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ORIGINAL PAPER

Use of Anti-aging Herbal Medicine, *Lycium barbarum*, Against Aging-associated Diseases. What Do We Know So Far?

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Abstract *Lycium barbarum* (Gouqizi, *Fructus Lycii*, Wolfberry) is well known for nourishing the liver, and in turn, improving the eyesight. However, many people have forgotten its anti-aging properties. Valuable components of *L. barbarum* are not limited to its colored components containing zeaxanthin and carotene, but include the polysaccharides and small molecules such as betaine, cerebroside, β-sitosterol, *p*-coumaric, and various vitamins. Despite the fact that *L. barbarum* has been used for centuries, its beneficial effects to our bodies have not been comprehensively studied with modern technology to unravel its therapeutic effects at the biochemical level. Recently, our laboratory has demonstrated its neuroprotective effects to counter neuronal loss in neurodegenerative diseases. Polysaccharides extracted from *L. barbarum* can protect neurons against β-amyloid peptide toxicity in neuronal cell cultures, and retinal ganglion cells in an experimental model of glaucoma. We have even isolated the active component of polysaccharide which can attenuate stress kinases and pro-apoptotic signaling pathways. We have accumulated scientific evidence for its anti-aging effects that should be highlighted for modern preventive medicine. This review is to provide background information and a new direction of study for the anti-aging properties of *L. barbarum*. We hope that new findings for *L. barbarum* will pave a new avenue for the use of Chinese medicine in modern evidence-based medicine.

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Introduction

L. barbarum (*Lycium barbarum L.* belongs to the Solanaceae family, also named *Fructus Lycii* or called Wolfberry) has been regarded as an upper class Chinese medicine in Chinese pharmacopoeia, indicating that the fruit of *L. barbarum* can be one of the ingredients in Chinese cuisine or formulated Chinese medicine. According to traditional Chinese medicine literature, *L. barbarum* can nourish liver and kidney, helping the re-balance of 'Yin' and 'Yan' in the body. Therefore, the biological effects of *L. barbarum* have increasingly received attention. Its value in Chinese and herbal medicine are high and significant, as long as we can provide much scientific evidence with modern technology.

L. barbarum's attractive red color has led us to believe that it must play a role in strengthening eyesight and protecting our eyes. According to Chinese medicine theory, *L. barbarum* can nourish the liver, which in turn, nourishes the eyes. This is supported by chemical analysis of *L. barbarum* showing that it contains lots of carotene and zeaxanthin which can provide nutrients and anti-oxidants directly to the eyes (Xie et al. 2001). However, our regular diet does not rely on *L. barbarum* to provide carotene. Therefore, protective effects of *L. barbarum* to the eyes should not limit to high carotene and zeaxanthine content. We will discuss other protective mechanisms, namely indirect and direct effects, below.

In fact, increasing lines of experimental studies have revealed that *L. barbarum* has a wide array of functions, which may be due to its high polysaccharide content instead of zeaxanthin and carotene. The polysaccharides in *L. barbarum* can exhibit anti-aging, anti-tumor, cytoprotective, neuromodulation, and immune modulation effects. We will summarize all these biological activities of *L. barbarum* below. In order elicit anti-aging effects, polysaccharides from *L. barbarum* modulate other organs or systems. We name this type of modulation as 'indirect effects'. Alternatively, polysaccharides can directly act on cells to antagonize toxins.

