11. Medicinal and nutraceutical uses of wolfberry in preventing neurodegeneration in Alzheimer's disease

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Abstract. In recent years, more people embrace complementary and alternative medicine as a possible mean for disease prevention. While wolfberry is considered to be a medicinal herb, it is also a common ingredient in oriental cuisines. Recently, there are many different lines of wolfberry products as dietary supplements in North America, South Africa and Europe. Chemical analysis suggests that wolfberry is composed of polysaccharides, carotenoids such as β-carotene, zeaxanthin, lutein, different vitamins and some trace elements. Owing to its multi-nutritional values, it would not be surprising that wolfberry exhibits a wide array of beneficial effects. Wolfberry has been reported to have anti-cancer and immune-modulating properties. More importantly, wolfberry is well-known for its anti-aging effects. Some studies have shown that wolfberry can ameliorate age-related conditions including glaucoma, hypertension and diabetes. These protective
effects actually agree with its traditional use in oriental medicine and as a dietary supplement. Some laboratories have suggested that wolfberry provides its protection via its anti-oxidative effect as it composes high content of β-carotene and zeaxanthin. Recent research suggests that wolfberry elicits protective effects against neurodegeneration in Alzheimer’s disease (AD). Studies have shown that wolfberry extract containing mainly polysaccharides can reduce neurotoxin β-amyloid peptide-induced neurodegeneration in vitro. Wolfberry can also protect neurons against some risk factors in AD. The role of wolfberry in AD prevention as well as in anti-aging deserves more exploration, and use of wolfberry may pave a new road in early intervention of AD pathogenesis.

Introduction

Complementary and alternative medicine (CAM) has become more popular in recent years. According to a survey released in 2004 by the National Center for Complementary and Alternative Medicine, 36% of adults in the United States are using some forms of CAM. Among these people, 19% of them have used natural products and the expenses on these products are about 5 billion US dollars [1]. More herbal products have become available as dietary supplements and wolfberry is one of these examples.

Wolfberry is the common name of the fruits *Lycium barbarum* or *Lycium chinense*, which are two very closely related species. It belongs to the family Solanaceae and it can be found in many regions of the world. There has been a long history for using wolfberry as a medicinal herb in Asian countries. In China, where it is named as *Gouqizi*, wolfberry has been used as a “yin-tonifying herb” and is believed to be beneficial to the eye, kidney and liver. People believe that the fruit is highly nutritional and has an important therapeutic role. More importantly, it has been regarded as anti-aging in Chinese pharmacopoeia. For a long time, wolfberry has been used to treat various diseases including diabetes and glaucoma in oriental medicine. As wolfberry has a bright red appearance and sweet taste, it is also a common ingredient in food dishes, soup, and even snacks.

Wolfberry is commonly sold as a dried fruit and it can be directly eaten without further processing. When it is used as medicinal herbs in oriental medicine, the dried fruit (Fig. 1) is usually boiled in hot water for hours with other herbs to obtain maximum effects. It can also be added into soup and tea to provide a pleasant flavor. As people are placing more attention on health food products, wolfberry juice, extract or essence capsule have gained increased popularity.

While manufacturers always claim that these products have multiple benefits, there is usually insufficient data to support their use as health-promoting supplements. The purpose of this review is to summarize the medicinal and
nutraceutical beneficial effects of wolfberry, and discuss its possible therapeutic effects on the prevention of neurodegeneration in Alzheimer’s disease (AD).

**Alzheimer’s disease - diverse pathology and multiple risk factors**

AD is a progressive neurodegenerative disease which can eventually lead to dementia in elderly. The classical symptoms of AD include memory impairment, language deterioration and visuospatial deficits [2]. These symptoms, however, may occur years or decades after the onset of pathological changes [3]. Evidence from brain imaging studies indicates that brain atrophy and neuronal dysfunction precede the onset of cognitive impairment [4; 5]. Therefore, prevention or slowing down the onset of AD may be more effective than reversing the disease process [6].

