Lipid profile and glucose changes after supplementation with astaxanthin: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Introduction: Many studies have shown that oral supplementation with astaxanthin may be a novel potential treatment for inflammation and oxidative stress in cardiovascular diseases, but evidence of the effects on lipid profile and glucose is still inconclusive. Therefore, we performed a meta-analysis to evaluate the efficacy of astaxanthin supplementation on plasma lipid and glucose concentrations.

Material and methods: The search included PubMed, Cochrane Library, Scopus, and EMBASE (up to November 27, 2014) to identify randomized controlled trials (RCTs) investigating the effects of astaxanthin supplementation on lipid profile and glucose levels. Two independent reviewers extracted data on study characteristics, methods and outcomes.

Results: Seven studies meeting inclusion criteria with 280 participants were selected for this meta-analysis; 163 participants were allocated to the astaxanthin supplementation group and 117 to the control group. A random-effect meta-analysis of data from 7 RCTs (10 treatment arms) did not show any significant effect of supplementation with astaxanthin on plasma concentrations of total cholesterol (weighted mean difference (WMD): –1.52 mg/dl, 95% CI: –8.69 to –5.66, $p = 0.679$), LDL-C (WMD: +1.25 mg/dl, 95% CI: –6.70 to +9.21, $p = 0.758$), HDL-C (WMD: +1.75 mg/dl, 95% CI: –0.92 to +4.42, $p = 0.199$), triglycerides (WMD: –4.76 mg/dl, 95% CI: –21.52 to +12.00, $p = 0.578$), or glucose (WMD: –2.65 mg/dl, 95% CI: –5.84 to +0.54, $p = 0.103$). All these effect sizes were robust, and omission of any of the included studies did not significantly change the overall estimate.

Conclusions: This meta-analysis of data from 10 RCT arms did not indicate a significant effect of supplementation with astaxanthin on plasma lipid profile, but a slight glucose-lowering effect was observed. Further, well-designed trials are necessary to validate these results.

Key words: astaxanthin, lipids, antioxidants, glucose.

Introduction

Astaxanthin (ASTX) is a lipophilic, pinkish-orange carotenoid (3,3'-dihydroxy-β,β-carotene-4,4'-dione) found in algae, seafood (crustacean

shells, crab, shrimps, fish) and various plants, giving them their exclusive colored aspect [1]. Presently, the main source of ASTX is the microalga *Haematococcus pluvialis*, containing the maximum concentrations [2]. Astaxanthin is also used as a dietary additive in the USA, Japan, South Korea and Sweden [3]. Like other carotenoids, ASTX manifests high protective antioxidant [4, 5] and anticancer [6–8] properties, reduces oxidative stress and inflammation [9–11], reduces rethrombosis after thrombolysis [12] and is efficient in ischemia-reperfusion [13, 14], arterial hypertension [15, 16] and dyslipidemia [15, 17]. Astaxanthin is considered the most powerful natural carotenoid antioxidant, being 65 times more potent than vitamin C, 54 times more than β-carotene, 14 times more than vitamin E, and 10 times more powerful than zeaxanthin, lutein and canthaxanthin [18, 19]. However, the powerful antioxidant capacity of ASTX is at least moderately caused by its distinctive chemical structure, its polar ends interacting with phospholipid head groups or water in the aqueous condition, suppressing radicals from the surface or inside the lipid bilayer [20]. Moreover, *cis*-ASTX usually accumulates in blood plasma compared with the *trans* form, as a consequence of evident smaller chain lengths [21].

In an *in vitro* membrane model, ASTX preserved the membrane consistency and successfully inhibited the formation of lipid peroxide, in contrast to lutein and β-carotene, which damaged the structure of the membrane and raised lipid hydroperoxide levels [22]. Moreover, ASTX reduces cellular lipid accumulation in lipid-loaded hepatocytes by acting as a peroxisome proliferator-activated receptor α (PPAR-α) agonist and PPAR-γ antagonist [23]. An experimental study proved that ASTX consumes increased peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) in skeletal muscle, leading to acceleration of lipid usage, as a result of initialization of mitochondrial aerobic metabolism [24]. Furthermore, it has been shown that ASTX is more efficient than many antioxidants for decreasing liver weight and abdominal fat-pad weight in obese mice [25].

The evidence of the effects of ASTX on lipid profile and glucose are based on relatively small sample sizes and are still inconclusive. Therefore, a meta-analysis was performed to evaluate the efficacy of ASTX supplementation on plasma lipid and glucose concentrations.

Material and methods

Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [1]. SCOPUS (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): ("randomized controlled trial" or randomized or placebo or cholesterol or triglyceride or LDL or LDL-C or LDL-cholesterol or HDL or HDL-C or HDL-cholesterol or hyperlipidemia or hyperlipidemic or hypolipidemic or dyslipidemia or dyslipidemic) and (astaxanthin). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in humans. The literature was searched from inception to November 27, 2014.

Study selection

Original studies were included if they met the following inclusion criteria: (i) a randomized clinical case-control or case-crossover trial, (ii) investigated the impact of ASTX on plasma/serum concentrations of at least one of the main lipid parameters (i.e. total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) or triglycerides), (iii) presentation of sufficient information on plasma/serum lipid levels at baseline and at the end of the study in both ASTX and control groups, and (iv) administering ASTX for a period of at least 2 weeks. Exclusion criteria were (i) non-clinical studies, (ii) uncontrolled trials, (iii) using non-standardized preparations containing ASTX, and (iv) lack of sufficient information on baseline or follow-up lipid concentrations. Exclusion of an article for the latter reason was applied if no feedback was received after contacting the author(s).

Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) number of participants in the spirulina and control groups; 5) age, gender and body mass index (BMI) of study participants; 6) circulating concentrations of total cholesterol, LDL-C, HDL-C, triglycerides and glucose; 7) systolic and diastolic blood pressures; 8) homeostasis model assessment-estimated insulin resistance (HOMA-IR) index; and 9) prevalence of smoking, type 2 diabetes, dyslipidemia, hypertension and coronary heart disease (CHD).

