Review

Anti-aging herbal medicine—How and why can they be used in aging-associated neurodegenerative diseases?

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A B S T R A C T

Aging is a universal biological process that leads to progressive and deleterious changes in organisms. From ancient time, mankind has already interested in preventing and keeping ourselves young. Anti-aging study is certainly not a new research area. Nowadays, the meaning of anti-aging has been changed from simply prolonging lifespan to increasing health span, which emphasizes more on the quality of life. This is the concept of healthy aging and prevention of pathological aging, which is associated with diseases. Keeping our brain functions as in young age is an important task for neuroscientists to prevent aging-associated neurological disorders, such as Alzheimer's diseases (AD) and Parkinson's disease (PD). The causes of these diseases are not fully understood, but it is believed that these diseases are affected by multiple factors. Neurodegenerative diseases can be cross-linked with a number of aging-associated conditions. Based on this, a holistic approach in anti-aging research seems to be more reasonable. Herbal medicine has a long history in Asian countries. It is believed that many of the medicinal herbs have anti-aging properties. Recent studies have shown that some medicinal herbs are effective in intervention or prevention of aging-associated neurological disorders. In this review, we use wolfberry and ginseng as examples to elaborate the properties of anti-aging herbs. The characteristics of medicinal herbs, especially their applications in different disease stages (prevention and intervention) and multi-targets properties, allow them to be potential anti-aging intervention in prevention and treatment of the aging-associated neurological disorders.

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1. Introduction

Aging is a natural process in all living organisms. Anti-aging has always been an interest to mankind. Today, the goal of anti-aging medicine shifts from prolonging lifespan to health span. We target at a healthy elderly life which is free of aging-associated diseases. Alzheimer's disease (AD) and Parkinson's disease (PD) are aging-associated neurodegenerative diseases that can greatly impair quality of life. These diseases affect the brain, which is the control centre of our body, and lead to cognitive impairment and motor deficits. Therefore, keeping our brains "young" is important. In recent years, study of herbal medicine has received increasing attention in aging research. It is suggested that some traditional herbs have anti-aging properties and they are potential candidates for the treatment of chronic and aging-associated diseases (Luo et al., 2004; Chan et al., 2007; Wu et al., 2006; Heo et al., 2008; Lee et al., 2008; Zhao et al., 2009). Studies show that these "anti-aging herbs", such as Panax ginseng and wolfberry (Lycium barbarum), are usually multi-functional and can protect our body through different mechanisms. Increasing lines of evidence suggested that these herbs are potential candidates for the prevention or treatment of aging-associated neurological disorders (Kim et al., 2007). Many reviews have already summarized the beneficial effects of these herbs comprehensively. The purpose of this review, on the other hand, is to link the traditional anti-aging concept with modern scientific evidence. We take two anti-aging herbs, ginseng and wolfberry, as examples on neurodegenerative disorders and try to explain the properties of these "anti-aging herbs".

2. What is aging?

Aging refers to the progressive, deleterious and universal changes in organisms. It was once regarded as an "unsolved problem in biology" in 1950s since its cause was unclear (Holliday, 2006). After much research being done in the field, it is now widely accepted that aging is a multifarious event resulting from the

Table 1
Summary of the direct and indirect protective effects of wolfberry and its active components against AD.

	Authors	Wolfberry extract/LBP	Experimental model	Effects	Possible mechanism
Direct effects	Yu et al. (2005)	Wolfberry aqueous extract, LBA	Rat primary cultured cortical neurons treated with $A\beta_{25-35}$ and $A\beta_{1-42}$	↓ Cell death; ↓ caspase-3	↓ Phosphorylations of JNK and c-Jun
	Yu et al. (2007)	LBP	Rat primary cultured cortical neurons treated with $A\beta_{25-35}$ and $A\beta_{1-42}$	↓ Cell death; ↓ caspase-3 and -2	↓ Phosphorylations of PKR
	Ho et al. (2007)	Wolfberry alkaline extract	Rat primary cultured cortical neurons treated with $A\beta_{25-35}$ and $A\beta_{1-42}$	↓ Cell death; ↓ caspase-3	↑ Phosphorylation of Akt
Indirect effects (on AD risk factors)	Luo et al. (2004)	LBP	Alloxan-induced diabetic or hyperlipidemic rabbits	↓ Blood glucose level; ↓ serum total cholesterol and triglyceride level; ↑ high density lipoprotein cholesterol	–
	Wu et al. (2006)	LBP	Rats with non-insulin dependent diabetes mellitus	↓ Blood glucose level; ↓ MDA; ↓ NO; ↑ serum SOD	–
	Ho et al. (2009)	Wolfberry aqueous extract, LBA	Rat primary cultured cortical neurons treated with homocysteine	↓ Cell death; ↓ caspase-3; ↓ tau cleavage; ↓ tau phosphorylation	↑ Phosphorylation of ERK; ↓ phosphorylations of JNK
	Ho et al. (in press)	Wolfberry aqueous extract, LBA	Rat primary cultured cortical neurons treated with glutamate	↓ Cell death	↓ Phosphorylations of JNK
	Amagase et al. (2009)	LBP	Healthy adults	↑ Serum SOD, GSH-Px; ↓ MDA	–
	Li et al. (2007b)	LBP	Aged-mice	↑ SOD; ↓ MDA; ↑ GSH-Px activity in brain	–

