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Safety of an Astaxanthin-Rich *Haematococcus pluvialis* Algal Extract: A Randomized Clinical Trial

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ABSTRACT

A growing body of scientific literature indicates that astaxanthin is a more powerful antioxidant than other carotenoids and vitamin E and may confer numerous health benefits. The purpose of this investigation was to conduct a human safety study with a *Haematococcus pluvialis* algal extract with high levels of astaxanthin. Thirty-five healthy adults age 35–69 years were enrolled in a randomized, double-blind, placebo-controlled trial of 8 weeks' duration. All participants took three gelcaps per day, one at each meal. Nineteen participants received gelcaps with an algal extract in safflower oil, containing 2 mg of astaxanthin each (treatment); 16 participants received gelcaps containing safflower oil only (placebo). Blood pressure and blood chemistry tests, including a comprehensive metabolic panel and cell blood count, were conducted at the beginning of the trial and after 4 and 8 weeks of supplementation. No significant differences were detected between the treatment and the placebo groups after 8 weeks of supplementation with the algal extract in the parameters analyzed, except for serum calcium, total protein, and eosinophils ($P < .01$). Although the differences in these three parameters were statistically significant, they were very small and are of no clinical importance. These results reveal that 6 mg of astaxanthin per day from a *H. pluvialis* algal extract can be safely consumed by healthy adults.

INTRODUCTION

ASTAXANTHIN IS A CAROTENOID that is common in the marine environment and is found in highest concentrations in *Haematococcus pluvialis* (10,000–40,000 mg/kg) and in the flesh of various salmon species (1–58 mg/kg).¹ A number of animal and cell culture studies have reported that astaxanthin shows antioxidant activity that is 10 times greater than that of other carotenoids such as zeaxanthin, lutein, canthaxanthin, and β -carotene² and 500 times greater than that of vitamin E.^{3,4}

Animal and cell culture studies have also indicated that astaxanthin can be protective

against several kinds of oxidative damage and may have beneficial health effects. These include protection from ultraviolet light-induced skin damage and certain cancers, amelioration of age-related macular degeneration, increased high-density lipoproteins (HDL) and decreased low-density lipoproteins (LDL), and enhancement of the immune system.^{5–12}

The consumption of *H. pluvialis* has never been associated with any toxicity in the reported literature. In addition, a number of animal studies have revealed no adverse effects of ingesting doses ranging from 5 to 18 g/kg/day.¹³ In the United States, *H. pluvialis* was reviewed and cleared for marketing by the

Food and Drug Administration (FDA) in August 1999 as a new dietary ingredient by means of the DSHEA (21 CFR Part 190.6). However, no human safety study has yet been conducted. We tested the safety of an *H. pluvialis* algal extract containing astaxanthin on healthy adults, at a dose of 6 mg astaxanthin per day.

MATERIALS AND METHODS

Participants

Forty-four healthy men and women (age 35–69 years) were initially recruited in the San Francisco Bay Area through local advertisements. The study protocol was approved by an independent investigational review committee and was explained to each subject, who then signed an informed consent. Of the 44 participants enrolled, 35 completed the study, and 9 left the study for reasons unrelated to the product.

Study design

The participants were randomly divided into two equal groups, and both the subjects and the principal investigator were blinded to which group received the algal extract and which received the placebo. All participants took three gelcaps per day, one with each meal, for 8 weeks. After 9 participants left the study, 19 received the algal extract and 16 received the placebo. The composition of the gelcaps with the algal extract was as follows: 460 mg high-oleic safflower oil; 40 mg *H. pluvialis* algal extract, containing a minimum of 2 mg astaxanthin and 35 μ g lutein; and approximately 0.4 mg rosemary oil to enhance stability (500 mg total contents). The placebo gelcap contained 500 mg high-oleic safflower oil. The gelcaps were manufactured in such a manner that it was not obvious to either the investigator or the subjects which contained the algal extract and which contained the placebo.

Blood samples were obtained at the beginning of the trial and after 4 and 8 weeks of treatment. Blood pressure and blood chemistry tests, including a comprehensive metabolic panel and blood cell count, were performed with standard clinical laboratory methods. Blood pressure was measured three times, at week 0, 4, and 8, and the results were averaged.

