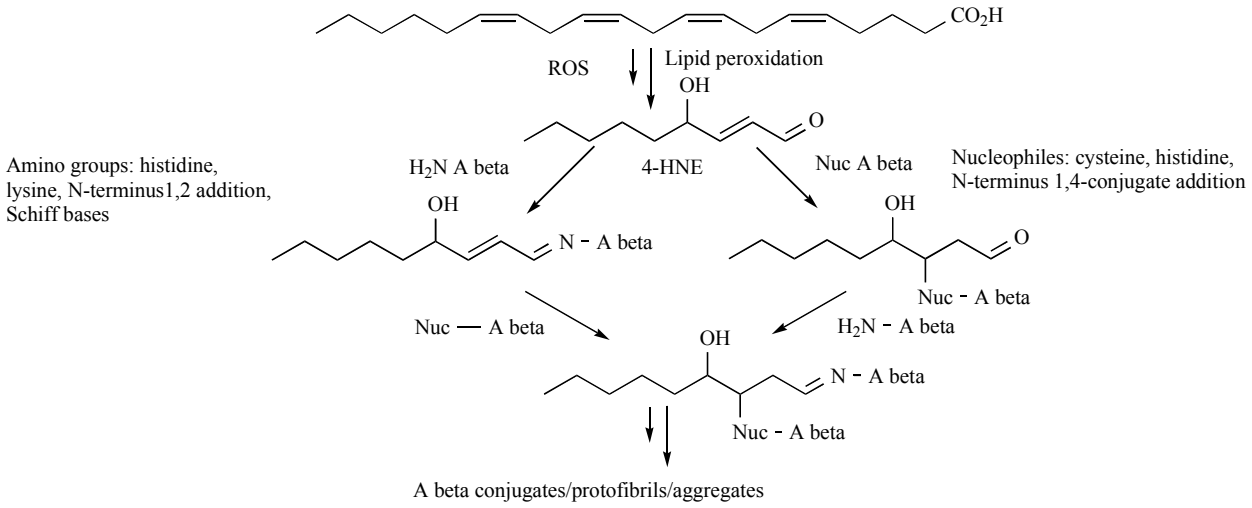
Related triterpenoids with inhibiting γ-secretase activity have been patented by Sartori Pharmaceuticals [40, 41].

Poria Cocos

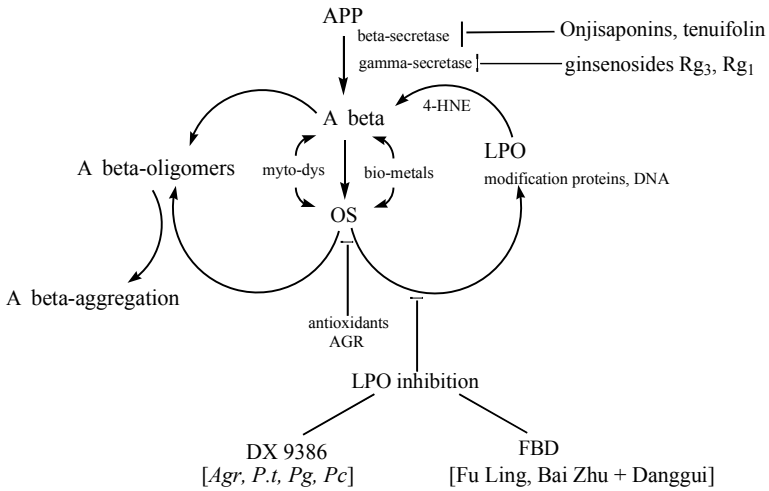
Poria cocos (Fu-ling) is used in China and some Asian countries, particularly Japan and Korea for herbal prescriptions as diuretics, sedatives and to improve cognitive and memory function in the elderly [53]. Lanostane-type triterpene acids (7-9%, 17 have been isolated, representative structures shown in Fig. **4**) and polysaccharides (93%) are the major chemical constituents of *P. cocos*. Evaluation [54] of tumor-promoting effects of poricoic acid G revealed that it was cytotoxic to leukemia HL-60 cells GI_{50} value 39.3 nM. It has been observed that the triterpene acids found in the sclerotium of *Poria cocos* that are hydroxylated at C-16α in combination with a 3,4-*seco*-3-oic acid functionality (as in porioic acid G) may be potential anti-cancer agents [55]. The water soluble 1,6-branched 1,3-α-D-galactan polysaccharide [56] from cultured mycelia of *Poria cocos* showed no cytotoxicity or antiangiogenic activity to endothelial cells and was found to dose-dependently suppress production of IP-10 the interferon (IFN)-γ-induced inflammation marker, suggesting it may have an anti-inflammatory function. Extraction and analysis of the polysaccharide from *Poria cocos* Wolf revealed it contained sugar (mole percentages): ribose (1.6%), arabinose (1.09%), xylose (0.54%)%, mannose (11.3%), glucose 85.9% and galactose 1.01% respectively. The experimental evidence [57] showed the polysaccharide significantly inhibited tumor cell growth, increased serum superoxide dismutase, catalase and glutathione peroxidase activities in rats.

