Received: 28 March 2019 | Revised: 12 August 2019 | Accepted: 4 September 2019

DOI: 10.1002/ptr.6514

REVIEW

WILEY

Astaxanthin: How much is too much? A safety review

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Astaxanthin (AX)-containing preparations are increasingly popular as health food supplements. Evaluating the maximum safe daily intake of AX is important when setting dose levels for these products and currently, there are discrepancies in recommendations by different regulatory authorities. We have therefore conducted a review of approved dose levels, clinical trials of natural AX, and toxicological studies with natural and synthetic AX. Recommended or approved doses varied in different countries and ranged between 2 and 24 mg. We reviewed 87 human studies, none of which found safety concerns with natural AX supplementation, 35 with doses ≥12 mg/day. An acceptable daily intake (ADI) of 2 mg as recently proposed by European Food Safety Authority was based on a toxicological study in rats using synthetic AX. However, synthetically produced AX is chemically different from natural AX, so results with synthetic AX should not be used in assessing natural AX safety. In addition, few safety studies have been conducted in either humans or animals with synthetic AX. We therefore recommend the ADI for natural AX to be based only on studies conducted with natural AX and further studies to be conducted with synthetic AX (including human clinical trials) to establish a separate ADI for synthetic AX.

KEYWORDS
astaxanthin, dosage, *Haematococcus pluvialis*, *Paracoccus carotinifaciens*, *Pfaffia rhodozyma*, safety, synthetic astaxanthin, toxicity

1 | INTRODUCTION

Astaxanthin (AX) is a carotenoid pigment found in some algae, mainly *Haematococcus pluvialis*, and the aquatic animals that feed on them: the yeast *Pfaffia rhodozyma* (*Xanthophyllomyces dendrorhous*) and the bacterium *Paracoccus carotinifaciens*. Astaxanthin-containing products are increasingly popular as human health food supplements, with a market size of over US$100 million in 2018 and double-figure annual growth rates (Schultz, 2018). They are taken for many different reasons, including to improve eye health and vision, skin health, and exercise performance and recovery. Some regulatory authorities allow limited health claims for these indications. Commercial AX preparations are mainly sourced from *H. pluvialis* cultivation, but synthetic AX is becoming an important product, given the ecological issues surrounding krill harvesting and limitations on yields from cultivated algae.

Astaxanthin is routinely found in the human diet, from salmon, trout and other fish, and crustaceans. In the wild, animals obtain AX from dietary algae. If farmed, to produce the required pink color to the flesh, AX is added to feed. Thus, evaluating the maximum safe human daily intake of AX is important when setting recommended doses for nutritional supplements. Some toxicity studies have examined synthetic AX and some have been extrapolated to natural AX, as discussed below. The purpose of this review is to evaluate studies of safety, toxicity, and dose-related effects for natural AX-containing supplements.

2 | MATERIALS AND METHODS

For the regulatory review, websites and publications of national competent authorities (European Union [EU], the U.S. Food and Drug Administration [FDA], Health Canada, Australia's Therapeutic Goods

Administration, and the Ministry of Health of Japan and South Korea) were searched.

For the clinical and toxicological reviews, PubMed, Google Scholar, Web of Science, and Scopus were searched using the keywords "astaxanthin," "*Haematococcus pluvialis*," "human," "trial," "RCT," "safety," and "toxicology." Given that the first AX supplements entered the marketplace in the 1990s, our search was limited to 1985–2019. The search included reviews and meta-analyses that were then searched manually for reports on han trials.

3 | RESULTS

3.1 | Recommended levels in feed additives and acceptable daily intake

3.1.1 | AX as a feed additive

Synthetic AX and AX-rich extracts of *P. rhodozyma*, *P. carotinifaciens*, and *H. pluvialis* are registered as feed additives for salmon and trout up to 100 mg/kg feed (European Food Safety Authority [EFSA], 2014a). In 1987, the US FDA approved the use of naturally derived AX as a feed additive at up to 80 mg/kg feed (Hoffmann la Roche, 1987).

3.1.2 | AX acceptable daily intake in humans

Synthetic AX

In 2014, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) established the human acceptable daily intake (ADI) for synthetic AX in foodstuffs as 2.0 mg/day for a 60-kg adult (EFSA, 2014a), which was derived from a study in rats by Buser, Jovanovic, Lenz, et al. (2003a).

Natural AX

EFSA estimated an ADI of 0.034 mg/kg body weight per day of natural AX (EFSA, 2014b), equating to about 2 mg/day for a 60-kg adult, derived from a study in rats by Takahashi, Tsukahara, and Minato (2005).

Recent human clinical studies have used doses of 4 mg of natural AX, and frequently 8 mg or higher, and in many cases, therapeutic outcomes depend on doses higher than 2 mg/day. It is necessary to address this discrepancy to clarify the evidence on the safety of doses above 2 mg/day and to update the recommendations. We have therefore reviewed:

1. Dose levels approved or recommended by regulatory authorities.
2. The clinical safety of natural AX in human trials at all doses.
3. Toxicity studies in animal studies and on synthetic AX.

3.2 | Regulatory review

Natural and synthetic AX have been assessed for safety and found safe for human consumption by multiple jurisdictions and in various regulatory categories.

3.2.1 | European Union

Substantial equivalence

Astaxin, containing a daily dose of 4 mg AX, was launched in Sweden by Astacarotene in 1995, which preceded Regulation (EC) 258/97, concerning ingredients without a history of use in the EU prior to May 1997. Since then, many other manufacturers have issued notifications on the basis of "substantial equivalence," at doses of 2 mg and above, and Table 1 shows these and their reliance on previous applications for other products. In 2018, the new Novel Foods Regulation (EU) 2015/2283 came into force, and the list entry for AX-rich oleoresin from *H. pluvialis* confirmed a maximum ADI level for AX of up to 8 mg (European Commission, 2017).

3.2.2 | USA

GRAS, FDA-affirmed

The FDA is satisfied with the safety-in-use of the AX derived from *H. pluvialis* and *P. carotinifaciens*, providing that consumption is below 6–7 mg AX per day.

GRAS, Self-affirmed

Self-affirmed generally recognized as safe (GRAS) procedures are generally not made public, nor is this an obligation, other than disclosure to the regulator. Several natural AX products are included in this category.

New dietary ingredient notifications (NDINs)

Over the last 20 years, FDA received, and had no objections to, a total of 17 NDINs addressing the safety of natural AX products in various preparations, with a recommended daily dose ranging from 2–24 mg/day. These are summarized in Table 2 and almost all are in excess of the recommended 2 mg/day.

3.2.3 | Canada

Health Canada's licensed natural health products database lists a total of 81 active registered products containing AX. Allowable claims include "helps to improve physical endurance," "source of/provides antioxidants," "helps to support eye health," and "helps to reduce eye strain and eye fatigue." The allowable daily dose is up to 12 mg.

3.2.4 | Australia/New Zealand

The Australian Register of Therapeutic Goods lists 40 registered products containing AX (Therapeutic Goods Administration, 2013) with an allowable daily dose of up to 12 mg.

