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Review

A review of botanical characteristics, phytochemistry, clinical relevance in efficacy and safety of *Lycium barbarum* fruit (Goji)

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ABSTRACT

Lycium barbarum has been used as a traditional Chinese medicine (TCM) to nourish liver and kidney, and brighten the eye. The fruits are dried or freshly squeezed for their juice and concentrated for beverages. Among various constituents, a group of polysaccharides (LBP) with a Glycan-O-Ser glycopeptide structure has been most researched and considered to be important for the efficacy of *L. barbarum*. Studies indicate effects of *L. barbarum* on aging, neuroprotection, general well-being, fatigue/endurance, metabolism/energy expenditure, glucose control in diabetics, glaucoma, anti-oxidant properties, immunomodulation, anti-tumor activity and cytoprotection. In addition to TCM, *L. barbarum* can be sold as a dietary supplement or classified as a food based upon the long and safe traditional usage. This review is to provide background and updated information of chemical constituents and efficacies with safety including a new direction for research and current regulatory situation of *L. barbarum*.

Contents

Abbreviations: L. barbarum, *Lycium barbarum* L.; LBP, *Lycium barbarum* polysaccharide; TCM, traditional Chinese medicine; SCAR, Sequence Characterized Amplified Region; RAPD, Random Amplified Polymorphic DNA; FTIR, Fourier-transform infrared spectroscopy; HPLC, high performance liquid chromatography; NMR, nucleic magnetic resonance; GCMS, gas-chromatographic–mass spectrometry; HRESIMS, high resolution electrospray ionization mass spectrometry; HPLC-DAD–MS, high performance liquid chromatography-photo diode array detection–mass spectrometry; APCI, atmospheric pressure chemical ionization; HPLC-DAD-ESI-MS, high-performance liquid chromatography-diode array detection-mass spectrometry method with electrospray ionization mode; LC–(APCI) MS, liquid chromatography–atmospheric pressure chemical ionization mass spectrometry; 2-GlcAsA, 2-O-glucosyl-L-ascorbic acid; PSQI, Pittsburgh Sleep Quality Index; LDH, lactate dehydrogenase; LiCl, lithium chloride; JNK, c-Jun N-terminal kinase; DTT, dithiothreitol; ER, endoplasmic reticulum; PERK, PKR-like ER kinase; NMDA, N-methyl-D-aspartate; LBP-III, arabinogalactan-protein; PKR, double-stranded RNA-dependent protein kinase; RBC, red blood cells; MMC, mitomycin C; CYP2E1, cytochrome P450 enzyme 2E1; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; MDA, malondialdehyde; H_2O_2, hydrogen peroxide; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; EDRF, endothelium-derived relaxation factor; LDL, low density lipoprotein; RBC-C_3bRR, RBC C_3b receptor rosette; IL, interleukin; NIDDM, non-insulin dependent diabetes mellitus; NO, nitric oxide; GLUT4, glucose transporter 4; AGEs, advanced glycation endoproducts; AMD, age-related macular degeneration; TUNEL, terminal deoxynucleotidyl transferase dUTP Nick End Labeling; NADPH, nicotinamide adenine dinucleotide phosphate; CAT, catalase; SSUV, solar simulated UV; TAOC, total antioxidant capacity; PBMCs, peripheral blood mononuclear cells; G-CSF, granulocyte colony-stimulating factor; TBARS, thiobarbituric acid-reactive substances; Xan/XO, xanthine/xanthine oxidase; ORAC, oxygen radical absorbance capacity; BMDC, bone marrow derived dendritic cells; DC, dendritic cells; Th1, T helper cells; TNF, tumor necrosis factor; AA-2betaG, 2-O-beta-D: -Glucopyranosyl-L: -ascorbic acid; RT-PCR, reverse transcription polymerase chain reaction; LAK, lymphokine-activated killer cell; HO-1, haem oxygenase-1; AA-2betaG, 2-O-beta-D: -Glucopyranosyl-L: -ascorbic acid; LD_{50}, 50% lethal dose.

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1. Introduction

Lycium barbarum L. (*L. barbarum*) is a Solanaceous defoliated shrubbery that grows in China, Tibet and other parts of Asia and its fruits are 1–2 cm-long, bright orange-red ellipsoid berries (Fig. 1). A ripe fruit has been used in Asian countries as a traditional herbal medicine and functional food (Bensky & Gamble, 1993; Bryan et al., 2008; Chang & But, 2001; Zhu, 1998). Concentrated extracts and infusions prepared from the berries have a history of use as ingredients in various soft or alcoholic drinks that were marketed (UK Food Standard Agency, 2007) for their benefits to anti-aging, vision, kidney and liver functions. In support of these traditional properties, recent studies indicate that extracts from *L. barbarum* fruit and one of its active compounds, polysaccharides (LBP) possess a range of biological activities, including effects on aging, neuroprotection, anti-fatigue/endurance, increased metabolism, glucose control in diabetics, glaucoma, anti-oxidant properties, immunomodulation, anti-tumor activity and cytoprotection (Bensky & Gamble, 1993; Bryan et al., 2008; Chang & But, 2001; Potterat, 2010; Zhu, 1998). Along with the growing number of studies of *L. barbarum*, we have conducted various clinical and basic studies to examine the traditional effects of *L. barbarum* fruits provided in the form of a juice that is standardized for LBP. To begin to address this, we examined directly the general effects of daily consumption of *L. barbarum* or a placebo. These were provided daily and changes in subjective ratings of feelings of general well-being, fatigue, stress, neurological/psychological traits, gastrointestinal and musculoskeletal complaints, cardiovascular effects (blood pressure and pulse rate), visual acuity (Amagase & Hsu, 2009; Amagase & Nance, 2008a), plasma levels of anti-oxidant factors (Amagase, Sun, & Borek, 2009), immune factors and any side effects (Amagase, Sun, & Nance, 2009) were determined at the end of the treatment period. *L. barbarum* fruit has recently been marketed as foods and dietary supplements in many countries including North America (Karp, 2009; McLaughlin, 2006; Sohn, 2008; Seeram, 2008), Caribbean countries, EU (Dutch Authorities, 2004; UK Food Standard Agency, 2007), Australia, New Zealand and Southeast Asia in various retail outlets, including major supermarkets and direct marketing channels.

This review article summarizes current knowledge and information of *L. barbarum* for its botanical characteristics, phytochemistry, clinical relevance in efficacy and safety aspects including our clinical and basic studies.

2. Botanical characteristics

L. barbarum has various vernacular names, such as Chinese wolfberry, Barbary wolfberry, boxthorn, Chinese boxthorn, matrimony vine, Chinese matrimony vine, kuko (Japanese), red medlar, the Duke of Argyll's Tea Tree, gou qi (Mandarin), kei tze (Cantonese), gugija (Korean), củ khởi (Vietnamese), gău gèe (Thai), and dretsherma (Tibetan). Its fruit is called *Lycium* Fruit, *Fructus lycii* ("fruit of Lycium"), lycii berries, lycii fructus, lycii fruit, dried wolfberries, gou qi zi (Chinese), gouqizi (Chinese), goji, Tibetan goji berry, goji berry, goji juice. Its dried root is called Di Gu Pi or Digupi. Other names are Bastard Jasmine, Box Throne, Common Matrimony Vine, Prickly Box, Tea Plant and Tea Tree (Bryan et al., 2008; PDR, 2007). The Chinese name for the *lycium* plant is gouqi and for the fruit is gouqizi. Zi represents small fruit. The common name "wolfberry" comes from the character gou as it is related to the one that means wolf. The spiny shrub has also been called matrimony vine, for reasons long lost. Botanical name, *L. barbarum* was assigned by the Swedish botanist, Carolus Linnaeus in 1753. He is responsible for the species name *barbarum*, while botanist Philip Miller described *Lycium chinense* 15 years later (Dharmananda, 2007). Taxonomy and nomenclature with taxonomic hierarchy are listed as

Fig. 1. Pictures of *Lycium barbarum* fruit.

Taxonomic Serial No. 503599 (Integrated Taxonomic Information System (ITIS), 2007) and set by United States Department of Agriculture (USDA) (2010a). *Lycium californicum*, *Lycium europeaum*, *Lycium halimifolium* Mill., *Lycium nodosum*, *Lycium parishii*, *Lycium ruthenicum*, *Lycium shawii*, *Lycium vulgare* Dunal, *Lycium exsertum*, and *Lycium fremontii* are all *Lycium* genus, but many are names of species other than *L. barbarum*.

Approximately 70 species of *Lycium* grow in separate and distinct regions distributed in temperate to subtropical parts of North America, South America, southern Africa, Eurasia, and Australia (Fukuda, Yokoyama, & Ohashi, 2001). The original habitat of goji is not known. *Lycium* spp. are part of the Solanaceae family, which includes tomatoes, potatoes, eggplants, and peppers (Bryan et al., 2008). Ten species and varieties of *Lycium* are found to be substitutes or adulterants of *L. barbarum* in the commercial market in Hong Kong and China. *L. barbarum* cv. 'Tianjinense' and *L. chinense* var. *potaninii* are the most common examples. It is difficult to differentiate among the *Lycium* species by traditional morphological and histological analysis. An easy and reliable approach based on Sequence Characterized Amplified Region (SCAR) analysis was developed to differentiate *L. barbarum* from other *Lycium* species. Two characteristic bands of about 700 and 650 bp were detected on the RAPD (Random Amplified Polymorphic DNA) profiles generated from samples of *L. barbarum* and *L. chinense* var. *potaninii*. Two primer sets, based on the sequences, could amplify a single specific band in samples of *L. barbarum* respectively while no bands were detected in samples of *L. chinense* var. *potaninii* (Sze et al., 2008; Zhang, Leung, Yeung, & Wong, 2001). A method of using Fourier-transform infrared spectroscopy (FTIR) to identify 7 species and 3 variations of genus *Lycium* (Gouqi) in China has been described. This method is based on the additive IR absorptions of the chemical components and the differences of their relative contents in various Gouqi. These differences are reflected in the FTIR spectra. The method provides a novel fingerprinting technique for the identification and differentiation of *Lycium* species and cultivars, and can serve as a rapid, simple, reliable and non-destructive analytical method for Gouqi (Peng, Sun, Zhao, & Leung, 2004).