Statistical analysis

Data were analyzed by the two-tailed paired *t* test at the $P < .05$ level of significance. All results are reported as mean \pm SD. The main comparisons were made between the treatment and the placebo groups at the beginning of the trial and after 8 weeks of treatment.

RESULTS

The baseline characteristics of the participants are presented in Table 1. Subjects in the treatment group did not significantly differ from those in the placebo group in age, weight, or height.

The results of the blood chemistry and blood pressure analyses are shown in Table 2 (metabolic panel), Table 3 (blood cell count), and Table 4 (blood pressure). No significant differences were detected between the treatment and the placebo groups in blood pressure, metabolic markers, or blood cell count at the beginning of the trial ($P < .05$). After 8 weeks of supplementation with the algal extract, there were no significant differences between the two groups, except for serum calcium, total serum protein, and eosinophils ($P < .01$). These differences, however, were very small and represented a 0.3 mmol/L difference in serum calcium, a 3 g/L difference in total serum protein, and a 0.01 difference in eosinophils. Although statistically significant, they carry little or no clinical importance.

TABLE 1. BASELINE CHARACTERISTICS OF THE SUBJECTS (MEAN \pm SD)

Characteristic	Treatment group (n = 19)	Placebo group (n = 16)
Age (yr)	58 \pm 9	55 \pm 8
Weight (kg)	79 \pm 14	77 \pm 16
Height (cm)	172 \pm 10	170 \pm 9

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TABLE 2. BLOOD CELL COUNT AT 0, 4, AND 8 WEEKS (MEAN \pm SD)

Parameter	Treatment group (n = 19)	Placebo group (n = 16)
White blood cells (WBC) ($n \times 10^{12}/L$)		
0 weeks	6.0 \pm 1.6	5.9 \pm 1.2
4 weeks	6.1 \pm 1.4	5.8 \pm 1.0
8 weeks	6.2 \pm 1.5	6.1 \pm 1.0
Red blood cells (RBC) ($n \times 10^{12}/L$)		
0 weeks	4.9 \pm 0.5	5.0 \pm 0.0
4 weeks	4.7 \pm 0.9	5.0 \pm 3.0
8 weeks	5.0 \pm 0.5	8.0 \pm 11.0
Hemoglobin (Hb) (nmol/L)		
0 weeks	2.26 \pm 0.23	3.08 \pm 3.02
4 weeks	2.29 \pm 0.22	2.45 \pm 0.60
8 weeks	2.26 \pm 0.20	2.45 \pm 0.7
Hematocrit (HCT)		
0 weeks	0.45 \pm 0.04	0.56 \pm 0.40
4 weeks	0.44 \pm 0.04	0.45 \pm 0.03
8 weeks	0.45 \pm 0.04	0.45 \pm 0.03
Mean corpuscular value (MCV) (fL)		
0 weeks	93 \pm 6	94 \pm 3
4 weeks	91 \pm 6	93 \pm 3
8 weeks	91 \pm 6	92 \pm 3
Mean corpuscular hemoglobin (MCHC) (pg)		
0 weeks	29.8 \pm 2.4	30.4 \pm 1.3
4 weeks	30.7 \pm 2.6	30.8 \pm 1.2
8 weeks	29.6 \pm 1.9	30.0 \pm 1.3
Mean corpuscular hemoglobin concentration (MCHC)		
0 weeks	0.32 \pm 0.01	0.32 \pm 0.01
4 weeks	0.34 \pm 0.01	0.33 \pm 0.01
8 weeks	0.32 \pm 0.01	0.33 \pm 0.01
Platelets ($n \times 10^9/L$)		
0 weeks	272 \pm 60	248 \pm 48
4 weeks	257 \pm 49	240 \pm 35
8 weeks	265 \pm 59	235 \pm 32
Neutrophils		
0 weeks	0.53 \pm 0.07	0.54 \pm 0.10
4 weeks	0.55 \pm 0.06	0.55 \pm 0.09
8 weeks	0.55 \pm 0.06	0.55 \pm 0.09
Absolute neutrophils ($n \times 10^{12}/L$)		
0 weeks	3.2 \pm 1.0	3.3 \pm 1.3
4 weeks	3.4 \pm 1.0	3.2 \pm 0.9
8 weeks	3.4 \pm 1.0	3.4 \pm 1.0
Lymphocytes		
0 weeks	0.36 \pm 0.06	0.35 \pm 0.09
4 weeks	0.34 \pm 0.04	0.33 \pm 0.09
8 weeks	0.34 \pm 0.05	0.34 \pm 0.08
Absolute lymphocytes ($n \times 10^{12}/L$)		
0 weeks	2.1 \pm 0.7	2.0 \pm 0.5
4 weeks	2.1 \pm 0.5	1.9 \pm 0.5
8 weeks	2.1 \pm 0.5	2.0 \pm 0.4
Monocytes		
0 weeks	0.08 \pm 0.02	0.08 \pm 0.02
4 weeks	0.08 \pm 0.02	0.08 \pm 0.02
8 weeks	0.08 \pm 0.02	0.08 \pm 0.02
Absolute monocytes ($n \times 10^{12}/L$)		
0 weeks	0.5 \pm 0.1	0.5 \pm 0.1
4 weeks	0.5 \pm 0.1	0.5 \pm 0.1
8 weeks	0.5 \pm 0.2	0.5 \pm 0.2
Eosinophils		
0 weeks	0.03 \pm 0.01	0.03 \pm 0.02
4 weeks	0.03 \pm 0.01	0.03 \pm 0.02
8 weeks	0.03 \pm 0.01	0.04 \pm 0.01