Different mechanisms and hypotheses have been proposed to explain the pathological changes and clinical symptoms of AD. It is generally accepted that protein misfolding, aggregation, beta-amyloid (Aβ) peptide accumulation and tau accumulation in neurofibrillary tangles (NFT) play important roles in AD development [7]. Based on the pathological characteristics of the disease, several targets have been suggested for disease-modifying therapy. Current development on disease-modifying agent for AD focuses on production of Aβ and tau protein [8]. While Aβ and tau are involved in the initial stage of AD, it is possible that secondary pathological cascades such as inflammation and oxidative stress can occur and cause further damage to brain [9; 10].
Therefore medication or nutritional intervention targeting these secondary changes may also be helpful in slowing down disease processes. Apart from these pathological changes, AD is also believed to be associated with a number of risk factors such as hyperhomocysteinemia, diabetes, midlife hypertension, cardiovascular diseases, hypercholesterolemia and viral infections [11-17]. Although the exact linkage between AD and these risk factors remains unclear, pharmaceutical or nutritional interventions that minimize these risk factors may be benefit to AD prevention. In view of the diverse pathology and multiple risk factors, effective disease-modifying agent should be multifunctional and targets different aspects during AD progression.

**General effects of wolfberry**

Wolfberry belongs to the “Yin-tonifying” herbs in traditional Chinese medicine. In Chinese pharmacopoeia, it is listed as an upper class herb, implicating that it has multiple beneficial effects but little side effects. The fruit is used to provide a general tonic effect and is especially beneficial to kidney, liver and eye. Although it has a good reputation for vision improvement, its effects is not limited to the eye. It helps to restore body homeostasis (balance “Yin” and “Yang”) and strengthen body energy. Interestingly, this idea is supported by a recent clinical study, which suggests that daily consumption of wolfberry juice for 2 weeks increases subjective feelings of general well-being and improves gastrointestinal functions [18].

Wolfberry is also famous for its anti-aging properties. Up to date, there is no research in rodents to investigate if taking wolfberry can enhance longevity. However, increasing lines of evidence suggest that wolfberry can improve diverse aging-associated conditions as follow: Zhang et.al. (2005) have reported that polysaccharides from wolfberry can have anti-tumor effects on hepatoma QGY7703 cell line probably by inducing cell cycle arrest in S phase and increasing intracellular calcium to induce apoptosis [19]. Another study suggests that wolfberry extract can inhibit hepatocarcinoma cell proliferation and stimulate p53-mediated apoptosis [20]. Degeneration of organs is also involved in aging processing, and the degenerative processes may be attenuated by wolfberry. In a study of glaucoma, an aging-associated eye disease, oral feeding of wolfberry extract protects rat retinal ganglion cells from ocular hypertension-induced damage [21].

Wolfberry can provide beneficial effects on different organs and body systems. Traditional literatures of oriental medicine also describe its anti-aging effects. Therefore, our laboratory hypothesizes that wolfberry can be a potential therapeutic agent for the prevention of neurodegenerative diseases such as AD. More importantly, findings from our group support the idea that
Wolfberry as disease-modifying agent for AD

Wolfberry has multi-target effects on neurodegeneration of AD. The results imply that wolfberry can protect brain cells from neurodegeneration of AD by modulating different AD-related pathogenesis [22-24]. We will discuss these effects in this review.

Chemical compositions of wolfberry and their beneficial effects

Wolfberry is made up of a group of components including polysaccharides, betaine, zeaxanthin, beta-carotene, groups of vitamin, 19 kinds of amino acid and trace minerals. Many of these components are helpful in maintaining body health and some of their benefits are listed as follows.

Polysaccharides

It is believed that the polysaccharides of wolfberry, also named as *Lycium barbarum* polysaccharides (LBP), are the active components responsible for its various biological activities, especially the immune-modulating and anti-oxidative functions [25]. LBP is not a single compound but a group of proteoglycans made up of monosaccharides. The carbohydrate content of wolfberry is found to contain arabinose, rhamnose, xylose, galactose, glucose, glucoronic acid, galacturonic acid and mannose [23, 26]. This composition is not fixed. By using different extraction methods, such as using water or alcohol or alkaline solutions, LBP can be purified and isolated into different sub-fractions [22]. Studies have found that these LBP can have diverse biological activities and they may affect cell signaling pathways [22, 27]. The beneficial effects of LBP will be further discussed in the later part.

