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Lycium barbarum (goji) juice improves in vivo antioxidant biomarkers in serum of healthy adults

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Abstract

Although *Lycium barbarum* (goji) and active compounds, *Lycium barbarum* polysaccharides (LBP), have a high in vitro antioxidant score as determined by simple chemical reaction methods, their in vivo antioxidant effects in humans have not been extensively examined. After our earlier report that an LBP-standardized *Lycium barbarum* preparation (GoChi) helps prevent oxidant stress-related conditions in humans, our present study examined the hypothesis that the antioxidant effects of GoChi result from its ability to enhance endogenous antioxidant factors. We investigated the effects of GoChi in a 30-day randomized, double-blind, placebo-controlled clinical study. The study population included 50 Chinese healthy adults aged 55 to 72 years. In vivo antioxidant markers, consisting of serum levels of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and lipid peroxidation (indicated by decreased levels of malondialdehyde, MDA) were examined preintervention and postintervention with GoChi or placebo (120 mL/d). In the GoChi group, antioxidant markers significantly increased by 8.4% for SOD and 9.9% for GSH-Px between the preintervention and postintervention measurements, whereas MDA were significantly decreased by 8.7%. In addition, the SOD, GSH-Px, and MDA levels in the GoChi group were significantly different from those in the placebo group at the postintervention time point, with increases of 8.1% and 9.0% and a decrease of 6.0%, respectively. No significant differences were detected between the preintervention and postintervention time points in the placebo group. These results indicate that GoChi increased antioxidant efficacies in humans by stimulating endogenous factors and suggest that continued use beyond 30 days might help prevent or reduce free radical-related conditions.

Keywords: *Lycium barbarum*; Humans; Reactive oxygen species; Superoxide dismutase; Glutathione peroxidase; Malondialdehyde
Abbreviations: GSH-Px, Glutathione peroxidase; IL-1, interleukin 1; LBP, *Lycium barbarum* polysaccharide; MDA, Malondialdehyde; SOD, Superoxide dismutase..

1. Introduction

Lycium barbarum fruit (goji) has become more popular for the last few years due to its public acceptance as a "super food" with highly advantageous nutritive and antioxidant properties. Although *Lycium barbarum* fruit extracts/fractions and its main active constituents (*Lycium barbarum* polysaccharides, LBP) have been shown to generate high scores in vitro by simple chemical reaction methods [1], their antioxidant effects in humans under normal conditions have not been well evaluated. Although an in vitro assay system can be used to evaluate the effects of complex ingredients with slow and fast-acting

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antioxidants, as well as ingredients with combined effects that cannot be precalculated, the results of such methods do not always mimic actual physiologic effects in vivo [2]. Alternative markers of antioxidant capacity include endogenous changes in glutathione-related enzymes (eg, glutathione peroxidase [GSH-Px]), and superoxide dismutase [SOD] and changes in DNA oxidation, prostaglandin levels, and lipid peroxidation (as indicated by malondialdehyde [MDA] and other markers). Although the physiologic significance of these antioxidant markers in vivo has yet to be fully understood, these markers are widely used as the first step in evaluating the role of in vivo antioxidants in disease-associated conditions. Identification of these markers may be important for reducing risk and preventing or slowing disease processes [2]. *Lycium barbarum* is a solanaceous defoliated shrubbery, and its fruit is a famous traditional medicine in Asian countries. It has been widely used in these countries for medicinal purposes and as a functional food for more than 2500 years [3,4]. The ancient herbalist classics recorded that *Lycium barbarum* nourishes the liver and kidney and brightens the eye. In support of such traditional properties, modern studies indicate that extracts from *Lycium barbarum* possess a range of biologic activities, including antioxidant properties [3,4]. The extracts also exhibit antiaging effects, neuroprotection, promotion of endurance, increased metabolism, improved control of glucose and other diabetic symptoms, antiglaucoma effects, immunomodulation, antitumor activity, and cytoprotection [3,4].