3.2.5 | Japan

Astaxanthin is listed as an "existing food additive," due to it being widely used in Japan and having a long history of consumption by

TABLE 1 Substantial equivalence notifications for natural astaxanthin under Regulation (EC) 258/97

Manufacturer	Year	Daily dose (mg)	Authority	Opinion
US Nutra/Valensa (Zanthin)	2004	4	ACNFP (UK)	"The AX-rich carotenoid oleoresin produced by US Nutra can be considered substantially equivalent to the existing algal meal produced by Astacarotene"
AstaREAL (L-10)	2006	8	NFA (Sweden)	"AstaREAL-L 10 meets the criteria for equivalence as defined in Article 3(4) (EC) 258/97"
Cyanotech (BioAstin)	2007	4	ACNFP (UK)	"Cyanotech has demonstrated the equivalence of their astaxanthin-rich oleoresin (…) to be used with an AX content of no more than 4mg per capsule"
Alga Technologies	2008	4	ACNFP (UK)	"Demonstrated the equivalence of their astaxanthin-rich oleoresin from *H. pluvialis*"
Parry (AstaNatural)	2009	4	ACNFP (UK)	No opinion published
Fenchem (AstaMarin)	2014	2–12 (4)	FSAI (Ireland)	"AX marketed by Fenchem Biotek Ltd. is substantially equivalent to the astaxanthin product (BioAstin®)"
Fenchem (AstaSuper)	2015	2–12 (4)	FSAI (Ireland)	As for 2014 Astamarin application
InnoBio	2016	2–4	FSAI (Ireland)	"InnoBio® Astaxanthin substantially equivalent to the EU-authorized astaxanthin (Zanthin®)"
BGG (AstaZine)	2016	4	FSAI (Ireland)	"AstaZine produced by the Beijing Gingko Group (BGG) in China is substantially equivalent to the authorized astaxanthin-rich oleoresin (Zanthin®)"
BGG (AX Oil, CO2 extract)	2016/2017	n.a.	FSAI (Ireland)	"Astaxanthin oil (supercritical CO2 extraction) produced by BGG is substantially equivalent to the EU-authorized Zanthin®"
Algalif	2017	4	FSAI (Ireland)	No opinion published
Algalo	2017	4	ACNFP (UK)	"Demonstrated the equivalence of their oleoresin product from dried biomass obtained from *H. pluvialis* with the existing oleoresin products …"
Algamo (Algastin)	2017	4	Ministry of Agriculture (Czech Republic)	"AX from *Haematococcus pluvialis* produced by Algamo is substantially equivalent to AX from BioAstin®"
Yunnan Alphy (AstAlphy)	2017	8	FSAI (Ireland)	"Astaxanthin from *Haematococcus pluvialis* (AstAlphy™) is substantially equivalent to the astaxanthin-rich oleoresin (AstaREAL®L10)"

Abbreviations: ACNFP, Advisory Committee on Novel Foods and Processes; FSAI, Food Safety Authority of Ireland; NFA, National Food Administration.

humans. Competent authorities are conducting safety testing on substances in this category but AX has not yet been assessed.

3.2.6 | South Korea

Astaxanthin derived from *H. pluvialis* is listed at an allowable daily dose of 4–12 mg. The associated health claim is "help to improve eye fatigue."

3.3 | Natural versus synthetic AX

Natural and synthetic AX are not identical in chemical composition, bioavailability, purity, or organoleptic qualities. Natural AX is variable, existing as 3*S*,3′*S*- and 3*R*,3′*R*-stereoisomers (see Figure 1) and in free and esterified form. The alga *Haematococcus* synthesizes mainly the 3*S*,3′*S*-isomer, also predominant in wild Atlantic salmon and occurring mainly in the free form. The yeast *P. rhodozyma* produces mainly the 3*R*,3′*R*-isomer, also the primary stereoisomer found in the Antarctic krill (*Euphausia superba*), but mainly in the esterified form (Ambati, Phang, Ravi, & Aswathanarayana, 2014). As shown in Table 2, the vast majority of new dietary ingredient notifications for natural AX filed with FDA were regarding *H. pluvialis* extracts. Natural AX extracts usually contain other carotenoids (beta-carotene, canthaxanthin, and lutein), depending on source, that possess related and other biological activities.

Synthetic AX comprises a mixture of the isomers 3*S*, 3′*S*, 3*R*, 3′*S*, and 3*R* and 3′*R*. *It* may also contain trace amounts of residual solvents and chemical reagents (Capelli, Bagchi, & Cysewski, 2013; Edwards, Bellion, Beilstein, Rümbeli, & Schierle, 2016).

3.3.1 | Clinical safety of natural AX

The effects of natural AX in humans have been reviewed in more than 20 publications over the last 10 years and include studies on antioxidation, hepatoprotection, eye function, skin health, immune response, inflammation, gastric ulcer, cardiovascular system, muscle endurance, cancer, central nervous system, male fertility, metabolic syndrome, diabetes, and mitochondrial dysfunction (Ekpe, Inaku, & Ekpe, 2018; Fakhri, Abbaszadeh, Dargahi, & Jorjani, 2018;

TABLE 2 New dietary ingredient notifications for natural astaxanthin filed with Food and Drug Administration

NDIN	Applicant	Year	Source	RDI astaxanthin (mg)
45(52), 50(58)	Cyanotech	1999	*Haematococcus pluvialis*	6
65(75)	Aquasearch	2000	*Haematococcus pluvialis*	5
119(143)	Micro Gaia	2002	*Haematococcus pluvialis*	1–2
236(281)	Fuji	2004	*Haematococcus pluvialis*	12
237(282)	Nutraceuticals	2004	*Haematococcus pluvialis*	n.d.
274(319)	Fuji	2005	*Haematococcus pluvialis*	7.6
278(323)	US Nutra	2005	*Haematococcus pluvialis*	5
372(417), 406(466)	Algatechnologies	2006/2007	*Haematococcus pluvialis*	5
632	Yamaha	2010	*Haematococcus pluvialis*	1–12
717	Cyanotech	2011	*Haematococcus pluvialis*	12
742	Fuji	2012	*Haematococcus pluvialis*	4–12
815	Genovia	2014	*Haematococcus pluvialis*	12
829	JX Nippon	2014	*Paracoccus carotinifaciens*	6
884	BGG	2015	*Haematococcus pluvialis*	12
943	BGG	2016	*Haematococcus pluvialis*	24
957	Algatechnologies	2017	*Haematococcus pluvialis*	12
1,067	Yunnan Alphy	2018	*Haematococcus pluvialis*	12

Abbreviation: NDI, new dietary ingredient; RDI, recommended daily intake.