Indirect Effects of Immune Modulation by *L. barbarum*

Modulation of body immunity is often the first line of study for Chinese herbal medicine. This is probably because body immunity is an important readout for us to investigate how Chinese medicine modulates 'Qi' (energy flow). In fact, body immunity often gradually decreases during the aging process because of the reduction of 'Qi' (Frasca et al. 2005). The immune modulation effects of *L. barbarum* are attributed to its polysaccharides, but not zeaxanthin and carotene. High polysaccharide content (~40%) is a unique chemical characteristic of *L. barbarum*. Crude polysaccharides can be extracted by boiling *L. barbarum* in water. The polysaccharides can up-regulate both innate and adaptive immune responses. It has been shown that polysaccharides from *L. barbarum* (LBP) can increase ConA-triggered proliferation of splenocytes and cytotoxicity of natural killer (NK) cells (Wang et al. 1995). In addition, a report has shown an increase in interleukin-2 (IL-2) receptors on isolated human peripheral lymphocytes (Hu et al. 1995). Further isolation and purification of crude polysaccharides by size and ion-exchange chromatography into different fractions, the LBP_{3P} and LbGp4 fractions, (which constitute galactose, glucose, rhamnose, arabinose, mannose, and xylose with β-D-glucose linkage), demonstrate immune stimulatory properties. LBP_{3P} can increase expression of mRNA for IL-2 and tumor necrosis factor-α (TNFα) in human peripheral blood mononuclear cells (Gan and Zhang 2002; Gan et al. 2003). Since high levels of these two cytokines can exhibit anti-tumor immunity, it has been considered that LBP encompasses anti-tumor effects. LbGp4 with the above carbohydrate contents has been shown to stimulate proliferation of isolated splenocytes and B-lymphocytes (Peng et al. 2001). Such stimulation may be explained by up-regulation of NF-κB and activator protein-1 (AP-1) expression (Peng et al. 2001). An independent study from another group has shown that polysaccharides with a main chain of α-(1 $\rightarrow$ 4)-D-polygalacturonans strongly activate proliferation of splenocytes (Duan et al. 2001). These results suggest that the format of linkage between different carbohydrates or even among carbohydrates and proteins is an important factor to determine the biological activity of polysaccharides from *L. barbarum*.

LBPs from another source are recently demonstrated to have the ability to stimulate bone marrow-derived dendritic cells (BMDC) to secrete IL-12 and expression of CD11c (Zhu et al. 2006). It should be noted that the procedures for preparing LBP and subsequent purified fractions are not identical among different groups (Huang et al. 1998). Nevertheless, they all demonstrate immune stimulatory effects to enhance the whole body's immunity. Indeed, our recent findings also reveal that polysaccharides from *L. barbarum* can activate microglial cells (brain macrophages) in the central nervous system (CNS) (Chiu et al. 2005). Increasing lines of evidence have demonstrated that modulation of immune responses can affect the degenerative processes of neurons in the CNS (Schwartz and Kipnis 2005; Butovsky et al. 2006). Moreover, parameters for immune responses and body immunity are often regarded as the first line index to assess how a Chinese medicine improves our overall body health (Kuroiwa et al. 2004; Xu et al. 2004). Therefore, it is important to understand and elucidate how *L. barbarum* modulates our body immunity.

One may question that many Chinese medicine can enhance our body immunity. Thus, why should one take *L. barbarum* instead of other Chinese medicines? Answering this question should be based on the health, age, and environmental conditions of individuals. Indeed, many Chinese medicines, such as Ling-zhi and Ginseng can strongly stimulate our body immunity (Bao et al. 2002; Chen et al. 2004; Lin and Zhang 2004; Tan and Vanitha 2004). However, Chinese medicine is used to adjust the 'Qi' inside our body so that energy flow will not run into extreme condition toward 'Yan' or 'Yin'. Therefore, strong immune stimulation may not always be useful to improve 'Qi' in our body. According to the scientific studies so far, polysaccharides in *L. barbarum* seem to moderately stimulate body immunity. This may be the reason why *L. barbarum* can be used to moderately affect our body immunity. In fact, our recent study also shows that *L. barbarum* can moderately stimulate immune responses in the CNS (Chiu et al. 2005; So et al. 2005). Animals fed with polysaccharides of *L. barbarum* induce an activation of microglia (brain macrophages) in retina (Chiu et al. 2005; Chan et al. 2007).

