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Review Article

Effects of Astaxanthin Supplement on Cardiovascular Health: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: The objective of this study was to evaluate the effects of astaxanthin intake on the cardiovascular disease-related indicators. **Materials and Methods:** Fives databases, including PUBMED, CNKI, WEIPU, WAN FANG and Clinical Trials were searched up to June 30, 2023. The random-effects model was used to calculate the summary risk. A total of 17 studies were included in this meta-analysis and a total of 1101 subjects' data were included in the analysis. In all included literature studies, a randomly assigned placebo group was established as the control. In the literature included, the average intervention dose of ASTX in the experimental group was 10.14 mg/day, with an average duration of administration of 68 days. **Results:** The overall study did not show a significant association between Astaxanthin (ASTX) and Systolic Blood Pressure (SBP) (standardized mean difference, SMD: -0.03, 95% CI: -0.22 to 0.17, *p*=0.771), Diastolic Blood Pressure (DBP) (SMD: -0.16, 95% CI: -0.35 to 0.03, *p*=0.100), the glucose concentration (SMD: -0.12, 95% CI: -0.39 to 0.15, *p*=0.398) and Body Mass Index (BMI) (SMD: -0.02, 95% CI: -0.22 to 0.18, *p*=0.821). However, the results revealed that astaxanthin can significantly reduce total cholesterol concentration (SMD: -0.20, 95% CI: -0.37 to -0.04, *p*=0.000), low-density lipoprotein cholesterol concentration (LDL-C) (SMD: -0.25, 95% CI: -0.41 to -0.09, *p*=0.003) and triglyceride concentration (SMD: -0.17, 95% CI: -0.32 to -0.01, *p*=0.033). Furthermore, astaxanthin could increase the concentrations of high-density lipoprotein cholesterol (HDL-C) (SMD: 0.18, 95% CI: 0.05 to 0.32, *p*=0.008). **Conclusion:** The results of this meta-analysis indicate that astaxanthin intake can significantly improve hyperlipidemia. Further studies are needed to validate these findings and investigate the potential cardiovascular benefits of astaxanthin.

Keywords: Astaxanthin, Cardiovascular Health, Efficacy, Hyperlipidemia, Meta-Analysis.

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INTRODUCTION

Astaxanthin (ASTX) is a type of axanthophyll carotenoid known as the "miracle of red". There are more than five natural sources of ASTX, including yeast, algae, crops, crustaceans and protozoans, as well as some types of bacteria.[1] ASTX was firstly discovered in lobsters in 1938 and was the only pigment used in aquaculture.[2] ASTX manifests high antioxidant[3] and anticancer properties,[4,5] reduces oxidative stress and inflammation,[6-9] prevents carotid artery rethrombosis and *ex vivo* platelet activation.[10] It is also an efficient treatment for ischemia-reperfusion injury,[11,12] arterial hypertension[13,14] and dyslipidemia.[15] ASTX is considered to be the most powerful natural carotenoid antioxidant, exhibiting 65 time's greater potency than that of Vitamin C, 54 times greater than that of β-carotene, 14 times greater than that of vitamin E and about 10 times more powerful than that of zeaxanthin, lutein and canthaxanthin.[16,17]

Cardiovascular diseases are leading causes of mortality world wide. The progression of cardiovascular diseases is frequently accompanied by alterations in blood lipids, blood pressure, blood glucose and other indicators.[18-20] ASTX has been demonstrated to improve lipid levels,[21-24] reduce blood pressure and decrease blood glucose concentrations[25-28] in these patients. Additionally, ASTX has been found to play crucial roles in anti-inflammatory and antioxidant activities. ASTX has been shown to increase the

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expression of Nrf2 regulatory enzymes, which are involved in combating oxidative stress by activating the signaling pathways of PI3K/Akt and extracellular signal-regulated kinase ERK, promoting the dissociation and nuclear translocation of nuclear erythroid 2-related factor Nrf2. It also negatively regulates the Sp1/NR1 signaling pathway, thereby reducing intracellular Reactive Oxygen Species (ROS) and oxidative stress production.[29-32]

Although research on the effects of ASTX on cardiovascular disease has been increasing,[21-23,25-28] there are still some controversies regarding the conclusions. Meta-analysis is a statistic method which can systematically evaluate and summarize the findings of multiple studies on the same subject,[33,34] Therefore, a meta-analysis was conducted in the present study to assess the efficacy of ASTX in treating cardiovascular disease.Seventeen studies were included in this meta-analysis and the analysis showed that ASTX was an effective treatment in relieving hyperlipidemia.

MATERIALS AND METHODS

Search strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements checklist, PUBMED, CNKI, WEIPU, WANFANG and Clinical Trials were searched from their inception to June 30, 2023. In addition, an online search of published literature was conducted through PubMed using the Medical Subject Headings (MeSH) term and additional grey literature. The search terms and keywords used were as follows: (astaxanthin or ASTX or haematococcus pluvialis) and (randomized controlled trial or randomized) and (cholesterol or total cholesterol) and (triglyceride) and (HDL-cholesterol or HDL or High-Density Lipoprotein) and (LDL-cholesterol or LDL or Low-Density Lipoprotein) and (cardiovascular system or cardiovascular or angiography or heart and blood vessels) and (blood glucose or plasma glucose or FBG or hyperglycemia or hyperglycaemia or hyperglycemic) and (hyperlipidemia or hyperlipidemic or dyslipidemia) and (blood pressure or diastolic pressure or diastolic blood pressure or systolic pressure or systolic blood pressure) and (Body Mass Index or BMI). There are no restrictions on the type of language. This study was limited to human studies and the retrieved articles were screened manually.