Zeaxanthin

Apart from LBP, zeaxanthin is also abundant in wolfberry. Zeaxanthin is an oxygenated carotenoid and is found specially located in the human macula [28]. Findings indicate that zeaxanthin is beneficial to eye and can protect the eye against age-related macula degeneration and aged-related cataract formation [29, 30]. Zeaxanthin can be obtained from fruits and vegetables [31]. However, its bioavailability is varied from different food. In wolfberry, zeaxanthin presents as an esterified from, zeaxanthin diaplmitate. Its content varies depending on the grade and source of the berry [32]. There are several advantages of using wolfberry as the source of zeaxanthin. Firstly, zeaxanthin content in wolfberry is very high. It has been reported that the content of
zeaxanthin in wolfberry can be as high as 30 mg/100g of the material [33], which is much higher when comparing to that found in egg yolk (210 µg/yolk). Secondly, wolfberry intake does not affect plasma lipid levels. When taking egg yolk to supplement zeaxanthin, the plasma low density lipid (LDL)-cholesterol level increases and this would increase the risk of heart diseases [32; 34]. Thirdly, the bioavailability of zeaxanthin from wolfberry is good and can directly increase plasma zeaxanthin concentrations after intake [35]. Fourthly, studies have shown that zeaxanthin diaplmitate from wolfberry can have hepatoprotective effects. In a rat model of hepatic fibrosis, oral feeding of the compound can slow down collagen deposition and reduce the activities of aspartate transaminase and alkaline phosphatase in serum [36]. These unique characteristics of wolfberry regarding to its zeaxanthin content enable the fruit to act as a medicinal herb as well as a highly nutritional food.

Betaine

Wolfberry contains 0.797-1.18% of betaine [37]. Betaine is important for maintaining the health of cardiovascular system. It works with other nutrients such as folic acid, vitamin B6 and B12 to break down homocysteine, a substance which can increase the risk of atherosclerosis and hence heart attack [38]. Recent studies have suggested that betaine supplementation may protect liver cells from ethanol-induced steatosis [39]. A pilot study also suggested that betaine may provide biological and histological improvement in patients with nonalcoholic steatohepatitis [40].

Beta-carotene

Wolfberry also contains a high content of beta-carotene. Every 100 g of wolfberry contains 19.6 mg of carotene [41], which is even higher than that in carrot (about 5.6 mg/100 g) [42]. Beta-carotene is the most common form of carotene. It is a precursor of vitamin A and can provide strong anti-oxidative effects. A recently randomized trial suggested that long-term beta-carotene supplement might provide cognitive benefits [43].

Wolfberry as a potential disease-modifying agent for prevention of AD

As mentioned in the previous section, LBP from wolfberry is responsible for many biological functions. Recent findings have shown that these polysaccharides may have protective effects against AD-associated conditions
Wolfberry as disease-modifying agent for AD [22-24]. We summarize these effects in two categories: direct protective effects and indirect protective effects. Direct protective effects refer to actions that target on neurons. Indirect effects, which can also be considered as global effects, refer to those that target AD risk factors.

**Direct protective effects against Aβ-peptide neurotoxicity**

Base on the hypothesis that wolfberry can provide protection against neurodegeneration in AD through multiple mechanisms, our laboratory has conducted a comprehensive research on the polysaccharides of this fruit. We found that neurons pretreated with LBP reduced neurotoxicity induced by Aβ-peptide [23]. It is generally accepted that Aβ-peptide and its aggregation are related to AD progression [44]. Experiments have shown that Aβ-peptide can induce apoptosis, tau phosphorylation and activation of microglia [45]. Surprisingly, this protective effect is only provided by the polysaccharide fraction of wolfberry. We have examined other fractions from wolfberry including betaine and β-sitosterol, none of them provide protective effects against Aβ-peptide neurotoxicity [22-24], suggesting that LBP is the active component for neuronal protection. Moreover, LBP provides an additional advantage as it has a wider effective and safety dosage when comparing to a well-known Western neuroprotective medicine, lithium chloride (LiCl) [23; 24]. The ability of LBP to protect neurons against Aβ toxicity enables it to be a potential candidate for AD prevention.

The mechanisms mediated by LBP for its protective effects against Aβ remains unclear. Our data suggested that LBP can inhibit some pro-apoptotic signaling pathways, including the c-Jun N-terminal kinase (JNK) and double-stranded RNA-dependent protein kinase (PKR) in Aβ peptide neurotoxicity [23; 24]. If we extract LBP by a different solvents, such as an alkaline solvents, the resulting LBP shows different properties and can stimulate the survival Akt signaling pathway [22]. This kind of changes for the biological effects may reflect conformational changes of LBP during extraction.

