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ORIGINAL ARTICLE

Goji Berry Effects on Macular Characteristics and Plasma Antioxidant Levels

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ABSTRACT

Purpose. Goji berry (*Lycium barbarum* L.) is purported to benefit vision because of its high antioxidant (especially zeaxanthin) content, although this effect has not been demonstrated in high-quality human studies. The purpose of this study was to evaluate the effects of daily supplementation with a proprietary milk-based formulation of goji berry, Lacto-Wolfberry (LWB), on macular characteristics and plasma zeaxanthin and antioxidant capacity levels in elderly subjects.

Methods. This was a double-masked, randomized, placebo-controlled trial in healthy elderly subjects (range, 65 to 70 years) receiving 13.7 g/d of LWB (n = 75) or placebo (n = 75) for 90 days. Subjects underwent direct ophthalmic examination to assess pigmentation and soft drusen count in the macula and a blood draw to measure plasma zeaxanthin level and total antioxidant capacity.

Results. The placebo group demonstrated hypopigmentation and soft drusen accumulation in the macula, whereas the LWB group remained stable. Both plasma zeaxanthin level and antioxidant capacity increased significantly in the LWB group, by 26% and 57%, respectively, but did not change in the placebo group. No product-related adverse events were reported in either group.

Conclusions. Overall, daily dietary supplementation with goji berry for 90 days increases plasma zeaxanthin and antioxidant levels as well as protects from hypopigmentation and soft drusen accumulation in the macula of elderly subjects. However, the mechanism of action is unclear, given the lack of relationship between change in plasma zeaxanthin and change in macular characteristics.

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Key Words: age-related macular degeneration, antioxidant, elderly, goji berry, *Lycium barbarum*, zeaxanthin

Age-related macular degeneration (AMD) is a primary cause of vision loss in the elderly, negatively impacts quality of life, and raises the risk of clinical depression, falls, hip fractures, and placement in nursing homes.[1–3] The prevalence of AMD ranges from 1.5% in people older than 40 years to >15% in women older than 80 years.[4,5] The number of AMD diagnoses is expected to almost double by 2020.[4] Unfortunately, there is no cure for AMD and current treatment options have limited effectiveness and introduce significant patient risk.[6,7] Therefore, AMD prevention strategies should be identified and implemented. A number of AMD risk factors have been determined including older age, AMD family history, cigarette smoking, white race, and low dietary intake of antioxidants in the form of fruits and vegetables.[8] Given that cigarette smoking and low antioxidant intake are the only modifiable risk factors, increasing antioxidant intake may arguably be the most easily used AMD prevention strategy.

Goji berry (*Lycium barbarum* L.), well known as a traditional Chinese medicine, is a small red fruit that is widely consumed in China and by Chinese abroad[9] because of its benefits on vision as well as kidney and liver function.[10,11] Goji berry is the richest natural source of the antioxidant carotenoid, zeaxanthin, which composes the preretinal pigment. Zeaxanthin intake increases plasma zeaxanthin concentrations, which subsequently increases preretinal pigment concentration, i.e., lutein and zeaxanthin, and ultimately lowers AMD risk.[12,13] Therefore, regular consumption of goji berry may play a role in the prevention of AMD and help to maintain preretinal pigment density.[14]

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Although Chinese consumers believe in the benefits of goji berry on eyesight, very few human studies on the effects of goji berry supplementation on visual parameters have been reported. A 15-day regimen of goji berry juice supplementation had no effect on visual acuity in healthy young adults.[15] Although general endogenous antioxidant markers increased with 30 days of goji berry juice supplementation,[16] no measures of plasma antioxidant activity were performed. A possible confounding factor in these trials is zeaxanthin bioavailability. Several human studies have investigated the bioavailability of zeaxanthin from goji berry fruit,[17–19] and the milk-based goji berry formulation tested by Benzie et al.[17] had three times better bioavailability than a goji berry preparation made with traditional hot water extraction.

The objective of this prospective, double-masked, randomized, placebo-controlled study was to evaluate the effect of 90-day supplementation with a proprietary milk-based goji berry formulation, Lacto-Wolfberry (LWB), on clinical risk factors for AMD in healthy elderly subjects. We hypothesized that subjects who consumed LWB would show reduced macula hypopigmentation and accumulation of soft drusen as well as significant improvements in plasma zeaxanthin and antioxidant activity levels vs. placebo.