L. barbarum grows up to 3 m high, and its gray-green leaves are alternate, lanceolate and gradually narrow to the petiole (Fig. 1). There are 1 to 3 axillary, radical flowers. The calyx and pistils are fused; the calyx is bilabial with a double-toothed lower lip. The corolla is funnel-shaped, light purple or violet with a 5-lobed margin. There are 4 stamens, which are hairy at the base. The ovary is 2-chambered with 1 style (PDR, 2007). The fruit is fusiform with acute apex, 6–20 mm in length, 3–8 mm in diameter, pericarp red to dark red (Japanese Pharmacopoeia, 2006) (Fig. 1). It naturally grows in Asia, primarily in northwest China (mainly in Qinghai, Gansu, Ningxia, and Inner Mongolia, east as far as Hebei and west to Tibet and Xinjiang) (Bensky & Gamble, 1993; PDR, 2007; Wu, 2005; Zhu, 1998). The fruits are collected in the summer and autumn, dried in the shade till the skin shrinks and are then exposed to the sun until the outer skin becomes dry and hard but the pulp still soft (PDR, 2007; Zhu, 1998). *Lycium* is extensively cultivated, especially in Ningxia Province, a small autonomous region formerly part of Gansu in China, with several production projects initiated since 1987. China, the main supplier of *L. barbarum*/wolfberry products in the world, had total exports generating US$120 million in 2004. This production derived from 82,000 ha farmed nationwide, yielding 95,000 tons of wolfberries (China Daily Staff reporter, 2004). The fruits are dried to yield the market herb, or the fresh fruits may be squeezed for their juice that is then concentrated to preserve it for future use in making various beverages. The cultivation of *L. barbarum* in the United Kingdom is reported (UK Food Standard Agency, 2007) to date back to its

introduction in the 1730s. The plant appears in Scottish botanist Philip Miller's eighth edition of The Gardener's Dictionary, published in 1768, and is now widely established as a naturalized species in the UK, being found in hedgerows in some parts of the country. *L. barbarum* is also available for cultivation from UK plant nurseries and it is listed by the Royal Horticultural Society with various synonyms, such as Chinese boxthorn, barbary boxthorn, barbary wolfberry, common matrimony vine, and vicar's tea party.

There were 38 species of *L. barbarum* pests and 23 species of natural enemies, the occurrence of them were closely related, but natural enemies can control Aphis and Paratrioza effectively (Ale-Agha, Brassmann, & Jensen, 2009; Chen, Cheng, Zhang, Zhang, & Ding, 2003; Zhao et al., 2009). Sensitive analytical methods using GC/mass spectrometry detection in the selected-ion monitoring mode for organophosphorus pesticides have been developed (Li et al., 2007).

3. Chemical constituents

3.1. Polysaccharides

Among the chemical constituents of *L. barbarum* fruit, the most well researched components are a group of water-soluble glycoconjugates, (*L. barbarum* polysaccharides or LBP), which are estimated to comprise 5–8% of the dried fruits (Wang, Chen, & Zhang, 1991). The LBP group has a molecular weight range of 8–241 kDa, and several LBP have been isolated and purified from aqueous *L. barbarum* extracts by methods such as DEAE ion-exchange cellulose, gel-permeation chromatography and high performance liquid chromatography (HPLC) (Luo, Yan, & Zhang, 2000; Ouyang, Li, & Xiao, 2007; Peng & Tian, 2001; Peng, Wang, & Tian, 2001; Tian & Wang, 2006). Their structural composition has been studied by SDS-PAGE gel electrophoresis, gas chromatography, amino acid automatic analysis, partial acid hydrolysis, periodate oxidation and nucleic magnetic resonance (NMR) spectrum regio-selective enzymatic, alkaline and acidic hydrolyses and spectroscopic methods involving gas-chromatographic–mass-spectrometry (GCMS), high resolution electrospray ionization mass spectrometry (HRESIMS) and 1D and 2D NMR (Gao, Ali, & Khan, 2008), and they have been found to be complex glycopeptides consisting of acidic heteropolysaccharides and polypeptides or proteins. Although they differ somewhat in composition, the LBP contain 6 monosaccharides (Ara, Rha, Xyl, Man, Gal and Glc), mainly containing xylose and glucose with smaller amounts of arabinose, rhamnose, mannose and galactose. LBP also contain galacturonic acid and 18 amino acids. They share a Glycan-O-Ser glycopeptide structure (Tian & Wang, 2006). The main chains of the glycan backbones of LBP have been found to be either alpha-(1–>6)-D-glucans or alpha-(1–>4)-D polygalacturonans (Duan et al., 2001). These were recently summarized and listed by Potterat (2010).

According to the Chinese understanding of *Lycium* extracts and products, the content of LBP is important in the efficacy of *L. barbarum*. Many plant- and fungal-derived bioactive polysaccharides with a broad range of immunomodulatory activities are found in traditional Chinese medicine, and therefore, a high content of polysaccharides with proven pharmacological activities is considered to be an indicator of the medicinal status of a natural product (Chang, 2002; Wong, Leung, Fung, & Choy, 1994). Sulfated LBP polysaccharides showed greater efficacies on immune enhancements in cultured chicken peripheral lymphocytes proliferation compared by MTT assay. *In vivo*, sulfated modification also significantly enhanced the immune-enhancing activity of LBP indicated by the changes of peripheral lymphocytes proliferation and serum antibody titer in chickens expected as the component drug of a new-type immunopotentiator (Wang et al., 2010). LBP content in *L. barbarum* was increased by abamectin (Yu, Zhou, Chen, & Xu, 2009).

The clinically tested commercially available product, GoChi® is a liquid dietary supplement containing reconstituted juice from fresh whole *L. barbarum* fruit. It is standardized to contain, in a daily 120 ml serving, a content of LBP equivalent to that found in at least 150 g of fresh fruit, the amount customarily consumed in Traditional Chinese Medicine (Dharmananda, 2007; Zhu, 1998). The types of analyses applied to the assay and identification of LBP are not standardized worldwide. A general method has been applied based upon identification by Fourier transform near-infrared spectroscopy, the gravimetric assay of the isolated polysaccharide fraction, and a determination of sugars after hydrolysis using gas chromatography (German Foodstuffs and Commodities Act, 1986) and/or high performance liquid chromatography with the glucan analysis reported (AOAC International, 2008).

3.2. Carotenoids and related compounds

The reddish-orange color of *L. barbarum* fruits is derived from a group of carotenoids, which make up only 0.03–0.5% of the dried fruit (Peng et al., 2006). A total of 11 free carotenoids and 7 carotenoid esters were detected from unsaponified and saponified *L. barbarum* extracts. The predominant carotenoid is zeaxanthin, mainly as dipalmitate (also called physalien or physalin), comprising about one-third to one-half of the total carotenoids. Zeaxanthin dipalmitate (1143.7 μg/g) was present in the largest amount, followed by beta-cryptoxanthin monopalmitate and its two isomers (32.9–68.5 μg/g), zeaxanthin monopalmitate and its two isomers (11.3–62.8 μg/g), all-trans-beta-carotene (23.7 μg/g) and all-trans-zeaxanthin (1.4 μg/g) analyzed by a high performance liquid chromatography-photo diode array detection–mass spectrometry (HPLC-DAD–MS) method with atmospheric pressure chemical ionization (APCI) mode for qualitative and quantitative analyses of carotenoids in *L. barbarum* fruits (Inbaraj et al., 2008). *Lycium* fruit is considered to be a good food source of zeaxanthin. Zeaxanthin is a yellow pigment, an isomer of lutein and a derivative of β-carotene. When ingested, zeaxanthin accumulates in fatty tissues, but especially in the macula, a region of the retina. It has been reported that this compound may help to protect the macula from degeneration, which can be induced by excessive sun exposure (UV light) and by other oxidative processes (Cheng, Chung, Szeto, & Benzie, 2005; Rosenthal et al., 2006; Trieschmann et al., 2007).

In a study investigating potential genetic engineering targets in the pathway of beta-carotene biosynthesis in *L. barbarum*, the effects of five carotenogenic genes from *L. barbarum*, encoding proteins including geranylgeranyl diphosphate synthase, phytoene synthase and delta-carotene desaturase gene, lycopene beta-cyclase and lycopene epsilon-cyclase were functionally analyzed in transgenic tobacco (*Nicotiana tabacum*) plants. All transgenic tobacco plants constitutively expressing these genes showed enhanced beta-carotene contents in their leaves and flowers to different extents (Ji, Wang, Wang, & Wang, 2009).

3.3. Other compounds

Various small molecules are found in *L. barbarum* fruit, such as betaine, cerebroside, beta-sitosterol, p-coumaric acid, and various vitamins. Other minor components include glutamine; asparagine; stigmasterol; cholest-7-enol; campesterol; cholestanol; 24-methylene cholesterol; 28-isofucosterol; 24-methylcholesta-5,24-dienol; 24-ethylcholesta-5,24-dienol; 31-norcycloartanol; 31-norcycloartenol; cycloeucalenol; obtusifoliol; 4a,14a,24-trimethylcholesta-8′24-dienol; 4a-methylcholest-8-enol; 4-methylcholest-7-enol; 24-ethyllophenol; 4,24-methyllophenol; gramisterol; citrostadienol; 4a-methyl-24-ethylcholesta-7,24-dienol; lanost-8-enol; cycloartanol; lanosterol; b-amyrin; lupeol; 24-methylenelanost-8-enol; 24-methylenecycloartanol; taurine and gamma-aminobutanoic acid. K, Ca, Zn, Fe, Co, Mn, Se, Mg and other minerals are also present in inorganic forms (NHI, 2007). As the amount of betaine in *lycium* fruit, is about 1% (Zhu, 1998), to

obtain a significant amount, a large dose of *lycium* fruit would need to be consumed (e.g., 20–30 g). A method based on capillary electrophoresis with amperometric detection and far infrared-assisted extraction has determined rutin, gentisic acid, and quercetin in the leaves of *L. barbarum* (Duan, Chen, & Chen, 2010). A high-performance liquid chromatography-diode array detection-mass spectrometry method with electrospray ionization mode (HPLC-DAD-ESI-MS) was recently developed for simultaneous determination of phenolic acids and flavonoids in fruits of *L. barbarum*. By employing a Vydac C18 column, a total of 52 phenolic acids and flavonoids were separated. Of 52 compounds, 15 phenolic acids and flavonoids were positively identified based on both absorption and mass spectra, with the remaining 37 tentatively identified by comparison of absorption spectra with reported values in the literature. Among the 15 positively identified compounds, quercetin-rhamno-di-hexoside was present in largest mass fraction (438.6 μg/g), followed by quercetin-3-O-rutinoside (281.3 μg/g), dicaffeoylquinic acid isomers (250.1 μg/g), chlorogenic acid (237.0 μg/g), quercetin-di-(rhamnohexoside) (117.5 μg/g), quercetin-di-(rhamno)-hexoside (116.8 μg/g), kaempferol-3-O-rutinoside (97.7 μg/g), isorhamnetin-3-O-rutinoside (72.1 μg/g), p-coumaric acid (64.0 μg/g), caffeic acid (23.7 μg/g) and vanillic acid (22.8 μg/g) (Inbaraj, Lu, Kao, & Chen, 2010). The main flavonoids present in the leaves were separated and identified by HPLC, liquid chromatography–atmospheric pressure chemical ionization mass spectrometry (LC–(APCI) MS) and ultraviolet–visible spectra with shift additives. The predominant flavonoid was identified as rutin. Leaves are the rutin-rich parts (16.03–16.33 mg/g). In the wild and cultivated *L. barbarum* fruits, contents of rutin were determined to be very low (0.09–1.38 mg/g). The contents of total flavonoids (21.25 mg/g) of cultivated *L. barbarum* leaves were much higher than those in the wild *L. barbarum* leaves (17.86 mg/g) (Dong, Lu, & Wang, 2009). 2-O-glucosyl-L-ascorbic acid (2-GlcAsA) was isolated from the fruit of *L. barbarum*, and this is different from the ones in *Cucurbita pepo* L. (zucchini) (Hancock, Chudek, Walker, Pont, & Viola, 2008). The reported compounds were summarized and listed with structure by Potterat (2010).