collective effects of genetic variation, environmental risk factors, nutritional factors and lifestyle (Harman, 1998). With the inferences of these factors, our bodies undergo progressive deterioration of physical functions, loss of homeostasis and increased susceptibility to diseases. Many theories have been proposed to explain aging. For example, the free radical theory, which was first proposed by Harman (1956), proposed that increased levels of free radicals with age would cause a progressive accumulation of cellular damage (DNA, protein and lipid). In normal oxidative phosphorylation, free radicals are produced as by-products. Our brains consume high levels of oxygen, in the same time produce high levels of free radicals (Prasad et al., 1999). It is therefore not surprising that this organ is particularly susceptible to oxidative stress and easily become "aged".

3. Normal and pathological aging of the brain

The brain is the most vital organ in our body, not only because it controls all the involuntary functions such as heart beating and breathing, but also due to its unique role in memory, cognition and emotion. Aging has a great impact on brain functions. Aged people are found to have decreased memory, including recognition memory (James et al., 2008), short term recall (Gilchrist et al., 2008; Gazzaley et al., 2007), long-term memory and speed of processing (Park et al., 2002). Although aging is always associated with decline in physiological functions, it is not necessary associated with diseases (Anton et al., 2005). Aging can be divided into normal and pathological. The former is a result of natural maturational process. During the process, there are gradual changes in cognitive functions. Some scientists think that these cognitive changes may be inevitable, and human will eventually experience deterioration in memory even they are not diagnosed with dementia (Christensen, 2001). The later is always associated with non-normative factors such as diseases and brain trauma (Reese et al., 2000). The causes of aging-associated brain diseases are certainly linked with numerous factors such as lifestyle and genetics variation. If we can modify these factors, perhaps we can prevent these diseases and hence aging. In this review, we focus on the pathological aging process taking place in the brain only.

4. Alzheimer's disease and Parkinson's disease as two common aging-associated neurological disorders

With the improvement in hygiene and advance in medicine, people nowadays have increased average lifespan. The aging population, in the same time, is facing the challenge of aging-associated diseases. Neurodegenerative diseases that affect our brain particularly draw the attention of many developed countries (Dartigues et al., 2002; Brookmeyer et al., 1998). The age-specific incidence rates of neurodegenerative diseases such as AD and PD increase exponentially with age (Morens et al., 1996; Jorm and Jolley, 1998; Kawas et al., 2000). AD is the major cause of dementia and it accounts for 60–80% of cases. In 1997, the prevalence of AD in United States was 2.32 million (Brookmeyer et al., 1998); 10 years later, however, the prevalence has already jumped to 5.2 million (Alzheimer's Association, 2008). PD is the second most common neurodegenerative disorder and can lead to motor dysfunction. It affects approximately 1% of population aged 65–69 and the prevalence increases to 3% in the 80-year-old or above group (Tanner and Goldman, 1996). The prevalence of PD varies in different ethnic and geographic groups (Zhang and Roman, 1993). Nevertheless, it is expected that the number of PD cases in the five most populous nations in Western Europe will double from 2005 (between 4.1 and 4.6 million) to 2030 (between 8.7 and 9.3 million) (Dorsey et al., 2007). With these diseases, elderly are unable to take care themselves and must rely on other family members or caregivers, thus increasing financial and psychological burden to the society (Alzheimer's Association, 2008).

4.1. Neuropathology of AD and PD

AD is characterized by neuronal loss, the presence of extracellular senile plaques and intracellular accumulation of neurofibrillary tangles (NFTs). Senile plaque are composed of fibrillar β-amyloid peptide (Aβ) produced by cleavage of the β-amyloid precursor protein (APP). NFTs are made up of hyperphosphorylated microtubule-associated tau protein. Neuronal loss is particularly severe in the cortex and hippocampus (for review, see Selkoe, 2001).

Table 2
Summary of some studies of the beneficial effects of ginseng and its active components regarding to AD and PD.