METHODS

This single-center, double-masked, randomized, placebo-controlled trial was conducted at XuShe Community Day Care Center for Elderly Persons (Yi Xing, Zhejiang Province, China). All research procedures performed in this trial were in strict accordance with the guidelines outlined in the Declaration of Helsinki and in a predefined protocol that was approved by all researchers and the local ethics committee.

Subjects

Healthy volunteers aged 65 to 70 years were recruited between November and December 2007. Inclusion criteria included ability to understand the study procedures, ability to comply with study requirements including follow-up, and informed consent provided after receiving verbal and written information about the study. Key exclusion criteria included terminal disease, significant chronic disease (e.g., respiratory, cardiovascular, metabolic, organ failure), deteriorating health status at time of enrollment in the study (e.g., unstable blood pressure, uncontrolled diabetes, or major cardiovascular and/or neurological event in the past 6 months), presence of glaucoma or cataract, lactose intolerance, or participation in any clinical trial within the 3 months prestudy or in a trial of *L. barbarum* supplement at any time in the past.

Interventions

During the 90-day study period, each subject consumed 13.7 g of study product (LWB or placebo) per day in the form of freeze-dried powder mixed with 200 ml of soup or hot water at lunch under supervision of the research staff. The active product, LWB, was a milk-based goji berry formulation (Nestlé R&D Centre Shanghai, Shanghai, China) produced by a proprietary process using goji berry fruit (530 mg/g), skim milk (290 mg/g), and maltodextrin (180 mg/g). Placebo was produced using skim milk (290 mg/g), maltodextrin (200 mg/g), sucrose (476 mg/g), and colorants (yellow, caramel) (34 mg/g). The LWB product contained 0.73 mg/g (10 mg/d) goji berry-derived zeaxanthin and 5 mg/g (68.5 mg/d) goji berry-derived vitamin C precursor. To obtain a placebo with similar sensory properties as LWB, the ingredients were dry mixed, dissolved in water, and then freeze dried and milled to a fine powder. Masked study products were supplied to the study site by Nestlé and were stored at the study site in a dry environment under controlled temperature. The study products were provided in single-serving sachets labeled with the subject ID number and instructions for product preparation; each product provided 24 kcal per 100 ml when prepared as directed.

Subjects underwent detailed ophthalmic examinations before and after the 90-day supplementation period by a single experienced ophthalmologist (ZG). Direct ophthalmic evaluation was used to rule out presence of glaucoma, cataracts, and eye injury. Soft drusen were identified in the area of the central fovea of the macula. Assessments for macula pigmentation were conducted with the funduscope focused on the central fovea and the posterior pole was visually segmented into quadrants for evaluation. Pharmacological pupil dilation was occasionally performed (LWB, 13.3%; placebo, 16.0%).

After an overnight fast, blood samples (20 ml) were drawn and collected in serum-separating tubes with (antioxidant capacity) or without (zeaxanthin) heparin. The tubes were centrifuged at 1200g for 15 min at 4°C. All samples were stored at −20°C and analyses were performed within 2 days of sampling. Plasma zeaxanthin was assessed by high-performance liquid chromatography (LC-20A, Shimadzu, Duisburg, Germany). Total antioxidant capacity measurements were made to assess the cumulative effect of all antioxidants present in the plasma including enzymes (superoxide dismutase, catalase, and glutathione peroxidase), macromolecules (albumin, ceruloplasmin, and ferritin), and a number of small molecules (ascorbic acid, α-tocopherol, β-carotene, reduced glutathione, uric acid, and bilirubin). Total plasma antioxidant capacity was measured by estimating the ability of antioxidants to prevent oxidation of 2,2′-Azino-di-[3-ethylbenzthiazoline sulfonate] using an antioxidant assay kit (Cayman Chemical Company, Ann Arbor, MI).

Outcomes

Study endpoints included number of soft macular drusen, macula hypopigmentation, plasma zeaxanthin and antioxidant activity levels, and adverse events.

Randomization

Eligible subjects were randomized in a 1:1 ratio to LWB or placebo treatment. Randomization was stratified by gender and age (65 to 67.5 years, 67.6 to 70 years). A computer program was used to create four permuted block randomization lists, stratified by age and gender and with a block size of six, which assigned a unique study ID number and a treatment group to each subject. The unique subject ID number was printed on each set of subject-specific study product sachets, with the contents of the sachets as specified on the randomization lists. The study site received the lists of subject ID numbers without the treatment assignments and was instructed to enroll subjects in numerical order from the appropriate list according to the two stratification factors.