Various chemical constituents are found in *Lycium barbarum* fruit. Its reddish orange color is derived from a group of carotenoids, which make up only 0.03% to 0.5% of the dried fruit [5]. The predominant carotenoid is zeaxanthin, which exists mainly as dipalmitate (also called *physalien* or *physalin*). This carotenoid comprises about one third to one half of the total carotenoids. Various small molecules, such as betaine, cerebroside, β-sitosterol, p-coumaric acid, various vitamins, and minerals, are also present [6]. Among these chemical constituents of *Lycium barbarum* fruit, the most valuable and well-researched components are a group of unique, water-soluble glycoconjugates—collectively termed *Lycium barbarum polysaccharides* (LBP)—that are estimated to comprise 5% to 8% of the dried fruit [7]. *Lycium barbarum* polysaccharides have a molecular weight range of 24 to 241 kDa, and several LBP have been isolated and purified from aqueous *Lycium barbarum* extracts by methods including DEAE ion-exchange cellulose and gel permeation chromatography [8-11]. *Lycium barbarum* polysaccharides have been focused on as the active compounds responsible for the various effects of the *Lycium barbarum*, as mentioned above [3,4]. According to the Chinese understanding of *Lycium* spp extracts and products, the content of LBP is important for the efficacy of *Lycium barbarum*. Many plant and fungal-derived bioactive polysaccharides that possess a broad range of immunomodulatory activities are found in traditional Chinese medicine. Pharmacologically active concentrated polysaccharides are considered to be an indicator of the medicinal status of a natural product [12,13].

In accordance with the growing number of studies on *Lycium barbarum*, our recent randomized, double-blind, placebo-controlled clinical study has shown that daily consumption of GoChi juice, which was made from *Lycium barbarum* fruit and standardized for LBP, for 14 days significantly increased feelings of well-being and improved neurologic/psychologic performance and gastrointestinal function [3]. Because GoChi and LBP have been shown to improve conditions in which oxidant stress may play a role, our hypothesis for the present study is that LBP-standardized *Lycium barbarum* fruit juice may improve these conditions in normal human subjects by influencing endogenous antioxidant factors, such as serum SOD, GSH-Px, and MDA.

2. Methods and materials

2.1. Lycium barbarum and placebo preparation

FreeLife International LLC in Phoenix, Arizona, supplied LBP-standardized *Lycium barbarum* fruit juice (GoChi; lot no. ASA07120), which was produced from fresh ripe *Lycium barbarum* fruit grown in the People's Republic of China. As a finished product, the juice contains 1632 mg/daily serving (120 mL) of LBP. The juice was kept refrigerated at 2°C to 8°C until use. A description of the standardization procedures for this test material was previously published [3].

Placebo control material (lot no. A198) was supplied by FreeLife International LLC. The placebo matched the color, flavor, and taste of GoChi in a formulation of sucralose (10 mg), artificial fruit flavor (30 mg), citric acid (60 mg), and caramel color (12 mg) in 30 mL of purified water. It was packaged in the same type of container; however, it provided no nutritional value or LBP.

2.2. Study population

The recruited subjects were healthy Chinese adults residing in Hunan Province in the People's Republic of China. Subjects were men and women between 55 and 72 years of age. The subjects declared that they had no brain, heart, liver, lung, kidney, or blood diseases; no history of long-term medication; and no prior experience with GoChi intake. Subjects were instructed to discontinue use of any *Lycium barbarum* or *Lycium barbarum*–containing foods throughout the study. Fifty participants were enrolled in the study and randomly assigned to either the GoChi treatment group (n = 25; average age = 57.40 ± 4.79 years) or the placebo control group (n = 25; average age = 58.77 ± 4.81 years). The male-female ratio was 12:13 in the GoChi group and 13:12 in the placebo group. All subjects were fully informed of the purpose of the study and signed the Human

Subjects Informed Consent forms approved by the Internal Review Board of the Hunan Provincial Center for Disease Control and Prevention in The People's Republic of China provided under the Helsinki Declaration. No participants were pregnant during the study. All subjects consumed a typical Chinese diet with an average daily energy intake of about 598 kJ, as determined by use of a 24-hour dietary recall and a questionnaire. The regular diets of the subjects included digestible foods, such as milk, egg, soybean milk, noodles, gruel, vegetables, and fruit (>80% of the daily intake), as well as deep-fried greasy foods (<5% of the daily intake). The original dietary habits of the subjects were not changed during the trial period. All subjects were given a medical examination, and physical measurements (eg, body weight, blood pressure, heart rate) were assessed. In addition, background information, including disease history, was recorded for each participant. Abdominal B-ultrasounds, electrocardiograms, and chest x-ray examinations of these subjects were performed immediately before the trial; the results were all within normal ranges. Mood and sleep parameters were normal for these subjects. There were no dropouts during the trial.