Authors	Ginsenosides/crude extract	Experimental model	Effects	Possible mechanism
Heo et al. (2008)	Korean red ginseng	AD patients	Improved MMSE and ADAS score	–
Shieh et al. (2008)	Rh2	Type I rat brain astrocytes (RBA1) cells treated with $A\beta_{1-42}$	Promote cell survival and proliferation	↑ PACAP gene expression (an neurotrophic factor)
Chen et al. (2008)	Rb1	Primary cultured cortical neurons treated with $A\beta_{25-35}$	↓ Tau phosphorylation	Down regulate p25, ↓ CDK5 activity
Tohda et al. (2004)	Metabolites of ginsenoside (M1)/Rb1	$A\beta_{25-35}$ injected mice	Recover the impaired spatial memory	Promote axonal extension activity in degenerated neurons; preserved phosphorylated NF-H and synaptophysin, hence synaptic loss
Joo et al. (2008)	Rg3	BV-2 microglial and Neuro-2a neuroblastoma cells treated with $A\beta_{1-42}$	↑ Cell survival	↓ Inflammatory/pro-inflammatory cytokine expression; ↑ macrophage scavenger receptor type A expression
Joo and Lee (2005)	Rg3	Brain microglia treated with $A\beta$	Promote phagocytosis of $A\beta$	↑ Expression of macrophage scavenger receptor
Chen et al. (2006)	Re, Rg1, and Rg3	APP transgenic mice	↓ $A\beta_{1-42}$ in brains	–
Wang et al. (2009)	Rg1	Mice injected with MPTP	↓ Dopamine and its metabolites contents in striatum	↓ Nigral iron levels; regulate expression of iron transporters
Chen et al. (2005)	Rg1	Mice injected with MPTP	↓ Neuronal loss in substantia nigra	↓ Phosphorylations of JNK and c-Jun
Radad et al. (2004a,b)	Rb1 and Rg1	Primary mesencephalic culture treated with glutamate/MPP^+	↓ Dopaminergic cells loss; ↑ lengths of neurites	Neurotrophic action
Van et al. (2003)	Ginseng extract G115	Mice injected with MPTP; rats infused with MPP^+	↓ Dopaminergic cells loss; ↓ locomotor dysfunction	–
Rudakewich et al. (2001)	Rb1, Rg1	SN-K-SH cells treated with MPTP	↓ Cell death	Neurotrophic action
Jia et al. (2005)	Ginseng crude extract	PC12 cells treated with 6-OHDA	↓ Cell death; ↑ cell proliferation	Anti-apoptosis
Kim et al. (2002)	Rg3; ginseng total saponins	Primary cultured hippocampal neurons treated with glutamate	Neuroprotection	Inhibition of NMDA receptors
Li et al. (2007a)	Rg2	PC12 cells treated with glutamate	↑ Cellular viability; ↓ level of MDA, NO; ↓ level of calpain II, caspase-3 and $A\beta_{1-40}$	Anti-oxidation Anti-apoptosis
Kim et al. (1998)	Rb1, Rg3	Rat primary cultured cortical neurons treated with glutamate	↓ Neuronal cell damage	Anti-oxidant; preserve level of SOD, ↓ MDA
Lee et al. (2003)	Rd	ICR mice injected with kainic acid	↓ KA-induced lethal toxicity; ↓ neuronal damage in hippocampus	↑ Phosphorylation of ERK; ↓ phosphorylation of CREB
Lin et al. (2007a,b)	Rd	Mesencephalic primary cultures exposed to lipopolysaccharide	↓ Cell death	Anti-inflammatory; ↓ iNOS; ↓ PGE2 synthesis
Tsang et al. (1985)	Total ginsenoside	Rat brain synaptosomes treated with neurotransmitters	↓ Uptake of GABA, glutamate, dopamine, 5-HT, noradrenaline,	–
Xue et al. (2006)	Rb1	PC12 cells	↑ Neurotransmitter release	↑ Phosphorylation of synapsins through the PKA pathway

PD is characterized by the selective degeneration of pigmented, dopaminergic neurons in the pars compacta of the substantia nigra, with the presence of Lewy bodies, which are inclusion of α-synuclein, in the surviving neurons.

4.2. Current pharmacological intervention for the prevention and treatment of AD and PD

The U.S. Food and Drug Administration (FDA) approved drugs for AD treatment includes acetylcholinesterase inhibitors (AChEIs) e.g. donepezil, rivastigmine and galantamine for mild to moderate cases, and memantine for moderate to severe cases. AChEIs are developed based on the hypothesis that the deficiency in cholinergic neurotransmission contributes significantly to the expression of cognitive and non-cognitive symptoms of AD (Francis et al., 1999; Klafki et al., 2006). AChEIs increase the availability of the neurotransmitter acetylcholine by inhibiting its degradation enzyme acetylcholinesterase. Clinical studies have shown that these AChEIs can provide modest improvement on cognitive and global measures relevant to dementia (Rosler et al., 1999; Persson et al., 2009; Winblad et al., 2001; Almkvist et al., 2004; Wilcock et al., 2000; Raskind et al., 2004). Memantine is developed based on an anti-glutamatergic approach. Memantine acts as a specific, low to moderate, non-competitive NMDA antagonist to reduce glutamate excitotoxicity. It is also proposed that the combined use of memantine and AChEIs may provide additional benefit to AD patients (Tariot et al., 2004).