(continued)

TABLE 2. BLOOD CELL COUNT AT 0, 4, AND 8 WEEKS (MEAN \pm SD) (CONT'D)

Parameter	Treatment group (n = 19)	Placebo group (n = 16)
Absolute eosinophils ($n \times 10^{12}/L$)		
0 weeks	0.2 \pm 0.1	0.2 \pm 0.1
4 weeks	0.2 \pm 0.1	0.3 \pm 0.5
8 weeks	0.2 \pm 0.1	0.2 \pm 0.1
Basophils		
0 weeks	0.00 \pm 0.00	0.00 \pm 0.00
4 weeks	0.00 \pm 0.00	0.00 \pm 0.01
8 weeks	0.00 \pm 0.00	0.00 \pm 0.00
Absolute basophils ($n \times 10^{12}/L$)		
0 weeks	0.00 \pm 0.00	0.00 \pm 0.00
4 weeks	0.00 \pm 0.00	0.00 \pm 0.00
8 weeks	0.00 \pm 0.00	0.00 \pm 0.00

TABLE 3. METABOLIC PANEL AT 0, 4, AND 8 WEEKS (MEAN \pm SD)

Parameter	Treatment group (n = 19)	Placebo group (n = 16)
Glucose (mmol/L)		
0 weeks	5.7 \pm 0.6	5.7 \pm 0.4
4 weeks	5.6 \pm 0.7	5.4 \pm 0.5
8 weeks	5.6 \pm 0.6	5.5 \pm 0.3
Blood urea nitrogen (BUN) (mmol/L)		
0 weeks	5.7 \pm 1.4	6.4 \pm 1.4
4 weeks	6.0 \pm 1.4	5.7 \pm 1.8
8 weeks	5.7 \pm 1.4	5.4 \pm 2.1
Creatinine ($\mu\text{mol}/L$)		
0 weeks	88 \pm 18	88 \pm 18
4 weeks	88 \pm 26	106 \pm 9
8 weeks	88 \pm 26	97 \pm 9
Sodium (mmol/L)		
0 weeks	142 \pm 2	141 \pm 2
4 weeks	142 \pm 2	143 \pm 2
8 weeks	143 \pm 3	142 \pm 3
Potassium (mmol/L)		
0 weeks	4.8 \pm 0.5	4.7 \pm 0.4
4 weeks	4.7 \pm 0.5	4.6 \pm 0.3
8 weeks	4.7 \pm 0.3	4.5 \pm 0.4
Chloride (mmol/L)		
0 weeks	105 \pm 2	105 \pm 3
4 weeks	104 \pm 2	97 \pm 26
8 weeks	104 \pm 3	103 \pm 4
Calcium (mmol/L)		
0 weeks	9.8 \pm 0.3	9.6 \pm 0.3
4 weeks	9.7 \pm 0.2	9.5 \pm 0.3
8 weeks	9.4 \pm 0.4	9.1 \pm 0.3
Carbon dioxide (mmol/L)		
0 weeks	24 \pm 2	23 \pm 1
4 weeks	27 \pm 2	27 \pm 2
8 weeks	24 \pm 3	23 \pm 2
Total protein (g/L)		
0 weeks	74 \pm 6	73 \pm 3
4 weeks	73 \pm 4	71 \pm 3
8 weeks	73 \pm 5	70 \pm 3
Albumin (g/dL)		
0 weeks	4.3 \pm 0.3	4.4 \pm 0.2
4 weeks	4.5 \pm 0.3	4.6 \pm 0.3
8 weeks	4.4 \pm 0.3	4.4 \pm 0.2