Masking

This study was double masked. Subjects were masked to the treatment received and the two study products were identical in shape, size, taste, smell, color, and packaging. All investigators, study coordinators, other site personnel, clinical monitors, data managers, and biostatisticians remained masked to treatment allocation throughout the clinical study until all statistical analyses had been completed. This method provides the most effective and stringent means of minimizing study bias.

Statistical Analysis

All data were recorded on case report forms, double-entered, verified, and independently monitored for accuracy by Sprim Advanced Life Sciences (San Francisco, CA). Continuous variables were summarized as means or medians with appropriate measures of dispersion; categorical variables were summarized as frequencies and percentages. Baseline characteristics of the two study groups were compared descriptively and evaluated using independent-sample t-tests or χ^2 tests. Study outcomes were evaluated with χ^2 and McNemar test for categorical variables. Statistical analyses were performed using SAS (Cary, NC), S-Plus (Palo Alto, CA), GraphPad (La Jolla, CA), and LogXact software (Cambridge, MA).

RESULTS

Subject Compliance

Subject flow in each treatment group is displayed in Fig. 1. Ten (13.3%) subjects in the LWB group and seven (9.3%) in the placebo group discontinued early for reasons unrelated to the study or the study product.

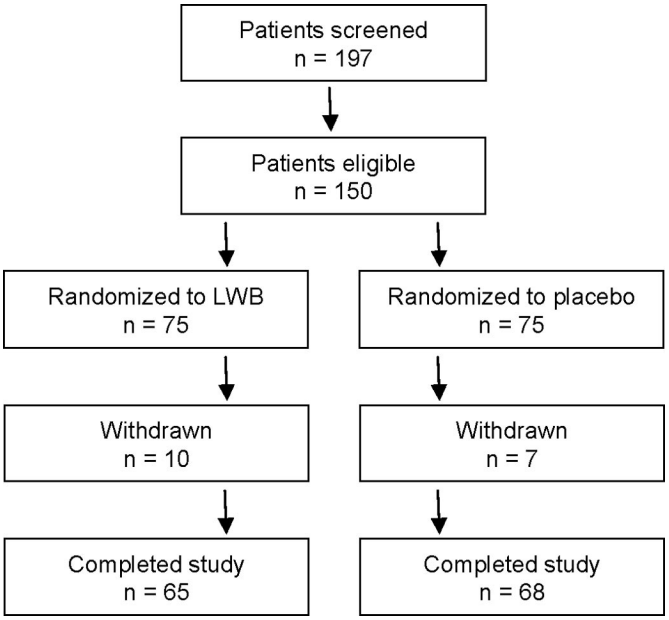

FIGURE 1.
Subject flow diagram.

TABLE 1.
Baseline subject characteristics

Variable	LWB (n = 75)	Placebo (n = 75)	p
Female gender	45 (60.0)	47 (62.7)	0.74
Age (yr)	67 ± 2	66 ± 2	0.31
Height (cm)	166 ± 8	166 ± 8	0.91
Weight (kg)	63 ± 5	62 ± 7	0.29
Body mass index (kg/m^2)	23 ± 2	23 ± 2	0.78
Systolic BP (mm Hg)	134 ± 15	131 ± 12	0.29
Diastolic BP (mm Hg)	77 ± 4	77 ± 3	0.51
Hypertension	4 (5.3)	1 (1.3)	0.17
AMD family history	19 (25.3)	19 (25.3)	1.0
Current smoker	24 (32.0)	24 (32.0)	1.0
Soft macular drusen per eye			0.47
None	56 (74.7)	52 (69.3)	
One	19 (25.3)	23 (30.7)	
Two or more	0	1 (1.3)	
Macula hypopigmentation			0.13
None	53 (70.7)	61 (81.3)	
Single quadrant	22 (29.3)	14 (18.7)	

Values are represented as mean ± SD or n (%).
BP, blood pressure.

TABLE 2.
Macular hypopigmentation by study day and treatment group

	LWB		Placebo	
Macular hypopigmentation	Day 0 (n = 75)	Day 90[a] (n = 65)	Day 0 (n = 75)	Day 90 (n = 68)
No	53 (70.7)	44 (67.7)	61 (81.3)	49 (72.1)
1 quadrant	22 (29.3)	21 (32.3)	14 (18.7)	12 (17.6)
2 quadrants	0	0	0	7 (10.3)
3 quadrants	0	0	0	0

Values are represented as n (%).
[a]$p < 0.01$, LWB vs. placebo at day 90.