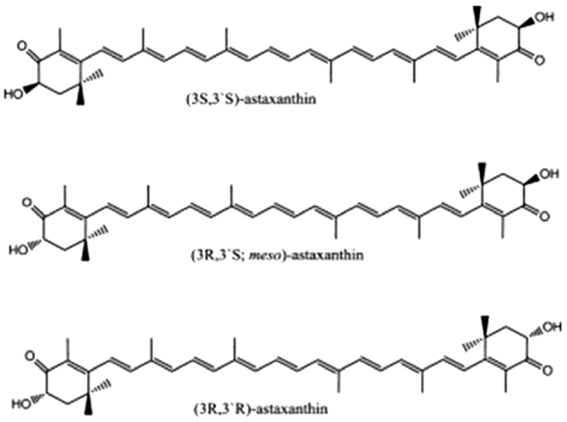

FIGURE 1 Isomers of astaxanthin

Fassett et al., 2008, Fassett & Coombes, 2012; Galasso et al., 2018; Visioli & Artaria, 2017; Brown, Gough, Deb, Sparks, & McNaughton, 2018; Capelli, Jenkins, & Cysewski, 2013; Davinelli, Nielsen, & Scapagnini, 2018; Kim & Kim, 2018; Yamashita, 2013).

We have identified and evaluated 87 clinical trials (Table 3), in which, 2,000+ participants received natural AX. In order to capture all adverse event reports, side effects, or other safety concerns, we did not exclude any studies on the basis of risk of bias or quality. Level of detail in reporting varied widely, which makes it near impossible to evaluate and compare the quality of the studies. Any attempt to rank would be flawed if based on the information available from the published literature. In general terms, however, it can be said that the more recent randomized clinical trials have been conducted with more scientific rigor than earlier open label and observational trials.

As shown in Table 3, eight human studies were conducted to look specifically at safety of high doses of natural AX, ranging from 8 to 45 mg/day and over 4 to 12 weeks (Aquasearch, 1999; Kajita et al., 2010; Kajita, Tsukahara, Kato, & Yoshimoto, 2009; Matsuyama et al., 2010; Ohgami et al., 2005; Satoh et al., 2009; Spiller & Dewell, 2003; Tsukahara et al., 2005). Twenty-eight studies were found, which used daily doses of at least 12-mg natural AX over a period of at least 4 weeks. These were general efficacy studies where adverse events were monitored.

No serious adverse events were observed in any of the clinical studies listed above, even at the highest dose tested (45 mg in 15 patients; Kajita et al., 2010). In one study, a red coloration of the stool was noted at a dose of 30 mg (Kajita et al. 2009b; Tsukahara, Kato, & Yoshimoto, 2009). This was also observed at a dose of 20 mg (Choi, Kim, et al., 2011) and an increased frequency in bowel movement in two patients (of 14). Kupcinskas et al. (2008) recorded 36 adverse events (in 131 patients taking 16 or 40 mg AX or placebo); however, compared with placebo, fewer events took place in the higher dose group.

No changes in liver parameters in humans have been reported. Natural AX has shown an excellent clinical safety profile at short-term daily doses up to 100 mg and long-term daily doses averaging between 8 and 12 mg. This is important in view of animal experimental results for synthetic AX discussed below.

3.4 | Toxicity studies in animals

3.4.1 | Natural AX

No changes in liver or other pathologies have been found in rats treated with AX-rich extracts of *H. pluvialis* (Takahashi et al., 2005;

TABLE 3 Clinical studies of natural astaxanthin (excluding topical applications)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
Andersen et al., 2007	Gastric inflammation in *Helicobacter pylori*-positive subjects	RCT	Biopsies examined IL-4, IL-6, IL-8, IL-10, IFN-g, CD4, CD8, CD14, CD19, CD25, and CD30. CD4 was significantly upregulated ($P < .05$) and CD8 significantly downregulated ($P < .01$) in patients with *H. pylori* when treated with 40 mg of AX daily	None reported	8 weeks	40	21
Anderson, 2014	Serum hormone levels in sedentary males	RCT	Serum profiles of testosterone, E2, and DHT were evaluated. No significant increase in serum testosterone but significant decrease in DHT and E2 levels versus placebo	No significant changes in systolic or diastolic blood pressure, no adverse side effects in both dose groups	2 weeks	n/a[b]	10/10
Angwafor & Anderson, 2008	DHT, testosterone, and ES levels in healthy males	OL	Blood samples were assayed for levels of endogenous testosterone, DHT, and ES. Significant increase of testosterone and decrease of DHT were observed in the lower dose group, additional significant decrease of ES in the higher dose group	No significant changes in systolic or diastolic blood pressure, no adverse side effects in both dose groups	2 weeks	n/a[b]	21/21
Aquasearch, 1999	Safety	OL	Blood and urine analyses and physical examinations were carried out at the beginning, after 3 to 7 days, and at the end of the 4-week period.	No changes of any clinical significance noted	4 weeks	3.85, 19.25	33
Baralic et al., 2013, 2015	PON1 activities, salivary IgA, oxidative stress, and inflammation in young soccer players	RCT	PON1 activities and oxidative stress status were assessed by substrates paraoxon and diazoxon and total –SH content, TBARS, advanced oxidation protein products, and redox balance, respectively. PON1 activities toward both substrates and SH increased significantly, TBARS and redox balance decreased significantly versus placebo. Authors also investigated salivary IgA and muscle enzyme levels for oxidative stress and inflammation. AX improved salivary IgA response, reduced plasma muscle enzyme levels, whereas placebo showed increase in neutrophil count and hs-CRP level	None reported	90 days	4	21
Belcaro, Cesarone, Cornelli, & Dugall, 2010	Menopause symptoms	RCT	Climacteric condition determined by 34-symptom questionnaire MSSQ. Signs and symptom scores were similar at baseline but showed significant reduction of many variables after 8 weeks versus placebo	Treatment well tolerated, compliance >97%	8 weeks	0.54	33
Bloomer et al., 2005	Muscle injury after eccentric exercise	RCT	Muscle soreness, CK, and muscle performance were measured at baseline after 3 weeks and through 96-hr post exercise. No significant difference in response was observed between groups	None reported	3 weeks	4	10

(Continues)

TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
Chalyk, Klochkov, Bandaletova, Kyle, & Petyaev, 2017	Skin parameters	OBS	Morphological analyses of the RSSCs were conducted and blood samples were taken for measuring plasma levels of MDA. Plasma MDA, corneocyte desquamation, and microbial presence decreased continuously and significantly, effects were more pronounced in overweight subjects	None reported	4 weeks	4	31
Chen & Kotani, 2017	Liver and leukocyte parameters in healthy climacteric women	RCT	Liver enzymes, levels of blood d-ROMs, 8-OHdG, and BAP were determined. Liver enzymes such as AST and ALT decreased and blood leucocytes increased significantly, whereas no significant changes were observed in d-ROMs and urinary 8-OHdG levels or BAP versus placebo	None reported	12 weeks	12	14
Choi, Kim, Chang, Kyu-Youn, & Shin, 2011	Oxidative stress in overweight subjects	RCT	MDA, ISP, SOD, and TAC were measured at baseline, 1, 2, and 3 weeks. MDA and ISP significantly decreased, SOD and TAC significantly increased in both groups	No adverse effects, changes in fecal color to red (n = 2)	3 weeks	5, 20	12/11
Choi, Youn, & Shin, 2011	Lipid profiles and oxidative stress in overweight subjects	RCT	TC, TG, HDL cholesterol, LDL cholesterol, ApoA1, and ApoB were measured at baseline and 12 weeks. MDA, ISP, SOD, and TAC were measured at baseline, 4, 8, and 12 weeks. LDL cholesterol, ApoB, MDA, and ISP were significantly lowered, TAC significantly increased versus placebo	Gastrointestinal adverse events: fecal color red (n = 2) and bowel movements increased (n = 2)	12 weeks	20	14
Cicero, Rovati, & Setnikar, 2007	Eulipidemic effects	RCT	TC, LDL, HDL, non-HDL, ApoB, ApoA, Lp(a), and TG were measured at baseline and after 4 weeks. TC, LDL, ApoB, and TG significantly decreased, HDL significantly increased	No adverse events or impairments of liver transaminases or of CPK	4 weeks	0.5	20
Comhaire, El Garem, Mahmoud, Eertmans, & Shoonjans, 2005	Male infertility	RCT	Semen parameters, ROS, zona-free hamster oocyte test, serum hormones including testosterone, LH, FSH, Inhibin B, and spontaneous or IUI-induced pregnancies were evaluated. ROS and Inhibin B decreased significantly, sperm linear velocity increased, and total and per cycle pregnancy rates were higher versus placebo	None reported	12 weeks	16	11
Coombes, Sharman, & Fassett, 2016; Fassett et al., 2008	Arterial stiffness, oxidative stress, and inflammation in renal transplant recipients	RCT	Arterial stiffness measured by aortic PWV, oxidative stress assessed by total plasma F2-ISPs, and inflammation assessed by plasma pentraxin-3 were primary, vascular function, carotid artery intima-media thickness, augmentation index, central blood pressure, subendocardial viability ratio, and additional measures of oxidative stress and inflammation	No adverse events were ascribed to the interventions during the trial	12 months	12	32

(Continues)

TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			were secondary outcomes. The study recorded no significant between-group differences in primary or secondary outcome measures				
Coral-Hinostroza, Ytrestøyl, Ruyter, & Bjerkeng, 2004	Appearance, pharmacokinetics and distribution of AX isomers	OBS	No AX esters were detected in plasma. Maximum levels were reached after 11.5 hr, elimination half-life was 52 ± 40 hr. Dose response was nonlinear. The relative proportion of AX *Z*-isomers was selectively increased before uptake in blood, and AX esters are selectively hydrolyzed during absorption	None reported	2 doses, 4 weeks in between	10, 100	3
Djordjevic et al., 2012	Muscle damage and oxidative stress	RCT	TBARS, AOPP, superoxide anion ($O_2^{\bullet}$), TAS, SH, SOD, CK, and AST were analyzed at baseline and after 90 days. Total SH increased, and SOD, CK, and AST significantly decreased with AX	None reported	90 days	4	18
Earnest, Lupo, White, & Church, 2011	Cycling time trial (TT) performance	RCT	A VO_{2max} test was conducted under various conditions. Significant improvements in 20 km TT and power output were observed with AX	None reported	4 weeks	4	7
Fleischmann, Horowitz, Yanovich, Raz, & Heled, 2017	Physiological and molecular influences on heat stress	RCT	Heat tolerance using the validated HTT and aerobic fitness using VO_{2max} were tested. No significant physiological inter-group differences were observed both in the response to heat stress exposure and in aerobic fitness	None reported	4 weeks	12	12
Fry, Schilling, Chiu, Hori, & Weiss, 2004	DOMS	RCT	DOMS was quantified by muscle soreness ratings (0–7 Likert scale). Muscle fiber characteristics were determined via mATPase histochemistry and digital imaging. No significant difference in DOMS was observed between groups. Fiber type areas were similar, but DOMS was positively related to Fiber Type I and negatively related to Types IIA and IIAB/B	No problems associated with dose	3 weeks	8	4
Hashimoto et al., 2013	Antioxidation in human aqueous humor	OBS	Changes in SSA, hydrogen peroxide, and total hydroperoxides levels in human aqueous humor were measured during bilateral cataract surgery before and after AX supplementation. After AX, SSA was significantly elevated, whereas total hydroperoxide production was suppressed	None reported	2 weeks	6	35
Hayashi, Ishibashi, & Maoka, 2018[d]	Cognitive function	RCT	Cognitive function was compared by word memory test, verbal fluency test, and Stroop test. There were no significant intergroup differences in the results, except in the subgroup <55 years, where the word memory test showed significant improvement with AX	No adverse events related to the supplement were observed	8 weeks	8	28
Imai et al., 2018	Daily fatigue	RCT			4 weeks	6	23

(Continues)

TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			Fatigue was evaluated using a VAS, daily subjective fatigue was evaluated by the Chalder fatigue questionnaire. Secondary outcomes included work efficiency, autonomic nerve activity, levels of plasma phosphatidylcholine hydroperoxide (PCOOH), and safety. Results showed significantly improved recovery from mental fatigue with AX. AX also attenuated increased PCOOH levels	No adverse effects associated with the supplementation were observed			
Ito, Saito, Seki, Ueda, & Asada, 2018	Mild cognitive impairment	RCT	CNSVS test and the Alzheimer's Disease Assessment Scale-Cog test were performed at baseline and after 6 and 12 weeks. Significant improvements in psychomotor speed and processing speed were demonstrated with AX	No adverse events related to the ingestion of AX	12 weeks	6	7
Ito, Seki, & Ueda, 2018	UV-induced skin deterioration	RCT	MED, UV-induced changes of moisture, TEWL, and subjective skin conditions were evaluated at baseline and after 9 weeks. MED increased, loss of skin moisture and subjective conditions were reduced with AX	No adverse events were observed	10 weeks	4	11
Iwabayashi et al., 2009	Increased oxidative stress in postmenopausal women	OL	Antiaging QOL common questionnaire, somatometry, hematological examination/ urinalysis, oxidative stress test, CAVI, ankle brachial pressure index (ABI), fingertip acceleration pulse wave, and FMD were conducted at baseline and at 4 and 8 weeks. Five of 34 physical symptoms listed in the common questionnaire significantly improved, blood pressure significantly decreased, ABI and BAB significantly increased, AST, LDH, and HbA1c levels significantly improved, DHEA-s, cortisol and adiponectin decreased with AX	No serious adverse events occurred	4 weeks	12	20
Iwamoto et al., 2000	Inhibition of LDL oxidation	OBS	Fasting venous blood samples were taken at baseline and Day 14. LDL lag time was longer, but there was no difference in oxidation of LDL with AX	None reported	2 weeks	1.8–21.6	5/5/3/5
Iwasaki & Tawara, 2006	Eye strain induced by accommodative dysfunction	RCT	Subjects were assigned a near visual task for 20 min. Accommodative function and subjective symptoms related to eyestrain were measured before and after the task and after a 10-min rest following the task. Accommodative contraction and relaxation times were significantly prolonged, however, eye fatigue and eye	None reported	2 weeks	6	5