Study selection

The included articles had to meet the following inclusion criteria: (1) Qualify as prospective cohort studies or case-control studies based on predetermined criteria; (2) Evaluate the effect of ASTX on cardiovascular disease-related indices, including total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, diastolic pressure, systolic pressure and plasma glucose; (3) ASTX was given in the experimental group, while the control group used either placebo control or blank control; (4) The limiting factor was a pure ASTX preparation with a precise dose or a dose that can be calculated based on data available in the literature.

The exclusion criteria were as follows: (1) Repetitive articles or articles that only provided titles and abstracts; (2) Systematic reviews, meta-analyses and case reports; (3) Letters and conference data; (4) Animal or cell experiments; (5) No control group.

Data extraction

Information was independently extracted by two investigators, with any disagreements adjudicated by a third investigator. The following data were reviewed and extracted from each eligible study: (1) first author; (2) year of publication; (3) country of origin; (4) age of study participants; (5) gender of study participants; (6) daily dosage of the ASTX given to the treatment groups and control groups; (7) number of participants in each group; (8) means and standard deviations of various health outcomes including total cholesterol concentration, HDL-C, LDL-C, triglyceride concentration, plasma glucose concentration, diastolic pressure, systolic pressure and Body Mass Index (BMI); and (9) follow-up time for cohort studies.

Quality assessment

The Cochrane Collaboration tool was utilized to assess the quality of each study, evaluating various factors that could potentially introduce bias. Two authors independently carried out the quality evaluation and a third author resolved any discrepancies.

Statistical analysis

The statistical analyses were conducted using the statistical software RevMan version 5.4 and StataMP-64 14.0 software. To obtain a more conservative estimate, a random-effects model was used to calculate the summary risk. The effect of ASTX was described using forest plots, which presented the Standardized Mean Difference (SMD) and 95% Confidence Interval (CI). Additionally, Heterogeneity among the studies was estimated using p-statistics and I^2 values. The p-statistic and the I^2 value are statistical measures used to assess the degree of heterogeneity. If the p-value is less than 0.05, indicating statistically significant heterogeneity, then a sensitivity analysis was conducted to explore the potential impact of individual studies on the overall results. This involved iteratively excluding each study and re-analyzing the remaining studies using forest plots to estimate the effect size. To assess the presence of publication bias, funnel plots were used to explore the studies included in the analysis. The Begg's test and the Egger's test were conducted to further evaluate whether publication bias exists. A symmetric funnel plot suggested no publication bias, while a p-value (pEgger and pBegg) less than 0.05 indicated the presence of potential publication bias.[35]

RESULTS

Characteristics of eligible studies

Literature search

A total of 7770 publications were initially collected from the four databases. Among them, 1281 were reviewed through titles and/or abstracts, 1058 articles were excluded because they were titles, abstracts, meta-analyses, case reports, systematic reviews, or irrelevant articles. The remaining 123 full-text articles were screened for eligibility and 49 articles fulfilled the inclusion criteria. The 32 studies were excluded from the remaining articles for the following reasons: 25 studies combined ASTX with other drugs and 7 studies did not have a control group. Finally, 17 studies were selected for the final meta-analysis. The flow chart illustrating the study selection process is shown in Figure 1.

Study Characteristics

The Characteristics of Prospective Cohort Studies Included in the Meta-Analysis are shown in Table 1. Fourteen studies were conducted in Asia (Korea, *n*=1; Thailand, *n*=1; Japan, *n*=6; Iran, *n*=2; China, *n*=4), two studies were conducted in Europe (Finland, *n*=1; Italy, *n*=1) and one study was conducted in America (Canada, *n*=1). The included studies provided other information on age range, sex, ASTX dose, placebo dose and follow-up period.

Quality assessment

The quality assessment results based on Cochrane standards was shown in Figure 2. The quality of the studies included in the analysis was varied. 61 information items were deemed to have a low risk bias, while 56 items had an unclear bias risk. Only 2 items were identified to be with high risk bias, but these did not