Baseline Subject Characteristics

Baseline subject characteristics were similar between the two groups (Table 1).

Macula Pigmentation

No macula pigmentation changes were observed in the LWB group during the 90-day supplementation period, whereas 13 subjects in the placebo group showed progression of macula hypopigmentation ($p < 0.001$). At the 90-day follow-up visit, LWB subjects showed significantly less macula hypopigmentation vs. placebo ($p < 0.01$; Table 2).

Soft Macular Drusen Count

All study subjects had zero or one soft drusen at the baseline examination. At the 90-day follow-up visit, eight subjects in the placebo group and no subject in the LWB group had two to five

TABLE 3.
Soft macular drusen count by study day and treatment group

Soft macular drusen count	LWB		Placebo	
	Day 0 (n = 75)	Day 90[a] (n = 65)	Day 0 (n = 75)	Day 90 (n = 68)
0	56 (74.7)	48 (73.8)	52 (69.3)	43 (63.2)
1	19 (25.3)	17 (26.2)	23 (30.7)	17 (25.0)
2–5	0	0	0	8 (11.8)

Values are represented as n (%).
[a]p = 0.02, LWB vs. placebo at day 90.

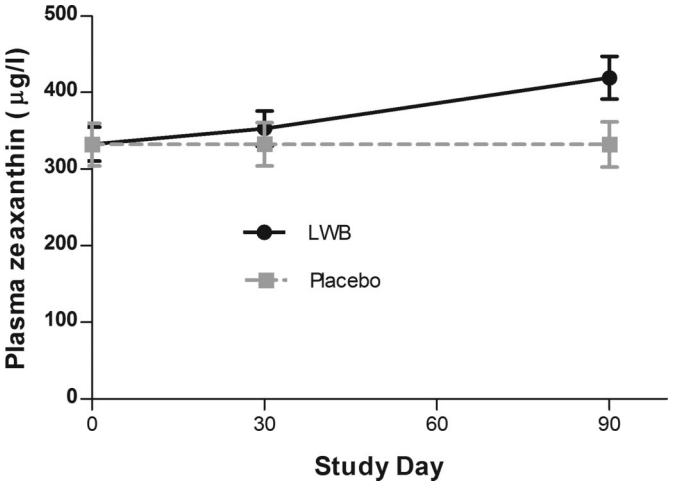

FIGURE 2.
Plasma zeaxanthin by study day and treatment group. Values are mean ± 95% confidence interval. LWB vs. placebo, $p < 0.01$ on day 90.

soft drusen; this difference was statistically significant ($p = 0.02$). Subjects in the LWB group had no change in soft drusen count during the study period whereas 11 subjects in the placebo group showed a significant increase ($p = 0.004$). At the 90-day follow-up visit, LWB subjects showed fewer soft drusen vs. placebo ($p = 0.02$; Table 3).

Plasma Zeaxanthin Levels

Plasma zeaxanthin levels were stable over time for the placebo group but increased 26% ($p < 0.01$) with LWB. The change in zeaxanthin levels was significantly greater in LWB vs. placebo ($p < 0.01$; Fig. 2). No significant relationship was observed between change in plasma zeaxanthin and change in macular characteristics during the 90-day supplementation period.

Plasma Antioxidant Capacity

Antioxidant capacity levels were stable over time for the placebo group but increased 57% ($p < 0.01$) with LWB. Antioxidant capacity levels were significantly greater in LWB vs. placebo on days 30 and 90 ($p < 0.01$; Fig. 3).

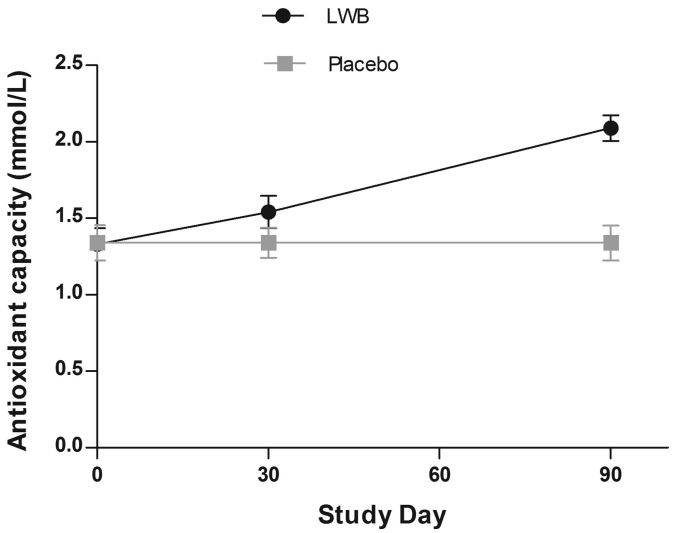

FIGURE 3.
Antioxidant level by study day and treatment group. Values are mean ± 95% confidence interval. LWB vs. placebo, $p < 0.01$ on study day 30 and day 90.