2.3. Trial design

A randomized, double-blind, placebo-controlled trial was used to compare the preintervention and postintervention effects of GoChi on serum antioxidant markers (SOD, GSH-Px, MDA) both within the GoChi group and compared to the placebo group. Subjects were randomly assigned to either the GoChi or placebo group to conduct a balanced trial and ensure intergroup comparability.

Each group consumed 60 mL of the sample twice daily (total, 120 mL/d) for 30 days, along with a meal. The dosage was established based upon the amount that is customarily consumed in traditional Chinese medicine, as previously described [3]. All participants were monitored daily to ensure full compliance with the protocol by checking the returned empty sample bottles. At the end of the 30-day treatment period, subjects were given a medical examination, morphometric data were recorded, and the questionnaire was again completed by each participant. The individuals that administered the physical examination or questionnaire were blinded to the treatment conditions, and the treatment codes were not broken until the study was completed. Randomization information was concealed from the investigators and subjects until the end of the study. At the end of the study, serum analysis was performed on the entire study population.

2.4. Safety indicators

2.4.1. General physical examination

At the beginning of the trial, detailed information was collected regarding the subjects' energy, sleep, diet, urine, stool, and weight. Blood pressure and pulse rate were measured before and after the trial to evaluate changes.

2.4.2. Blood panel

Standard clinical tests were used to assess the red blood cell count, leukocyte count, and classification and hemoglobin content.

2.4.3. Urine panel

The urine panel tests were performed with a Urine Analyzer (Shanghai Precision Instruments Co Ltd., Shanghai, PR China) to measure pH (5.5), leukocyte levels (±/−15 cells/L), and urine glucose levels (millimoles per liter).

2.4.4. Stool panel

Stool was tested by a yellow color indication, and characterization was checked using a strip. As there was no presence of grume, purulence, or helminthes, the stool sample results were normal. Microscopic examination indicated that the stool samples contained no erythrocytes or ovums and showed a few plant cells and muscle fibers.

2.4.5. Abdominal B-ultrasound, electrocardiogram, and chest x-ray examination

These tests were performed one time immediately before the trial.

2.4.6. Blood biochemical indicator tests

Routine analyses of blood included determination of erythrocyte numbers, leukocyte numbers and classification, and hemoglobin content. All tests were performed with a full automatic hemocyte analyzer (Tianjin Yixiangfa Technology Co Ltd., Tianjin, PR China). A standard clinical blood biochemical panel, including serum total protein, albumin, alanine transaminase, aspartate transaminase, cholesterol, triacylglycerols, uric acid, blood urea nitrogen, creatinine level, and blood glucose, was performed.

2.5. Observation indicators

Each observation indicator was tested once before intervention and again after intervention but not on a daily basis throughout the clinical trial.

2.5.1. Efficacy parameters

Analysis of the in vivo antioxidant efficacy parameters was performed both within and between groups. All parameters were tested in accordance with the methods provided by the manufacturer of the test kit at the beginning and end of the experiment. Serum SOD, GSH-Px, and MDA levels were measured individually by enzyme immunoassay using commercially available test kits (Northwest Life-science Specialties LLC, Vancouver, WA). The SOD activity assay (test kit code no. NWK-SOD02) monitors the autooxidation rate of hematoxylin, as was previously described [14], with modifications to increase robustness and reliability [15]. The GSH-Px assay (test kit code no. NWK-GPX01) was adapted from the method of Paglia and Valentine [16,17]. The MDA assay (test kit code no. NWK-MDA01) is based on the reaction of MDA with thiobarbituric acid, which forms an MDA-thiobarbituric acid adduct that absorbs strongly at 532 nm [18]. This method is commonly used to estimate MDA levels in biologic samples [19].