4. Traditional uses

Lycium fruits appear in Chinese lore as far back as 2800 B.C. in association with the legendary First Emperor, Shen Nung, who was an herbalist and the mythical father of agriculture. They are eaten as fresh berries, dried and soaked in liquor to make *Lycium* liquor. As a medicinal food, it is used as a condiment to steamed rice. Young soft leaves can be used as a food. The dried fruit is a well-known traditional medicine in Asian countries such as China, Korea, Japan, Vietnam, Thailand, and Tibet, which all have names for goji in their native languages. It has been widely used in these countries for medicinal purposes and as a functional food for more than 4500 years (Bensky & Gamble, 1993; Chang & But, 2001; Wang, 2006; Zhu, 1998). The ancient herbalist classics recorded that *L. barbarum* nourishes the liver and kidney and brightens the eye. In his "Compendium of Medica", Li Shi-zen named *L. barbarum* as a top-grade medicinal material that can nourish the liver and kidney, supplement energy and improve eyesight. "Shennong's Classic of Materia Medica (Shennong Bencaojing)" also mentioned that "long term use of goji can contribute to agility and longevity." Ni Zhu-Mo, the renowned Chinese herbalist, also said in his "Ben Cao Hui Yan (Convergent Speech on the Materia Medica)" that "Goji can supplement energy, blood, adjust Yin and Yang, reduce internal heat and resist wind and humidity, and enjoys ten magic functions" (Wang, 2006). Ethnobotanists have found that *Lycium* is still used by healers in Israel (Dafni & Yaniv, 1994).

Many of the herbal combination formulae are still made in the form of Chinese patent medicine. These formulae are also used in kampo (traditional Japanese medicine) in Japan where herbalists do not create medicine for each patient, but choose an herbal formula that has been standardized by the Japanese government (Japanese Pharmacopoeia, 2006). These formulae are based on the Chinese classic herbal formulae. They often vary slightly, however. Sometimes Chinese plants are substituted for plants found in Japan, or the proportions of the formula are changed slightly. Chrysanthemum flowers (*juhua*) is often combined with *Lycium* fruits in traditional Chinese herb formulae to benefit the eyes, including deteriorating vision that occurs with aging and may, in some cases, correspond to macular degeneration. One of the formula is Kogikujiougan (杞菊地黄丸 = *Lycii* Chrysanthemum Teapills = Qiju Dihuang Wan in Chinese), which is composed of *Rehmannia glutinosa* (5 portions for percolation, 5–8 for powder formula), *Cornus officinalis* (3, 3–4), *Dioscorea batatas* (3, 3–4), *Alisma plantago-aquatica* var. *orientale* (3, 3), *Poria cocos* (3, 3), *Paeonia suffruticosa* (2–3, 3), *Lycium* fruits (4–5, 4–5), *Chrysanthemum* flower (3, 3) for tired eyes, blurred vision, hot flashes, dizziness, head heaviness, difficulty in urination, frequent urination, and edema in people with moderate or below moderate physical strength who tire easily, but have no gastrointestinal problems or diminished urinary excretion (Japanese Ministry of Health Labour and Welfare, Pharmaceutical and Medical Safety Bureau, 2010a). Kogikumyokengan (杞菊妙見丸) is a slightly modified version of Kogikujiougan and also a traditional medicine in Japan using *L. barbarum* for tired eyes, blurred vision, hot flashes, dizziness, head heavy, difficulty in urination, frequent urination, and edema. Formulation per serving is *Rehmanniae* Radix (1200 mg), *Cornus officinalis* (600 mg), *Dioscoreae* Rhizoma (600 mg), *Poria* (450 mg), *Moutan* Cortex (450 mg), *Alismatis* Rhizoma (450 mg), *Lycium* fruits (300 mg), and *Chrysanthemum* flower (300 mg). As chrysanthemum flowers contain lutein, another yellow carotenoid that accumulates in the macula and provides similar protection, it is reasonable in combination with *Lycium* fruits. The expected effective daily dose of these two carotenoids has been estimated to be about 10 mg (Dharmananda, 2007). Although rarely, another plant in the Solanaceae family used in Chinese medicine is *Physalis alkekengi*, the Chinese lantern plant, which contains zeaxanthin dipalmitate as a major active component. In addition, the plant contains some steroidal compounds that have been named physalins, producing some confusion about the use of this term because of its former application to the carotenoid. *Physalis* is used as a treatment for viral hepatitis, and this effect may be attributed in part to zeaxanthin and also to the steroidal compounds. *Physalis* is used for treating a variety of inflammatory disorders, perhaps aiding treatment of infections; extracts of *Physalis* have been shown to increase natural killer cell activity when administered to mice. Benefits of carotenoid intake are thought to mainly arise from prolonged use. Therefore, *Lycium* fruit, as a source of zeaxanthin and other carotenoids, would be consumed regularly to complement dietary sources, boosting the amount of these components available from fruits and vegetables and egg yolks.

Lycium bark/root (Jikoppi) (Zhou et al., 1996) is formulated in the Kampo formula, and listed as one of the active ingredients approved by the Japanese government. One formula is Seishinrenshiin (清心蓮子飲), which is indicated for the relief of the following symptoms of those patients who have general malaise, dry mouth or tongue, and difficulty in urinating: Feeling of residual urine, pollakiuria, and micturition pain. It is composed of *Ophiopogon* Tuber (4 g), *Poria Sclerotium* (4 g), *Nelumbo* Seed (4 g), *Scutellaria* Root (3 g), *Plantago* Seed (3 g), Ginseng (3 g), Astragalus Root (2 g), *Lycium* Bark (2 g) and *Glycyrrhiza* (1.5 g) (Japanese Ministry of Health Labour and Welfare, Pharmaceutical and Medical Safety Bureau, 2010b). Another formula is Jiinshihoto (滋陰至宝湯) which is indicated for the relief of chronic coughing and sputum in patients with a delicate constitution. It is composed of *Cyperus* Rhizome (3 g), *Bupleurum* Root (3 g), *Lycium* Bark (3 g), Peony Root (3 g), *Anemarrhena* Rhizome (3 g), Citrus Unshiu Peel (3 g), Japanese Angelica Root (3 g), *Ophiopogon* Tuber (3 g), *Atractylodes* Rhizome (3 g), *Poria Sclerotium* (3 g), *Fritillaria* Bulb (2 g), *Glycyrrhiza* (1 g) and *Mentha* Herb (1 g) (Japanese Ministry of Health Labour and Welfare, Pharmaceutical and Medical Safety Bureau, 2010c).

5. Efficacies

5.1. General well-being, anti-aging, neuroprotection, anti-myelosuppression, enhancement of sleep quality, and reducing complaints during the menstrual period in women

Five recent randomized clinical studies conducted in USA (Amagase & Hsu, 2009; Amagase & Nance, 2008a, 2008b; Amagase & Nance, 2009) and China (Amagase, Sun, & Borek, 2009; Amagase, Sun, & Nance, 2009) have shown that daily consumption of standardized *L. barbarum* fruit juice (GoChi 120 ml = equivalent to 150 g of fresh fruit) for 14 or 30 days increases subjective feelings of general well-being, neurological/psychological traits, cardiovascular, joint/muscle functions and gastrointestinal regularity, without any adverse effects. Statistically significant differences between pre- and post-intervention period were consistently found in the *L. barbarum* group among all 5 studies showing the following effects: increased energy level, athletic performance, stamina/endurance, sleep quality, ease of awakening, ability to focus on activities, mental acuity, calmness, feelings of health, feelings of contentment, feelings of happiness, circulation, bowel regularity; reduced feelings of fatigue, stress, tiredness including after exercise, weakness, procrastination, headache, depression, daydreaming, impaired concentration, excess worry, unreasonable worry, memory loss, shortness of breath, backache, stiff shoulder, coldness in extremities, and complaints during menstrual cycle. Total efficacy of these primary assessments was improved in more than 63% of subjects. The placebo group showed only two changes in one study, but no improvements were found in the other four studies. Total number of the subjects in randomized, double-blind, placebo-controlled human clinical studies were 201, and each study has around 40 subjects on average. These improvements were confirmed by meta-analysis (Amagase & Hsu, 2009). *L. barbarum* group indicated better sleep evaluated by the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). High PSQI scores reflect poor sleep quality. A reduction of PSQI scores was found in *L. barbarum* group, with shortening of minutes to fall asleep, and a tendency of improving overall sleep quality. On the other hand, placebo group showed no improvement in sleep quality in PSQI, or in any of these four clinical studies (Amagase & Hsu, 2009; Amagase & Nance, 2008b). Better feelings of easing menstrual complaints were found in the female subjects in a randomized trial after consumption of a standardized *L. barbarum* fruit juice. In contrast, the placebo group showed no significant changes (Amagase & Nance, 2008a).

