

Shimada Y: Human safety study: oral dosage between 2-12 mg per day of extracted astaxanthin from *H. pluvialis*. Fuji Chemical Industry Co., Ltd. Internal Bulletin. 2003.



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Safety Study of Astaxanthin Consumption in Humans. Shimada et al., Fujita University, Japan.

Summary

The consumption of astaxanthin as part of the daily nutritional supplement is increasingly popular. Furthermore, this double-blind study supports existing literature that astaxanthin extracted from a natural source of freshwater microalgae called *Haematococcus pluvialis* does not cause any safety concerns over a range of doses for human consumption. This study forms part of an investigation whether astaxanthin can potentially help reduce symptoms of eyestrain. Furthermore, only the safety assessment is reported in this publication.

6, 4, 7 and 6 subject groups received daily dosage of 0, 2, 4, or 12 mg of astaxanthin respectively for up to four weeks in this double blind trial. A comprehensive biochemical markers and haematological examinations on the subjects' blood samples were performed before and after the trial period.

The analysis shows that there were no significant or adverse reactions in the analyses after receiving up to 12 mg of astaxanthin per day. It can be concluded that the range of astaxanthin intake of the described doses are safe for human consumption.

Test Group.

Healthy Japanese volunteers except with eyestrain were selected between the age of 40 and 50 years old. The group consisted of 15 males and 10 females and their consent was obtained and the study protocol approved and conducted by the Fujita Health University Ethics Committee and Fujita Health University of School of Medicine (Aichi, Japan) respectively. Volunteers taking medicines or supplements were excluded from this study. In addition, two volunteers could not give blood samples due to personal businesses at the end of the trial, thus reducing the group number to 23.

Dosage.

Two placebo and astaxanthin capsules containing 0.1, 2, 4 or 6 mg each (Fuji Chemical Ind. Co., Toyama, Japan) were taken orally after dinner. Placebo and astaxanthin capsules were identical in appearance and size.

Sample collection.

Venous blood samples were withdrawn from the volar cubital region. Initial baseline blood samples were withdrawn from all subjects 22 days in advanced of receiving astaxanthin. After four weeks of supplementation, a second sample was taken from the subjects for analysis 2-3 hours after lunch.

Measurement.

22 biochemical parameters of serum were analysed according. Electrolyte and haematological assessments were also conducted. Refer to appendix for full list of parameters tested.

Statistical Analysis.

All values are expressed as mean standard deviation from. A standard two-tailed t test was applied to assess the significance of differences in serum biochemical and haematological values before and after astaxanthin supplementation. P values less than 0.05 were considered significant.

Results.

Full table of results are listed in Appendix B.

Total Protein (TP), albumin (ALB) and Albumin to Globulin (A/G) ratio are given indicators for nutritional condition, protein leakage or reduction of protein synthesis in the liver and others. The A/G ratio results show statistically significant values ($P < 0.05$) after four weeks with in the control, 4 mg and 12mg groups. In these results, the A/G ratio increased, but not in a dose dependent manner and these values are also within normal ranges.

No significant changes detected in hepatic function (table 2), or creatine assay (CPK), for muscle breakdown (table 3). Renal function indicators (table 5) and blood electrolytes (table 7) were also within normal ranges. No trend could be established according to dosage intake compared to controls.

Haematological examinations (table 8) covered 8 tests that did not show any abnormalities in all treated groups including placebo group.

Conclusion.

Some significant values were observed in the biochemical parameters before and after the astaxanthin intake. However these changes were not dose related and within the normal ranges. Hence this study suggests that extracted astaxanthin consumed in the range of 2-12 mg per day up to four weeks displayed no undesirable reactions and deemed safe for human consumption.

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Appendix A - Abbreviations

TP: Total Protein
ALB: albumin
A/G: Albumin/globulin ratio

T-Bil: Total bilirubin
ALP: Alkaline phosphatase
GOT: Glutamic-oxaloacetic transaminase
GPT: Glutamic-pyruvic transaminase
LDH: Lactate dehydrogenase
 γ -GTP: γ -Glutamyltranspeptidase

CPK: Creatine phosphokinase

T-CHO: Total cholesterol
HDL: High density lipoprotein cholesterol
TG: Triglyceride
BUN: Blood urea nitrogen
CRE: Creatinine
UA: Uric acid

Na: Sodium
K: Potassium
Cl: Chloride
Ca: Calcium
Mg: Magnesium
GLU: Glucose

WBC: White cell count
RBC: Red cell count
PLT: Platelet
Hb: Haemoglobin concentration
Ht: Haematocrit
MCV: Mean corpuscular volume
MCH: Mean corpuscular haemoglobin
MCHC: Mean corpuscular haemoglobin concentration

Appendix B - Table of Results.