2.6. Statistical analyses

T tests were used to compare self-paired data, with a prerequisite of homogeneity of the variance between the GoChi and placebo groups. Group *t* tests were used to compare mean comparisons. For all other comparisons, *t* tests were performed after homogeneity of variance was achieved through variable conversion. Rank sum tests were used if the variance still lacked homogeneity. The data were processed using Statistica version 8 (StatSoft Inc, Tulsa, OK). Data are expressed as means ± SEM. Differences were considered significant at $P < .05$.

3. Results

3.1. Safety observations

There were no dropouts during this 30-day trial. Every subject successfully continued to consume the trial product throughout the study period. The effects of consumption were evaluated in both groups. After GoChi consumption, no abnormalities were seen in subjects' energy, urine, stools, or other examined physical parameters, as shown in Table 1. Thus, it provides evidence of no ill-consequences.

3.2. Parametric data

All parametric data, such as body weight, were analyzed using *t* tests for independent and dependent groups. There were no significant changes in any of these dependent measures between the preintervention and postintervention time points for either group, and no differences were observed between the groups.

3.3. In vivo antioxidant markers

The effects of GoChi on the serum SOD, GSH-Px, and MDA levels of subjects are shown in Table 2. Before proceeding with the tests, we confirmed that the serum levels of MDA, SOD, and GSH-Px in the GoChi and placebo groups were not significantly different at the preintervention time point ($P > .05$). The results indicated that the 2 groups were equivalent at baseline and therefore suitable for testing and analyses. At the postintervention time point, serum SOD activity was significantly higher in the GoChi group (by 8.10%) relative to the level observed in the placebo group ($P < .01$). Glutathione peroxidase had increased by 9.04% ($P < .01$) in the GoChi group relative to the placebo group. The MDA level had decreased by 5.95% in the GoChi group relative to that in the placebo group ($P < .05$).

Significant changes ($P < .05$) in the SOD, GSH-Px, and MDA levels, by 8.39%, 9.87%, and 8.7%, respectively, were observed in the GoChi group after intervention. In the placebo group, these markers at the postintervention stage had changed by 0.76%, 1.02%, and 0.6%, respectively, relative to the preintervention levels of the placebo group; these differences were not statistically significant.

4. Discussion

Various animal and in vitro cell culture studies have demonstrated the efficacy of *Lycium barbarum* and

Table 1
General effects, safety aspects, and biochemical parameters in the blood of GoChi or placebo subjects at preintervention and postintervention times in our randomized, double-blind, placebo-controlled human trial (30-day intervention trial)

Category	Placebo (n = 25)		GoChi (n = 25)		*P*
	Preintervention	Postintervention	Preintervention	Postintervention	
Body weight (kg)	60.91 ± 1.91	61.02 ± 1.90	61.78 ± 1.95	61.78 ± 1.90	NS
Systolic blood pressure (mm Hg)	118.33 ± 2.56	118.07 ± 2.40	118.63 ± 2.67	118.90 ± 2.38	NS
Diastolic blood pressure (mm Hg)	73.60 ± 1.60	74.07 ± 1.38	74.70 ± 1.61	74.90 ± 1.29	NS
Pulse	73.77 ± 13.24	74.13 ± 1.17	72.77 ± 1.14	73.03 ± 1.09	NS
White blood cell count (10^9/L)	6.36 ± 0.30	6.39 ± 0.38	6.28 ± 0.38	6.45 ± 0.32	NS
Red blood cell count (10^{12}/L)	4.33 ± 0.08	4.35 ± 0.09	4.27 ± 0.09	4.30 ± 0.07	NS
Total protein (g/L)	134.90 ± 2.12	133.07 ± 1.93	133.07 ± 2.43	132.20 ± 1.99	NS
Alanine transaminase (U/L)	23.63 ± 2.10	18.70 ± 1.99	23.60 ± 3.05	18.03 ± 1.95	NS
Aspartate transaminase (U/L)	26.47 ± 1.51	23.40 ± 1.46	25.87 ± 1.28	22.60 ± 0.90	NS
Cholesterol (mmo1/L)	4.99 ± 0.16	4.87 ± 0.17	5.35 ± 0.19	5.26 ± 0.21	NS
Triacylglycerols (mmo1/L)	1.41 ± 0.18	1.40 ± 0.22	1.66 ± 0.21	1.63 ± 0.18	NS
Total protein (g/L)	75.08 ± 1.12	70.65 ± 0.72	74.80 ± 0.93	69.56 ± 0.82	NS
Albumin (g/L)	46.70 ± 0.65	44.40 ± 0.49	46.14 ± 0.43	44.17 ± 0.49	NS
Blood urea nitrogen (mmo1/L)	4.55 ± 0.22	4.62 ± 0.24	5.00 ± 0.23	4.93 ± 0.23	NS
Creatinine (mmo1/L)	75.07 ± 2.95	68.07 ± 3.90	77.57 ± 15.69	67.00 ± 4.18	NS
Uric acid (mmo1/L)	257.37 ± 13.14	255.30 ± 10.61	245.23 ± 56.70	241.93 ± 13.54	NS
Blood glucose (mmo1/L)	4.98 ± 0.10	5.02 ± 012	5.12 ± 0.41	4.95 ± 0.09	NS
Urine	Normal	Normal	Normal	Normal	NS
Stool	Normal	Normal	Normal	Normal	NS