L. barbarum and LBP are reported to exhibit anti-aging effects, and exhibit neuroprotective effects against toxins in aging-related neurodegenerative diseases (Chang & So, 2008). It was found that *L. barbarum* and an arabinogalactan-protein (LBP-III) isolated from LBP exhibited cytoprotective effects against stress by reducing the phosphorylation of double-stranded RNA-dependent protein kinase (PKR) triggered by beta-amyloid peptide, and lowering the dithiothreitol (DTT)-induced LDH release and caspase-3 activity, but not caspase-8 and -9 (Ho et al., 2010). Since the phosphorylation state of PKR increased with age and PKR in beta-amyloid peptide neurotoxicity is significantly involved in Alzheimer's disease, reduction of its phosphorylation triggered by beta-amyloid peptide may implicate that LBP-III from *Fructus lycii* may be a potential neuroprotective agent (Yu, Ho, So, Yuen, & Chang, 2006; Yu et al., 2007). Pre-treatment of aqueous *L. barbarum* extract also reduced the phosphorylation of c-Jun N-terminal kinase (JNK)-1 (Thr183/Tyr185) and its substrates c-Jun-I (Ser 73) and c-Jun-II (Ser 63) (Yu et al., 2005), which are rapidly activated by beta-amyloid. An alkaline extract of *L. barbarum* protected neurons to attenuate beta-amyloid peptide neurotoxicity. Western blot analysis demonstrated that some of these fractions markedly enhanced the phosphorylation of Akt (Ho et al., 2007). This neuroprotective effect may come from both antioxidative and cytoprotective mechanisms, and by inhibiting pro-apoptotic signaling pathways. LBP also exerted neuroprotective effects against homocysteine (Ho et al., 2009) and glutamate (Ho et al., 2009). Elevated plasma homocysteine levels and glutamate excitotoxicity are suggested to increase the risk of Alzheimer's disease by damaging neurons by inducing apoptosis, DNA fragmentation, and tau hyperphosphorylation. Retina was also protected by LBP against ocular hypertension in a laser-induced glaucoma animal model. Effective dosage of *L. barbarum* extract in neuroprotective area was wider than that of lithium chloride (LiCl) medicinally used.

While bioavailability of *L. barbarum* and LBP must be considered in a series of the *in vitro* studies, *L. barbarum* and LBP have been reported *in vivo* to have neuroprotective effects against various toxicins and conditions and to enhance the learning and memory capability of manganese-poisoned mice by promoting neurogenesis in hippocampus. The average escape latency was higher and the times of passing through platform lower in LBP group than those in the control group. Bromodeoxyuridine-positive cells in LBP groups were significantly more than those in the manganese poisoning group (Wen, Yang, & Ren, 2010). *L. barbarum* has been reported to prevent brain oxidative mitochondrial damage in a prenatal stress model with rats and cognitive dysfunction associated with prenatal stress. Prenatal stress caused a significant decrease in cognitive function (Morris water maze test) in female offspring. Pretreatment of the mother rats with *L. barbarum* significantly prevented prenatal stress-induced cognitive dysfunction. LBP was effective on peripheral red blood cells (RBC) and platelet recovery of mitomycin C (MMC)-induced myelosuppressive mice. However, LBP showed no obvious effect on neutropenia (Hai-Yang, Ping, Li, Chang-Hong, & Fu, 2004).

5.2. Stimulation of metabolism

LBP composed of six kinds of monosaccharides enhanced food conversion rate and the content of zinc and iron in body, and reduced the body weight of weanling mice 21 days after oral consumption at the dose of 5, 10 and 20 mg/kg/day (Zhang, Wang, & Zhang, 2002). Administered to mice by stomach perfusion for seven consecutive days, LBP inhibited endoplasmic reticulum damages, promoted protein synthesis and detoxification, restored the normal function of hepatic cells, and promoted the regeneration of hepatic cells (Bian, She, & Wang, 1996). LBP also effectively prevented alcoholic fatty liver in rats. This may be due to its effects in inhibiting the hepatocyte cytochrome P450 enzyme 2E1 (CYP2E1) expression and prevention of lipid peroxidation. Serum levels of alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (GGT), the content of liver malondialdehyde (MDA), hydrogen peroxide (H_2O_2), CYP2E1 gene and protein expressions were all significantly reduced, and the activity of liver superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and GSH content were increased (Gu, Wang, & Jiang, 2007).

LBP-standardized *L. barbarum* fruit juice has been reported in several randomized clinical studies that it significantly increased postprandial energy expenditure compared to the placebo (Amagase, 2010). *L. barbarum* intake was effective to control waist circumference in the humans, and may reduce the risks of metabolic syndrome (Amagase & Nance, 2009). Subjects in the *L. barbarum* group maintained waist circumference at the starting point measurements even during the holiday overeating time at year's end. The placebo group showed no significant changes (Amagase & Handel, 2008). *L. barbarum* may stimulate metabolic rate through adrenocortical hormone control, and these effects may be related to the changes in waist circumference produced by daily consumption of *L. barbarum* in the form of fruit juice (Amagase, 2010). As these studies are preliminary and there are limitations, these did not include any functional measurements of substrate utilization, heart rate, muscle activity, temperature or respiratory quotient (RQ). These are additional relevant dependent measures that will need to be addressed in more detailed future studies. However, the absence of

these additional measures does not diminish the clear functional and statistical significance we observed in the present studies in terms of postprandial energy expenditure. Considering the overall effects of *L. barbarum*, it appears that the combination of nutritional ingredients with *L. barbarum* may be useful for increasing metabolic rate and body weight control. Thus, future studies with additional measures of energy balance and anthropometric parameters related to the body weight control will establish the possible effects of *L. barbarum* on glucose and fat metabolism, metabolic syndrome, and obesity-related hormone levels in humans in order to identify the mechanisms of actions of *L. barbarum*.

5.3. Cardiovascular benefits

The increase of blood pressure in hypertension rats was prevented significantly by LBP treatment tested in the two-kidney, one clip model *in vivo*. In isolated aortic rings of LBP-treated rats, the contraction of phenylephrine was reduced as compared with non-treated hypertensive rats. Removal of the endothelium abolished the difference of phenylephrine-induced vasoconstriction among groups. *In vitro* incubation of aortic rings from LBP-treated rats with methyl blue or N-nitro-L-arginine methyl ester increased the magnitude of phenylephrine-induced contraction. Role of LBP in decreasing vasoconstriction to phenylephrine may be mediated by increase of the effects and/or production of endothelium-derived relaxation factor (EDRF). LBP-induced EDRF formation may be related to increased substrate (Jia, Dong, Wu, Ma, & Shi, 1998). Meanwhile the response to acetylcholine was significantly increased in LBP-treated rats, but the response to nitroprusside had no significant difference among groups. Pretreatment with L-arginine partially restored acetylcholine-induced relaxation in hypertensive rats, but no effect in LBP-treated rats. LBP treatment resulted in a significant decrease in the concentration of fasting blood glucose levels, total cholesterol and triglyceride in diabetes mellitus mice (Jing, Cui, Feng, & Xiao, 2009).

L. barbarum significantly increased the maximum combination capacity of cardiac muscle b receptors in both 26-month-old mice and rats (Liu, Zhao, Liu, Weng, & Cao, 1996; Shi et al., 1998). Decoction of *L. barbarum* at various concentration levels (1 g/kg through 4 g/kg) administered by stomach perfusion to rats of experimental hyperlipidemia for 10 consecutive days lowered the levels of total cholesterol, triglyceride in both the serum and the liver, and the low density lipoprotein (LDL)-C level in serum (Wang, Xiao, & Xu, 1998). LBP reduced serum total cholesterol and triglyceride concentrations and at same time increased high density lipoprotein (HDL) cholesterol levels after 10 days treatment in rabbits (Luo, Cai, Yan, Sun, & Corke, 2004).

5.4. Diabetes

5.4.1. Clinical studies

There are several clinical and experimental reports showing an anti-diabetic effect of *L. barbarum* as it is well-known in traditional Chinese herbal medicine for diabetes. *L. barbarum* reduced oxidation in patients with retinopathy (Li et al., 2000). In a randomized diabetic retinopathy study, after intake of *L. barbarum* for 3 months, the serum content of lipid peroxide decreased by about 20%, and the contents of vitamin C and the activities of SOD increased by 61 and 87% compared with control group, respectively (He, Zhou, & Qiu, 1998a). *L. barbarum* was also effective to improve immunologic function of red blood cells in the patients with diabetic retinopathy (He et al., 1998a). In the 44 patients with diabetic retinopathy treated with *L. barbarum* for 3 months, RBC C_3b receptor rosette (RBC-C_3bRR) was decreased, RBC immunologic adherence accelerated rate was slightly decreased, RBC immunologic adherence suppress rate was increased, but there was no statistically significant change in RBC immune complex rosette (RBC-1CR). The deterioration of RBC-C_3bRR, suppressor rate of RBC immunological adherence rate, fasting blood–glucose levels, hemoglobin glycosylation and blood lipid showed negative correlations. After the treatment RBC-C_3bRR and RBC immunologic adherence accelerated rate was increased, RBC immunologic adherence suppress rate was decreased. LBP has been identified as one of the active ingredients responsible for its biological activities (He, Zhou, & Qiu, 1998b). LBP has been shown immunomudulary effect on patients with type-2 diabetes ($n = 40$), which reduced T8 and interleukin 6 (IL-6) by 23%, and increased T4/T8 and IL-2 significantly by 30 and 62% compared to the normal level, respectively. (Wang, Zhang, & Li, 2001). LBP also improved red blood cell fragility and abnormality indicated by cell membrane flexibility and evaluated by hypo-osmotic shock and Wright's blood stain under microscope in 50 non-insulin dependent diabetes mellitus (NIDDM) patients so that they either approached from 16.4 ± 0.9 (mean ± SE) to 10.0 ± 0.3% (normal condition ($n = 20$) was 8.3 ± 0.2%), or were restored to normal states, findings that may prove valuable as supplementary treatment for NIDDM (Li et al., 2000). This may be caused by anti-oxidant effects, cytoprotection and other mechanisms of *L. barbarum*.