The most effective symptomatic treatment for PD is levodopa. After administration, levodopa is converted to dopamine to replenish the diminished dopamine level in the body. In order to enhance its efficacy, levodopa is often co-administered with decarboxylase inhibitors to reduce its peripheral conversion to dopamine (Lewitt, 2008). Clinical trial shows that levodopa is effective in reducing parkinsonism in PD patients, but in the same time leads to motor complications in some patients (Fahn et al., 2004). Other drugs that have been used for PD treatment include dopamine agonist e.g. bromocripitine, monoamine oxidase-B (MAO-B) inhibitors e.g. rasagiline, catechol-O-methyl transferase (COMT) inhibitors and anticholinergics (Olanow et al., 2009).

Current therapies for AD and PD mainly provide symptomatic improvement by replacing neurotransmitters or controlling their metabolism to restore their imbalance. Since they are not altering the underlying disease process, they usually have little or no impact on disease progression (Lleo et al., 2006).

5. Herbal medicine and its theory on aging

Herbal medicine, which is also known as phytotherapy, refers to the use of plants or plant parts for its scent, flavor or therapeutic properties. There has been a long history of using medicinal herbs.

For instance, the Indian Ayurveda medicine has used the plant *Curcuma longa* (turmeric) for curing various diseases since 1900 BC (Aggarwal et al., 2007). Garlic has been used widely in ancient Egyptian, Greek and Korean medicine (Agarwal, 1996). Herbal medicine has played an important and irreplaceable role in human health care.

The use of medicinal herbs is based on unique traditional medical theories that had been developed in different geographical regions. Besides the holistic characteristic, these theories sometimes share certain similarities. For example, the concept of "channels" for the delivery of air, blood and nutrients to different body parts has been described in both Egyptian and Chinese medicine (Zhu, 2005). "Element balance" has been adopted in Chinese and American Indian medicine (Adams et al., in press). Nevertheless, many of these theories believe that balancing different body components is essential for health keeping, disease prevention and intervention (Schneider et al., 2002; Zhang and Wu, 1991). In order to have a better understanding of the properties of anti-aging herbs, it would be better for one to acquaint the concept on the aging theory in traditional medicine.

5.1. Herbal medicine: aging is a result of decline in vital energy

Herbal medicines of Asian geographical regions always share some similarities in theories and usage of herbs. Asian countries including China, Korea and Japan have a tradition to use medical herbs for anti-aging purpose. In these countries, aging is regarded as a process of progressive decline of "vital energy" in our body; and therefore leads to deterioration in functions and diseases. Unlike the concept adopted in Western medicine, "vital energy" in the traditional theory is a collective term for describing both the physical and mental energy. It has multiple functions and is believed to be essential for growth, daily activities, reproduction, cognitive functions and disease prevention (Ody, 2000). While recent advance allows the measurement of physical energy metabolism (energy expenditure) and assessment of mental state to a certain extent (Manini, in press; Lieberman, 2001), vital energy is usually accessed by multiple observational parameters in the traditional practice. However, modern research is now investigating the possibility to evaluate and quantify different components of vital energy. One possible approach is to use the oxidation and anti-oxidation states to explain imbalance in *yin* and *yang* (a form of vital energy) (Ou et al., 2003). The modulation of mitochondrial ATP generation may also be a modern explanation of the "energy-boost up effect" of tonic herbs (Leung et al., 2005). Furthermore, *Qigong*, which is a traditional exercise designed to control vital energy for health promotion, is found to be related to immune functions and may reduce the blood level of stress-related hormone cortisol (Jones, 2001). These changes might serve as measurable parameters for us to quantify vital energy by biochemical assays.

Preservation of vital energy is important according to the traditional theory. The ancient traditional Chinese medicine book *Yellow Emperor's Canon of Internal Medicine (Huangdi Neijing)* clearly points out that proper methods (maintain good lifestyle, exercise, reduce stress) can help us to preserve vital energy in our body, and human is able to obtain lifespan beyond 100-year-old (Wu et al., 1997). There are also theories of aging-associated diseases. They are caused by deficiency of certain essential components, which leads to imbalance in body functions (Gao et al., 2004). Neurodegenerative diseases that lead to dementia, for instance, are considered to be resulted from decline of vital energy in the brain (Gao et al., 2004). PD, which is characterized by movement disorders instead of dementia, is also considered to be the result of reduced vital energy (Xue, 2003). It is believed that neurodegenerative diseases all share the same fundamental cause i.e. decline of energy, hence allows them to be treated with the same therapeutic strategy. The differences in their symptoms are explained as the co-existence of other pathological factors; and hence additional herbs are added to form herbal formulas for disease treatment. The aim of anti-aging is to prevent or intervene aging-associated diseases through maintenance of vital energy.

5.2. Properties of anti-aging herbs

Some herbs are regarded as "anti-aging herbs" in Asian countries. These herbs usually have some common properties. (1) *Effects*: these herbs usually belong to the group of "tonifying" herb, which means they can help boosting up the level of vital energy in body. As deficiency of vital energy is thought to be the cause of aging, this property is especially important. (2) *Multi-stages intervention*: in healthy stage, some of these herbs act as food to provide certain essential nutrients; in disease stage, they help intervening disease and relieving symptoms. (3) *Multi-targets and holistic approach*: anti-aging herbs are often multi-targets and can be used in a number of diseases. They also achieve their therapeutic effects through modulating multiple pathological aspects.