**Indirect effects of wolfberry**

Although wolfberry can protect neurons against Aβ peptide-induced neurotoxicity, research shows that its beneficial effects are not limited to this neurotoxin. By modulating AD-related pathogenesis and reducing pathological changes in the associated risk factors, wolfberry may provide its beneficial effects in a holistic approach.
Attenuation of glutamate excitotoxicity

Glutamate is the most abundant excitatory neurotransmitter in the mammalian central nervous system. It is released from the presynaptic vesicles and binds to specific postsynaptic glutamate receptor (e.g. N-Methyl-D-Aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), kainate and some metabotrophic glutamate receptors) to trigger depolarization and action potential. Many studies have shown that glutamate receptors play important roles in AD pathogenesis [47-50]. The expression and functions of glutamate receptors can be impaired by Aβ peptide [51; 52]. It has been shown that NMDA receptor antagonist can reduce loss of hippocampal neurons induced by injection of Aβ1-40 [53], which further supports the involvement of glutamate excitotoxicity in AD development. One of the AD therapeutic strategies is targeting these receptors.

Since blockage of glutamate excitotoxicity is beneficial for AD treatment, our laboratory investigated the protective effects of LBP against glutamate-induced neuronal damage. We found that LBP could reduce necrotic and apoptotic cell death in cortical neurons treated with glutamate or NMDA. Its protective effect is comparable to memantine, which is a NMDA receptor antagonist. This is a good indication as memantine is a currently approved drug for AD treatment based on its effect on glutamate toxicity [54]. Our data also suggest that LBP can attenuate glutamate-activated JNK. Future research will be focused on the change of electrophysiological properties of neurons treated with LBP to find out its protective mechanisms. The protective effects of LBP against glutamate toxicity further support its potential role in preventing neurodegeneration in AD [54].

Protection against diabetes

Diabetes mellitus (DM) is a common and devastating health problem in the elderly. Epidemiological studies suggest that it is a risk factor for a number of diseases including AD. In a population-based cohort study, it is found that patients with adult onset diabetes mellitus have significant increased risk of AD [55]. Similar results were also found in another population-based cohort study, the Honolulu Asia Aging Study [56]. In this study, it suggests that type 2 diabetes together with the presence of APOE epsilon4 allele is associated with increase prevalence of AD. Several mechanisms are proposed to explain the association between AD and DM. It is generally believed that DM, being an atherogenic risk factor itself, can cause stroke and vascular change that is related to vascular dementia. DM
may exacerbate Aβ-neurotoxicity by advanced glycation end-product [57], insulin resistance [58] and impaired glutamate receptors functions [59]. Since it has been documented that a better glycemic control in DM patients may result in cognitive improvement [60], agents that can provide hypoglycemic effects or reduce DM-related pathology may provide some benefits to AD prevention or treatment.

Several studies have found that wolfberry has hypoglycemic effects or can attenuate hyperglycemia-induced damage. In one study, researchers have shown that feeding LBP can reduce blood glucose level, serum total cholesterol and triglyceride concentrations in alloxan-induced diabetic or hyperlipidemic rabbits [61]. Since hyperglycemia pathology is often associated with oxidative stress, some studies also investigate if wolfberry or LBP can attenuate the associated oxidative damages. It has been reported that LBP treatment for 4 weeks can reduce blood glucose level, DNA damage, malondialdehyde (MDA) and nitric oxide (NO) in serum of fasting rats with non-insulin dependent diabetes mellitus (NIDDM). It is proposed that LBP may have anti-oxidant properties which account for its protection against hyperglycemia-induced DNA damage [62]. Similar results are also found in another study, which shows that LBP can restore abnormal oxidative index to near normal level in blood, liver and kidney of streptozotocin-injected rats [63]. Apart from these, LBP can also ameliorate insulin resistance in a rat model of NIDDM. It is suggested that LBP can increase cell-surface level of GLUT4, improve GLUT4 trafficking and intracellular insulin signaling [64]. As wolfberry can normalize blood glucose level and reduce DM-associated pathological changes and DM is a risk factor for AD, it may help preventing AD and improve cognitive functions by targeting this risk factor.