5.4.2. Animal experiments

LBP orally taken from the drinking water for 30 days was effective to reduce streptozotocin-induced diabetes in rats. Administration of LBP restored abnormal oxidative indices to near normal levels. It was assumed to protect liver and kidney tissue from the damage caused by streptozotocin and suggested that LBP may work as an antihyperglycemia agent (Li, 2007). LBP also has been shown to control blood glucose and modulate the metabolism of glucose, leading to improvement of oxidative stress markers (SOD, MDA and nitric oxide (NO)) in rats with NIDDM. LBP also decreased DNA damage determined by the single cell gel (comet) assay with alkaline electrophoresis and was quantified by measuring tail length and tail moment possibly via a decrease in oxidative stress levels (Wu, Guo, & Zhao, 2006; Zhao, Li, & Xiao, 2005). LBP alleviated insulin resistance and the effect of LBP is associated with increasing cell-surface level of glucose transporter 4 (GLUT4) in skeletal muscle of NIDDM rats. Under insulin stimulus, GLUT4 content in plasma membrane in NIDDM control rats was lower than that of control, and GLUT4 content in the plasma membrane in NIDDM + LBP rats was higher than that of NIDDM control rats. LBP may ameliorate insulin resistance, and the mechanism may be involved in increasing cell-surface level of GLUT4, improving GLUT4 trafficking and intracellular insulin signaling (Zhao, Li, & Xiao, 2005). Hypoglycemic effect of purified LBP was more significant than those of water decoction and crude LBP in alloxan-induced diabetic or hyperlipidemic rabbits (Luo et al., 2004). Alloxan-induced significant decrease in SOD activity and increase in MDA production were inhibited by LBP (Xu, Zhang, & Wang, 2002). Decreased levels of serum advanced glycation end products (AGEs), hydroxyproline concentration in mouse skin and spontaneous motor activity in D-galactose mouse aging model were detected after treated with LBP, while lymphocyte proliferation and IL-2 activity, learning and memory abilities, and SOD activity of erythrocytes were enhanced. LBP inhibited non-enzymatic glycation in a D-galactose-induced mouse aging model *in vivo* (Deng et al., 2003). Diabetic rats treated with LBP showed increased activity of antioxidant enzymes and increased scavenging of oxygen radicals, while the activity of protein kinase C in the renal cortex was maintained at a physiological level. The decreased activation of extracellular signal-regulated kinases 1 and 2 in mesangial cells, through the involvement of protein kinase C, may explain the protective mechanism in kidneys of diabetic rats treated with LBP (Zhao, Li, Li, & Zhang, 2009). LBP treatment also resulted in a significant decrease in the concentration of fasting blood glucose levels, total cholesterol and triglyceride in diabetes mellitus mice (Jing et al., 2009).

5.5. Eye health benefits

Age-related macular degeneration (AMD) is a common disorder and one of the major neurological disorders in eye that causes irreversible loss of central vision in elderly. Increased intake of foods containing zeaxanthin, one of the carotenoids in *L. barbarum* may be effective in preventing AMD because the macula accumulates zeaxanthin and lutein, oxygenated carotenoids with antioxidant and blue light-absorbing properties. The increase in intraocular pressure seen in glaucoma has been considered to be the major risk factor for the progressive loss of retinal ganglion cells in retina. *L. barbarum* has been tested for an ocular hypertension model in rat by laser photocoagulation of episcleral and limbal veins. Oral administration of *L. barbarum* significantly reduced the loss of retinal ganglion cells, although elevated intraocular pressure was not significantly altered. Thus, the therapeutic function of *L. barbarum* against neurodegeneration in the retina of rat ocular hypertension model suggest that *L. barbarum* may be a potential candidate for the development of neuroprotective drug against the loss of retinal ganglion cells in glaucoma (Li, 2007). Other studies also showed that *L. barbarum* protected the subjects from light damages to the retinal pyramid, rod cell layer, outer nuclear layer, and retinal pigmented epithelium in rats (Liu, Li, & Tso, 1995). A single-blinded, placebo-controlled, human intervention trial of parallel design, was to provide data on how fasting plasma zeaxanthin concentration changes as a result of dietary supplementation with whole *L. barbarum*(15 g/day *L. barbarum*, estimated to contain almost 3 mg zeaxanthin) for 28 days. After supplementation, plasma zeaxanthin increased 2.5-fold significantly for the supplementation group, but placebo group did not show significant changes. Such increase in plasma zeaxanthin levels may cause eye benefits (Cheng et al., 2005).

Neuroprotective effect of LBP on the survival of retinal ganglion cells may be mediated via direct up-regulation of neuronal survival signal betaB2-crystallin (Chiu et al., 2010). Neuroprotective effects of LBP were partly due to modulating the activation of microglia (Chiu et al., 2009a; Chiu et al., 2009b). A combination of antioxidants (zeaxanthin, lutein, alpha-lipoic acid, glutathione, and *L. barbarum* extract) delayed the degeneration process in rd1 mouse retina. This combination treatment increased glutathione peroxidase activity and glutathione levels and decreased cystine concentrations in rd1 retinas. A high correlation was present between glutathione concentration and glutathione peroxidase activity, and there was a negative correlation between glutathione retinal concentration and number of terminal deoxynucleotidyl transferase dUTP Nick End Labeling (TUNEL)-positive cells. No difference was observed between the numbers of nNOS- and nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase-positive cells in treated and untreated rd1 mice. Thiol contents and thiol-dependent peroxide metabolism seem to be directly related to the survival of photoreceptors in rd1 mouse retina (Miranda et al., 2010).

5.6. Anti-oxidant effects

Several clinical studies, various pre-clinical *in vivo* animal and *in vitro* cell culture studies have shown the efficacy of *L. barbarum* and LBP as anti-oxidants in protecting against various peroxidation-related conditions (Gong, Shen, Jin, Xing, & Tang, 2005; Huang, Lu, Shen, & Lu, 1999; Huang, Tian, Wang, Dong, & Wu, 2001; Huang, Yang, Wu, & Yan, 2003; Huang et al., 1998; Li, Ma, & Liu, 2007; Li, Yang, Ren, & Wang, 2002; Luo et al., 2006; Ni, Qing, Kaisa, & Lu, 2004; Reeve, Allanson, Arun, Domanski, & Painter, 2010; Ren, Ma, Shen, & Gao, 1995; Sui et al., 1996; Wang et al., 2002; Wu, Ng, & Lin, 2004; Zhang, 1993; Zhang, Zhang, & Li, 1997; Zhao, Alexeev, Chang, Greenburg, & Bojanowski, 2005).

5.6.1. Clinical study

A randomized clinical trial showed intrinsic anti-oxidant effects of orally consumed *L. barbarum*, administered as a LBP-standardized *L. barbarum* fruit juice, in healthy old adults (Amagase, Sun, & Borek, 2009). Serum SOD and GSH-Px levels in the *L. barbarum* group were significantly increased over the starting point, and MDA was decreased significantly. SOD and GSH-Px in the *L. barbarum* group were also significantly improved over placebo. No significant differences were detected in the placebo group. Since free radical oxidations play a role in various diseases and symptoms (Borek, 2004), *L. barbarum* may be useful in preventing or reducing these oxidation-related conditions and these anti-oxidant effects are the possible mechanism. As elderly people have age-associated reduction of GSH-Px and SOD (Andersen, Nielsen, Nielsen, & Grandjean, 1997), *L. barbarum* fruit juice may have anti-aging effects consistent with the traditionally recognized effects of *L. barbarum*. As most of the anti-oxidant studies with other food materials or supplements have been done under disease conditions (Bose & Agrawal, 2007; Micke, Beeh, Schlaak, & Buhl, 2001; Wang, Adachi, Sim, & Wilcken, 1998) or deficient conditions (Machefer et al., 2007), it is meaningful that *L. barbarum* intake produced a nearly 10% increase in serum anti-oxidant capacities in human subjects under normal conditions. LBP also improved red blood cell fragility and abnormality in NIDDM patients so that they either approach or are restored to normal states, and may be useful as a supplementary treatment for NIDDM (Li et al., 2000).

5.6.2. Animal experiments

While *L. barbarum* treatment did not prolong the survival time, *L. barbarum* and LBP increased the activities of SOD, catalase (CAT), total anti-oxidative capacity (TAOC), and decreased MDA level, creatine kinase activities, endogenous lipid peroxidation, the oxidative stress induced by exhaustive exercise in murine models after administration of *L. barbarum* (Li, Ma, & Liu, 2007; Li et al., 2002; Lin, Wang, Chang, Inbaraj, & Chen, 2009; Niu, Wu, Yu, & Wang, 2008; Sui et al., 1996; Wu et al., 2010; Zhu, 1998). Pretreatment with *L. barbarum* significantly prevented the loss of myofibrils and improved the heart function of the doxorubicin-treated rats as evidenced from lower mortality, normalization of antioxidative activity and serum aspartate aminotransferase and creatine kinase, as well as improving arrhythmias and conduction abnormalities. *In vitro* cytotoxic study showed the antitumor activity of doxorubicin was not compromised by *L. barbarum*. *L. barbarum* was proposed to be used as an adjunct in combination with doxorubicin chemotherapy (Xin et al., 2007). Skin protection by *L. barbarum* against immune suppression and oxidative stress by solar simulated UV (SSUV) radiation was seen. Commercially available Himalayan Goji juice was administered to hairless mice in the drinking water. Mice drinking 1%–10% Goji juice were dose-dependently protected from SSUV-induced systemic immunosuppression, measured as the contact hypersensitivity reaction (CHS). It was confirmed that the protection was an innate property of the goji berry, because it was not observed with commercial apple/pear juice (0.2 mg/ml vitamin C), nor was it attributable to the high vitamin C content, nor to the preservative. It was observed that 5% GoChi juice induced the expression of haem oxygenase-1 (HO-1) mRNA in the mouse skin. Furthermore, inhibition of HO enzyme activity by injecting mice with the substrate antagonist, SnPP, abrogated the photoimmune protection. Therefore, drinking Goji juice has photoprotective effects by inducing the endogenous cutaneous antioxidant HO-1, and might protect humans against actinic skin damage leading to cancers (Reeve & Reeve, 2008; Reeve et al., 2010). LBP provided a protective effect against the testicular tissue damage induced by 43 °C heat exposure through improved SOD activity, and raised sexual hormone levels. LBP improved the copulatory performance and reproductive function of hemicastrated male rats. These findings support the folk reputation of *L. barbarum* fruits as an aphrodisiac and fertility-facilitating agent as well as the extensive use of *L. barbarum* fruits as a traditional remedy for male infertility in China (Luo et al., 2006). LBP promoted the peripheral blood recovery of irradiation or

chemotherapy-induced myelosuppressive mice, and the effects may be the result of the stimulation of peripheral blood mononuclear cells (PBMCs) to produce granulocyte colony-stimulating factor (G-CSF) (Gong et al., 2005). *L. barbarum* and betaine inhibited the lipid peroxidation of RBC membrane induced by hydrogenperoxide (H_2O_2) in rats in the following order of antioxidizing power: *L. barbarum* dry>LBP>Residue *L. barbarum*>betaine (Ren et al., 1995). A synergistic anti-oxidant effect with vitamin C was also reported (Zhu, 1998). The *L. barbarum* aggravated ischemia/reperfusion-induced liver injury by increasing hydroxyl radical release with no effect on NO release. *L. barbarum* may not directly scavenge the free radicals like ascorbic acid (Wang et al., 2009).