(continued)

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TABLE 3. (CONT'D)

Parameter	Treatment group (n = 19)	Placebo group (n = 16)
Globulin (g/dL)		
0 weeks	3.0 ± 0.5	2.9 ± 0.3
4 weeks	2.8 ± 0.4	2.5 ± 0.3
8 weeks	2.8 ± 0.5	2.6 ± 0.2
Albumin/globulin ratio		
0 weeks	1.5 ± 0.3	1.5 ± 0.2
4 weeks	1.7 ± 0.3	1.9 ± 0.3
8 weeks	1.6 ± 0.3	1.7 ± 0.2
Total bilirubin (μmol/L)		
0 weeks	14 ± 9	12 ± 5
4 weeks	12 ± 7	14 ± 5
8 weeks	10 ± 7	12 ± 5
Alkaline phosphatase (U/L)		
0 weeks	69 ± 12	63 ± 22
4 weeks	71 ± 14	60 ± 18
8 weeks	66 ± 19	61 ± 19
Aspartate aminotransferase (AST) (U/L)		
0 weeks	21 ± 6	19 ± 6
4 weeks	22 ± 4	18 ± 4
8 weeks	21 ± 4	20 ± 6
Alanine aminotransferase (AST) (U/L)		
0 weeks	20 ± 10	21 ± 15
4 weeks	22 ± 11	18 ± 7
8 weeks	19 ± 8	19 ± 8
Creatine kinase (U/L)		
0 weeks	101 ± 42	102 ± 53
2 weeks	109 ± 46	104 ± 46
4 weeks	98 ± 36	94 ± 41

DISCUSSION

This study was conducted to test the safety of ingesting an astaxanthin-rich product derived from *H. pluvialis* in healthy adults. After 8 weeks of supplementation with 6 mg/day of astaxanthin, no significant physiological differences were detected in blood pressure or serum safety markers between the participants receiving the extract and those receiving the placebo. This amount of extract is comparable to the average astaxanthin level that can be ob-

tained by consuming 0.25 kg of different salmon species (1.3 mg from Atlantic salmon to 10 mg from sockeye salmon).¹

To our knowledge, there are no published data on the safety of an astaxanthin-rich product in human subjects. A number of standard toxicity and safety studies have been conducted on rats with doses ranging from 5 to 18 g of *H. pluvialis* per kilogram body weight per day. These studies showed no adverse clinical signs, behavioral alterations, weight changes, or mortalities in the test animals.¹³

TABLE 4. BLOOD PRESSURE STUDIES AT 0, 4, AND 8 WEEKS (MEAN ± SD)

Parameter	Treatment group (n = 19)	Placebo group (n = 16)
Average systolic (mm Hg)		
0 weeks	118 ± 12	118 ± 16
4 weeks	117 ± 13	115 ± 10
8 weeks	123 ± 14	116 ± 12
Average diastolic (mm Hg)		
0 weeks	76 ± 11	70 ± 10
4 weeks	76 ± 10	73 ± 7
8 weeks	77 ± 10	73 ± 10

A growing body of literature has revealed that astaxanthin possesses potent antioxidant activity and may have numerous health benefits.⁵⁻¹² Although astaxanthin has been marketed in the United States and in Europe for many years and has never been reported to cause toxicity, it is important to establish its safety. Our findings show that, at doses of 6 mg/day, healthy adults can safely consume astaxanthin taken in the form of a *H. pluvialis* algal extract. Further investigations are needed to confirm these results in larger-scale clinical trials, as well as in subjects with specific clinical conditions that could benefit from a high-astaxanthin intake.

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