One may notice that many anti-aging herbs provide general health promotion to different organs and seems to be non-specific to the nervous system. In traditional medicine, herbs are classified according to their properties which allow them to correct the imbalance of vital energy components (e.g. *yin* and *yang*) (Ody, 2000). The theory adopts a holistic approach that during aging, energy deficiency or imbalance in one body system can affect the function of other systems; therefore herbs are not specifically targeting single organ but tend to be multi-functional. This is perhaps a different concept from Western pharmacology in which drugs should have specific targets of action. The holistic view for aging can be partly supported by research findings demonstrating that aging-associated neurological disorders can be affected by risk factors. For instance, the risk of AD increases with hyperhomocysteinemia, midlife hypertension, and even viral infections (McGuinness et al., 2006; Nurk et al., 2005; Stozicka et al., 2007). Factors which seem to have no direct relationship to the brain (or central nervous system) can certainly affect disease progression. Modulation of these risk factors can serve as indirect intervention for neurodegenerative diseases (Beeri et al., 2008; Zamrini et al., 2004). This may explain why the general health promotion effects of herbs can eventually benefit the aging brain. Anti-aging herbs which are described to have general tonic functions are therefore being investigated for their actions in the brain as anti-dementia drugs.

6. Anti-aging herbs and neurodegenerative diseases

In order to further elaborate the properties of anti-aging herbs, two herbs are used as examples. Wolfberry and *P. ginseng* are both regarded as anti-aging herbs in Asian countries. In the following sections, we will summarize their effects on neurodegenerative diseases and link their traditional properties in modern theories.

6.1. Wolfberry

6.1.1. General properties

The fruit of *L. barbarum*, also called wolfberry, is a commonly used herb in Asian countries. In China, where it is also named as *Gouqizi*, this fruit is particularly famous for its beneficial effects on eye and liver. According to the Chinese pharmacopoeia, wolfberry is regarded as upper class herb, indicating that it has good therapeutic effects and little side effects. The fruit belongs to "Yin-tonifying herb" and is believed to be effective in replenishing any deficient "Yin" (a kind of vital energy); hence balancing homeostasis in our body (Benzie et al., 2006; Chang and So, 2007).

6.1.2. Wolfberry is a food ingredient, yet more than just food

Wolfberry is not just used as medicinal herb in disease stage; it is also a common ingredient in Asian cooking recipe. It is taken as food not just because of its sweet taste, nor its beautiful red color. Many Asian think that it is good for health and recent research on its components may help to explain this thought. It has been reported that the fruit has a high content of zeaxanthin (30 mg/100 g), which is beneficial to the aging eye for prevention of age-related macula degeneration and aged-related cataract formation (Pratt, 1999; Mares-Perlman et al., 2002). The fruit also contains high content of β-carotene (up to 19.6 mg/100 g) (Qi and Li, 1981), and long-term β-carotene supplement may provide cognitive benefits (Grodstein et al., 2007). Betaine can also be found in *L. barbarum*. It works with other nutrients to break down excess homocysteine (Selhub, 1999), which is considered to be a risk factor for AD (Seshadri, 2006). With these nutritional components, it is not surprised that wolfberry has been taken as functional food and supplement in non-disease and sub-health stages.

6.1.3. Multiple protective effects on AD

The neuroprotective effects of wolfberry embody the multi-targets and holistic approaches of anti-aging herbs. It is suggested that wolfberry can provide direct cellular effects and indirect immune modulation in aging-associated conditions (Chang and So, 2007). In AD, wolfberry provides direct and indirect protective effects on neurons. (1) *Direct effects*: polysaccharides from wolfberry, the *L. barbarum* polysaccharides (LBP), are the active components of the fruit (Chang and So, 2007). Data from our laboratory has shown that LBP have direct cellular protection against Aβ neurotoxicity (Yu et al., 2007). Treatment with LBP attenuated Aβ-induced apoptosis and the effective and safety dosages were wider than lithium chloride (LiCl), a well-known Western neuroprotective agent (Yu et al., 2005). LBP could modulate the phosphorylation of double-stranded RNA-dependent protein kinase (PKR) and c-Jun-N terminal kinase (JNK), which are both involved in Aβ neurotoxicity (Yu et al., 2005; Yu et al., 2007). (2) *Indirect effects*: the protection of wolfberry against neurodegeneration in AD is not limited to its effect against Aβ neurotoxicity. Wolfberry actually has indirect effects and modulates a number of AD-associated risk factors. Diabetes mellitus, for example, is consider to be one of the risk factors to increase the prevalence of AD (Peila et al., 2002; Kalaria et al., 2008). A proper control of blood glucose level remains the principle of disease treatment. Tight blood glucose control can reduce disease complications (Holman et al., 2008), and may also result in cognitive improvement in diabetes patients (Beeri et al., 2008; Meneilly et al., 1993). Studies have shown that wolfberry has hypoglycemic effects. Oral feeding with its polysaccharides can reduce blood glucose level in alloxan-induced diabetic rabbits (Luo et al., 2004). The anti-oxidant properties of LBP also enable it to reduce DNA damage, malondialdehyde (MDA) and nitric oxide (NO) level in diabetic rats (Wu et al., 2006). Apart from diabetes, LBP also reduces serum cholesterol level, which is another risk factor involves in AD development. In patients with elevated serum cholesterol level, administration of the cholesterol-reducing drug statin can lead to a 39% lower risk of AD relative to non-statin users (Zamrini et al., 2004). In a study of alloxan-induced diabetic or hyperlipidemic rabbits, oral feeding of wolfberry extract (composed mainly LBP) reduces serum total cholesterol and triglyceride level in the animals and in the same time increases the levels of high density lipoprotein cholesterol (Luo et al., 2004). Recent data from our laboratory further demonstrate that LBP is able to attenuate homocysteine toxicity (Ho et al., 2009), which is associated with cardiovascular diseases, stroke and AD (Perry et al., 1995; den Heijer et al., 1995; Graham et al., 1997; Morris, 2003). It has been reported that increased plasma homocysteine