5.6.3. Tissue culture

L. barbarum extract had better inhibition among three popular traditional Chinese medicines on MDA formation in rat liver homogenate, and superoxide anion scavenging and anti-superoxide formation activities than *Angelica sinensis* or *P. cocos*. *L. barbarum* extract exhibited the lowest IC_{50} values (0.77–2.55 μg/ml) (Wu et al., 2004). Effective level of LBP *in vitro* was reported in 0.25–1.0 mg/ml (Ni et al., 2004). *L. barbarum* dose-dependently scavenged hydroxyl and superoxide radicals, and inhibited $FeCl_2$/ascorbic acid-induced dysfunction in brain tissue and tissue mitochondria, including increases in reactive oxygen species and lipid peroxidation and decreases in the activities of complex I, complex II, and glutamate cysteine ligase (Feng et al., 2010). LBP cleaned out the free-radicals and restrained the DNA damage caused by the oxidative stress without causing oxidative damage (Huang et al., 2003), inhibited time- and hyperthermia-induced structural damage in murine seminiferous epithelium (Wang et al., 2002), and improved the passive electrical membrane parameters of the injured membrane (Zhang, 1993; Zhang et al., 1997). As these direct scavenging effects are different from *in vivo* studies, further studies are necessary to confirm these *in vitro* effects. LBP also decreased the level of selective matrix metalloproteinase significantly in the whole human skin system, without compromising the viability of the skin (Zhao, Alexeev, et al., 2005). Consistently, it inhibited skin expansion under mechanical stress, which in this model depends on the activity of matrix metalloproteinase-1 under the condition of higher levels of collagen type I, the matrix metalloproteinase-1 substrate (Zhao, Alexeev, et al., 2005). These results are consistent with the recent *in vivo* results (Reeve et al., 2010). LBP stimulated human PBMCs to produce G-CSF for protective effect on irradiation- or chemotherapy-induced cultured PBMCs (Gong et al., 2005). Among LBP and their glycans, glycoconjugate LbGp5 showed the best effect on inhibiting LDL peroxidation measured by the oxidative production of thiobarbituric acid-reactive substances (TBARS) and their glycans showed no effects (Huang et al., 2001). As LBP containing several monosaccharides and 18 amino acids are considered to be major bioactive constituents of hypoglycemic effect, both polysaccharides and vitamin antioxidants from *L. barbarum* fruits are possible active principles of hypolipidemic effect. Further detailed studies are necessary to clarify the responsible compound(s) for specific effect.

Flavonoids from *L. barbarum* were also found to be anti-oxidants. The mitochondrial lipid peroxidation measured as MDA was significantly inhibited by total flavonoids from *L. barbarum* in a dose-dependent manner, and the fluidity of mitochondria membrane was also protected. The shape of RBC was protected (Huang et al., 1999). Scavenging effects were also found by ESR-spin trapping technique. Flavonoids scavenged free radicals in xanthine/xanthine oxidase (Xan/XO) system, and in Fenton reaction in concentration-dependent manner. It inhibited the heat output from PMA-stimulated polymorphonuclear leukocyte and inhibited the heat output from L1210 cells (Huang et al., 1998). Newer studies on flavonoids from *L. barbarum* have not seen after these publications.

In a simple fruit juice comparison, total antioxidant capacity was assessed using trolox equivalent antioxidant capacity and oxygen radical absorbance capacity (ORAC) assay. Total antioxidant capacity assay showed that raw (USDA, 2010b) and all three *L. barbarum* extracts/fractions possessed antioxidant activity. Water and methanolic fruit extracts and crude polysaccharide extracts exhibited stronger antioxidant activity than purified polysaccharide fractions because crude extracts were identified to be rich in antioxidants (Luo et al., 2004). Since ORAC is not purported to represent actual antioxidant capacity in the body, ORAC comparison *in vitro* does not necessarily translate to real anti-oxidant activities *in vivo*.

5.7. Immune modulation

Many studies have shown that goji and LBP have a wide variety of immuno-modulatory functions including activation of various immune cells (Xu et al., 2000). A review of research on *Lycium* fruit appearing in Recent Advances in Chinese Herbal Drugs (Zhou, 1991), indicates that LBP enhance both cell-mediated and humoral immune responses. It was reported, for example, that in laboratory animals, a dose of 5–10 mg/kg LBP daily for one week increased activity of T-cells, cytotoxic T-cells, and natural killer cells; other studies showed that part of the mechanism of action was via IL-2 stimulation. However, the end response to LBP administration did not appear to be solely a stimulation of immune activity. In a laboratory study of *Lycium* on IgE responses, it was noted that *Lycium* fruit reduced antibodies associated with allergy-type reactions, which was presumed to be accomplished through the mechanisms of promoting CD8 T-cells and regulating cytokines (Yin, Jin, Bai, & Hao, 1992). The following immune factors were significantly increased:

5.7.1. White blood cell count

L. barbarum extract suppressed cyclophosphamide-induced decrease in white blood cell count, and promoted its recovery, significantly delaying death (Pu, 1998).

5.7.2. Interleukin 12 (IL-12)

Compared to the control murine bone marrow derived dendritic cells (BMDC) which was not exposed to LBP, the co-expression of I-A/I-E, CD11c and secretion of IL-12 p40 by BMDC cultured with LBP were increased. The endocytosis of FITC-dextran by LBP-treated BMDC was impaired, whereas the activation of proliferation of allogenic lymphocytes by BMDC was enhanced. Since activation of T cells, B cells and NK cells through dendritic cells (DC) are potent antigen-presenting cells that play pivotal roles in the initiation of the primary immune response, this suggests that LBP seem to be capable of promoting both the phenotypic and functional maturation of murine BMDC *in vitro*. LBP promoted not only the maturation of cultured murine BMDC *in vitro*, but also the immune response initiation induced by BMDC (Zhu, Zhao, & Chen, 2006; Zhu, Zhao, Zhao, & Chen, 2007). LBP up-regulated DC expression of CD40, CD80, CD86, and MHC class II molecules; down-regulated DC uptake of Ag; enhanced DC allostimulatory activity; and induced IL-12p40 and p70 production. LBP developed enhanced T helper cells 1 (Th1) response, and LBP-treated DC enhanced Th1 and Th2 responses *in vitro* and *in vivo* (Chen, Lu, Srinivasan, Tan, & Chan, 2009).

5.7.3. Interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α)

Administration of LBP increased the expression of IL-2 and TNF-α at both mRNA and protein levels in a dose-dependent manner found in the study using human peripheral blood mononuclear cells in reverse transcription polymerase chain reaction (RT-PCR) and bioassay. Since these are two important cytokines in anti-tumor immunity, LBP may induce immune responses and possess potential therapeutic efficacy in cancer (Gan, Zhang, Liu, & Xu, 2003). A certain concentration (between 1.9 and 7.8 mg/ml), *L. barbarum* extract

promotes the expression of IL-2 receptors (Du & Qian, 1995). *L. barbarum* attenuated binding-caused reductions in body weight and TNF-α activity in rats (Li, Liu, Yang, & Zhu, 2007).

5.7.4. Phagocytic action

Isolated and purified LBP increased rate of phagocytic action and phagocytic index, promote lymphocyte translation and accelerated the production of serum hemolysin. LBP has distinct effect of antioxidation and the superoxide anion produced by DMSO-NaOH system was scavenged effectively. LBP was shown to be a kind of homogeneous glycoconjugate with immunoactivity and antioxidative activity (Peng et al., 2001). Administered to mice by stomach perfusion for seven consecutive days, LBP increased the weight of the immune organs, and significantly increased the reticuloendothelial system's phagocytotic capacity on Indian ink (Sui et al., 1996). LBP enhanced innate immunity by activating macrophages. LBP activated transcription factors NF-κB and AP-1 by RAW264.7 macrophage cells, induced TNF-α, IL-1β, IL-12p40 mRNA expression, and enhanced TNF-α production in a dose-dependent manner. Furthermore, LBP significantly enhanced macrophage endocytic and phagocytic capacities *in vivo*. The mechanism may be through activation of transcription factors NF-κB and AP-1 to induce TNF-α production and up-regulation of MHC class II costimulatory molecules (Chen, Soo, Srinivasan, Tan, & Chan, 2009).

5.7.5. Splenocyte proliferation

LBP were shown to enhance splenocyte proliferation induced by ConA evaluated with splenocyte proliferation by [^{3}H]-TDR incorperation *in vitro*. Polysaccharides with main chain of alpha-(1–>4)-D-polygalacturonans showed stronger immunomodulation activity (Duan et al., 2001).

5.7.6. Lymphocyte proliferation

Flow cytometry revealed that LBP enhanced the murine splenic lymphocyte proliferative reaction. Combined use of LBP and ConA had synergic effects. MTT demonstrated that LBP significantly promoted the murine splenic lymphocyte proliferative reaction as compared with control group, while LBP plus ConA combination also enhanced the lymphocyte proliferation at a high dose. LBP with ConA had immunocompetence (Du et al., 2004). LBP activated T cells and stimulated mouse splenocyte proliferation, but not B cells. Cell cycle profile analysis indicated that LBP markedly reduced sub-G1 cells. LBP activated transcription factors NFAT and AP-1, prompt CD25 expression, and induce IL-2 and IFN-γ gene transcription and protein secretion. Activation of T lymphocytes by LBP may contribute to one of its immuno-enhancement functions (Chen, Kwong, & Chan, 2008). LBP reverses apoptotic resistance of aged T cells by modulating the expression of apoptosis-related molecules. LBP increased the apoptotic rate of T cells from aged mice and showed a similar DNA ladder pattern to that in young T cells. The reversal of apoptotic resistance was involved in down-regulating the expression of Bcl-2 and FLIP, and up-regulating the expression of FasL (Yuan, Deng, Chen, Li, & He, 2008).