Examples of its immune modulation effects can also be found in its anti-tumor property. *L. barbarum* has been reported to inhibit the growth of transplantable sarcoma in mice (Gan et al. 2004). Its anti-tumor functions can be attributed to its immune stimulatory effects on macrophages and lymphocytes by the polysaccharide (Cao et al. 1994) and sub-fraction of polysaccharide LBP_{3P} (Gan et al. 2004). These are the examples to demonstrate that modulation of immune responses is an important parameter to elucidate its indirect effects to affect different organs.

Direct Cellular Effects of *L. barbarum*

While modulation or nourishment of one organ to affect other organs can be considered to be ''indirect'' effects of anti-aging, many studies have demonstrated *L. barbarum*'s ''direct'' anti-aging effects on cells. It has been considered to be an anti-oxidant to prevent oxidation-induced cell injury (Huang et al. 2001; Luo et al. 2004). It has been shown that polysaccharides of *L. barbarum* can increase anti-apoptotic protein Bcl-2 level in lens epithelial cells of the whole lens incubated in culture medium and exposed to hydrogen peroxide (Wang et al. 2003). Increased ratio of Bcl-2 to Bax (pro-apoptotic protein) in the lens may be due to direct anti-oxidative effects of LBP (Wang et al. 2003). Besides retinal epithelial cells, LBP has also been reported to protect cultured seminiferous epithelium from hyperthermia-induced damage (Wang et al. 2002b; Zhao et al. 2005). It has been demonstrated that LBP can attenuate breakage of DNA by oxidation in testicle cells in mice (Huang et al. 2003). Crude extract of polysaccharides have been shown to protect DNA damage of peripheral blood lymphocytes against oxidative stress in non-insulin-dependent diabetes mellitus (NIDDM) (Wu et al. 2006). They have demonstrated that crude extracts of polysaccharides (10 mg/kg) from *L. barbarum* can significantly reduce blood glucose, nitric oxide, and malondoaldehyde (MDA) levels in streptozotocin-induced diabetic rats (Wu et al. 2006). An independent study also shows that 20–50 mg/kg of *L. barbarum*'s polysaccharides protects liver and kidney tissue in streptozotocin-induced diabetics (Li et al. 2006). Apart from experimental models of diabetes, it has been shown that *L. Chinense* (same family as *L. barbarum*) fruit protects hepatocytes from carbon tetrachloride toxicity (Ha et al. 2005). All the evidence suggests that polysaccharides in *L. barbarum* exhibits cytoprotective effects probably via attenuation of oxidative stress. Indeed, we have shown that *L. barbarum* exhibits neuroprotective effects against endoplasmic reticulum stress in neurons (Yu et al. 2006). Taken together of what we have learnt about *L. barbarum* in animal and cell culture studies, polysaccharides of *L. barbarum* exhibit an indirect effects via modulating vital organs, such as the liver and kidneys to globally adjust the health of the whole body, and direct effects on cells to exhibit cytoprotection.

Global Anti-aging Effects of *L. barbarum*

It has been considered that accumulation of oxidative stress will contribute to aging processes (Zou et al. 2000; Squier et al. 2001; Poon et al. 2004). Therefore, experiments showing the anti-aging effects of *L. barbarum* often use free-radicals as experimental toxin agents. One of the experimental models for aging is an injection of D-galactose into rats or mice for six to eight weeks (Ho et al. 2003). The metabolism of D-galactose as well as non-enzymatic glycation on D-galactose will gradually exert oxidative stress to the whole body including the brain, the bone, the liver and the immune system (Ho et al. 2003). Crude polysaccharides from *L. barbarum* have been shown to recover D-galactose-attenuated IL-2 levels from splenocytic lymphocytes in mice (Deng et al. 2003). Feeding the mice with LBP at 100 mg/kg daily can reduce (1) serum advanced glycation-end products (AGE) levels, (2) restore motor activity, (3) restore memory index for animals and (4) increase superoxide dismutase (SOD) levels in erythrocytes (Deng et al. 2003). Another model for aging study is to investigate the life span of Drosophila *melanogaster* (Fruit-fly). It has been surprisingly demonstrated that LBP at 16 mg/kg can significantly increase the maximal and average life span of the male fruit-fly (Wang et al. 2002a, b). Apart from life span, 200–500 mg/kg polysaccharides from *L. barbarum* can markedly reduce age-related oxidative stress in aged mice (Li 2007). All these experimental aging studies have suggested the anti-aging effects of *L. barbarum*. Perhaps, concrete evidence of its anti-aging effects can be found in a human study by showing that taking dietary *L. barbarum* for a total of 500 mg in ten days can significantly reduce plasma triglyceride levels and increase plasma cAMP and SOD levels (Dai et al. 1994). The study suggests that dietary supplementation of *L. barbarum* can maintain the health of our body.