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [26]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing dropouts (incomplete outcome data), selective

outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

Quantitative data synthesis

A meta-analysis was conducted using the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [27]. Plasma lipid (total cholesterol, LDL-C, HDL-C and triglycerides) and glucose concentrations were collated in mg/dl. Multiplication by 38.6 and 88.5 was used to convert cholesterol (total cholesterol, HDL-C or LDL-C) and triglyceride, respectively, expressed in mmol/l into mg/dl. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. In case of reporting SEM, SD was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel and crossover trials, as follows: (measure at end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at end of follow-up in the control group – measure at baseline in the control group). A random-effects model and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of study design, ASTX dose and demographic characteristics (e.g. age, gender, underlying disease and comorbidities) of populations studied. In order to avoid double counting of subjects and consequent unit-of-analysis error in the trials with more than 1 treatment arm, the control group was evenly (where possible) split. Effect size was expressed as weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach [28, 29].

Meta-regression

Random-effects meta-regression was performed using the unrestricted maximum likelihood method to evaluate the association between calculated WMD in plasma lipids and glucose concentrations with ASTX dose in individual studies.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie's "trim and fill" method was used to adjust the analysis for the effects of publication bias [30].

Results

Search results and trial flow

The initial screening for potential relevance removed articles whose titles and/or abstracts were obviously irrelevant. Among the 26 full text articles assessed for eligibility, 19 studies were excluded: 15 because of not assessing lipid parameters, 2 because of not having a controlled design, and 2 because of not having a randomized design (Figure 1). After final assessment, 7 randomized con-

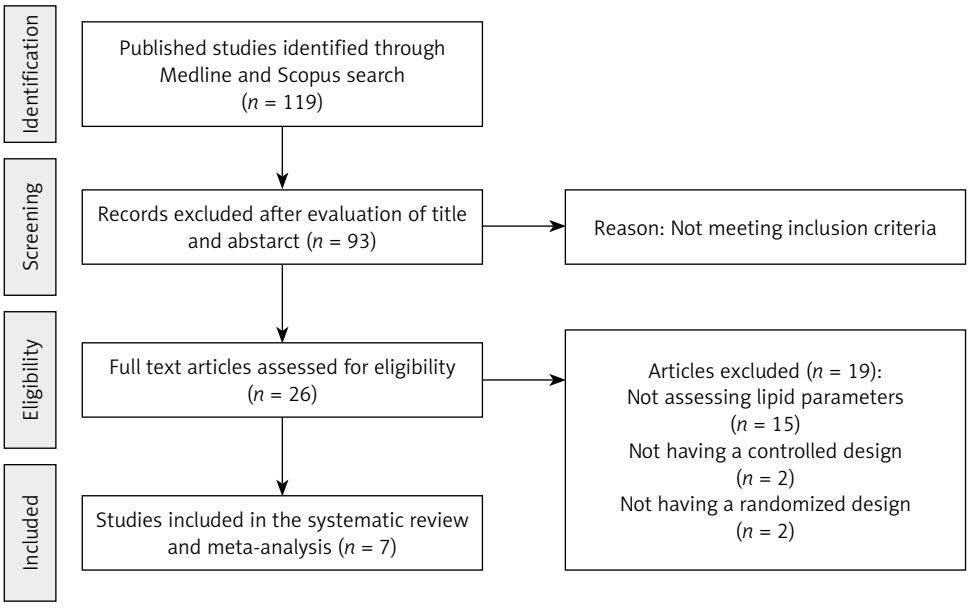


Figure 1. Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of the impact of astaxanthin supplementation on plasma lipid concentrations

trolled trials (RCTs) fulfilled the inclusion criteria and were preferred for the final meta-analysis. In total, 280 participants were randomized, of whom 163 were allocated to the ASTX supplementation group and 117 to the control group in the selected studies. The number of participants in these trials ranged from 20 to 63. Included studies were published between 2007 and 2013, and were conducted in Serbia, South Korea, Finland, Canada and Japan (3 trials). Doses ranging from 4 mg to 20 mg ASTX/day were administered in the included trials. Duration of supplementation with ASTX ranged from 4 weeks to 3 months. All 7 trials were designed as parallel-group studies, comprising a total of 10 treatment arms. Demographic and baseline parameters of the included studies are shown in Table I. The risk of bias of the included trials according to Cochrane quality assessment tool is shown in Figure 2.

Quantitative data synthesis

The random-effect meta-analysis of data from 7 RCTs (10 treatment arms) did not show any significant effect of supplementation with ASTX on plasma concentrations of total cholesterol (WMD: –1.52 mg/dl, 95% CI: –8.69 to –5.66, p = 0.679) (Figure 2), LDL-C (WMD: +1.25 mg/dl, 95% CI: –6.70 to +9.21, p = 0.758) (Figure 3), HDL-C (WMD: +1.75 mg/dl, 95% CI: –0.92 to +4.42, p = 0.199) (Figure 4), triglycerides (WMD: –4.76 mg/dl, 95% CI: –21.52 to +12.00, p = 0.578) (Figure 5), and glucose (WMD: –2.65 mg/dl, 95% CI: –5.84 to +0.54, p = 0.103) (Figure 6). All these effect sizes were robust, and omission of any of the included studies did not significantly change the overall estimate (Figures 2–7).

Meta-regression analysis

Since different doses of ASTX were used among the included trials, a meta-regression analysis was conducted to evaluate the association between changes in plasma lipids and glucose concentrations and ASTX dose as a potential moderator variable. The results of the meta-regression did not suggest any significant dose-response association for the impact of ASTX on evaluated parameters, i.e. total cholesterol (slope: –0.44; 95% CI: –2.80 to +1.91; p = 0.712), LDL-C (slope: –0.054; 95% CI: –1.45 to +1.34; p = 0.940), HDL-C (slope: +0.119; 95% CI: –0.34 to +0.58; p = 0.609), triglycerides (slope: –2.50; 95% CI: –4.74 to –0.25; p = 0.029) and glucose (slope: –0.19; 95% CI: –1.19 to +0.80; p = 0.701) (Figure 8).

Publication bias

Visual inspection of the funnel plot of the study precision (inverse SEM) by effect size (mean difference) suggested asymmetry for the impact of ASTX on total cholesterol, LDL-C, HDL-C and glucose. Using the trim-and-fill method, 3, 4, 1 and 3 potentially missing studies were imputed for the analysis of total cholesterol, LDL-C, HDL-C and glucose, respectively. The imputed effect size of ASTX on plasma levels of total cholesterol (WMD: –3.32 mg/dl, 95% CI: –8.70 to +5.66), LDL-C (WMD: –2.32 mg/dl, 95% CI: –9.08 to +4.45), and HDL-C (WMD: +1.85 mg/dl, 95% CI: –0.79 to +4.49) was not significant, but a slight glucose-lowering effect was observed following imputation (WMD: –4.01 mg/dl, 95% CI: –6.78 to –1.25). As for plasma triglyceride concentrations, there was no sign of asymmetry in the funnel plot (Figure 9).