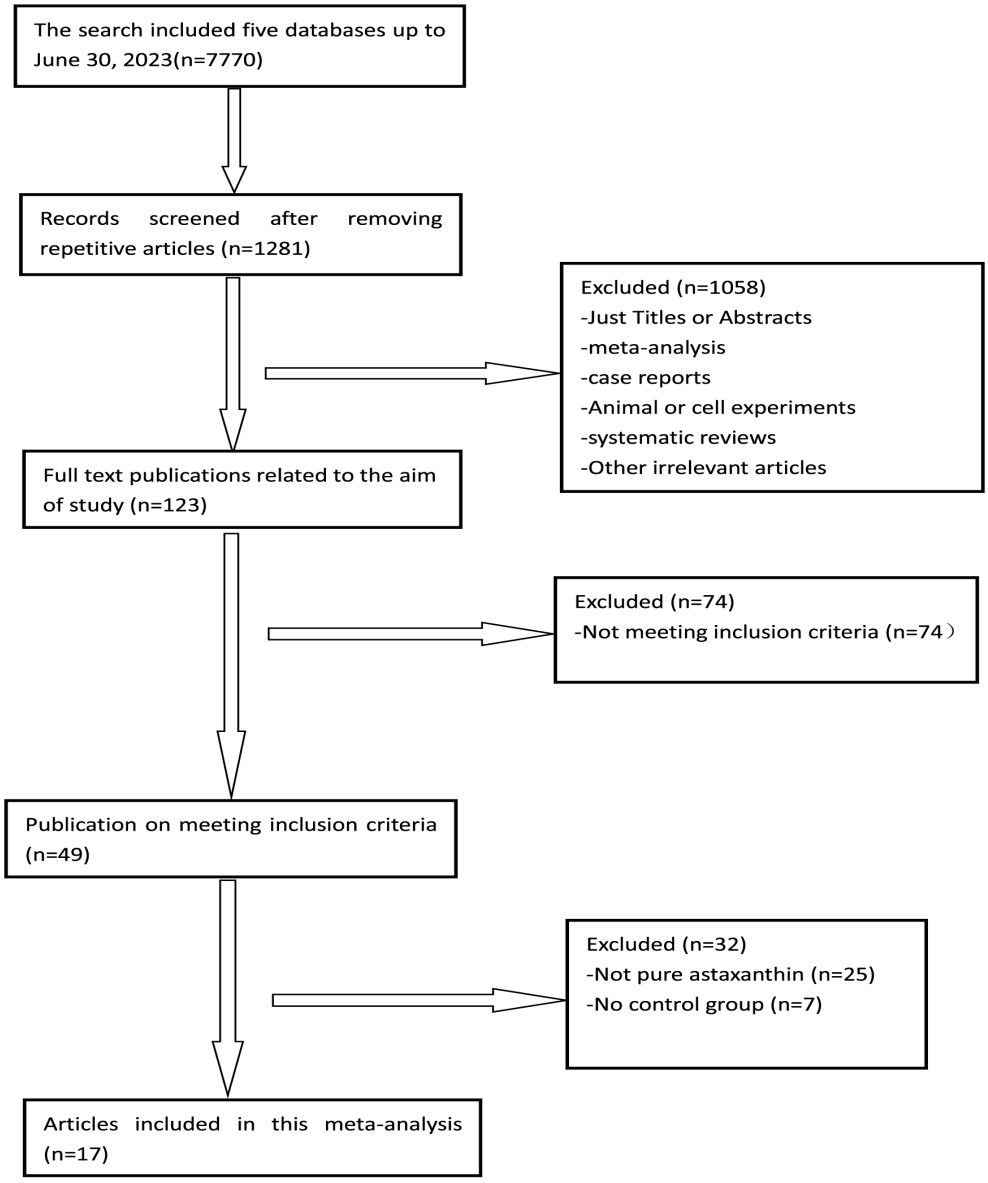

Figure 1: Flow diagram of the study selection procedure in this meta-analysis, which show the process of screening relevant studies based on the inclusion and exclusion criteria.

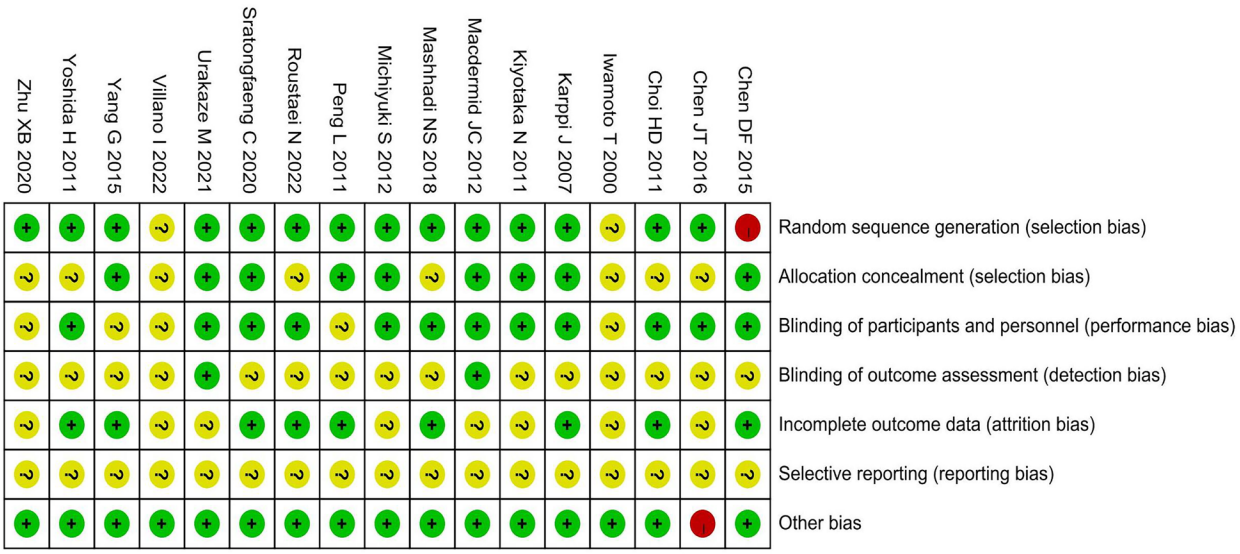

Figure 2: Cochrane criteria as the evaluation criteria for quality assessment.