Adverse Events

No adverse events were reported in the placebo group. One adverse event, vomiting and fever of 6-day duration, was reported in the LWB group. This adverse event was classified as mild by the principal investigator (LS) and unrelated to the study product.

DISCUSSION

The results of this clinical study demonstrated that daily dietary LWB supplementation increases plasma zeaxanthin and total antioxidant levels as well as protects against macula hypopigmentation and accumulation of soft drusen in elderly subjects. Strengths of this clinical trial included the double-masked, randomized, placebo-controlled design, stringent data management procedures, and a long supplementation duration in comparison with similar trials examining goji berry's effects in humans.

There is a clear relationship of macula hypopigmentation and soft drusen number with AMD risk.[20] Oxidative stress may play a role in AMD development by targeting the junctional proteins vital to retinal pigment epithelium integrity.[21] A possible mechanism of action of LWB on these parameters is the transfer of zeaxanthin and other antioxidants from the plasma to the retinal pigment epithelium. High macular zeaxanthin levels are suggested to lower AMD risk.[17] Interestingly, blood zeaxanthin levels rose 26% in the LWB group, in striking contrast to another human study in which blood zeaxanthin levels showed a three-fold increase after 28 days treatment with 15 g/d of goji berry supplementation[19]; however, the effective amount of goji berry-derived zeaxanthin in the LWB used in this study was only about 10 mg/d. Another reason for the smaller increase in blood zeaxanthin level could be related to age-related declines in nutrient absorption and bioavailability; the mean age of subjects was 28 years for the study conducted by Cheng et al.[22] vs. 67 years in this study. Of note, the effective amount of goji berry in the LWB (about 7 grams per day) is far less than what Chinese doctors prescribe in traditional Chinese medicine-related formulas with goji berry (typically a dose of 9 to 15 g, 2 to 3 times daily).

Interestingly, the mean increase in blood antioxidant capacity levels was much greater than that of blood zeaxanthin levels in the LWB group (57 vs. 26%, respectively) whereas the means of both parameters remained stable in the placebo group. One possible reason is that LWB contains significant amounts of other antioxidants, in particular a heat-stable vitamin C precursor unique only to the goji berry.[23] In fact, the daily dose of LWB added the equivalent of about 40 mg of ascorbic acid to the daily diet of the LWB group. Although the stable vitamin C precursor has been shown to be metabolized to ascorbic acid in rats,[23] it remains unknown how much of the precursor is converted to ascorbic acid in humans. Nevertheless, LWB has been shown to stimulate antioxidant activity. In vitro studies demonstrated that LWB can directly scavenge hydroxyl and superoxide radicals, two of the most important biological free radicals. Furthermore, the hydroxyl radical-scavenging ability of LWB is similar to that of mannitol and its superoxide radical scavenging ability is of the same order of magnitude as that of superoxide dismutase. LWB also inhibited $FeCl_2$/ascorbic acid-induced dysfunction in brain tissue and mitochondria, indicating that it may be effective in preventing brain oxidative mitochondrial damage and cognitive dysfunction.[24] However, no trials have assessed the potential antioxidant ability of LWB in the retina.

A limitation of this study included a subject pool of only healthy Chinese subjects within a narrow age range. Also, we did not directly assess the optical density of the preretinal pigment. Furthermore, no significant relationship was observed between change in plasma zeaxanthin and change in macular characteristics. Therefore, the notion that increases in plasma zeaxanthin directly affected the macula is speculative.

CONCLUSIONS

Daily dietary supplementation with LWB, a goji berry formulation, for 90 days increases plasma zeaxanthin and total antioxidant levels as well as protects from hypopigmentation and accumulation of soft drusen in the macula of elderly subjects. However, the mechanism of action is unclear given the lack of relationship between change in plasma zeaxanthin and change in macular characteristics.

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