In addition to visual inspection of funnel plots, presence of publication bias was explored using Begg's rank correlation test and Egger's linear regression test. None of these tests indicated evidence of publication bias for the impact of ASTX on the evaluated parameters, apart from significant evidence of bias for the effects of ASTX on plasma glucose levels according to Egger's test (Table II).

Discussion

To our knowledge, the present systematic review and meta-analysis is the first to assess the effects of ASTX supplementation on lipid profile and glucose concentrations and provides a thorough synthesis of results from RCTs. In contrast to the findings from some studies [31, 32], no significant effect of supplementation with ASTX on plasma lipid profile, but a slight glucose-lowering effect was observed. This effect size was robust in sensitivity analysis, and omission of each individual study did not have a significant effect.

Astaxanthin improved lipid metabolism in a few experimental and human studies [33]. It was speculated that the underlying molecular mechanisms for the supposed hypolipidemic effect of ASTX may be modulated by peroxisome proliferator-activated receptors (PPARs). A recent study investigated the effects of ASTX on key molecules in cholesterol efflux from macrophages, such as ATP-binding cassette transporters (ABC) A1 and G1. The study revealed that ASTX did not modify PPAR-γ, liver X receptor (LXR) α and LXRβ levels, but increased the expression of ATP-binding cassette transporter A1/G1 and the efflux of cholesterol from macrophages [34]. Another study showed that ASTX increases the levels of apoA1- and HDL-mediated macrophage cholesterol efflux via upregulation of expression of ABCA1 and ABCG1 [34]. Since ASTX is a PPAR-α agonist and PPAR-γ antagonist, it has been shown to be able to reduce hepatic lipid deposits by rewiring the

Table I. Demographic characteristics of the included studies

Parameter		Study						
	Case/Control	Baralic *et al.* [49]	Choi *et al.* [9]	Karppi *et al.* [50]	MacDermid *et al.* [51]	Nakagawa *et al.* [52]	Saito *et al.* [53]	Yoshida *et al.* [33]
Year		2013	2011	2007	2012	2011	2012	2010
Jadad score		4	4	4	5	4	4	4
Location		Serbia	South Korea	Finland	Canada	Japan	Japan	Japan
Design		Randomized double-blind, placebo-controlled parallel-group trial	Randomized double-blind, placebo-controlled, parallel-group trial	Randomized double-blind, placebo-controlled parallel-group trial	Randomized triple-blind controlled parallel-group trial	Randomized, double-blind placebo-controlled, parallel-group trial	Randomized, double-blind placebo-controlled, parallel-group trial	Randomized, double-blind placebo-controlled, parallel-group trial
Duration of trial		12 weeks	12 weeks	3 months	12 weeks	12 weeks	4 weeks	12 weeks
Inclusion criteria		Healthy male soccer players, non-smokers, with no ongoing or previous (during last year) injuries and no use of any medication or antioxidant supplements for at least 3 months	Overweight adults (aged 20–55 years; BMI > 25.0 kg/m^2)	Healthy non-smoking male volunteers aged 19–33 years with no severe diseases or malabsorption	Patients presenting with symptoms of primary carpal tunnel syndrome aged 18–65 years	Subjects recruited from the Anti-Aging Science volunteer database	Healthy volunteers	Healthy subjects with serum triglyceride levels of 120–200 mg/dl
Astaxanthin form		Capsules	Capsules	Capsules	Capsules	Capsules	Capsules	Capsules
Astaxanthin intervention		4 mg/day	20 mg/day	2 × 4 mg/day	4 mg/day	6 mg/day[a]	2 × 6 mg/day	6 mg/day[a]
						12 mg/day[b]		12 mg/day[b]
								18 mg/day[c]
Participants	Case	21	14	20	32	10[a]	10	15[a]
						10[b]		15[b]
								16[c]
	Control	19	13	19	31	10	10	15
Age [years]	Case	17.91 ±0.16	31.1 ±9.4	23.1 ±2.3	49 ±7	56.3 ±6.6[a]	38.2 ±11.7	47.0 ±7.0[a]
						56.1 ±5.1[b]		42.8 ±8.8[b]
								43.8 ±10.4[c]
	Control	17.62 ±0.14	30.1 ±9.5	25.7 ±3.3	49 ±9	56.6 ±4.4	38.8 ±6.8	44.3 ±7.0

Table I. Cont.

Parameter	Study						
	Case/Control	Baralic *et al.* [49]	Choi *et al.* [9]	Karppi *et al.* [50]	MacDermid *et al.* [51]	Nakagawa *et al.* [52]	Saito *et al.* [53]	Yoshida *et al.* [33]
Male (%)	Case	100.0	85.71	100.0	30.0	50.0[a]	20.0	66.67[a]
						50.0[b]		66.67[b]
								68.75[c]
	Control	100.0	84.61	100.0	25.0	50.0	30.0	66.67
BMI [kg/m^2]	Case	22.37 ±0.33	28.1 ±2.4	23.8 ±2.2	NS	27.4 ±2.2[a]	25.4 ±5.0	23.6 ±3.2[a]
						27.6 ±2.1[b]		23.0 ±2.2[b]
								23.9 ±7.0[c]
	Control	22.24 ±0.41	26.3 ±1.3	23.8 ±2.3	NS	27.7 ±2.1	26.0 ±4.1	25.1 ±2.8
Total cholesterol [mg/dl]	Case	165.21 ±7.72	178.3 ±3.54	174.47 ±25.86	223.88 ±27.02	226.0 ±39.0[a]	190.1 ±32.9	219.0 ±29.0[a]
						203.0 ±23.0[b]		215.0 ±22.0[b]
								234.0 ±29.0[c]
	Control	175.24 ±8.88	174.8 ±30.6	180.65 ±25.48	193.0 ±34.74	218.0 ±44.0	194.7 ±24.1	209.0 ±31.0
LDL-C [mg/dl]	Case	101.52 ±7.33	127.9 ±35.0	99.59 ±22.0	142.82 ±19.3	132.0 ±37.0[a]	NS	141.0 ±26.0[a]
						117.0 ±20.0[b]		136.0 ±27.0[b]
								157.0 ±25.0[c]
	Control	114.64 ±9.26	120.1 ±39.7	108.08 ±23.93	111.94 ±27.02	135.0 ±35.0	NS	135.0 ±32.0
HDL-C [mg/dl]	Case	49.02 ±1.93	47.2 ±10.2	48.64 ±12.74	46.32 ±11.58	68.8 ±19.0[a]	72 ±17.4	51.0 ±11.0[a]
						58.8 ±12.1[b]		55.0 ±8.0[b]
								51.0 ±6.0[c]
	Control	49.79 ±2.70	48.6 ±8.19	49.02 ±7.33	46.32 ±15.44	58.8 ±14.7	74.7 ±17.7	52.0 ±10.0
Triglycerides [mg/dl]	Case	74.34 ±10.62	110.6 ±51.5	107.08 ±73.45	168.5 ±70.8	111.0 ±78.0[a]	56.0 ±21.6	151.0 ±23.0[a]
						125.0 ±73.0[b]		147.0 ±21.0[b]
								151.0 ±26.0[c]
	Control	84.07 ±12.39	113.4 ±40.5	95.58 ±30.09	221.25 ±194.7	125.0 ±52.0	81.1 ±48.9	145.0 ±21.0
Glucose [mg/dl]	Case	NS	NS	NS	NS	102.0 ±11.0[a]	88.0 ±6.6	95.0 ±7.0[a]
						101.0 ±6.0[b]		98.0 ±5.0[b]
								98.0 ±10.0[c]
	Control	NS	NS	NS	NS	101.0 ±6.0	83.8 ±6.4	98.0 ±12.0