levels are associated with memory deficit in elderly (Nurk et al., 2005), dementia, AD and mild cognitive impairment (MCI) (Quadri et al., 2005). Pre-incubation with LBP reduces the level of apoptosis, hyperphosphorylation and cleavage of tau induced by homocysteine in primary cortical neurons (Ho et al., 2009). Apart from providing protection against Aβ and some AD risk factors, wolfberry may also slow down AD progression by reducing glutamate excitotoxicity (Ho et al., in press). It has been suggested that over-activation of NMDA receptors is one of the final common pathways that lead to neuronal dysfunction and neuronal loss in acute and chronic neurodegenerative diseases. Agents that can reduce glutamate excitotoxicity are potential candidate for disease treatment. Therapeutic agents that act on NMDA glutamate receptor, such as memantine for the treatment of mild to severe AD, have been developed (Muir, 2006). It is found that LBP can attenuate glutamate excitotoxicity *in vitro*, and its protective effect is comparable to memantine (Ho et al., in press). The protective effects of LBP on glutamate suggested that it has potential therapeutic use on different neurodegenerative diseases. The protective effects of wolfberry and its active components against AD are listed in Table 1.

By using wolfberry as an example, we have shown that anti-aging herbs can modulate disease at a multi-target approach. Wolfberry provides direct protection against Aβ neurotoxicity, which plays a central role in AD pathology. In the same time, its modulation on AD-related risk factors and glutamate toxicity (indirect effects) is a reflection of the traditional Asian medicine theory. Anti-aging herbs such as wolfberry is used to balance the energy in different body systems during aging, therefore their "general health promotion effects" eventually help to preserve the aging brain.

6.2. Panax ginseng

6.2.1. General properties

Ginseng is another well-known anti-aging herb and it is the second most commonly used natural products in the United States (Barnes et al., 2008). Ginseng refers to a group of 11 species within the *Panax* genus. In Greek, Panax means "all-cure". *P. ginseng* and *P. quinquefolius* are the most commonly used ones and they are characterized by the presence of ginsenosides. They are viewed as adaptogenic herbs, which means they increase body's resistance to stress, trauma, anxiety and fatigue (Winston and Maimes, 2007). In oriental medicine, ginseng is classified as a "*Qi*-tonifying herb" and can boost up vital energy in different body parts to delay aging (Kathi, 1996).

6.2.2. Beneficial effects of ginseng on multiple neurodegenerative diseases

Ginseng or ginsenosides has shown protective effects in various neurodegenerative diseases even though the symptoms and pathogenesis are quite different from each others. Research has shown that ginseng is effective in attenuating pathological changes in cellular/animal models of AD, PD or even Huntington's diseases. The beneficial effects of ginseng on AD have been demonstrated in human as well as animal studies. In an open label trial carried out in Korea, AD patients who consumed high dose (9 g/day) of Korean red ginseng for 12 weeks showed significant improvement of clinical test performance. The scores for mini-mental state examination (MMSE) and Alzheimer disease assessment scale (ADAS) of the ginseng group were significantly higher than that of control group during the 12 weeks of ginseng consumption, and they declined after discontinuing ginseng intake (Heo et al., 2008; Lee et al., 2008). Studies have been conducted to investigate the protective mechanisms of ginseng. Researchers have found that even single oral feeding of ginsenosides Re, Rg1, and Rg3 to APP transgenic mice could reduce the level of Aβ$_{1-42}$ in mice brains