Effects of pure LBP on immunological activity were compared with crude LBP. The pure LBP were divided into different doses, lower doses (5–20 mg/kg/day) of pure LBP showed a remarkable effect on immunological enhancement. Especially, 10 mg/kg/day had a highly significant difference compared with crude LBP on immune indices in mice. LBP might have optimum dosage in immunological effects. (Luo, Yan, & Zhang, 1999) The sulfated modification of LBP significantly promoted lymphocytes proliferation and enhance serum antibody titer both *in vitro* and *in vivo* and more effective than LBP (Wang, Hu, Wang, Liu, et al., 2010; Wang, Hu, Wang, Zhang, et al., 2010).

Furthermore, a clinical study has been reported in immunological treatment combining with lymphokine-activated killer cell (LAK)/IL-2 combining with LBP in 79 advanced cancer patients. Initial results of the treatment from 75 evaluable patients indicated that objective regression of cancer was achieved in patients with malignant melanoma, renal cell carcinoma, colorectal carcinoma, lung cancer, nasopharyngeal carcinoma, malignant hydrothorax. The response rate of patients treated with LAK/IL-2 plus LBP was 40.9% while that of patients treated with LAK/IL-2 was 16.1%. The mean remission in patients treated with LAK/IL-2 plus LBP also lasted significantly longer. LAK/IL-2 plus LBP treatment led to more marked increase in NK and LAK cell activity than LAK/IL-2 without LBP. The results indicate that LBP can be used as an adjuvant in the biotherapy of cancer (Cao, Yang, & Du, 1994). Recent 2 randomized, double-blind, placebo-controlled human clinical studies conducted in USA and China have examined the immunomodulatory effects of orally consumed *L. barbarum* fruit in a form of LBP-standardized juice (GoChi) provided to healthy adults. The *L. barbarum* group significantly increased the number of lymphocytes by 27%, IL-2 by 58%, and IgG levels by 19% compared to starting point, whereas the number of CD4, CD8, or NK cells, or IL-4, and IgA levels were not significantly changed. No adverse reactions, abnormal symptoms, changes in body weight, blood pressure, pulse rate, visual acuity, urine, stool, or blood biochemistry were seen during the trial. No significant improvements were found in any of the indications in the placebo group. Thus, daily consumption of *L. barbarum* significantly increased several measures of immunological function without any adverse reactions (Amagase, Sun, & Nance, 2009).

5.8. Anti-inflammation (including skin protection from UV radiation)

The *in vivo* immunostimulatory action of *L. barbarum*, as well as its anti-inflammatory effect in response to a septisemia endotoxin challenge with regard to TNF and IL-6 was seen in male SD rats (Nance, Amagase, & Luczy-Bachman, 2009). *L. barbarum* produced a small but significant increase in basal plasma and splenic levels of IL-6 and plasma levels of IL-1β. Endotoxin increased levels of all cytokines and corticosterone; however, the increase in splenic levels of IL-6 and TNF-α was attenuated in the *L. barbarum* group. Consumption of *L. barbarum* produced a significant reduction in body weight gain and an increase in plasma and splenic levels of IL-6 and plasma levels of IL-1β. In contrast to the immunostimulatory effects of *L. barbarum* treatment alone, *L. barbarum* attenuated endotoxin-induced IL-6 and TNF-α levels in the spleen. *L. barbarum* had no effect on endotoxin-induced increases in IFN-γ and corticosterone levels. Thus, *L. barbarum* juice can have both an immunostimulatory and an anti-inflammatory action on basal and stimulated cytokine production. Since the anti-cancer effect of LBP was proposed to be via an immunostimulatory action (Cao et al., 1994), the immunostimulatory effects seen in this study is reasonable and consistent with previous observations.

L. barbarum has photoprotective effects by inducing the endogenous cutaneous antioxidant haem oxygenase-1 (HO-1), and might protect humans against actinic skin damage leading to cancers. A standardized *L. barbarum* fruit juice (GoChi) was administered to hairless mice in the drinking water. It was found that mice drinking 1%–10% *L. barbarum* were dose-dependently protected from SSUV radiation-induced systemic immunosuppression, measured as the contact hypersensitivity reaction. It was confirmed that the protection was an innate property of the goji berry, because it was not observed with any excipients of *L. barbarum* fruit juice or vitamin C, which is found high concentration in *L. barbarum* berry. It was observed that 5% *L. barbarum* juice induced the expression of HO-1 mRNA in the mouse skin. Furthermore, inhibition of HO enzyme activity by injecting mice with the substrate antagonist, SnPP, abrogated the photoimmune protection. *L. barbarum* offers skin protection against immune suppression and oxidative stress by SSUV radiation. (Reeve & Reeve, 2008; Reeve et al., 2010).

5.9. Antibacterial effects

According to the preliminary *in vitro* study, *L. barbarum* extract has been reported to have antibacterial effects on 17 kinds of bacteria, including *Staphylococcus aureus, Staphylococcus epidermidis*, *Salmonella* Typhi, *Salmonella* Paratyphi *A through C, Salmonella* Typhimurium, *Bacillus subtilis*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, *Bacillus dysenteriae* (*Shigella dysenteriae*), *E. coli*, *Candida albicans* and *Typhoid bacillus* (Jin, Jia, Wang, & Li, 1995). Considering crude extract and large molecules in the material, such as LBP, bioavailability is the issue for the *in vivo* effect. Antibiotic effects shown in this preliminary study may be applied to gastrointestinal or external usage. A typical antibiotic drug was needed to be compared in the same experiment system as a positive control. As it was a simple study and no follow-up studies have been published so far, further studies are needed to clarify these efficacies.

5.10. Anti-cancer and cytoprotection

5.10.1. Animal experiments

Most of the animal studies were done with LBP and expected to cause anti-cancer effects through immune enhancements. LBP may prevent the development of complications or even tendency to carcinogenesis in NIDDM rats (Wu et al., 2006). Anti-tumor effect of LBP may be caused by increasing the numbers of CD4(+) and CD8(+) T cells in tumor-infiltrating lymphocytes to relieve the immunosuppression and enhance the anti-tumor function of the immune system. However, whether LBP recovers the phenocyte and function of dendritic cells in H22-bearing mice is not known (He et al., 2005). LBP significantly increased the numbers of CD4(+) and CD8(+) T cells in TIL as compared with those in the control group. In the control group, the number of dendritic cells in tumor microenvironment decreased markedly, while LBP tended to increase number of dendritic cells and B7-1 expression. LBP (10 mg/kg) significantly reduced tumor weight and improved the immune system (Gan, Hua, Liang, & Bi, 2004). LBP significantly inhibited the growth of transplantable sarcoma and increase macrophage phagocytosis, the form of antibody secreted by spleen cells, spleen lymphocyte proliferation, cytotoxic T lymphocyte activity, IL-2 mRNA expression level and reduced the lipid peroxidation in sarcoma-bearing mice. The effect is not dose-dependent in a linear fashion. The radiosensitizing effects of LBP were observed by the model transplanted Lewis lung cancer. The significant radiosensitizing effects were obtained by combination of LBP and radiation. The mean numerical value of the dose modifying factors was 2.05. LBP also enhanced radiation effects to acute hypoxic cells of Lewis lung cancer without severe toxicity to the mice (Lu & Cheng, 1991). LBP significantly inhibited human prostate cancer cell growth in nude mice. Both the tumor volume and weight of the LBP-treated group were significantly lower than those of the control group (Luo et al., 2009).

5.10.2. Cell-culture and mechanism studies

Various *in vitro* studies were reported on *L. barbarum* and LBP to evaluate their mechanism of actions. While the estrogen receptor positive breast cancer cells significantly increased growth after treatment with estrogens, treatment with 1% *L. barbarum* (maximum cytostatic concentration) exhibited a dose-dependent growth inhibition. The estrogen receptor positive breast cancer cells retain their mitogenic and metabolic response to 17 β-estradiol and *L. barbarum* down-regulates 17β-estradiol-stimulated growth via the formation of antiproliferative 2-hydroxyestrone and accelerated conversion of mitogenic 16α-hydroxyestrone to antimitogenic estriol. Thus, *L. barbarum* inhibited growth of estrogen receptor positive human breast cancer cells by favorably altering estradiol metabolism (Li, Sepkovic, Bradlow, Telang, & Wong, 2009). LBP inhibited the growth of human prostate cancer cell lines in a dose- and time-dependent manner. LBP caused the breakage of DNA strands of prostate cancer cells; the tail frequency and tail length were significantly higher than that of control cells. LBP also markedly induced prostate cancer cell apoptosis, with the highest apoptosis rates at around 40%. The ratio of Bcl-2/Bax protein expression following LBP treatments decreased significantly with a dose-effect relationship, which suggested that LBP may regulate the expression of Bcl-2 and Bax to induce apoptosis of prostate cancer cells (Luo et al., 2009). LBP also induced apoptosis of human leukemia cells (Gan, Wang, & Zhang, 2001). Hot water-extracted *L. barbarum* inhibited proliferation and stimulate p53-mediated apoptosis in human hepatocellular carcinoma cells (Chao, Chiang, Wang, Tsai, & Wu, 2006). A stable vitamin C analog found in *L. barbarum* fruit, 2-O-β-D: -Glucopyranosyl-L: -ascorbic acid (AA-2βG), selectively induced cell death repressed the proliferation of Hela cells by apoptosis and cell cycle arrest induced through stabilizing p53 protein. AA-2βG and vitamin C may share a similar mechanism of inducing Hela cell apoptosis, which is dependent on a cell type, time and dose (Zhang et al., 2010). LBP treatment caused inhibition of human hepatoma cell growth with cycle arrest in S phase and apoptosis induction. The amount of RNA in cells and the concentration of intracellular Ca^{2+} were increased. The distribution of calcium in cells was also changed. It is suggested that the induction of cell cycle arrest and the increase of intracellular calcium in apoptotic system may participate in the antiproliferative activity of LBP in hepatoma cells (Zhang et al., 2005). LBP inhibited the growth of human colon carcinoma cells in dose-dependent manner and decrease the membrane fluidity of the cell. Agarose gel electrophoresis of DNA from the cells treated with LBP revealed a "DNA ladder" and positive TUNEL test. Cells were arrested at the G0/G1 phase. The changes in cell-cycle-associated protein, cyclins, and cyclin-dependent kinases were consistent with the changes in cell-cycle distribution (Mao et al., 2010). LBP inhibited growth of human gastric cancer cell, with cell-cycle arrest at the G0/G1 and S phase. LBP arrested different cell lines from the same types of cancer at different phases. The changes in cell-cycle-associated protein, cyclins, and cyclin-dependent kinases were consistent with the changes in cell-cycle distribution. Induction of cell-cycle arrest participates in the anticancer activity of LBP on gastric cancer cells (Miao et al., 2009). A p53-mediated apoptosis and cell cycle arrest may be its possible mechanisms on anti-tumorgenesis. *L. barbarum* also inhibited the apoptosis of rat spleen cells induced by hydrocortisone in a dose-dependent manner (Lu, Xian, Lu, Wu, & Gu, 1999).