Values are expressed as mean ± SD. BMI – body mass index, NS – not stated, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, [a]6 mg/day astaxanthin group; [b]12 mg/day astaxanthin group; [c]18 mg/day astaxanthin group.

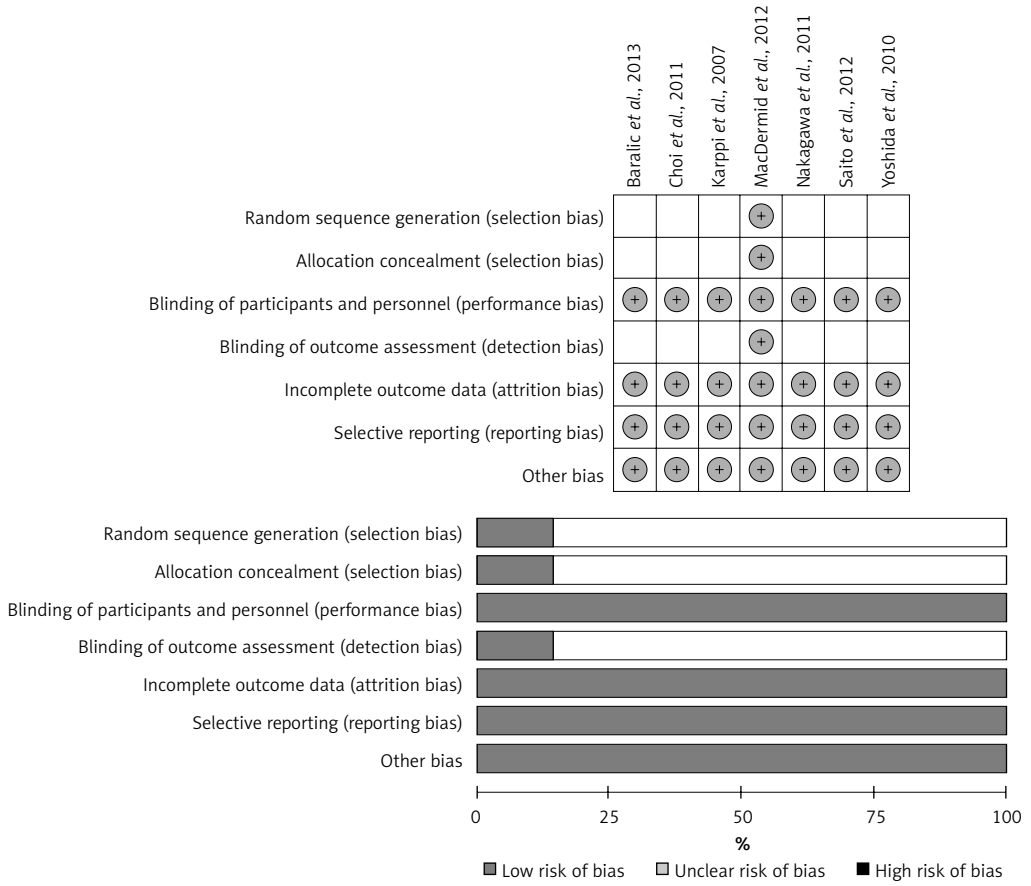
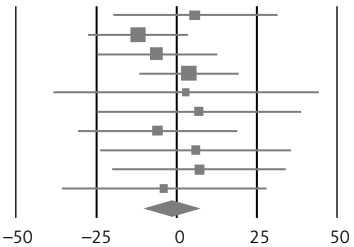


Figure 2. Plots showing the risk of bias of the included trials according to Cochrane quality assessment tool

Study name	Statistics for each study							Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value	
Baralic *et al.*, 2013	5.790	12.944	167.548	–19.580	31.160	0.447	0.655	
Choi *et al.*, 2011	–12.000	7.992	63.866	–27.663	3.663	–1.502	0.133	
Karppi *et al.*, 2007	–6.180	9.577	91.727	–24.951	12.591	–0.645	0.519	
MacDermid *et al.*, 2012	3.860	7.837	61.421	–11.501	19.221	0.493	0.622	
Nakagawa *et al.*, 2011a	3.000	21.074	444.115	–38.304	44.304	0.142	0.887	
Nakagawa *et al.*, 2011b	7.000	16.115	259.685	–24.584	38.584	0.434	0.664	
Saito *et al.*, 2012	–5.900	12.671	160.548	–30.734	18.934	–0.466	0.641	
Yoshida *et al.*, 2010a	6.000	15.123	228.711	–23.641	35.641	0.397	0.692	
Yoshida *et al.*, 2010b	7.000	13.804	190.548	–20.055	34.055	0.507	0.612	
Yoshida *et al.*, 2010c	–4.000	16.206	262.624	–35.763	27.763	–0.247	0.805	
	–1.518	3.662	13.411	–8.695	5.660	–0.414	0.679	