### Protection against high cholesterol level

Elevated plasma cholesterol levels are also considered as another risk factor for AD. This is supported by in vivo and in vitro studies. In animals, it has been shown that cholesterol rich diet can increase brain intraneuronal Aβ level, and this effect can be reversed by returning the animals to normal diet [65; 66]. In vitro data also show similar results. In one study, a cholesterol-lowering drug has reduced Aβ production in hippocampal and mixed cortical neurons [67]. These data have suggested that cholesterol plays an important role in AD development. Currently, cholesterol-reducing drug statin is being investigated for its protective effects in AD. In a case-control study, statin users have shown a 39% lower risk of AD relative to non-statin users. This association between the use of statin and AD is affected by the presence of certain chronic medical conditions including hypertension, ischemic heart
disease and cerebrovascular disease [11]. It is still uncertain if cholesterol-reducing strategy is protective in AD prevention. Nevertheless, maintaining appropriate low serum cholesterol level is beneficial to health as there is a close relation between serum cholesterol level and atherosclerosis, a risk factor for many diseases. Wolfberry may have hypolipidemic effects. There is a report showing that wolfberry water extract and its crude LBP extract can reduce serum total cholesterol and triglyceride level in hyperlipidemic rabbits. In the same time, researchers have found that there is an increase in high density lipoprotein cholesterol levels after wolfberry feeding [61]. Oral feeding with wolfberry also dose-dependently attenuates the level of total cholesterol, total triglyceride and hepatic cholesterol in experimental hyperlipidemic mouse, while no adverse effect on liver and kidney function can be observed [68]. Further studies are required to demonstrate the effect of wolfberry on maintaining serum cholesterol level. Its potential hypolipidemic effect deserves more investigation.

Attenuation of hyperhomocysteinemia neurotoxicity

Homocysteine is a non-essential sulfur-containing amino acid that is derived from methionine metabolism. Its metabolism depends on folate, vitamin B6 and vitamin B12. Elevated plasma homocysteine is associated with cardiovascular disease and stroke [69; 70]. Recent studies suggest that hyperhomocysteinemia is a risk factor for AD [71, 17]. In fact, homocysteine can induce a direct neurotoxicity to neurons. It has been reported that homocysteine can activate NMDA receptors to cause excessive influx of calcium ions and generation of reactive oxygen species (ROS) [72]. An oxidized metabolite of homocysteine, homocysteic acid, may also induce intraneuronal accumulation of $\text{A}\beta_{1-42}$ [73]. Rats with elevated plasma homocysteine are also found to have tau hyperphosphorylation, and this change in tau pathology may link to alteration in protein phosphatase 2A activity [74-77]. As hyperhomocysteine is one of the important risk factor leading to AD, we will investigate whether wolfberry can protect neurons against this kind of toxicity.

Protective mechanisms of wolfberry

Antioxidant effects

Wolfberry provides beneficial effects in different body systems. Its benefit is not limited to the nervous system, it can also protect the liver [20; 78], the eyes [21], and the kidney [63]. In many reports, wolfberry or its
polysaccharides are shown to provide strong anti-oxidative effects. Wolfberry can provide protection against oxidative damage induced by hydrogen peroxide [79; 80]. It has been shown that treatment with LBP protects mice testicle cells from oxidative stress-induced DNA damage [80]. The anti-oxidative properties of wolfberry may be due to its direct free-radical scavenging effect [81; 82] or its ability to increase anti-oxidant enzyme activities [83; 84]. LBP administration can reduce exhaustive exercise-induced oxidative stress in rats, and it increases anti-oxidant enzyme activities [83]. Wolfberry also protects hepatocytes from carbon tetrachloride (CCL4). This toxin can decrease the activities of glutathione reductase and glutathione peroxidase in hepatocytes. After wolfberry treatment, the hepatocytes can maintain a relatively normal level of these enzymes [84]. Oxidative stress is suggested to be involved in normal aging process as well as many degenerative diseases [85; 86]. In an aging-induced oxidative stress study, reports have shown that aged-mice have decreased superoxide dismutase, catalase, glutathione peroxidase activities and total antioxidant capacity. Feeding LBP to rat can restore the aged-induced changes in these anti-oxidant enzymes and its anti-oxidant activity is comparable to vitamin C [87]. In a human study, dietary consumption of wolfberry for 10 days also significantly increases superoxide dismutase activity in elderly [88]. Since increased levels of oxidative stress in the brain have been considered to be the important factor mediating Aβ toxicity, anti-oxidative effects of wolfberry can provide protective effects to neurons.

Although wolfberry can act as anti-oxidant, its functions and neuroprotective mechanisms is certainly not simply due to its anti-oxidative effects. The immune-modulation ability of wolfberry may also account for its multiple beneficial effects on the CNS and other body systems.