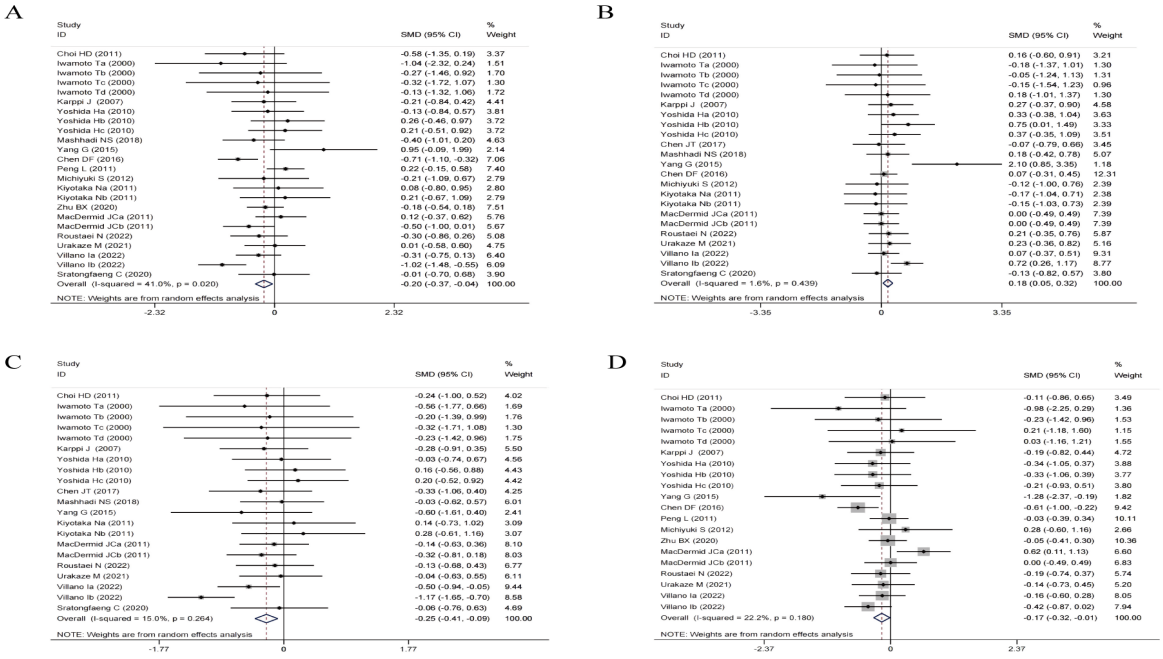

Figure 3: Forest plots detailing standardized mean difference (SMD) and 95% confidence intervals (95%CI) for the effect of astaxanthin on different indicators. The p value < 0.05 indicated the existence of heterogeneity among studies. (A) Total cholesterol concentrations; (B) HDL-C concentrations (C) LDL-C concentrations; (D) Triglyceride concentrations.

affect our findings. Thus, the included articles were high-quality studies.

Effect of ASTX supplementation

Blood lipid

Sixteen studies on the relationship between ASTX and cholesterol concentration were shown in Figure 3. ASTX remarkably recovered the plasma concentration of total cholesterol (SMD: -0.20, 95% CI: -0.37 to -0.04, p=0.000, Z=3.61), LDL-C (SMD: -0.25, 95% CI: -0.41 to -0.09, p=0.003, Z=2.99) and triglyceride (SMD: -0.17, 95% CI: -0.32 to -0.01, p=0.033, Z=2.13), while also increased HDL-C levels (SMD: 0.18, 95% CI: 0.05 to 0.32, p=0.008, Z=2.63). Table 2 showed that the heterogeneity was not statistically significant for triglycerides, HDL-C and LDL-C (Triglycerides: I^2=22.2%, p=0.180; HDL-C: I^2=1.6%, p=0.439; LDL-C: I^2=15.0%, p=0.264) but the heterogeneity was low for total cholesterol (I^2=41.0%, p=0.02). The sensitivity analysis was performed to assess the impact of individual studies on the overall results of the comprehensive assessments. According to the results presented in Figure 5, substantial heterogeneity was not observed in this analysis, as each study was within the confidence interval and no publication bias was detected in the four analyzed studies. (Total cholesterol: pBegg=0.823, pEgger=0.456; HDL-C: pBegg=0.895, pEgger=0.812; LDL-C: pBegg=0.651,