Study name	Statistics with study removed							Difference in means (95% CI) with study removed
	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value	
Yoshida *et al.*, 2010a	–1.986	3.774	14.246	–9.383	5.412	–0.526	0.599	
Yoshida *et al.*, 2010b	–2.162	3.798	14.426	–9.607	5.282	–0.569	0.569	
Yoshida *et al.*, 2010c	–1.384	3.759	14.132	–8.752	5.984	–0.368	0.713	
Saito *et al.*, 2012	–1.118	3.825	14.633	–8.616	6.379	–0.292	0.770	
Nakagawa *et al.*, 2011a	–1.658	3.719	13.828	–8.947	5.630	–0.446	0.656	
Nakagawa *et al.*, 2011b	–1.981	3.760	14.141	–9.352	5.389	–0.527	0.598	
MacDermid *et al.*, 2012	–3.020	4.142	17.156	–11.138	5.099	–0.729	0.466	
Karppi *et al.*, 2007	–0.719	3.963	15.707	–8.487	7.048	–0.181	0.856	
Choi *et al.*, 2011	1.269	4.120	16.975	–6.807	9.344	0.308	0.758	
Baralic *et al.*, 2013	–2.153	3.818	14.577	–9.637	5.330	–0.564	0.573	
	–1.518	3.662	13.411	–8.695	5.660	–0.414	0.679	

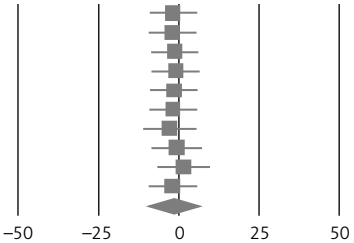
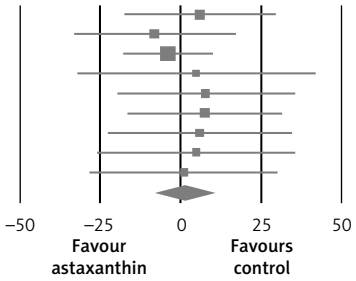


Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of astaxanthin supplementation on plasma total cholesterol concentrations (upper graph). Leave-one-out sensitivity analysis is shown in the lower graph

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Baralic *et al*., 2013	6.180	11.990	143.765	–17.320	29.680	0.515	0.606
Choi *et al*., 2011	–8.000	12.878	165.840	–33.240	17.240	–0.621	0.534
MacDermid *et al*., 2012	–3.860	7.069	49.968	–17.715	9.995	–0.546	0.585
Nakagawa *et al*., 2011a	5.000	18.869	356.054	–31.983	41.983	0.265	0.791
Nakagawa *et al*., 2011b	8.000	14.108	199.038	–19.651	35.651	0.567	0.571
Saito *et al*., 2012	7.720	12.276	150.711	–16.341	31.781	0.629	0.529
Yoshida *et al*., 2010a	6.000	14.578	212.504	–22.571	34.571	0.412	0.681
Yoshida *et al*., 2010b	5.000	15.655	245.067	–25.682	35.682	0.319	0.749
Yoshida *et al*., 2010c	1.000	14.989	224.659	–28.377	30.377	0.067	0.947
	1.253	4.059	16.473	–6.702	9.208	0.309	0.758



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Yoshida *et al*., 2010a	0.098	4.516	20.931	–8.752	8.949	0.022	0.983
Yoshida *et al*., 2010b	0.255	4.487	20.134	–8.540	9.049	0.057	0.955
Yoshida *et al*., 2010c	0.580	4.504	20.285	–8.247	9.408	0.129	0.897
Saito *et al*., 2012	–0.386	4.607	21.226	–9.415	8.644	–0.084	0.933
Nakagawa *et al*., 2011a	1.704	4.578	20.956	–7.269	10.676	0.372	0.710
Nakagawa *et al*., 2011b	–0.146	4.530	20.524	–9.026	8.733	–0.032	0.974
MacDermid *et al*., 2012	3.270	5.444	29.642	–7.401	13.941	0.601	0.548
Choi *et al*., 2011	1.704	4.578	20.956	–7.269	10.676	0.372	0.710
	0.615	4.313	18.605	–7.839	9.069	0.143	0.887

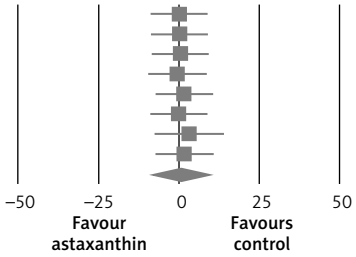
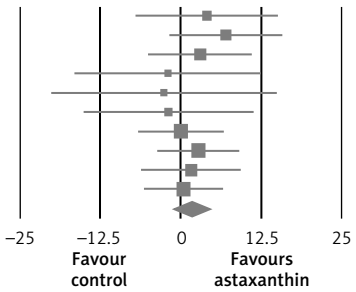


Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of astaxanthin supplementation on plasma LDL-C concentrations. Leave-one-out sensitivity analysis is shown in the lower graph

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Yoshida *et al*., 2010a	4.000	5.628	31.674	–7.031	15.031	0.711	0.477
Yoshida *et al*., 2010b	7.000	4.456	19.852	–1.733	15.733	1.571	0.116
Yoshida *et al*., 2010c	3.000	4.112	16.911	–5.060	11.060	0.730	0.466
Saito *et al*., 2012	–2.000	7.405	54.828	–16.513	12.513	–0.270	0.787
Nakagawa *et al*., 2011a	–2.600	8.931	79.755	–20.104	14.904	–0.291	0.771
Nakagawa *et al*., 2011b	–1.900	6.695	44.826	–15.022	11.222	–0.284	0.777
MacDermid *et al*., 2012	0.000	3.431	11.774	–6.725	6.725	0.000	1.000
Karppi *et al*., 2007	2.700	3.259	10.623	–3.688	9.088	0.828	0.407
Choi *et al*., 2011	1.600	3.910	15.285	–6.063	9.263	0.409	0.682
Baralic *et al*., 2013	0.390	3.148	9.909	–5.780	6.560	0.124	0.901
	1.748	1.361	1.853	–0.920	4.416	1.284	0.199



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Yoshida *et al*., 2010a	1.608	1.403	1.968	–1.142	4.358	1.146	0.252
Yoshida *et al*., 2010b	1.207	1.430	2.044	–1.595	4.009	0.844	0.399
Yoshida *et al*., 2010c	1.594	1.443	2.081	–1.234	4.421	1.105	0.269
Saito *et al*., 2012	1.879	1.385	1.918	–0.836	4.593	1.357	0.175
Nakagawa *et al*., 2011a	1.851	1.377	1.897	–0.849	4.551	1.344	0.179
Nakagawa *et al*., 2011b	1.905	1.390	1.933	–0.820	4.630	1.370	0.171
MacDermid *et al*., 2012	2.074	1.483	2.200	–0.833	4.981	1.399	0.162
Karppi *et al*., 2007	1.546	1.498	2.245	–1.390	4.483	1.032	0.302
Choi *et al*., 2011	1.768	1.452	2.109	–1.078	4.614	1.218	0.223
Baralic *et al*., 2013	2.060	1.510	2.280	–0.899	5.019	1.364	0.172
	1.748	1.361	1.853	–0.920	4.416	1.284	0.199