As the anti-aging effects of *L. barbarum* have a wide array of target tissues, it can protect cells against oxidants, hyperglycemia, and hyperlipidemia conditions. In agreement with the above findings in the human study (Dai et al. 1994), an animal study using alloxan to induce diabetes in rabbits also show that crude and purified fractions of LBP can significantly reduce blood glucose levels (Luo et al. 2004). The results suggest that *L. barbarum* can globally modulate different organs to reduce blood glucose and lipid. According to the theory of Chinese medicine, modulation of one vital organ, such as the liver or the kidney can eventually affect other organs or the whole body. Therefore, it is possible to use *L. barbarum* for the treatment against aging-related diseases as *L. barbarum* has a wide array of effects reducing all the risk factors in aging-related diseases.

Neuromodulation Effects of *L. barbarum*

In order demonstrate the effects of Chinese medicinal herbs in our body, we often use immune responses as a parameter for assessing, whether the energy flow 'Qi' is up-regulated (Kuroiwa et al. 2004; Xu et al. 2004). However, we often overlook the potential significance of Chinese medicine in the CNS. There are only a few studies reporting the effects of polysaccharides from *L. barbarum* in the CNS. It has been shown that injection of LBP (60 lg/0.5 ml i.p.) can reduce stroke index and neurological score in an experimental ischemia and reperfusion model (Song et al. 1995). Apart from disease states, injection of LBP (i.p.) can enhance the spontaneous electrical activity of the hippocampus, implying that LBP can improve cognitive functions (Peng et al. 2002).

In view of the direct cytoprotective and anti-aging effects of *L. barbarum*, our research group has initiated a comprehensive investigation of *L. barbarum* against β-amyloid (Aβ) peptide toxicity. It is known that Aβ peptide is one of the toxic factors triggering progressive neuronal loss in Alzheimer's disease (AD) (Selkoe 1993; Yankner 1996; Sullivan et al. 2005). Aβ peptide activates pro-apoptotic signaling pathways such as c-Jun N-terminal kinase (JNK) and double-stranded RNA-dependent protein kinase (PKR) (Zhao et al. 2001; Chang et al. 2002a, b; Suen et al. 2003). Since *L. barbarum* is an anti-aging Chinese medicine and AD is an aging-associated disease, we have investigated its polysaccharide fraction on primary cultured neurons to examine its neuroprotective effects (Yu et al. 2005, 2007). Surprisingly, polysaccharides from *L. barbarum* exhibit a wide range of effective dosages to prevent neuronal death in both necrosis and apoptosis (Yu et al. 2006). The effective range of neuroprotection is even wider than a more commonly used neuroprotective agent, lithium chloride. Recently, we have isolated the major active component of LBP which provides neuroprotection against PKR (Yu et al. 2007). Among different carbohydrates in the components, abundant amounts of galacturonic acid and arabinose are found. Perhaps, these two key carbohydrates attribute to elicit neuroprotective effects. This direction of research is still undergoing active investigation in our laboratory. The neuroprotective effects of *L. barbarum* is not due to its anti-oxidative effects as the polysaccharide can inhibit two key pro-apoptotic signaling pathways (JNK and PKR) in Aβ peptide neurotoxicity (Chang et al. 2002a; Suen et al. 2003; Yu et al. 2005, 2006; Zhao et al. 2001). It is still a major focus in this laboratory to elucidate the molecular mechanisms of the neuroprotective effects of *L. barbarum*. Apart from direct neuroprotective effects, we are investigating into how *L. barbarum* exhibits indirect neuroprotective effects by regulating immune responses in the body to prevent another type of neurodegeneration, glaucoma (Chiu et al. 2005; So et al. 2005; Chan et al. 2007). As stated before, animals fed with *L. barbarum* exhibit a moderate increase in immune responses in the CNS. This may be an example of the indirect effects of *L. barbarum* in preventing neurodegeneration.