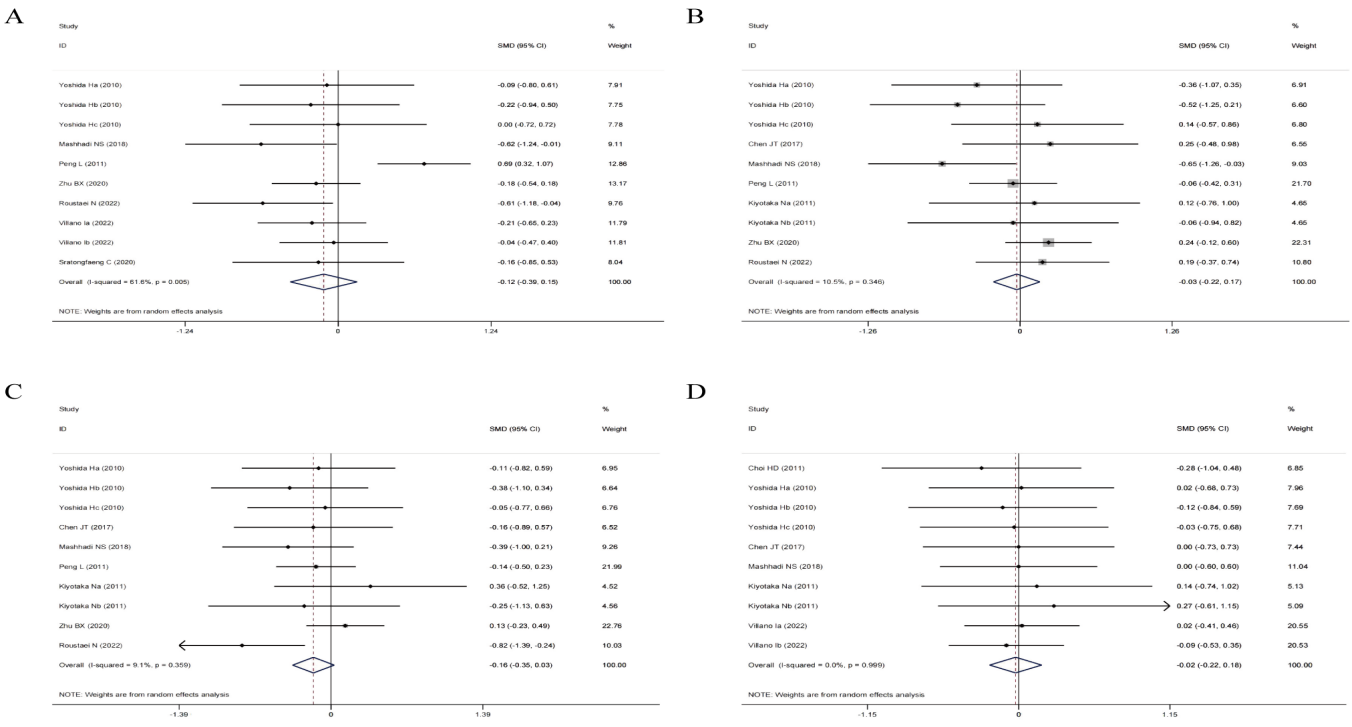

Figure 4: Forest plots detailing standardized mean difference (SMD) and 95% confidence intervals (95% CI) for the effect of astaxanthin on different indicators. The p value < 0.05 indicated the existence of heterogeneity among studies. (A) Plasma Glucose, (B) Systolic blood pressure; (C) Diastolic blood pressure; (D) BMI.

Table 1: Characteristics of Included Studies.

First author, year	Country	Age	Sex (Male/Female)	Astaxanthin dose (mg/day)	Placebo dose (mg/day)	Follow-up (day)
[21]Choi HD, 2011	Korea	20-55	23/4	20	20	84
[22]Iwamoto T, 2000	Japan	20-36	—	1.8	0	14
[22]Iwamoto T, 2000	Japan	20-36	—	3.6	0	14
[22]Iwamoto T, 2000	Japan	20-36	—	14.4	0	14
[22]Iwamoto T, 2000	Japan	20-36	—	21.6	0	14
[43]Karppi J, 2007	Finland	19-33	—	8	8	90
[23]Yoshida H, 2011	Japan	20-65	41/20	18	0	84
[23]Yoshida H, 2011	Japan	20-65	41/20	12	0	84
[23]Yoshida H, 2011	Japan	20-65	41/20	6	0	84
[26]Chen JT, 2016	Japan	46-56	0/29	12	12	90
[25]Mashhadi NS, 2018	Iran	30-60	17/27	—	—	56
[44]Yang G, 2015	China	17-23	16/0	9	9	28
[45]Chen DF, 2015	China	38-54	60/47	3.72	0	45
[38]Peng L, 2011	China	45-65	53/62	40	0	90
[28]Michiyuki S, 2012	Japan	26-50	5/15	12	12	28
[27]Kiyotaka N, 2011	Japan	50-63	10/10	6	6	84
[27]Kiyotaka N, 2011	Japan	51-62	10/10	12	12	84
[39]Zhu XB, 2020	China	37-64	57/63	9	9	90
[46]Macdermid JC, 2012	Canada	29-74	18/45	4	4	42

First author, year	Country	Age	Sex (Male/Female)	Astaxanthin dose (mg/day)	Placebo dose (mg/day)	Follow-up (day)
[46]Macdermid JC, 2012	Canada	29-74	18/45	4	4	84
[47]Roustaei N, 2022	Iran	20-60	22/25	10	0	84
[48]Urakaze M, 2021	Japan	20-74	15/29	12	0	84
[49]Villano I, 2022	Italy	25-67	36/44	0.1	0	84
[49]Villano I, 2022	Italy	25-67	36/44	0.1	0	168
[50]Sratongfaeng C, 2020	Thailand	21-54	—	4	0	84

pEgger=0.185; Triglyceride: pBegg=0.581, pEgger=0.632). The funnel plots are shown in Figure 6.

Plasma glucose

The included seven studies were focused on the effect of ASTX on plasma glucose concentrations, as shown in Figure 4. The findings revealed that ASTX did not affect the plasma glucose levels (SMD: -0.12, 95% CI: -0.39 to 0.15, p=0.398). However, there was a notable degree of heterogeneity in the Plasma glucose results (I^2=61.6%, p=0.005), as outlined in Table 2. The sensitivity analysis in Figure 5 showed no substantial heterogeneity among the included studies, with each study's effect size estimate falling within the confidence interval. These results demonstrated evidence of no publication bias (pBegg=1.000, pEgger=0.225). The funnel plots were shown in Figure 6.

Blood pressure

Seven studies investigated the role of ASTX in controlling blood pressure was presented in Figure 4. The results showed that ASTX has no effect on reducing the DBP (SMD: -0.16, 95% CI: -0.35 to 0.03, p=0.10, Z=1.64) and the SBP (SMD: -0.03, 95% CI: -0.22 to 0.17, p=0.771, Z=0.29). The heterogeneity was not significant in this study (DBP: I^2=9.1%, p=0.359; SBP: I^2=10.5%, p=0.346), as shown in Table 2. Also, no significant publication bias was observed in this analysis (DBP: pBegg=0.858, pEgger=0.512; SBP: pBegg=0.721, pEgger=0.378), as evidenced by the funnel plots presented in Figure 6.