(Continues)

TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			heaviness were increased. Overall subjective symptoms rating decreased with AX				
Kajita, Tsukahara, & Kato, 2009	Accommodation function of the eye	OL	Uncorrected VA and near response (by TriIRIS C9000) were measured at baseline and 4 weeks. Symptoms including difficulty to see nearby objects, difficulty to see far objects, eye strain, ocular pain, blurred vision, eye redness, flashing vision, lacrimation, shoulder and low back stiffness, and dull headache were scored at baseline and 4 weeks. Uncorrected VA showed no significant changes. Pupillary constriction ratio showed a significant increase for both eyes. Symptoms also improved significantly with AX, except for eye redness and lacrimation	None reported	4 weeks	6	22
Kajita, Tsukahara, Kato, & Yoshimoto, 2009	Safety of excessive intake	RCT	Hematological and biochemical tests, ophthalmological examinations including intraocular pressure, and questionnaires were conducted. No statistical differences and no clinically meaningful adverse effects between the groups were shown	Red-colored stool	4 weeks	30	12
Kajita, Kato, Yoshimoto, & Masuda, 2010	Safety of high-dose intake	RCT	Hematological, serum chemistry, or urinalysis parameters were tested. Tonometry, slit-lamp biomicroscopy and fundoscopy were performed. No significant changes were observed	No serious adverse events were observed	4 weeks	45	15
Kaneko et al., 2017	Vocal fold injury and inflammation	OBS	A 60-min vocal loading session and vocal assessments prior to, immediately after, and 30 min post vocal loading were performed at baseline and 4 weeks. All parameters were significantly worse after loading at baseline but not after 4 weeks with AX	No allergic responses or adverse effects	4 weeks	24	10
Karppi, Rissanen, Nyyssönen, Kaikkonen, & Voutilainen, 2007	Lipid peroxidation	RCT	Effects on lipid peroxidation, absorption, and safety were evaluated. Plasma levels of 12- and 15-hydroxy fatty acids were reduced significantly with AX. Supplementation was well tolerated. No significant changes in liver enzymes, blood profile, or blood pressure were observed	None reported	12 weeks	8	40
Katagiri, Satoh, Tsuji, & Shirasawa, 2012	Effect of AX on cognitive function	RCT	Somatometry, hematology, urine screens, and CogHealth and Groton Maze Learning Test were performed at baseline and after every 4 weeks of administration. CogHealth scores and Groton Maze Learning Test scores improved with both	No adverse effects were observed	12 weeks	6, 12	29/29

(Continues)

TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			doses of AX but not significantly due to small sample size				
Kim & Chyun, 2004	Lipid peroxidation and antioxidant status in postmenopausal women	OL	TC, LDL, HDL, TG, plasma TBARS, total antioxidant status (TAS), and urinary 8-ISPs were analyzed. HDL and TAS increased significantly, TG and TBARS decreased significantly with AX	None reported	8 weeks	2, 8	5/5
Kim et al., 2011	Oxidative stress in healthy smokers	RCT	MDA, ISP, SOD, TAC, and ASX levels in plasma were measured at baseline and after 1, 2, and 3 weeks. Plasma MDA and ISP decreased significantly, SOD level and TAC increased with AX	None reported	3 weeks	5, 20, 40	13/13/13
Komori, 2015	Effect on late life depression	OL	Seventeen-item HAMD17 and the basal levels and circadian rhythm of salivary cortisol were measured at baseline and 12 weeks. HAM-D17 was significantly improved after 12 weeks, basal levels and circadian rhythm of salivary cortisol were normalized in 8 responders	None reported	12 weeks	6	18
Kupcinskas et al., 2008	Functional dyspepsia with or without *H. pylori*	RCT	Gastroscopy and urea breath test were performed before treatment. Questionnaires GSRS and SF-36 were performed at baseline and Weeks 4 and 8. No difference between the three treatment groups was observed regarding GSRS. Reduction of reflux syndrome was significant in the higher dose of AX	Thirty-six adverse events occurred, 12 possibly related to the study drug, but no prevalence could be detected between treatment groups	4 weeks	16, 40	43/44
Liu, Ali, & Campbell, 2018	Strength, endurance, and mobility in the elderly	RCT	Strength was measured as MVC in ankle dorsiflexion exercise, tibialis anterior muscle size (CSA) was determined from magnetic resonance imaging at baseline, after 1 month of supplementation only, and at 4 months of supplementation and 3 months training. AX improved muscle strength and CSA elderly in addition to positive effects of training alone	None reported	4 months	12	21
MacDermid, Vincent, Gan, & Grewal, 2012	Carpal tunnel syndrome	RCT	SSS, physical impairments, disability, and health status were measured at baseline and 6 and 12 weeks. Electrodiagnostic testing was performed at baseline and 12 weeks. A reduction in symptoms as measured by SSS was observed for both groups but no statistically significant difference between groups	No moderate/severe adverse events reported	9 weeks	4	32
Malmsten & Lignell, 2008	Strength and endurance	RCT	Fitness, strength/endurance and strength/explosivity were measured by standardized exercises at baseline, 3, and 6 months. Only	None reported	6 months	4	19

(Continues)

TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			increase in knee bending was significantly higher with AX				
Mashhadi et al., 2018	Glucose metabolism and blood pressure in patients with Type 2 diabetes mellitus	RCT	Serum adiponectin, visceral body fat mass, TG, LDL, systolic blood pressure, fructosamine, and plasma glucose concentration were measured at baseline and 8 weeks. Serum adiponectin was significantly increased, all other parameters significantly decreased with AX.	No adverse events observed	8 weeks	8	22
Matsuyama, Takahashi, & Itakura, 2010	Long-term safety	OL	Physiological, biochemical, hematological, and urinary markers were analyzed at baseline, 4, 8, and 12 weeks. No clinical changes were observed over the study period	No adverse effects reported	12 weeks	9	50
Mercke Odeberg, Lignell, Pettersson, & Höglund, 2003	Bioavailability and pharmacokinetics	OL	Bioavailability was examined for AX and AX + lipid bases. Blood sampling from healthy volunteers and subsequent analyses elucidated plasma concentrations. Highest bioavailability of AX was observed with polysorbate 80	Headache, which was not attributed to the treatment.	1 dose	40	32
Miyawaki et al., 2008	Effects on human blood rheology	OL	A blood rheology test was conducted, which measures whole blood transit by a microchannel array flow analyzer at baseline and 10 days. Blood transit times were shortened significantly with AX	None reported	10 days	6	20
Nagaki et al., 2002	Effects in visual display terminal workers	RCT	Accommodation, CFF and PVEP were evaluated at baseline and 4 weeks. Accommodation amplitude was significantly larger with AX, compared with control and placebo	None reported	4 weeks	5	13
Nagaki, Mihara, & Takahashi, 2005	Retinal capillary blood flow	RCT	Retinal capillary blood flow, blood pressure, blood cell counts, fasting plasma glucose level, and intraocular pressure were measured at baseline and 4 weeks. Significant increase in retinal capillary perfusion with AX, intraocular pressure, and physical and biochemical parameters remained unchanged	None reported	4 weeks	6	18
Nagaki, Mihara, Tsukahara, & Ono, 2006	Accommodation and asthenopia	RCT	Visual accommodation was evaluated by questionnaire and examination at −2 weeks, baseline, 2, and 4 weeks. Blood work was done at −2 and 4 weeks. Amplitude of accommodation improved significantly with AX	No difference in safety parameters, no adverse events. One case of tinnitus was not causally related to AX	4 weeks	6	25
Nagaki, Tsukahara, Yoshimoto, & Masuda, 2010	Accommodation and asthenopia	RCT	Accommodation ability was tested at baseline and 4 weeks. Value and rate of change of accommodation ability was significantly higher	No clinically relevant problems or adverse events observed	4 weeks	9	42