(*,** * P value <0.05, <0.01 in t-test: Pre.vs. Post)

Table 1. Nutritional Condition.

			0mg (N=6)	2mg (N=4)	4mg (N=7)	12mg (N=6)
TP	Pre.	Mean	7.28	7.28	7.04	7.27
		SD	0.19	0.46	0.43	0.45
	Post	Mean	7.18	7.20	7.00	7.35
		SD	0.31	0.35	0.36	0.27
ALB	Pre.	Mean	4.60	4.45	4.57	4.48
		SD	0.11	0.10	0.31	0.12
	Post	Mean	4.68	4.50	4.74	4.73*
		SD	0.19	0.14	0.26	0.15
A/G ratio	Pre.	Mean	1.70	1.63	1.86	1.65
		SD	0.11	0.34	0.17	0.23
	Post	Mean	1.88*	1.68	2.13*	1.82*
		SD	0.18	0.22	0.21	0.18

Table 2. Hepatic Function.

			0mg (N=6)	2mg (N=4)	4mg (N=7)	12mg (N=6)
T-BIL Mg/dl	Pre.	Mean	1.22	0.55	0.43	0.65
		SD	0.46	0.30	0.16	0.18
	Post	Mean	1.20	0.55	0.49	0.65
		SD	0.67	0.17	0.12	0.16
ALP IU/l	Pre.	Mean	166.2	220.8	220.7	234.0
		SD	29.6	39.2	43.5	65.4
	Post	Mean	163.8	202.5	227.9	231.7
		SD	31.9	22.6	65.7	60.9
GOT IU/l	Pre.	Mean	18.5	19.0	23.1	22.8
		SD	2.3	0.8	5.2	5.2
	Post	Mean	18.5	18.8	25.3	22.8
		SD	1.9	2.2	6.3	6.2
GPT IU/l	Pre.	Mean	18.3	12.0	26.1	31.8
		SD	5.6	2.0	15.1	24.2
	Post	Mean	18.0	13.0	26.9	29.8
		SD	5.7	4.5	17.3	23.0
LDH IU/l	Pre.	Mean	164.5	173.8	177.9	193.3
		SD	17.6	21.4	30	25.3
	Post	Mean	158.0	174.5	183.6	189.5
		SD	15.6	22.8	35.5	27.5
γ-GTP IU/l	Pre.	Mean	23.7	20.8	33.6	49.8
		SD	14	12.2	21.9	35.3
	Post	Mean	24.2	23.8	35.9	51.3
		SD	15.5	16.2	22.3	37.9

Table 3. Lesion Detection in Skeletal muscle.

			0mg (N=6)	2mg (N=4)	4mg (N=7)	12mg (N=6)
CPK IU/l	Pre.	Mean	87.2	119.3	104.1	137.0
		SD	27.8	28.3	51.6	40.8
	Post	Mean	93.2	133.0	110.0	119.2
		SD	32.2	30.1	56.8	21.8

Table 4. Arteriosclerosis.

			0mg (N=6)	2mg (N=4)	4mg (N=7)	12mg (N=6)
TG mg/dl	Pre.	Mean	109.3	202.8	168.6	179.5
		SD	35.9	203.1	104.5	122.5
	Post	Mean	179.5	190.0	149.9	191.7
		SD	128.2	137.6	75.7	108.5
T-CHO mg/dl	Pre.	Mean	213.3	197.0	199.0	210.8
		SD	32.8	23.3	32.2	38.7
	Post	Mean	220.3	185.0	192.9	218.3
		SD	32.3	12.2	33.2	26.1
HDL	Pre.	Mean	58.75	62.48	53.39	48.77
		SD	13.91	8.29	20.30	10.62
	Post	Mean	57.02	58.08**	53.83	49.05
		SD	12.08	8.03	16.94	12.02
HDL ratio	Pre.	Mean	27.92	31.78	27.40	24.37
		SD	7.56	2.79	11.12	8.73
	Post	Mean	26.42	31.35	28.87	23.18
		SD	7.18	3.29	11.14	7.60
Arteriosclerosis index	Pre.	Mean	2.82	2.18	3.19	3.67
		SD	0.99	0.30	1.69	1.95
	Post	Mean	3.08	2.20	2.91	3.88
		SD	1.31	0.41	1.43	2.07

Table 5. Renal Function.