The question whether oxidative stress (OS) is the causative factor or a consequence of AD is unresolved. Researchers [58] have reported that 4-hydroxynonenal (4-HNE) illustrated in Scheme **3** is a product from lipid peroxidation (LPO) of ω-6 polyunsaturated fatty acids, reacts/modifies Aβ to produce protein conjugates that may be cross-linked with other Aβ peptides, contributing to the transformation of the Aβ's physical and chemical properties leading to its aggregation.

The triterpene saponins of *Polygala tenuifolia, Panax ginseng,* are metabolized/bioavailable with sufficient physiochemical characteristics to access the intracellular



Scheme 3. The chemical peroxidation of ω-6 polyunsaturated fatty acids leading to Aβ aggregation.



Scheme 4. Outline of herbal interventions in Aβ pathology.

regions and modulate the secretase enzymes (Scheme **4**). These phytochemicals and related compounds that can alter APP cleavage and reduce production of pathogenic forms of amyloid β are useful anti Alzheimer agents. Their target specificity, poly-pharmacological activities/toxicity requires further investigation. Studies on the multiple herbal prescription FBD [59] suggest it exerts its protective effects against neuronal oxidative stress, largely *via* inhibiting LPO and maintaining endogenous antioxidant system instead of scavenging free radicals. The traditional Chinese herbal medicine DX-9386, composed of four herbs (*Acorus gramineus, Polygala tenuifolia, Panax ginseng,* and *Poria cocos*) has shown favorable effects in relation to AD symptoms in several animal models. DX-9386 improved motor activity, reduced lipid peroxidation, ameliorated memory impairment and prolonged the lifespan of senescence accelerated mice, and ameliorated the ethanol- and scopolamine-induced memory impairment in mice [60].

Bioavailability

The efficacy of Chinese herbs for treating dementia and AD requires the identification and quantification of the bioactive plant metabolites administered. The degree to which the herbal constituents become available to the brain after oral administration has essentially been ignored in most studies and remains a challenging task.

CONCLUSION

In summary, the results indicate that:

- the pharmacological bioactivities of these four Chinese herbal plants appear to reflect their traditional uses for treatment of neurodegenerative and cognitive disorders
- saponins from *P ginseng and P tenuifolia* have tremendous potential for the development of therapeutic drugs that can be used to improve cognition in patients with cognitive deficit diseases
- further structure activity/function studies are necessary to establish whether the antioxidant activity, lipid peroxidation and APP secretase modulation correlates with the saponin content of *P. ginseng, P. tenuifolia and Poria cocos*
- the structure of metabolites, their oral bioavailabilities [brain concentration] of the saponins, and also the other herbal constituents has to be established
- studies are needed to clarify the contribution of each of the four herbs in DX-9386 to the observed pharmacological activities
- evidence regarding the efficacy/optimal therapeutic effect and safe doses of these four herbs is required [herb combinations, efficacy/quantities/quality control, synergistic activity]
- modified phytochemicals that target highly specific pathways may have substantial safety and therapeutic advantages over less specific compounds.

It is anticipated that the application of modern chemical synthesis linked to plant constituents can form a platform technology to promote the linkage of herbal-medicinal science research advancing the discovery of novel phytochemical based compounds and therapeutics for the treatment of Alzheimer's diseases.

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