(Continues)

TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			with AX. Subjective questionnaire significantly improved in four conditions with AX				
Nagata, Tajima, & Takahashi, 2006	Antifatigue and task performance	RCT	Trail Making Test and exercise test stepwise with three maximum heart rates were performed at baseline, 2, and 4 weeks (crossover after 2 weeks). Blood parameters and HRV were also measured. A significantly higher recovery rate could be shown with AX. Plasma TC and TG significantly decreased with AX. HRV spectrum improved significantly with AX	None reported	4 weeks	5	38
Nakagawa et al., 2011	Effect on phospholipid peroxidation	RCT	Anthropometric data and blood samples were collected at baseline and 12 weeks. Phospholipid hydroperoxides (PLOOH) and erythrocyte antioxidant status improved with AX	None reported	12 weeks	6, 12	10/10
Nakamura, Isobe, Otaka, et al., 2004	Changes in visual function	RCT	Far VA, refraction, flicker fusion frequency, accommodation, and pupillary reflex were tested at baseline and 4 weeks. Uncorrected VA improved significantly, and positive accommodation time was shortened significantly with AX	No changes in physical condition or other adverse effects were reported	4 weeks	2, 4, 12	12/14/13
Nir, Spiller, & Multz, 2002a	Carpal tunnel syndrome	RCT	Pain rate and duration were measured by questionnaire at baseline, 4, and 8 weeks. A nonsignificant trend toward decreased pain rate and duration was observed for AX	None reported	8 weeks	12	13
Nir, Spiller, & Multz, 2002b	Rheumatoid arthritis	RCT	Pain rate and ability to perform daily activities were measured by questionnaire at baseline, 4, and 8 weeks. Pain rate and satisfaction scores improved significantly with AX	None reported.	8 weeks	12	14
Nitta et al., 2005	Accommodation and asthenopia	RCT	Allocation, general ophthalmology, asthenopia, and blood chemistry were examined, accompanied by interviews and questionnaires (VAS), at Weeks -1, 0, 2, 4, and 8. Amplitude of accommodation and accommodation speed improved significantly with AX, VAS items decreased significantly with AX	No difference in safety parameters, no adverse events	4 weeks	6, 12	10/10
Ohgami et al., 2005	Safety of high dose administration	OL	Hematological, biochemical, urine, physical, and ophthalmological examinations were performed at baseline, Weeks 2 and 4, and after supplementation at Weeks 6 and 8. No relevant changes were recorded for any of the parameters at any time point	No difference in safety parameters, no adverse events. Reddish-colored stools were reported at the beginning of the supplementation. Other symptoms indicated were causally not attributed to AX	4 weeks	30	10

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TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
Okada, Ishikura, & Maoka, 2009	Bioavailability	OL	Blood samples were analyzed at baseline and 4, 6, 8, 24, 72, and 168 hr after administration. Analyses included platelet count, number of white and red blood cells, hemoglobin content, hematocrit, corpuscular volume, and hemoglobin and hemoglobin concentration. AST, ALT, GGT, TC, HDL, LDL, TG, uric acid, urea nitrogen, creatinine and fasting blood glucose levels were also measured. Bioavailability was affected by timing of administration (significantly better after a meal), smoking affected pharmacokinetic parameters and reduced AX elimination half-life significantly	No adverse events. Red coloration of feces reported. Hematological and blood-biochemical parameters showed no abnormalities or significant changes	1 dose	48	15
Østerlie, Bjerkeng, & Liaaen-Jensen, 2000	Bioavailability	OL	Blood samples were analyzed at baseline and 2, 4, 6, 8, 10, 12, 24, 32, 48, and 72 hr after administration for AX concentration in the plasma and composition in VLDL, LDL and HDL fractions. AX was absorbed into plasma without any appreciable metabolic transformation. Maximum levels were observed were reached ~7 hr after administration, elimination half-life was ~21 hr	None reported	1 dose	100	3
Parisi, Tedeschi, Gallinaro, et al., 2008	Age- related macular degeneration (AMD)	RCT	Multifocal electroretinograms in response to 61 M-stimuli presented to the central 20° of the visual field were assessed at baseline, 6, and 12 months. At baseline, multifocal electroretinogram RADs were significantly reduced compared with healthy controls at baseline. RADs representing dysfunction in the central retina (0°–5°) improved significantly with AX	No adverse events	12 months	4	15
Park, Chyun, Kim, Line, & Chew, 2010	Immune response	RCT	Blood tests were performed at baseline and Weeks 4 and 8, a tuberculin test was performed at Week 8. AX decreased DNA damage biomarker. Plasma C-reactive protein concentration was significantly lower with AX. AX stimulated mitogen-induced lymphoproliferation, increased natural killer cell cytotoxic activity, and increased total T and B cell subpopulations. AX led to higher tuberculin response, and increased IFN-γ and IL-6	None reported	8 weeks	2, 8	28
Petyaev et al., 2018	Markers of hypoxia and oxidative stress	RCT	Serum AX, nitric oxide (NO), malonic dialdehyde, and oxidized LDL were quantified, and oxygenation parameters were evaluated at baseline and 4 weeks. AX decreased serum levels	None reported	4 weeks	7	24