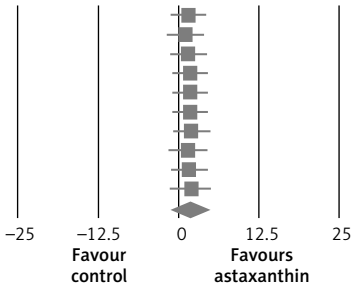
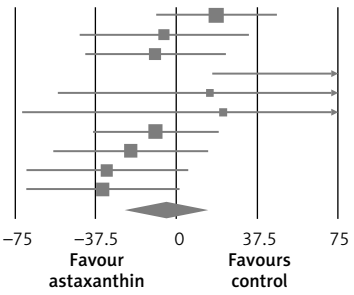


Figure 5. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of astaxanthin supplementation on plasma HDL-C concentrations. Leave-one-out sensitivity analysis is shown in the lower graph

Study name	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Baralic *et al.*, 2013	18.580	14.277	203.840	–9.403	46.563	1.301	0.193
Choi *et al.*, 2011	–5.500	20.045	401.790	–44.787	33.787	–0.274	0.784
Karppi *et al.*, 2007	–9.730	16.677	278.126	–42.417	22.957	–0.583	0.560
MacDermid *et al.*, 2012	79.650	32.399	1049.691	16.149	143.151	2.458	0.014
Nakagawa *et al.*, 2011a	16.000	36.311	1318.500	–55.169	87.169	0.441	0.659
Nakagawa *et al.*, 2011b	22.000	47.807	2285.515	–71.700	115.700	0.460	0.645
Saito *et al.*, 2012	–9.300	14.886	221.599	–38.476	19.876	–0.625	0.532
Yoshida *et al.*, 2010a	–21.000	18.274	333.956	–56.817	14.817	–1.149	0.250
Yoshida *et al.*, 2010b	–32.000	19.301	372.533	–69.830	5.830	–1.658	0.097
Yoshida *et al.*, 2010c	–34.000	17.959	322.516	–69.198	1.198	–1.893	0.058
	–4.757	8.552	73.142	–21.520	12.005	–0.556	0.578



Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Baralic *et al.*, 2013	–9.347	8.761	76.747	–26.517	7.824	–1.067	0.286
Yoshida *et al.*, 2010c	–1.011	8.795	77.345	–18.248	16.226	–0.115	0.908
Choi *et al.*, 2011	–4.252	9.639	92.919	–23.145	14.641	–0.441	0.659
Karppi *et al.*, 2007	–3.535	9.854	97.108	–22.849	15.779	–0.359	0.720
MacDermid *et al.*, 2012	–9.235	6.486	42.064	–21.947	3.477	–1.424	0.154
Nakagawa *et al.*, 2011a	–5.602	9.028	81.511	–23.297	12.093	–0.621	0.535
Nakagawa *et al.*, 2011b	–5.412	8.921	79.578	–22.896	12.072	–0.607	0.544
Saito *et al.*, 2012	–3.453	10.017	100.331	–23.085	16.179	–0.345	0.730
Yoshida *et al.*, 2010a	–2.328	9.494	90.143	–20.937	16.281	–0.245	0.806
Yoshida *et al.*, 2010b	–1.441	8.984	80.719	–19.050	16.168	–0.160	0.873
	–4.757	8.552	73.142	–21.520	12.005	–0.556	0.578

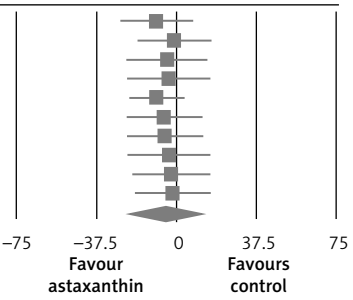
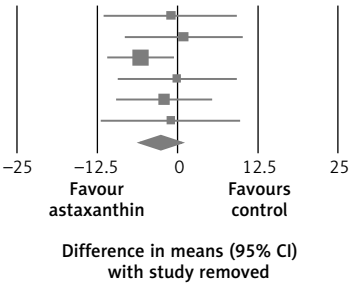


Figure 6. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of astaxanthin supplementation on plasma triglyceride concentrations. Leave-one-out sensitivity analysis is shown in the lower graph

Study name	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Nakagawa *et al.*, 2011a	–1.000	5.291	27.992	–11.370	9.370	–0.189	0.850
Nakagawa *et al.*, 2011b	1.000	4.665	21.762	–8.143	10.143	0.214	0.830
Saito *et al.*, 2012	–5.700	2.607	6.797	–10.810	–0.590	–2.186	0.029
Yoshida *et al.*, 2010a	0.000	4.667	21.778	–9.146	9.146	0.000	1.000
Yoshida *et al.*, 2010b	–2.000	3.783	14.311	–9.415	5.415	–0.529	0.597
Yoshida *et al.*, 2010c	–1.000	5.509	30.353	–11.798	9.798	–0.182	0.856
	–2.652	1.627	2.649	–5.841	0.538	–1.629	0.103



Study name	Statistics with study removed						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*P*-value
Nakagawa *et al.*, 2011a	–2.824	1.710	2.926	–6.177	0.528	–1.651	0.099
Nakagawa *et al.*, 2011b	–3.158	1.737	3.016	–6.561	0.246	–1.818	0.069
Saito *et al.*, 2012	–0.705	2.083	4.340	–4.788	3.378	–0.338	0.735
Yoshida *et al.*, 2010a	–3.019	1.737	3.015	–6.422	0.385	–1.738	0.082
Yoshida *et al.*, 2010b	–2.800	1.803	3.250	–6.333	0.734	–1.553	0.120
Yoshida *et al.*, 2010c	–2.809	1.704	2.902	–6.148	0.529	–1.649	0.099
	–2.652	1.627	2.649	–5.841	0.538	–1.629	0.103