Body mass index

The effect of ASTX on BMI was evaluated in five studies. As illustrated in Figure 4, ASTX had no statistically significant effect on BMI (SMD: -0.02, 95% CI: -0.22 to 0.18, p=0.821). The analysis also revealed no significant heterogeneity (I^2=0%, p=0.999) and no publication bias on BMI (pBegg=0.721, pEgger=0.534). The funnel plots were displayed in Figure 6.

DISCUSSION

This meta-analysis included a total of 17 studies to assess the impact of ASTX supplementation on the cardiovascular disease-related indicators. The results showed that the intake of ASTX significantly reduced the concentrations of total cholesterol, LDL-C and triglycerides, while significantly increased the concentrations of HDL-C. These findings were consistent with the results of previous animal and human studies. For instance, Kishimoto Y *et al.* found that ASTX supplementation significantly reduced triglyceride levels (12 and 18 mg/day of ASTX) and increased HDL-cholesterol (6-and 12-mg doses) in a dose-dependent manner.[34] In a systematic review and meta-analysis of animal studies conducted by Radice RP *et al*, ASTX intake in animal models of NAFLD significantly improved blood concentrations of disease biomarkers (including cholesterol, triglycerides, ALT and AST, p<0.05). These results suggested that ASTX exhibited a beneficial effect on NAFLD animal models. The effects of ASTX on lipids showed consistent results in both animal models and humans.[3,35,36] Therefore, our study supports the notion that ASTX has a significant effect on hyperlipidemia.

However, our meta-analysis did not find any significant association between ASTX intake and blood glucose concentration, blood pressure, or BMI. Our search only identified a limited number of research trials on the effect of ASTX on BMI. Due to the relatively small sample size of the studies included, it was uncertain whether ASTX has an effect on BMI. Notably, our analysis showed ASTX has no direct effect on blood glucose concentrations. However, only one of the included studies supported this conclusion (the study by Peng L *et al.*), while the remaining studies did not directly investigate this relationship. After removing this study and re-analyzing the included studies, we reached a different conclusion: ASTX may reduce blood sugar levels. Nonetheless, further studies are required to confirm this finding.

There are two categories of ASTX, natural and synthetic forms. Currently, the majority of ASTX available in the market is chemically synthesized, which lower absorbability and antioxidant capacity has compared to the natural form.[37] However, the extraction method, purity and other factors of ASTX used in different experiments may also affect the final results. For example, in the study by Peng L *et al.*, the ASTX used were extracted from Rhodiaceae with a purity of 95%, provided by a biologics company.[38] The low purity may be one of the influencing factors in the study results. Therefore, it is essential to consider the source and quality of ASTX when interpreting the results of different studies.

Studies at the molecular and cellular levels have also demonstrated that ASTX exhibited a protective effect on blood lipids in the