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TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			of oxidized LDL and malonic dialdehyde and increased NO levels				
Piermarocchi et al., 2012	AMD	RCT	VA, CS, and NEI VFQ-25 scores were established at baseline, 12 and 24 months. VA stabilized significantly, CS and final mean NEI VFQ-25 composite scores also showed significant improvement with AX	No significant systemic or ocular adverse events	24 months	4	84
Pirro et al., 2016	Low-grade systemic inflammation	OL	TC, triacylglycerols, LDL, and HDL were determined by enzymatic-colorimetric method, plasma hs-CRP levels were measured using the hs-CRP assay by nephelometry at −4 weeks, baseline, and 3 months. Significant reductions of TC, LDL, and hsCRP were observed with AX	No adverse events	12 weeks	0.5	50
Res et al., 2013	Fat use and endurance performance	RCT	Well-trained cyclists performed 60 min of exercise (50% W_{max}), followed by a time trial of approximately 1 hr at baseline and 4 weeks. No augmented antioxidant capacity, increase fat oxidative capacity, or improved time trial performance were observed with AX	No adverse events	4 weeks	20	16
Rüfer, Moeseneder, Briviba, Rechkemmer, & Bub, 2008	Bioavailability	OBS	Plasma AX concentration and isomer distribution were measured by HPLC using a reversed and a chiral stationary phase. AX plasma concentrations varied between sources (wild and farmed salmon) and a selective process of isomer absorption was observed	None reported	4 weeks	1.25	28
Saito et al., 2012	Choroidal blood flow velocity	RCT	Hemodynamics of the choroidal circulation were measured with LSFG. SBR, a quantitative index for relative blood flow velocity was calculated at baseline, 2, and 4 weeks. Macular SBR was significantly increased at 4 weeks with AX	No subjective or objective adverse events	4 weeks	12	10
Satoh et al., 2009	Toxicity and efficacy	OBS	Biochemical and blood parameters were measured, and brain function assessed using CogHealth and P300 at baseline, 4, and 12 weeks. No statistically significant changes were noted for any of the measured parameters. CogHealth and P300 measures improved with AX	No adverse events. Reddening of feces was observed	4, 12 weeks	4, 8, 12, 20	73/38/10/16
Sawaki et al., 2002	VA and muscular fatigue	RCT	Deep vision, CFF, static and kinetic VA, blood biochemical, and hematological parameters were measured at baseline, 4, and 12 weeks. For CFF, the visual sensation significantly sharpened, and	No adverse events observed	4 weeks	4	9/8

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TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			serum lactate levels significantly decreased with AX				
Seya, Takahashi, & Imanaka, 2009	Visual fatigue and reaction time	OL	An eye pursuit movement test was conducted, and reaction times were measured at baseline, 2, and 4 weeks. No significant differences were observed, but long-term AX reduces reaction time and visual fatigue	None reported	4 weeks	6	10
Shiratori et al., 2005	Accommodation, asthenopia and safety	RCT	Subobjective accommodation power, positive accommodation time, and negative accommodation time were measured to evaluate asthenopia. Asthenopia was subjectively evaluated using VAS. Lab tests of safety parameters (blood chemistry and biochemistry) were performed at −3, baseline, 2, and 4 weeks. Accommodation power, positive and negative accommodation times, and VAS significantly improved with AX	No difference in safety parameters, no adverse events	4 weeks	6	20
Spiller & Dewell, 2003	Safety	RCT	Blood chemistry and blood pressure were analyzed at baseline, 4, and 8 weeks. No significant physiological differences were detected in blood pressure or serum safety markers	No adverse events	8 weeks	6	19
Takahashi & Kajita, 2005	Accommodative recovery	OL	Objective diopter value, accommodative reaction volume, and HFC in accommodative microfluctuation were examined and questionnaires given at baseline and 2 weeks. HFC value decreased significantly with AX.	None reported	2 weeks	6	9
Talbott et al., 2019	Depression and fatigue	RCT	Subjects completed POMS and related subscales Vigor (*V*), Tension (*T*), Depression (*D*), Anger (*A*), Fatigue (*F*), and Confusion (*C*) at baseline and 8 weeks. POMS, *V*, *D*, *F*, *T*, *A*, and C improved significantly with AX	No adverse events related to AX recorded	8 weeks	12	14
Tominaga, Hongo, Karato, & Yamashita, 2009	Skin parameters	OL	Wrinkle topography measurements were taken, skin elasticity and size of age spots quantified, skin topography measurements made, and cell size in the corneocyte measured at baseline and 8 weeks. Size of age spots was reduced, skin texture and the size of cells in the stratum corneum corneocyte substantially improved. Improvements were also found with acne, excessive sebum secretion, and pregnancy-induced skin changes	None reported	8 weeks	6	28/30/29/30/30
Tominaga, Hongo, Karato,	Skin parameters	OLm RCT	AX caused improvements in skin wrinkle, age spot size, elasticity, skin texture, moisture content of	None reported	6 weeks	6	30/18

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TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
& Yamashita, 2012			corneocyte layer, dry skin, and corneocyte condition at 8 weeks. For methods, see above				
Tominaga, Hongo, Fujishita, Takahashi, & Adachi, 2017	Skin parameters	RCT	Wrinkle grade measurements were performed at baseline and Weeks 8 and 16. Wrinkle grade, skin moisture, and IL-1α levels in the stratum corneum significantly deteriorated in placebo but not in AX	No serious adverse events were reported	16 weeks	6, 12	22/19
Trimarco et al., 2017	Plasma lipid and cardiovascular risk factors	RCT	BP, heart rate, body weight, waist circumference, lipid and glucose profile, plasma levels of insulin, and HbA1c were assessed at baseline and 16 weeks. LDL, TC, and TG levels, as well as plasma glucose levels, HbA1c,and insulin, and average BP were significantly reduced with AX	7 reported minor adverse events, none of which could be directly attributed to AX	16 weeks	0.5	170
Tsukahara, Fukuhara, & Takehara, 2005	Long-term safety	OL	Body weight, BMI, BP, and comprehensive hematological and urine analyses were conducted at baseline, 4, 8, and 12 weeks. No clinically relevant negative effects on any of the measured parameters were observed	No adverse events observed	12 weeks	6	15
Tsukahara et al., 2008	Blood flow and shoulder stiffness	OL	Blood flow change and subjective questionnaires were measured at baseline and 4 weeks. Blood flow in shoulders increased significantly, physical symptoms including stiffness, fatigue, irritation coldness, and so forth significantly improved with AX	No clinical differences in safety parameters, no adverse events observed	4 weeks	6	13
Uchiyama, 2008	Metabolic syndrome	OL	Subjective symptoms, hematology, blood chemistry, blood coagulation system, glucose and lipid metabolism, physical parameters, and urinalysis were investigated at baseline and 3 months. HbAc1 and TNF-α significantly decreased, adiponectin significantly increased with AX	No adverse events related to AX, other than red stool.	3 months	16	17
Urakaze et al., 2018a	Glycemic control and lipid profile	RCT	TG, TC, HDL, LDL, glucose, and HbA1c levels were measured at baseline and 12 weeks. Glucose, HbA1c, and LDL were significantly reduced with AX	None reported	12 weeks	12	22
Urakaze, Kobashi, Satou, et al., 2018b	Glucose tolerance in nondiabetic subjects	RCT	Matsuda index, hepatic insulin resistance, muscle insulin sensitivity, glucose, and HbA1c were measured at baseline and 4 weeks. Glucose level and HbA1c were reduced, Matsuda index and hepatic insulin resistance improved with AX	None reported	12 weeks	12	16
Yamashita, 2002	Skin parameters	RCT	Questionnaire, inspection, skin moisture content, sebum content, and skin surface measurements were conducted at baseline and 4 weeks. Self-assessment and inspection reported	None reported	4 weeks	2	8