Other Components of *L. barbarum*

While research in *L. barbarum* often focuses on the polysaccharide fractions (as content of polysaccharide is about 40%), the effects of its other components should not be neglected. As mentioned in the introduction, *L. barbarum* is rich in zeaxanthin which can function as an anti-oxidant. Therefore, having *L. barbarum* in the diet can increase plasma zeaxanthin levels which can maintain macular pigment density in the retina (Cheng et al. 2005; Benzie et al. 2006). However, a recent study has shown that total carotenoid concentrations is about 0.03–0.5% only (Peng et al. 2005). Apart from zeaxanthin, other components such as betaine, cerebroside, β-sitosterol or *p*-coumaric acid can also be obtained from *L. barbarum* (Kim et al. 1999; Xie et al. 2001). Betaine has been shown to inhibit NF-κB and MAP kinase to attenuate oxidative stress signaling in vivo and in vitro (Go et al. 2005). It has also been reported to attenuate glutamate-induced neurotoxicity (Park et al. 1994). A small pilot clinical trial has been done for using betaine in Alzheimer's disease patients, in which reduction of serum homocysteine levels is the major target for betaine (Knopman and Patterson 2001). Cerebroside from *L. barbarum* has been reported to preserve the glutathione redox system in hepatocytes (Kim et al. 1999). All these components have anti-oxidative properties leading *L. barbarum* to exhibit anti-oxidative effects (Ren et al. 1995; Huang et al. 2001; Choi et al. 2002; Kanski et al. 2002; Wu et al. 2004). As accumulation of oxidative stress is a common theory in the aging processes, one may draw a conclusion that anti-aging properties of *L. barbarum* may be derived from its rich anti-oxidative components. However, its nourishment of vital organs (liver and kidney) and its enhancement on body immunity cannot be simply explained by the anti-oxidative effects of *L. barbarum*. In fact, if *L. barbarum* can provide anti-oxidation only, one may not need to take *L. barbarum* to improve our health as there are other dietaries supplements which function as anti-oxidants.