(Chen et al., 2006). Another study shows that metabolites of ginsenoside (M1) is able to antagonize memory impairment, axonal atrophy and synaptic loss in Aβ injected mice (Tohda et al., 2004). Since ginsenosides are a group of compound, each ginsenoside may provide protection through different mechanisms. For instance, ginsenoside Rh2 could stimulate pituitary adenylate cyclase-activating polypeptide (PACAP) gene expression (an neurotrophic factor) in type I rat brain astrocytes after Aβ treatment, hence promoting cell survival (Shieh et al., 2008). Ginsenoside Rg3 could promote the phagocytic responses of microglia to remove Aβ (Joo and Lee, 2005). Other ginsenosides such as Rg2 could attenuate glutamate-induced toxicity and may slow down AD progression (Li et al., 2007a). The above studies suggest that ginseng components act on different disease stages or mediators to fight against AD. Ginseng attenuates Aβ toxicity, enhances clearance of Aβ and promotes cell survival. It also enhances cognitive performance and relieves symptoms. The non-specific and multi-targets properties of ginseng are typical characteristics of anti-aging medicinal herbs.

Apart from AD, ginseng also shows protective effects on PD. Many studies use 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or its active metabolite 1-methyl-4-phenylpyridinium (MPP$^+$) as the neurotoxins or parkinsonism mimetics in cell culture or animal PD models. These toxins induce oxidative stress and lead to cell death of dopaminergic neurons to mimic the situation in PD (Zhou et al., 2008). Some ginsenosides are able to reduce toxicity induced by the above agents and reduce neuronal cell loss. For example, mice with ginsenoside Rg1 injected into their body have less neuronal cell loss in their substantia nigra after MPTP injection. It is suggested that Rg1 can attenuate oxidative stress and activation of stress kinase JNK in these mice (Chen et al., 2005). Another group of researchers found that Rg1 is able to protect neurons probably through suppression of MPTP-induced elevation of iron level and regulation of iron transport proteins (Wang et al., 2009). It is also found that both ginsenoside Rb1 and Rg1 can protect neuroblastoma SN-K-SH cells from MPTP toxicity and promote neurite outgrowth in PC12 cells (Rudakewich et al., 2001). Others report that Rg1 and Rb1 can attenuate MPP$^+$ or glutamate-induced neurodegenerative changes in dopaminergic neurons in vitro and promote their neurite outgrowth (Radad et al., 2004a,b). Crude extract from ginseng is neuroprotective against 6-OHDA-induced apoptosis of PC12 cells (Jia et al., 2005).

In summary, ginseng provides protection against neurodegeneration in several PD models. Similar to wolfberry, ginseng employs multiple neuroprotective mechanisms: it acts as anti-oxidant, attenuates activation of caspase-3, suppresses activation of stress kinases and may promote cell survival through elevation of NGF mRNA expression (Van et al., 2003). It may also protect neurons in different disease stages; it interferes stress kinase signaling pathway and attenuates activation of caspases, which are considered to be up-stream and down-stream events in apoptosis cascade. It also inhibits NMDA receptor and may slow down progression of neurodegenerative diseases (Kim and Rhim, 2004; Kim et al., 2002). The multiple protective mechanisms and multi-disease stage intervention properties perhaps explain why ginseng is a well-known "anti-aging herb". The beneficial effects of ginseng and its active components against AD and PD are summarized in Table 2.

7. What should we be aware when studying the neuroprotective effects of anti-aging herbs?

In the above sections, we have listed some neuroprotective properties of wolfberry and ginseng. We propose that the scientific evidence of their properties is matched with the traditional theory. Aging is an "energy decline" process that involves the whole body.

The decline of vital energy in the brain is often accompanied with dysfunctions in other body systems. Neurodegenerative diseases that appear to affect mainly the brain can be influenced by changes in other body parts (e.g. elevation of blood glucose may increase the risk for AD, exposure to toxins may increase the risk for PD). Therefore traditional medicine use anti-aging herbs to preserve energy; hence prevent or treat aging-associated diseases in multi-stages and multi-targets manner.

The central therapeutic action of anti-aging herbs is their ability to preserve vital energy. Owing to the differences of interpretation of "energy" by modern Western medicine and traditional Asian medicine, it is not easy to provide direct experimental evidence to support the "energy preservation" statement. One direction that neuroscientists have recently explored is the mitochondrial dysfunction theory. Mitochondria are responsible for the generation of cellular energy and are believed to play a central role in aging and neurodegenerative diseases (Lopez-Lluch et al., 2008). In vivo experiments have shown that some herbs which have "tonifying" effects could promote mitochondrial ATP generation in various types of tissue including the brain in rats (Leung et al., 2005). These herbs may also increase the activities of mitochondrial anti-oxidant components under oxidative stress (Chiu et al., 2008). Although these studies can just partly explain the vital energy preservation concept, they demonstrate the possibility to use modern scientific approach to explain traditional theories. Elucidation of biological mechanisms of herbs remains the central and important part of anti-aging research.