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TABLE 3 (Continued)

References	Investigation	Study design	Therapeutic endpoints and outcomes	Adverse effects	Duration	Daily AX (mg)	Subjects[a]
			improvement, moisture content increased significantly with AX				
Yamashita, 2006	Skin parameters	RCT	Questionnaire, inspection, skin moisture content, elasticity, and surface measurements were conducted at baseline, 3, and 6 weeks. Self-assessment and inspection reported improvement, moisture content increased significantly, elasticity and skin surface improved with AX	None reported	6 weeks	4	28
Yoon et al., 2014	Skin parameters	OBS	Elasticity and hydration properties of facial skin were evaluated noninvasively, further, expression of Procollagen Type I, fibrillin-1, MMP-1 and -12, and UV-induced DNA damage in artificially UV-irradiated buttock skin were evaluated at baseline and 12 weeks. Skin elasticity and TEWL improved, expression of Procollagen Type I increased and expression of MMP-1 and -12 decreased with AX	No subjective adverse events were reported	12 weeks	2	44
Yoshida et al., 2010	Dyslipidemia and metabolic syndrome	RCT	Venous blood was collected, and all subjects underwent anthropometric and blood pressure measurements at baseline and 12 weeks. Fasting plasma glucose, adiponectin, TC, TG, LDL, and HDL were determined. TG decreased, HDL increased, and serum adiponectin increased significantly with AX	None reported	12 weeks	6, 12, 18	15/15/16

Abbreviations: 8-OHdG, urinary 8-hydroxy-20-deoxyguanosine; AOPP, advanced oxidation protein products; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ALT, aspartate aminotransferase; AST, alanine aminotransferase; AX, astaxanthin; BAP, biological antioxidant potential; BMI, body mass index; BP, blood pressure; CAVI, cardio ankle vascular index; CFF, critical flicker fusion; CK, creatine kinase; CNSVS, Central Nervous System Vital Signs; CPK, creatine phosphokinase; CS, contrast sensitivity; CSA, cross-sectional area; DHT, dihydrotestosterone; DOMS, delayed onset muscular soreness; d-ROMs, diacron-reactive oxygen metabolites; ES, estradiol; FMD, flow-mediated dilation; FSH, follicle stimulating hormone; GSRS, gastrointestinal symptom rating scale; HAMD17, Hamilton depression scale; HDL, high-density lipoprotein; HFC, high-frequency component; HPLC, high-performance liquid chromatography; HRV, heart rate variability; hs-CRP, high-sensitivity C-reactive protein; HTT, heat tolerance test; IFN, interferon; IL, interleukin; ISP, isoprostane; IUI, intrauterine insemination; LDL, low-density lipoprotein; LH, luteinizing hormone; LSFG, laser speckle flowgraphy; MDA, malondialdehyde; MED, minimal erythema dose; MMP-1, matrix metalloproteinase-1; MSSQ, Medical Student Stressor Questionnaire; MVC, maximal voluntary force; NEI VFQ-25, National Eye Institute visual function questionnaire; OBS, observational study; OL, open label; POMS, Profile of Mood States; PON1, paraoxonase; PVEP, pattern visual evoked potential; PWV, pulse wave velocity; QOL, quality of life; RADs, response amplitude densities; RCT, randomized controlled trial; ROS, reactive oxygen species; RSSCs, residual skin surface components; SBR, square blur rate; SF-36, short-form survey; −SH, sulphydryl group; SSS, Symptom Severity Scale; SOD, superoxide dismutase; SSA, superoxide scavenging activity; TAC, total antioxidant capacity; TBARS, thiobarbituric acid-reactive substances; TC, total cholesterol; TEWL, transepidermal water loss; TG, triglyceride; TNF, tumor necrosis factor; UV, ultraviolet; VA, visual acuity; VAS, visual analog scale.

[a]Number of subjects who received AX and completed the study

[b]According to U.S. Patent #6277417B1, which provides the basis for the composition of the trial product, AX content may have ranged from 0.8–48 mg/day.

[c]According to U.S. Patent #6277417B1, which provides the basis for the composition of the trial product, AX content may have ranged from 0.8–80 mg/day.

[d]AX-rich extract derived from Paracoccus carotinifaciens.

Stewart, Lignell, Pettersson, Elfving, & Soni, 2008), *P. rhodozyma* (Tago et al., 2014), or *P. carotinifaciens* (Katsumata, Ishibashi, & Kyle, 2014) at any dose.

3.4.2 | Synthetic AX

A carcinogenicity study for nongenotoxic and genotoxic effects in mice found no tumorigenic effects, neither benign nor malignant (Buser, Jovanovic, et al., 2003a), even at high dosages (≤1,400 mg/kg body weight per day). However, two rat carcinogenicity studies (Buser, Schierle, Schüep, et al., 2003b; Buser, Schierle, Schüep, et al., 2003c) found hepatocellular vacuolation, hypertrophy, and incidence of multinuclear hepatocytes to be increased in female rats at doses of 200 and 1,000 mg/kg body weight per day. Histological changes and an increase in hepatocellular adenoma, a nonmalignant tumor, occurred in female rats only at very high doses (Buser, Schierle, et al., 2003c). Females showed higher plasma levels of AX compared with male rats. No increase in the incidence of hepatocellular carcinomas was seen and longevity was not affected.

Other studies have found no association between liver or any other organ injury and synthetic AX intake (e.g., Buesen et al., 2015; Vega, Edwards, & Belstein, 2015).

Edwards et al. (2016) conclude that the effects of AX appear to be "species specific" and of "doubtful human relevance," notwithstanding the fact that the only studies describing liver toxicity used very high doses of synthetic AX.

4 | DISCUSSION

Natural AX is marketed in the EU in multiple products at daily doses up to 12 mg and has been approved by national competent authorities around the world at daily doses up to 24 mg. Human studies have not identified any significant toxicity at any doses over any length of time for natural AX in at least 87 clinical trials involving 2,000+ participants using short-term daily doses (up to 100 mg) and long-term daily doses averaging between 8 and 12 mg. No severe adverse events were recorded. No indicators of liver toxicity (such as elevated enzymes) were reported in any clinical studies. Reddening of stool is a minor adverse event occurring at high doses.

Considering the available regulatory, preclinical, and clinical data, there appear to be no applicable safety concerns for natural AX supplementation at levels of at least 12 mg/day. Regarding synthetic AX, the rat toxicity study by Buser, Jovanovic, et al. (2003a) used doses of 200 and 1,000 mg body weight per day, whereas a daily intake of 12 mg for a 50-kg human equates to 0.24 mg/kg body weight per day. Although synthetically produced AX has only demonstrated species-specific effects at very high doses, it must be considered unique and should not be introduced for direct human use (in contrast to animal feed) until safety parameters are established and human clinical trials showing potential benefits have been conducted.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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How to cite this article: Brendler T, Williamson EM. Astaxanthin: How much is too much? A safety review. *Astaxanthin: how much is too much?*. 2019;1–22. https://doi.org/10.1002/ptr.6514