			0mg (N=6)	2mg (N=4)	4mg (N=7)	12mg (N=6)
BUN mg/dl	Pre.	Mean	13.0	16.3	14.6	14.8
		SD	4.7	3.8	1.8	2.4
	Post	Mean	15.7	13.8	13.7	14.5
		SD	5.3	3.4	1.3	2.3
CRE mg/dl	Pre.	Mean	0.788	0.875	0.880	0.777
		SD	0.094	0.202	0.066	0.113
	Post	Mean	0.798	0.823	0.876	0.805
		SD	0.125	0.166	0.055	0.119

Table 6. Metabolism.

			0mg (N=6)	2mg (N=4)	4mg (N=7)	12mg (N=6)
GLU mg/dl	Pre.	Mean	105.2	101.0	100.3	90.5
		SD	19.3	8.8	25.6	16.2
	Post	Mean	110.8	96.3	124.6*	101.0
		SD	15.3	4.5	38.5	21.5
UA mg/dl	Pre.	Mean	5.18	4.70	5.30	4.92
		SD	1.28	0.76	1.30	0.99
	Post	Mean	5.32	4.35	5.07	5.53
		SD	1.42	0.49	1.48	1.53

Table 7. Electrolyte.

			0mg (N=6)	2mg (N=4)	4mg (N=7)	12mg (N=6)
Na mEq/l	Pre.	Mean	142.8	143.3	143.4	143.2
		SD	1.3	2.1	2.3	1.5
	Post	Mean	143.0	143.5	143.4	142.8
		SD	2.4	1.0	2.5	1.9
K mEq/l	Pre.	Mean	4.00	4.10	3.87	3.92
		SD	0.28	0.29	0.24	0.28
	Post	Mean	3.98	4.13	3.93	3.90
		SD	0.16	0.43	0.24	0.24
Cl mEq/l	Pre.	Mean	104.0	105.5	105.7	106.2
		SD	1.5	1.3	1.7	1.5
	Post	Mean	106.0*	106.3	106.4	106.5
		SD	2.3	1.0	2.6	1.9
Ca mg/dl	Pre.	Mean	9.12	8.98	8.94	8.83
		SD	0.29	0.29	0.42	0.22
	Post	Mean	9.05	9.08	9.14	9.02
		SD	0.14	0.39	0.31	0.36
Mg mg/dl	Pre.	Mean	2.25	2.18	2.24	2.23
		SD	0.08	0.13	0.14	0.18
	Post	Mean	2.22	2.15	2.23	2.25
		SD	0.15	0.17	0.16	0.05

Table 8. Haematological Assessment. (One sample was excluded in 4mg group due to coagulation).

			0mg (N=6)	2mg (N=4)	4mg (N=6)	12mg (N=6)
WBC 10 ² /mm ³	Pre.	Mean	61.0	58.8	66.6	75.3
		SD	8.5	9.9	24.6	16.5
	Post	Mean	60.7	51.0	63.3	74.8
		SD	4.2	12.6	23.2	14.2
RBC 10 ⁴ /mm ³	Pre.	Mean	451.7	457.8	455.0	464.3
		SD	37.9	18.3	42.2	36.6
	Post	Mean	445.8	439.0	460.8	464.2
		SD	52.9	23.9	41.0	48.4
PLT 10 ⁴ /mm ³	Pre.	Mean	25.52	21.10	21.69	22.87
		SD	4.70	3.92	6.50	3.72
	Post	Mean	24.72	21.80	20.65	24.97
		SD	4.88	5.03	6.46	2.24
Hb g/dl	Pre.	Mean	13.63	13.48	13.90	13.83
		SD	0.98	1.09	1.25	1.33
	Post	Mean	13.47	12.98	14.02	13.72
		SD	1.33	1.32	1.25	1.47
Ht %	Pre.	Mean	41.82	42.25	42.54	42.27
		SD	2.84	3.86	4.09	3.66
	Post	Mean	40.85	40.48	42.32	42.00
		SD	3.52	3.63	3.78	3.95
MCV fl	Pre.	Mean	92.70	92.15	93.57	91.03
		SD	3.15	5.33	4.90	3.74
	Post	Mean	91.95	92.05	91.93	90.65
		SD	4.03	3.47	4.89	5.26
MCH pg	Pre.	Mean	30.22	29.43	30.59	29.80
		SD	1.11	1.60	1.46	1.81
	Post	Mean	30.27	29.48	30.43	29.58
		SD	0.93	1.52	1.51	1.89
MCHC %	Pre.	Mean	32.60	31.90	32.70	32.70
		SD	0.72	0.73	0.75	0.70
	Post	Mean	32.93	32.00	33.13	32.65
		SD	0.58	0.62	0.63	0.67