The following points deserved our attention when we investigate and develop potential neuroprotective agents from anti-aging herbs:

(1) *Extraction and purification of active compounds*. One of the most significant differences between tradition and Western medicine is their usage of drugs. Traditional medicine often uses plant parts directly in their prescription, while Western medicine tends to extract the active compounds from herbs. The fundamental challenge for both clinical and basic pharmacological researchers would be their choices of single compound or crude extract as the research target. The advantage of using single compound with well-defined chemical structure is that this can facilitate the generation of basic pharmacological information such as molecules interaction, degradation, post GI tract modification, pharmacokinetic and metabolism. However, one must be reminded that the holistic and multi-target actions of anti-aging herbs are actually the unique properties which differentiate them from conventional Western medicine. Yet, these beneficial effects are unlikely to be achieved by single component. Hundreds of chemical compounds are found in plant, and the interaction between each component is not well-studied. These raise the possibilities that some useful ingredients may loss during extraction process. It is not uncommon that single component extracted from plants is less protective than the crude extract (Luo et al., 2004) as these compounds may have synergistic effects (Lin et al., 2007a). Take wolfberry as an example, β-carotene may provide cognitive benefit and LBP could protect neurons from Aβ-toxicity. The traditional anti-aging effects of wolfberry may be resulted from the combined effects of all its components. Instead of purification of single compound, extraction for standardized extracts may be more practical. One example is the EGB 761 (contains 24% flavone glycosides and 6% terpene lactones) from Ginkgo biloba. While there are reports focus on individual components of G. biloba, many clinical trials used the standardized formula (Birks and Grimley, 2009).

Quality control of herbal crude extract is essential for producing solid scientific evidence. Herbal authentication is

therefore necessary to determinate the correct origin, species and to assess the quality of herbs. Besides, all plant material extract should undergo chemical and biological standardization. By using mass spectrometry, it is possible to generate a three-dimensional fingerprint of herbal extract. The chemical composition such as the percentage of lipids, amino acid and carbohydrates should also be determined by HPLC. The chemical profile can be used as a reference to compare the quality of subsequence batch of extract. Further analysis is then followed to produce a biological fingerprint. Well-defined cell lines are treated with the extract and the mRNA expression are measured with microarray. These procedures allow the identification of important biologically active subset of molecules in the herbal extract (Sinha, 2005). With the advance in technology and standardization method, herb extracts are manufactured in a good-quality-controlled manner, which can serve as the foundation for basic and clinical research.

(2) *Proper choice of biomarkers for effectiveness evaluation.* Some "anti-aging" herbs like wolfberry and ginseng are actually taken as food in Asian countries. Therefore their usage is not purely for disease treatment, but for health maintenance and disease prevention. They may act as disease-modifying agents for pre-symptomatic individuals, and those with earliest manifestations of neurodegenerative diseases. The problem is whether there are sufficient biomarkers or methods to evaluate the effectiveness of these agents in pre-symptomatic stages. Since disease-modifying agents are not just providing symptomatic benefit, they also target underlying neuropathology, new biomarkers and clinical trial design are needed to evaluate their effectiveness. It is essential to develop reliable biomarkers that is able to predict disease progression in pre-symptomatic stages for outcome measures in clinical trials (Mani, 2004).

(3) *The differences between clinical trial, pharmacological experiment and expectation from traditional theories.* In Western medicine/ herbology, herbs are used in a symptomatically approach; which means herbs are chosen according to particular symptoms or diseases (Tierra, 1992). In traditional theory, however, the use of herbs is based on their energy profile, which matches with that of the patient. When conducting clinical trials and pharmacological experiment, the characteristic of energy profile is often neglected. Therefore, it is not surprised to see that some "anti-aging herbs" cannot demonstrate their effects when using modern scientific methods. One possible solution for this would be the modification of clinical trials in which traditional theory and diagnosis are also considered in the participant recruitment process. This would facilitate the exclusion of participants that are actually not suitable for receiving the tested active treatment. Besides, the inclusion of traditional diagnosis may help in clinical trial design. Participants can be further divided into several treatment arms according to their "energy profile" in traditional medicine. Nowadays, guidelines for traditional medicine diagnosis have already been established in some countries (e.g. the "guidelines for diagnosis and treatment of common internal diseases in Chinese medicine" in China). Essential information of participants e.g. appetite, the characteristic of pulse and tongue can be collected, which help further classification of participants into proper treatment groups. This personalized medicine approach allows the investigation of anti-aging herbs in a traditional and modern science integrated way.

8. Concluding remarks

Taken together, we use ginseng and wolfberry as examples to demonstrate the properties of anti-aging herbs. According to the traditional theory, these herbs can help us to maintain the level of vital energy in our body; and they have multiple neuroprotective mechanisms that enable them to be used in different health stages for disease prevention and even curing. These properties can sometimes be proved by using modern scientific methods, such as pharmacological experiments and clinical trials. If we understand the vital energy concept of herbal medicine, we can use modern scientific knowledge to disclose the biological mechanisms of anti-aging herbal medicine. On one hand, we use scientific language to explain tradition dogma of why some herbs can be named as "anti-aging". On the other hand, we may help prevention and intervention of aging-associated neurodegenerative diseases.

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