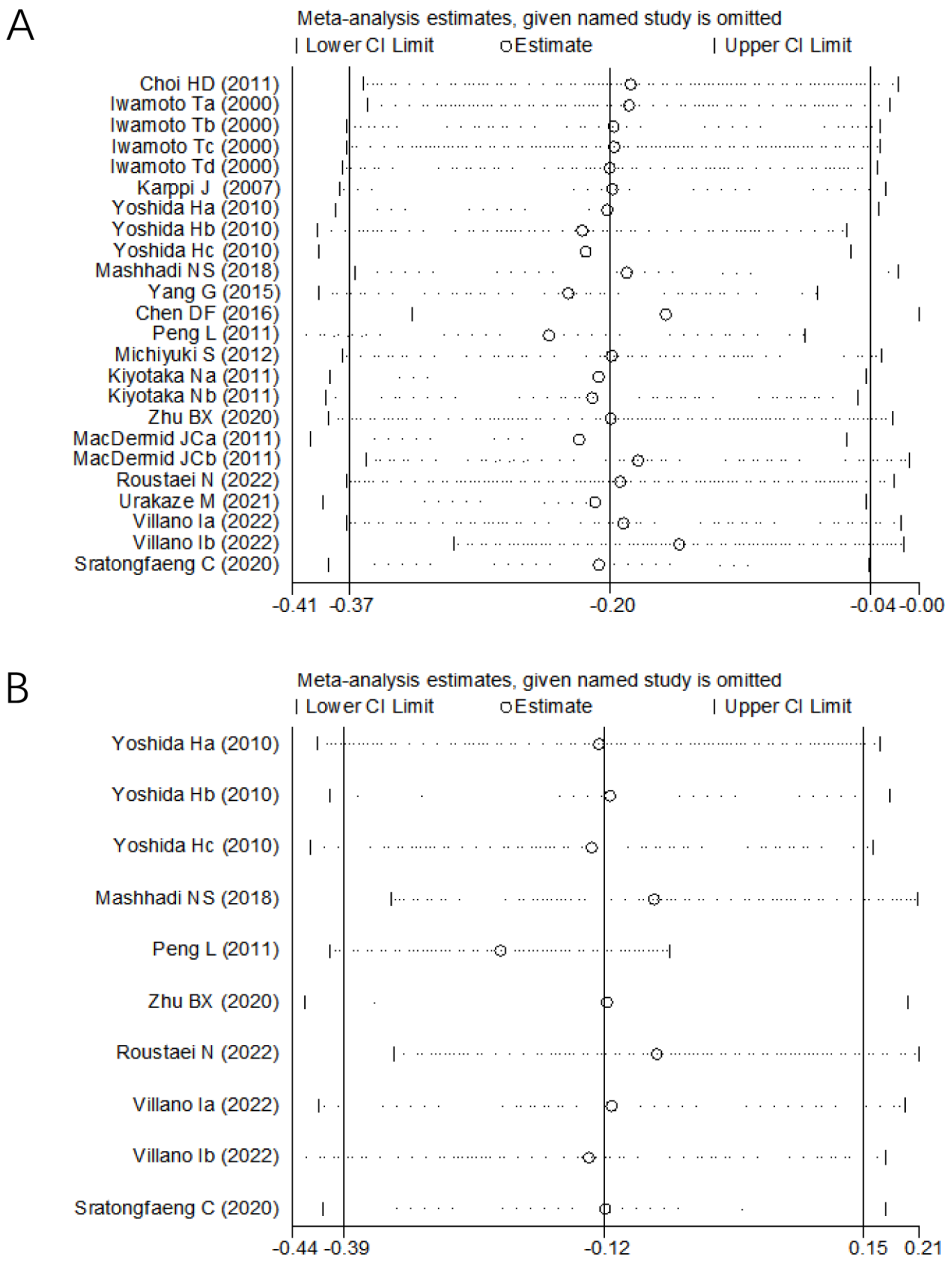

Figure 5: Sensitivity analysis was conducted using the one-study remove (leave-one-out) approach to evaluate the influence of each study on the overall effect size. (A) Total cholesterol; (B) Plasma glucose.

Table 2: The basis for Basis for heterogeneity and publication bias.

	Point estimate (95% CI)	I^2	*P* Begg		Egger
Total cholesterol	-0.20 (-0.37, -0.04)	41.0%	0.020	0.823	0.456
HDL-C	0.18 (0.05, 0.32)	1.6%	0.439	0.895	0.812
LDL-C	-0.25 (-0.41, -0.09)	15.0%	0.264	0.651	0.185
Triglyceride	-0.17 (-0.32, -0.01)	22.2%	0.180	0.581	0.632
Glucose	-0.12 (-0.39, 0.15)	61.6%	0.005	1.000	0.225
SBP	-0.03 (-0.22, 0.17)	10.5%	0.346	0.721	0.378
DBP	-0.16(-0.35, 0.03)	9.1%	0.359	0.858	0.512
BMI	-0.02 (-0.22, 0.18)	0%	0.999	0.721	0.534

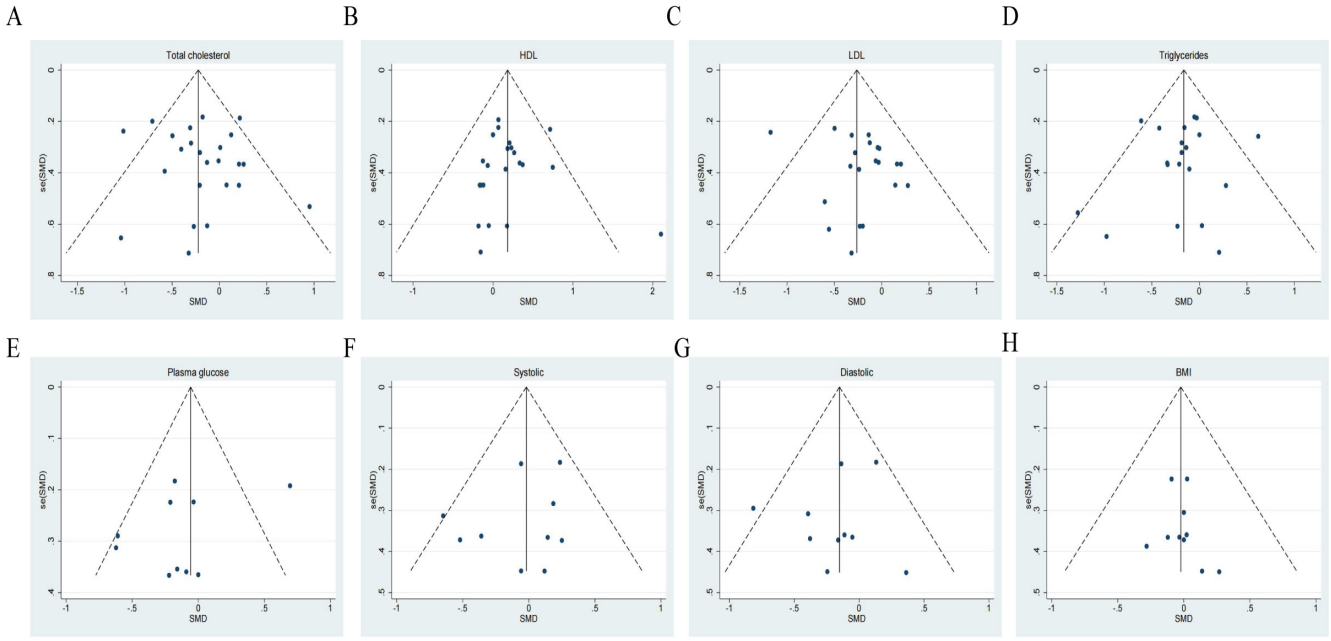

Figure 6: Funnel plots detailing publication bias about different indicators in the studies selected for analysis. Circles represent observed published studies. (A) Total cholesterol concentrations; (B) HDL-C concentrations (C) LDL-C concentrations; (D) Triglyceride concentrations; (E) Glucose, (F) Systolic blood pressure; (G) Diastolic blood pressure; (H) BMI.