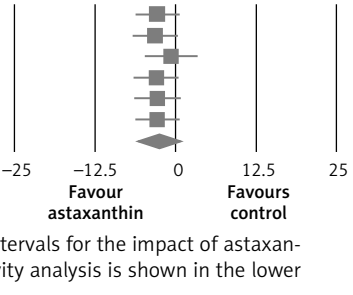


Figure 7. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of astaxanthin supplementation on plasma glucose concentrations. Leave-one-out sensitivity analysis is shown in the lower graph

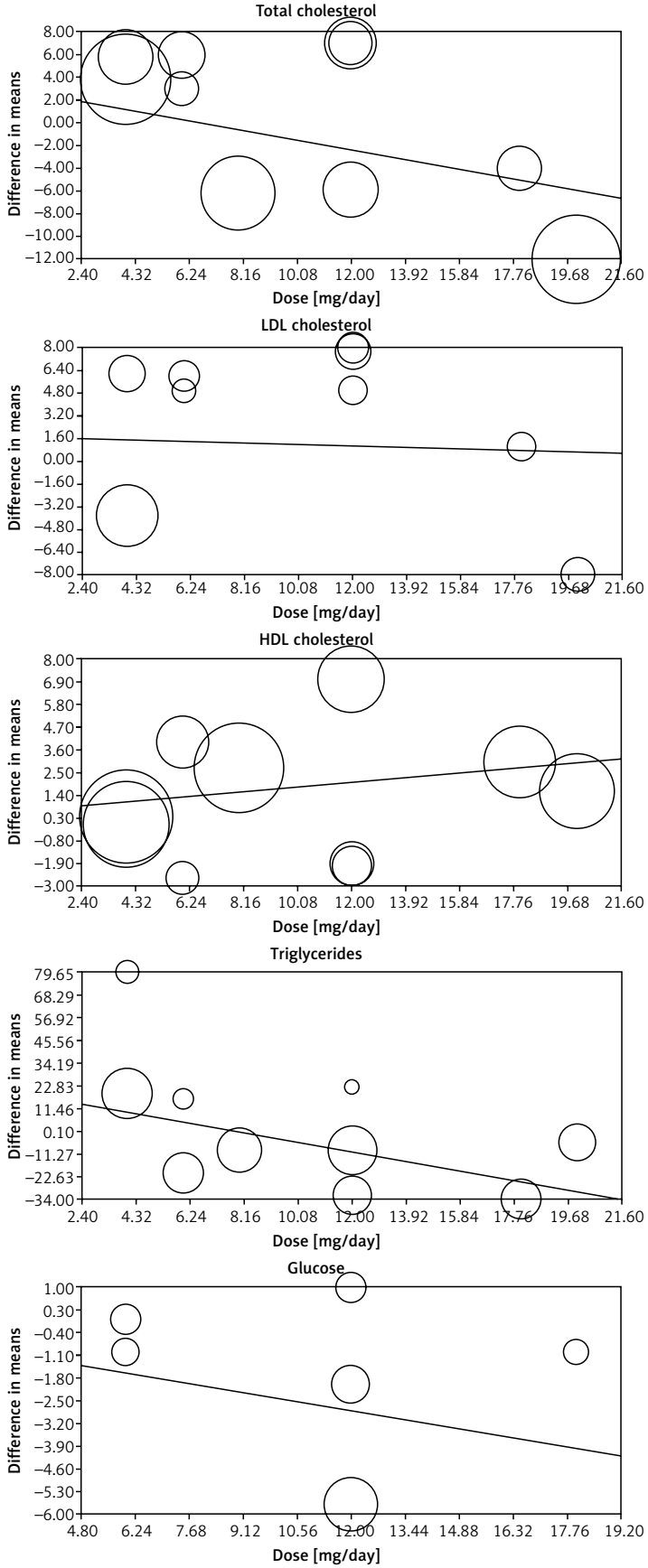


Figure 8. Meta-regression plots of the association between mean changes in plasma lipids and glucose concentrations and administered astaxanthin dose. The size of each circle is inversely proportional to the variance of change