Values are expressed as means ± SEM. *T* tests revealed no statistical differences after homogeneity of variance was achieved through variable conversion. Rank sum tests were used if the variance still lacked homogeneity. NS indicates not significant.

Table 2
In vivo antioxidant effects of GoChi in human serum as indicated by SOD, GSH-Px, and MDA levels obtained in our randomized, double-blind, placebo-controlled clinical study (30-day intervention trial)

	Placebo (n = 25)		GoChi (n = 25)	
	Preintervention	Postintervention	Preintervention	Postintervention
SOD (U/mL)	129.96 ± 2.55	130.95 ± 2.38	130.6 ± 2.34	141.56 ± 3.32[a,b]
GSH-Px (activity unit)	105.38 ± 4.00	106.45 ± 2.07	105.65 ± 2.29	116.08 ± 2.71[a,b]
MDA (nmol/mL)	3.72 ± 0.14	3.70 ± 0.12	3.81 ± 0.13	3.48 ± 0.14[c]

Serum SOD, GSH-Px, and MDA levels were measured individually in enzyme immunoassay by commercially available test kits (Northwest Lifescience Specialties LLC, Vancouver, WA). Values are expressed as means ± SEM. *T* tests were used for self-paired data. Group *t* tests were used for mean comparisons, with homogeneity of variance between the GoChi group and placebo group as a prerequisite. Otherwise, *t* tests were performed after homogeneity of variance was achieved through variable conversion. Rank-sum tests were used if the variance still lacked homogeneity. Differences were considered significant at $P < .05$.

[a] Significant difference compared to preintervention ($P < .01$).

[b] Significant difference compared to placebo ($P < .01$).

[c] Significant difference compared to preintervention ($P < .05$).

identified LBP as the major active antioxidants that protect against various peroxidation-related conditions, including lipid peroxidation [20-30]. In the present randomized, double-blind, placebo-controlled trial, the ability of the LBP-standardized GoChi to significantly increase endogenous antioxidant capacities in healthy elderly human subjects in vivo was indicated by changes in multiple major endogenous antioxidant markers (GSH-Px, SOD, and MDA). Because these markers typically respond in parallel to oxidative stress and antioxidants [22,30-31], we measured a representative subset of oxidative markers. Additional markers, such as the comet assay, measure of oxidation products in urine, and DNA adduct analyses should be investigated in future studies.

Individual polysaccharides isolated from *Lycium barbarum* (LBP) [9,30] have shown various effects including antioxidant activities. In vitro studies show that LBP significantly inhibited mitochondrial lipid peroxidation, which was measured as MDA in a dose-dependent manner [27]. LBP have been also reported to increase the destruction of free radicals [26]. The results of the other study indicated that LBP protect the structure of the murine seminiferous epithelium [29]. A study on testicular degeneration in vitro showed that, although oxygen radicals significantly damaged the shape of the murine seminiferous epithelium, the addition of LBP prevented this damage [29]. Thus, one of the mechanisms of action of LBP may be direct protection of membranes from oxygen radical damage. The structure of the LBP molecules may be necessary for their antioxidant effects. The glycoconjugates (LbGp) inhibited low-density lipoprotein peroxidation, whereas the glycans showed no effects on low-density lipoprotein peroxidation [9,30].