5.10.3. Cytoprotection

L. barbarum improved *in vitro* attachment and growth of human gingival fibroblast to root surfaces, on the planed diseased root surfaces. When exposed to *L. barbarum* cells on the diseased root surfaces increased markedly in number, with more even distribution, better spread, and more exuberant growth. (Liu, 1992). LBP have nutritional and protective effects on *in vitro* cultivated chorionic membrane cells (Wang, Lu, & Xu, 1998). LBP can be used as the vitrification solution for immature porcine oocytes (Huang et al., 2008). A 2-week study on various hematological and biochemical markers revealed that a standardized *L. barbarum* fruit juice (GoChi) in rats after daily administration by oral gavage for 14 consecutive days increased hemoglobin concentration and total red blood cell counts in both female and male rats. This may increase oxygen-carrying capacity in red blood cells. GoChi also increased plasma levels of calcium and potassium, and decreased Na/K ratio while maintaining sodium levels in the females. It may improve kidney functions and electrolyte balance. GoChi intake reduced SGPT and SGOT levels in the female rats. It thus may increase liver functions. Plasma albumin, globulin and total protein were all increased by GoChi in the male rats (Amagase, 2008a).

6. Dosage

Lycium fruit is most often incorporated into complex herb formulae in traditional medicines, in which its dose is in the range of 6–18 g as dried material. In case of decoction, NHI monograph

indicates 5–15 g of *Lycium* (NHI, 2007), equivalent to 25–120 g of fresh berries. There have been a few reports of using *Lycium* fruit as a single herb or as a major component in a small recipe. In the folk medicine for atrophic gastritis or diabetes, 10 g of *Lycium* fruits each time, two or three times daily is recommended (Wang & Dong, 1990; Xu, 1989). As a food therapy for strengthening the elderly or debilitated, it is cooked with lean pork, bamboo shoots, and typical Chinese flavorings, and the daily dose would be 15–30 g (Zhang, 1988). As a dietary supplement for eye health (Cheng et al., 2005), a dose of 15 g per day was deemed beneficial in supplying adequate zeaxanthin (estimated at 3 mg/day). A simple tea for decreased visual perception is made from 20 g *Lycium* fruit as a daily dose (Zong & Liscum, 1996). A Chinese clinical cancer study used polysaccharide-standardized amount of *L. barbarum* (Cao et al., 1994). Thus, the dose in complex formulas of 6–18 g shifts to a dose of 15–30 g when it is the main herb, or about a 2.5-fold increase in the dose (Dharmananda, 2007). Based on these dose information, we have set a recommended amount/volume at 30 ml four times daily (total 120 ml/day), which is equivalent to approximately 150 g of fresh berries. Servings can be combined, if desired (Amagase, 2008a, 2008b, 2010; Amagase & Handel, 2008; Amagase & Hsu, 2009; Amagase & Nance, 2008a, 2008b, 2009; Amagase, Sun, & Borek, 2009; Amagase, Sun, & Nance, 2009).

7. Toxicity

Like other commonly eaten fruits, *L. barbarum* is non-toxic. *L. barbarum* has been used traditionally as a food and as an herbal medicine for over 2500 years without any specific toxicity. There is no known toxicity reported on *L. barbarum* in the scientific literature or in traditional Asian herbal medicine textbooks (Bensky & Gamble, 1993; Chang & But, 2001; Inagaki, Shimada, Shimano, & Nagasawa, 1979; Wang, 2006; Wang & Dong, 1990; Zhu, 1998). Under the Dietary Supplement Health and Education Act of 1994, *L. barbarum* can be sold without restriction in the USA as an ingredient in dietary supplements and foods. Recently, Dutch authorities in 2004 and the UK Food Standard Agency (2007) classified *L. barbarum* as a food and not as a novel food, based upon the long traditional usage without toxicity. The various review articles and textbooks have cited the traditional beneficial aspects of *L. barbarum* and do not mention any toxicity aspects (Bensky & Gamble, 1993; Chang & But, 2001; Inagaki et al., 1979; Wang, 2006; Wang & Dong, 1990; Zhu, 1998). A review article on *L. barbarum* including translated Chinese papers concluded *L. barbarum* fruit is not toxic, according to their basic toxicological studies (Dharmananda, 2007).

Our five recent randomized, blind, placebo-controlled human clinical studies confirmed the safety of *L. barbarum* fruit juice, equivalent to at least 150 g of *L. barbarum* fresh fruit, provided to 201 healthy adults in total for 14–30 days in USA (Amagase & Hsu, 2009; Amagase & Nance, 2008a, 2008b) and China (Amagase, Sun, & Borek, 2009; Amagase, Sun, & Nance, 2009). No adverse reactions, abnormal symptoms, changes in body weight, blood pressure, pulse rate, visual acuity, urine, stool, or blood biochemistry were seen in either *L. barbarum* or placebo group.

A recent toxicological study in rats performed by a subcontracted research organization showed no toxicity or 50% lethal dose (LD_{50}) when given *L. barbarum* fruit juice (GoChi) orally (Amagase, 2008b). This basic short-term toxicological study was performed in rats after daily administration of GoChi by oral gavage for 14 consecutive days. Three different dosage treatments and a control group were assigned to 4 groups. There were no statistically significant differences in average body weights or food consumption between groups at any time points. Even at the maximum dosage (10 ml/kg/day), there was no death in animals, and no damage to organs. Therefore, LD_{50} has not been found. There were no differences between groups in tissue weights. No histopathological lesions of toxicological significance were observed in the tissues examined. Thus, no toxicity was found from this short term study, and it is concluded that, as previously experienced and expected, GoChi is safe for oral ingestion (Amagase, 2008b).

Two weeks after being treated with *L. barbarum* decoction by stomach perfusion at 20 g/kg and 30 g/kg for a period of 4 weeks, the subjects were found to have only an elevated count of white blood cells, increased numbers of monocytes and lymphocytes, and increased thymus gland parameters (Wang et al., 2001). The injection of 2.4 g/kg of *L. barbarum* fruit extract did not cause adverse reactions; the LD_{50} by injection was determined to be about 8.3 g/kg (Zhu, 1998).

There were two recent case reports of a possible interaction of *Lycium* fruit tea with warfarin (Coumadin) (Leung, Hung, Hui, & Chan, 2008; Li et al., 2000). However, given the high frequency of use of *L. barbarum* fruit and of warfarin, the lack of more reports of interaction suggests that the incidence may be very low (Yu et al., 2007). In China, patients with loose stool due to insufficiency of the spleen are suggested to use *L. barbarum* with caution. In clinical practice, there have been rare case reports of the following side effects upon taking *L. barbarum*: fever, allergic reactions, spontaneous nosebleed and blood in urine (Ding & Wang, 1994; Shen, Zhang, & Li, 1998; Xing, 1998; Yang, 1985; Zhu, 1985).

An independent lab analysis has shown that atropine has not been detected in *L. barbarum* including GoChi, even though it is in the family of *Solanaceae* (Adams, Wiedenmann, Tittel, & Bauer, 2006). In conclusion, considering all the efficacy and safety information, *L. barbarum* fruit juice may be taken safely without serious adverse effects.

8. Legal status

Marketed primarily as goji berry, *L. barbarum* has achieved widespread popularity in the past decade due to its acceptance by the public as a “super fruit” or “super food” with highly advantageous nutritive properties (Karp, 2009; McLaughlin, 2006; Sohn, 2008). In addition to the continued use of goji in soft drinks and others, this has led its sales to extend out from traditional Chinese communities and from specialized health food stores into the mainstream market in many countries. There is no known toxicity reported on goji in the leading scientific databases such as Medline, TOXNET, or in traditional Asian herbal medicine text books and review articles on *L. barbarum* (Bensky & Gamble, 1993; Chang & But, 2001; Inagaki et al., 1979; Wang, 2006; Wang & Dong, 1990; Zhang, 1988; Zhu, 1998). Under the Dietary Supplement Health and Education Act of 1994, *L. barbarum* can be sold in the USA as an ingredient of the dietary supplement or foods. Recently, Dutch authorities (Dutch Authorities, 2004) and the Food Safety Agent in the UK (UK Food Standard Agency, 2007) classified *L. barbarum*/goji as a food, not as a novel food based upon the long traditional usage without toxicity after their thorough evaluation of all the additional evidence supplied. While none of the individual pieces of information alone appears to provide incontrovertible proof of a substantial history of consumption, the overall picture is sufficient to indicate that *L. barbarum* berries were being consumed to a significant degree in the UK before May 1997, in which case the requirements of the novel foods regulation do not apply (June 2007 Novel Foods, Additives and Supplements Division). Documentary evidence was provided of the supply of more than 25 MT of such extracts during 1996–1997, which were produced from several metric tons of berries imported from Hong Kong to UK. *L. barbarum* fruit is used an ingredient in Ginseng tea. *L. barbarum* fruit were sold in Germany and the Netherlands before 1997. An Asian supermarket in France was one of the first companies in the EU to commercialize *L. barbarum* fruit (under the names *F. lycii* or Gou Qi Zi). An official decree issued in Belgium in August 1997, in which *L. barbarum* fruit appears on a list of herbal products authorized in foodstuffs. A German court decision from October 2002, that *L. barbarum* fruit should be

classified as a foodstuff. Evidence presented in this case showed that an importer had purchased *L. barbarum* fruit from China during 1993–1997 and the berries were distributed mainly via pharmacies. In 2005, *L. barbarum* was removed from an official list of prohibited plants in the Netherlands. Figures for the export of goji berries from China to various EU Member States were also provided. The export data provide useful figures for trade between China/Hong Kong and the UK. Although the quantities imported from China are low in relation to the size of the UK, more significant amounts arrived in the UK from Hong Kong, having been grown in China or perhaps in other Asian countries. Import of the berries does not automatically mean that they were consumed as such, however, since it is known that dietary supplements containing goji berries were being marketed in the EU before 1997, and in the US before 1994.

9. Conclusion

L. barbarum is an interesting herb and food, and has wide variety of biological effects shown in various human clinical, *in vivo* animal and *in vitro* studies. Further studies are needed to clarify detailed mechanisms of these various actions, including synergistic effects and contraindication with other food and medications.

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