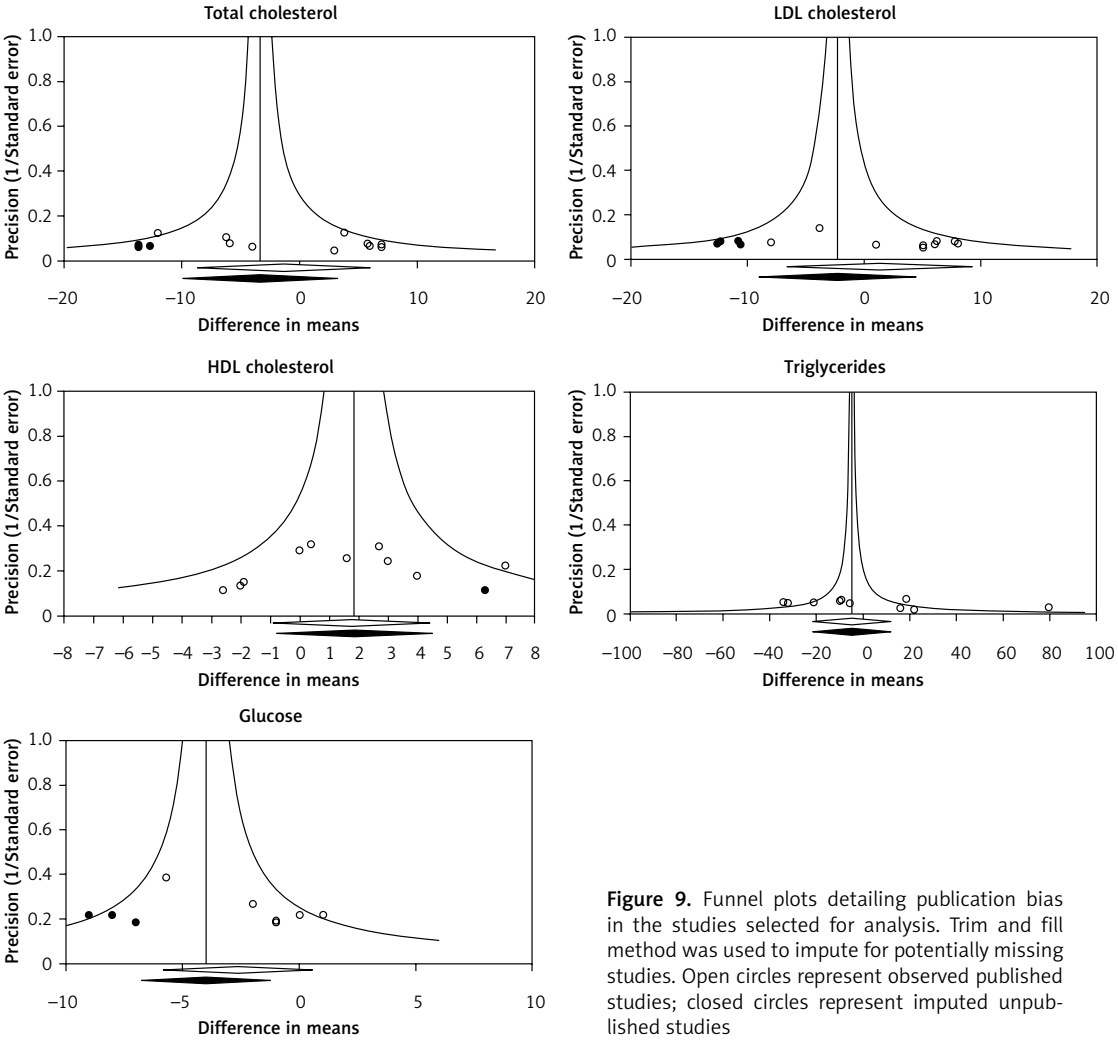


Figure 9. Funnel plots detailing publication bias in the studies selected for analysis. Trim and fill method was used to impute for potentially missing studies. Open circles represent observed published studies; closed circles represent imputed unpublished studies

Table II. Assessment of publication bias in the impact of astaxanthin supplementation on plasma lipids and glucose concentrations

Parameter	Begg's rank correlation test			Egger's linear regression test				
	Kendall's Tau[a]	*z*-value	*p*-value[b]	Intercept	95% CI	*t*	d*f*	*p*-value[b]
Total cholesterol	0.04	0.18	0.86	0.89	–0.62 to 2.39	1.36	8	0.21
LDL-C	–0.03	0.10	0.92	0.94	–0.19 to 2.08	1.96	7	0.09
HDL-C	0.00	0.00	1.00	–0.37	–1.80 to 1.06	0.60	8	0.57
Triglycerides	0.18	0.72	0.47	1.41	–1.67 to 4.48	1.06	8	0.32
Glucose	0.13	0.38	0.71	2.13	0.73 to 3.53	4.22	4	0.01

[a]*With continuity correction;* [b]*Two-tailed.*

transcriptome in lipid-loaded hepatocytes [35]. In diet-induced obesity in mice, ASTX significantly increased the hepatic mRNA expression of antioxidant nuclear factor erythroid-related factor 2 and reduced plasma triacylglycerol (TAG), alanine transaminase (ALT) and aspartate transaminase (AST) levels [36]. Furthermore, ASTX reduced plaque macrophage infiltration and apoptosis in the atheroma and enhanced plaque stability in hyperlipidemic rabbits. *In vivo* and *in vitro* studies have shown that ASTX inhibits the oxidation of LDL [37, 38] and limits the activation of mac-

rophage activation and the production of proinflammatory cytokines [39]. It was speculated that ASTX generates its hypotriglyceridemic effect by decreasing VLDL TG secretion consecutive to increased fatty acid β-oxidation in the liver [32]. Indeed, ASTX raises fat consumption in muscle by activating carnitine palmitoyltransferase-1 (CPT-1), thus lowering adiposity in mice.

Antidiabetic effects of ASTX could be explained by means of several mechanisms. In a diabetic db/db mice model, ASTX may protect pancreatic β-cells against glucose toxicity by decreasing blood glucose levels and hyperglycemia-induced oxidative stress and by increasing serum insulin levels [40]. In an experimental model of high fructose-fat diet (HFFD)-fed mice, ASTX enhanced insulin sensitivity by lowering serine phosphorylation of insulin receptor substrates (IRS), raising the association of IRS and phosphatidylinositol 3-kinase (PI3K), and raising Akt phosphorylation in the liver, consecutively promoting the hepatic IRS-PI3K-Akt pathway of insulin signaling [41]. Another study showed that ASTX modulates endoplasmic reticulum (ER) stress, reactive oxygen species (ROS) production, phosphorylation of c-Jun-N-terminal kinase 1 (JNK1), reactive oxygen species (ROS) production, and nuclear factor-κB-mediated inflammation in the liver of HFFD-fed mice [42]. A recent *in vitro* study evaluated whether ASTX alleviates cytokine- and free fatty acid-induced insulin resistance. The results obtained showed that ASTX ameliorates insulin resistance by defending cells from oxidative stress developed by different stimuli consisting of TNF-α and palmitate [43]. Furthermore, ASTX may be able to prevent the progression of diabetic nephropathy by reducing glomerular mesangial area and by decreasing hyperglycemia and oxidative stress [44].

The presence of dietary fat influences the magnitude of ASTX assimilation in the small intestine [45]. Furthermore, the bioavailability of ASTX is increased after meals and decreased by about 40% in smokers [45]. In experimental and human studies, ASTX seems to be well tolerated, and no notable toxicity has been described. It has been shown that persons with an allergy to sea foods may experience hypotension, hypersensitivity reactions, pigmentation of the skin, hypocalcemia, abnormal hair growth or decreased libido after consuming ASTX [46].

In 1987, the US Food and Drug Administration (FDA) authorized ASTX as a feed additive for the aquaculture industry and since 1999 as a dietary supplement [47]. The safety of ASTX extracted from *H. pluvialis* has been confirmed by several toxicological studies, leading to its affirmation as a Generally Recognized as Safe (GRAS) compound by the FDA in 2010. Following a demand from the European Commission, the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) recommended a maximum intake of 4 mg of ASTX per day [48]. Human clinical trials have utilized oral ASTX in a dose that varies from 4 mg up to 100 mg/day.

This meta-analysis has some limitations. Most significantly, the qualified RCTs generally had modest populations and limited follow-up [54, 55]. Moreover, the studies involved were heterogeneous concerning the population similarities, the concept of the study, and ASTX quantity. Finally, the smoking status, an important determinant of bioavailability of ASTX, could not be considered in this meta-analysis due to lack of data.

In conclusion, this meta-analysis of data from 10 RCT arms did not indicate a significant effect of supplementation with ASTX on plasma lipid profile, but a slight glucose-lowering effect was observed. Further, well-designed trials are necessary to validate these results.

Conflict of interest

The authors declare no conflict of interest.

This meta-analysis was written independently; no company or institution supported it financially. No professional writer was involved in the preparation of this meta-analysis.

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