Lycium barbarum polysaccharides may exert their effects in other ways, such as acting as bioactive fibers or prebiotics, by contributing to the synthesis and release of antioxidants by probiotic bacteria and inhibiting inflammation [32]. Thus, the gastrointestinal effects of LBP may lead to antioxidant actions within the gastrointestinal tract before absorption of the LBP or its degraded compounds. Absorption of LBP and the active constituents of GoChi in the gut are important to GoChi's effects in vivo. Various in vivo animal studies have demonstrated the antioxidant efficacy of *Lycium barbarum* and identified LBP as being responsible, at least partially, for the antioxidant effect [22-25,28]. An unpublished observation from a rat in vivo study indicated that the interleukin 1 (IL-1) level was significantly increased in the plasma and only slightly increased, to an insignificant degree, in the spleen by the administration of GoChi [33]. This observation suggests that the GoChi may stimulate basal IL-1 production in a region other than the spleen, such as the gut. GoChi consumption was also found in the same unpublished study to significantly increase both plasma and splenic IL-6 level [33]. That splenic IL-6 levels respond to GoChi consumption suggests that a component of GoChi is absorbed via the gut. GoChi or some of its constituents would need to reach the spleen via the splenic artery to increase cytokine production [33]. The bioavailability and kinetic behavior of LBP are important for understanding its in vivo bioactivity. However, these behaviors have not been characterized due to their complex nature and a lack of validated methods of the measurement of LBP in biologic specimens. For this reason, we did not measure blood levels of LBP in the present study and plan to address this deficiency in the future.

Our earlier clinical studies showed that GoChi significantly increased feelings of well-being and improved neurologic/psychologic performance, including improvement of the quality of sleep, and gastrointestinal function [3]. In that study, we did not evaluate antioxidant markers. The antioxidant effects of GoChi found in the present study may be associated with mechanisms that underline the physiologic effects of GoChi, as reported in our previous study; with regard to sleep quality, for example, alterations in the metabolism of reactive oxygen species result in prolonged sleep deprivation [34]. Other observed improvements after consumption of GoChi may result from its antioxidant effects. We suggest that these antioxidant

actions of GoChi are at least partially responsible for its clinical benefits.

Because free radical oxidation plays a role in the development of various diseases [2], GoChi may be useful in preventing or reducing the development, severity or symptoms of these conditions. As elderly people demonstrate age-associated decreases in GSH-Px and SOD levels [35], GoChi may have antiaging effects that are consistent with the traditionally recognized effects of *Lycium barbarum*. As most antioxidant studies of other food materials and supplements have been conducted under disease [36-38] or deficiency [39] conditions, it is meaningful that GoChi intake produced a nearly 10% increase in serum antioxidant capacities in human subjects under normal conditions. However, due to the following limitations in our current study, further investigation is necessary. First, the major endogenous antioxidant markers (GSH-Px, SOD, and MDA) that we have studied may not be sufficient to fully support our hypothesis. This is, however, the first in vivo study of the antioxidant effects of GoChi in humans, and, as such, it provides preliminary findings. Additional in vivo antioxidant markers, such as the comet assay, measures of oxidation products in urine, and DNA adduct analyses will be evaluated in future studies. Second, the bioavailability of individual active compounds derived from LBP and its related bioactivities are not known. Third, the mechanism of actions of GoChi has not yet been fully elucidated. Fourth, the current study was a 30-day intervention study. Continued long-term (beyond 30 days) consumption of GoChi is necessary to determine whether it results in a continued increase in endogenous antioxidant markers or an asymptotic approach to a plateau. Fifth, the relationship between our clinically significant observation of changes in endogenous antioxidant capacity and disease prevention or treatment, antiaging, or other benefits was not investigated in the current study. These relationships will be investigated in future studies.

In conclusion, because free radicals are implicated in many diseases and age-related conditions, the antioxidant-dependent actions of *Lycium barbarum* may have a wide range of beneficial effects. The LBP-standardized *Lycium barbarum* fruit juice GoChi may support health by increasing endogenous factors, such as SOD and GSH-Px, reducing the MDA level and protecting membranes from oxygen radical-mediated damage.

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