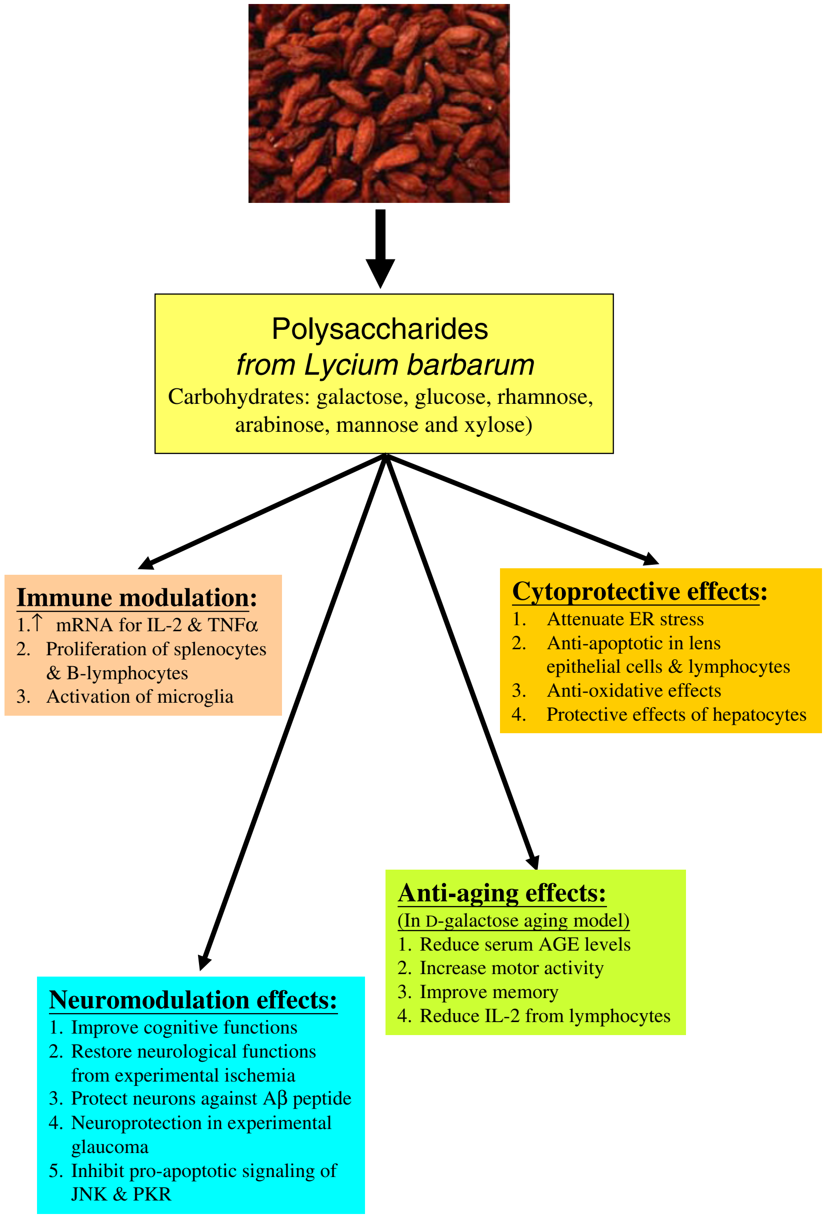

Fig. 1 Summary of biological effects of polysaccharides from *Lycium barbarum*. Six types of carbohydrates are the major constituents in polysaccharide of *Lycium barbarum*. They exert indirect effects on immune modulation and direct effects on cytoprotection, anti-aging and neuromodulation

Concluding Remark and Future Studies

Having reviewed different biological effects of *L. barbarum*, we should now realize that the functions of *L. barbarum* are multi-targets with direct and indirect effects. As an anti-aging herbal medicine, the fruit of *L. barbarum* can macroscopically regulate immune responses in our body so that appropriate activation of immunocompetent cells may re-adjust the severity of injury or damage. In addition, improvement of health by *L. barbarum* can be accomplished by nourishment of vital organs such as the liver and kidneys. In order modulate one organ by affecting other organs can be considered as an indirect effect. In this notion, *L. barbarum* may modulate the energy flow like 'Qi' in our body according to the theory of Chinese medicine. This may be the reason why *L. barbarum* is classified as an upper class Chinese medicine which can be used in the diet, as well as a therapeutic agent. In order to consolidate the scientific rationales of why *L. barbarum* can be an anti-aging Chinese medicine, we have proposed to investigate its biological effects by examining ''direct'' and ''indirect'' effects on different organs so that we can obtain a global picture of how *L. barbarum* improves our health (Fig. 1). Our recent discovery of its new usage in preventing neuronal death in neurodegenerative diseases is an example for this direction of research. If we can comprehensively study both ''direct'' and ''indirect'' effects of *L. barbarum* and elucidate its biological mechanisms, we may have the opportunity to use anti-aging *L. barbarum* for therapeutic intervention in the near future.

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