Providing immune-modulation effects

It has been known that modulation of the immune system can help fighting against AD and even improve the learning ability [89; 90]. It has been recently proposed that systemic infections and inflammation affect chronic neurodegeneration [91-93]. Therefore, it is important to investigate whether wolfberry can modulate body immunity or inflammatory responses. In fact, wolfberry is found to have immune-modulation effects. This property is contributed by the high content of LBP in wolfberry rather than other components like zeaxithine and carotene [25]. LBP has been recently demonstrated to stimulate murine bone marrow derived dendritic cells (BMDC) maturation as reflected by the co-expression of I-A/I-E, CD11c and secretion of IL-12 p40 [26]. Purified wolfberry polysaccharides also show diverse immune
stimulating effects. LBP3P can increase macrophage phagocytosis and interleukin-2 (IL-2) mRNA expression level in transplantable sarcoma S180-bearing mice [94]. This polysaccharide also increases the expression of IL-2 and tumor necrosis factor-alpha (TNF-α) in human peripheral blood mononuclear cells [95]. Another report has also shown that wolfberry can increase IL-2 receptor expression in isolated human peripheral lymphocytes [96]. LbGp4 can stimulate splenocytes proliferation in mice, which is associated with up-regulation of nuclear factor κB (NF-κB) and activator protein 1 (AP-1) [97]. It is clear that wolfberry demonstrates immune-modulation effects on the whole body immune system. However, not many study has been focused on its effects on the CNS. Whether the changes in the peripheral immune systems induced by wolfberry would contribute to its neuroprotective properties remains unclear, this certainly would be an interesting area for further exploration.

Adverse effects and drug interaction of wolfberry

At present, there is no report showing that intake of wolfberry would cause any side effect. This is agreed with the general thought that traditional Chinese medicine (TCM) has fewer side effects than single pure drug used in Western medicine [98]. Its characteristics of diverse biological effects and little adverse effect have also been described in ancient Chinese pharmacopoeia. Despite the safe nature of wolfberry, it is still possible for it to interact with other medications. There are two reports showing that wolfberry may interact with warfarin. In the first report, a patient who received warfarin therapy developed an elevated international normalized ratio (INR) after consumption of wolfberry tea. INR is used for the measuring of prothrombin time and hence blood clotting tendency. The increase in INR indicates an increased chance of bleeding. In vitro studies suggested that wolfberry may slightly inhibit the metabolism of S-warfarin through CYP2C9, the isoenzyme responsible for its metabolism [99]. The second report showed similar observation, in which a patient taking warfarin experienced 2 episodes of INR elevation after wolfberry-containing herbal tea consumptions. Since impairment of warfarin metabolism would lead to excessive bleeding, it has been suggested that patients should avoid taking warfarin together with herbal products including wolfberry [100].

Concluding remarks

Wolfberry and its polysaccharides have been shown to exhibit multifaceted protective effects against Aβ neurotoxicity. Based on current evidence on wolfberry and its components, we propose that this fruit can provide protection through direct and indirect approaches (Fig. 2). Wolfberry can protect neurons directly by attenuating Aβ-induced neurotoxicity. Through targeting at certain
Figure 2. Multifaceted protective effects of wolfberry against neurodegeneration in AD. Wolfberry has a long history for being used as medicinal herb in oriental medicine. It acts as a tonifying herb to nurture the kidney and liver, which may account for its anti-aging properties. It can also modulate body immune response and act as anti-oxidant. These may be responsible for its neuroprotective effects against several conditions related to AD pathogenesis. Wolfberry is able to attenuate Aβ peptide toxicity and glutamate excitotoxicity. It can also reduce pathological changes cause by high cholesterol level and diabetes mellitus. All of these beneficial effects enable wolfberry to become a potential disease-modifying agent for the prevention or treatment of AD.

AD risk factors, it may prevent or ameliorate devastating neurodegeneration process in an indirect approach. The neuroprotective mechanism of wolfberry is not completely elucidated, but its ability to suppress pro-apoptotic signals, reducing oxidative stress and regulating the immune system may account for its biological benefits. Besides polysaccharides, wolfberry also contains a number of components such as zeaxanthine, betaine and beta-carotene. The high content of these compounds in wolfberry further support its role in the prevention of aging-associated diseases. Although wolfberry is a potential herbal dietary supplement for the prevention of neurodegeneration in AD, most of its research has been carried out in cell culture or animal models. Its effects on human need further investigation. Its long-term safety and its interaction with other medicine also deserve proper address.

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