context of cardiovascular health. Firstly, ASTX possesses both polar and nonpolar groups that enable it to adopt a transmembrane alignment in biofilms, thereby shielding cell membranes from oxidative damage caused by Reactive Oxygen and Nitrogen Species (RONS), due to its unique chemical structure. Secondly, the conjugated bonds in the central non-polar region of ASTX allow it to transport free radicals along its own carbon chain, facilitating their removal from the cell interior and subsequent neutralization by extracellular antioxidants. Thirdly, ASTX has been shown to neutralize peroxynitrite, inhibit lipid peroxidation and LDL oxidation, reduces the production of superoxide anion radicals released by NADPH oxidase and increase Nitric Oxide (NO). Fourthly, Free radicals are highly reactive and can trigger lipid peroxidation, ultimately impairing normal physiological activities.[31,32] ASTX plays a crucial role in antioxidant defense by quenching singlet oxygen and scavenging radicals to terminate chain reactions.[32] Thus, ASTX appears to delay the progression of cardiovascular disease.[31] The results of this meta-analysis confirmed that ASTX has a protective effect on the cardiovascular system. Moreover, the absence of significant adverse effects reported in animals or humans following ASTX consumption, even at a high dose of 45 mg/d.[38-42] supports the safety of ASTX for future clinical studies.

This meta-analysis has several limitations that should be taken into consideration. Firstly, the included studies and sample size were relatively small, consisting of only 17 articles with 847 cases; Consequently, the limited sample size of clinical studies may increase the risk of false positive or false negative results. Secondly, confounding factors such as age, gender, environmental factors, lifestyle and medication doses should be considered and adjusted for future studies. Specifically, further analysis is required to verify whether a dose-dependent relationship exists in the protective effects of ASTX on cardiovascular disease. Thus, a larger sample size and further adjustments for confounding factors are necessary to provide more accurate and robust conclusions. Thirdly, it should be noted that the quality, purity and extraction method of ASTX used in different experiments may affect the results. Fourthly, additional *in vitro* and animal experiments are necessary to validate the effects of ASTX on cardiovascular disease.

In summary, this meta-analysis suggests that ASTX supplementation may have a positive effect on hyperlipidemia. However, further studies are required to examine the effects of ASTX on other cardiovascular risk factors, such as blood glucose concentration, blood pressure and BMI. To advance the research on the cardiovascular effects of ASTX, ongoing collection of literature and updating of data is necessary to stay abreast of the latest scientific findings.

CONCLUSION

ASTX supplementation may have a positive effect on hyperlipidemia by significantly reducing total cholesterol, LDL cholesterol and triglyceride levels, while increasing HDL cholesterol concentrations. However, no significant associations were found between ASTX intake and SBP, DBP, glucose concentrations or BMI. These findings highlight the potential benefit of ASTX in managing Cardiovascular Health. Nonetheless, due to the limitations of this study, further data from large-scale clinical trials are necessary and well-designed trials

are needed to fully understand its effectiveness and potential side effects.

AUTHOR CONTRIBUTIONS

XZG, LD, YJL and WYM designed the research; YJL, WYM, HQY, RZC, RH and ZL extracted data and conducted meta-analyses; YJL, WYM, XZG, LD, RRK, RLM, MHB and PYQ wrote the paper; YJL and WYM had primary responsibility for the final content. All authors read and agreed with the final manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ASTX: Astaxanthin; SBP**:** Systolic Blood Pressure; **DBP:** Diastolic Blood Pressure; **BMI:** Body Mass Index; **LDL-C: l**ow-density lipoprotein cholesterol; **HDL-C:** high-density lipoprotein cholesterol; **ROS:** Reactive Oxygen Species; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analysis; **RONS:** Reactive Oxygen and Nitrogen Species; **NO:** Nitric Oxide.

SUMMARY

This study aimed to assess the effects of astaxanthin intake on cardiovascular - disease - related indicators. The meta-analysis included 17 studies with data from 1,101 subjects, using randomized placebo-controlled trials. In conclusion, this meta - analysis suggests that astaxanthin intake can significantly improve hyperlipidemia, though further research is required to confirm these results and explore astaxanthin's potential cardiovascular benefits.

REFERENCES

1. Zhu XL, Qiu H. Distribution and source of astaxanthin. Hunan Feed. 2008;3(35-37):12.
2. Fakhri S, Abbaszadeh F, Dargahi L, Jorjani M. Astaxanthin: A mechanistic review on its biological activities and health benefits. Pharmacol Res. 2018;136:1-20. doi: 10.1016/j.phrs.2018.08.012, PMID 30121358.
3. Kim B, Ku CS, Pham T, *et al.* Supplementation of astaxanthin, a xanthophyll carotenoid, improved metabolic and inflammatory abnormalities associated with obesity in diet-induced obese mice. FASEB J. 2014;28 Suppl 1:645.8.
4. Demirel PB, Tuna BG. Anticancer properties of astaxanthin: A molecule of great promise. Nutraceuticals Hum Health A Prospectus. 2021.
5. Lu Q, Liu JZ. Enhanced astaxanthin production in *Escherichia coli* via morphology and oxidative stress engineering. J Agric Food Chem. 2019;67(42):11703-9. doi: 10.1021/acs.jafc.9b05404, PMID 31578056.
6. Augusti PR, Conterato GM, Somacal S, Sobieski R, Quatrin A, Maurer L, *et al.* Astaxanthin reduces oxidative stress, but not aortic damage in atherosclerotic rabbits. J Cardiovasc Pharmacol Ther. 2009;14(4):314-22. doi: 10.1177/1074248409350136, PMID 19846890.
7. Li X, Qi Z, Zhao L, Yu Z. Astaxanthin reduces type 2 diabetic-associated cognitive decline in rats via activation of PI3K/Akt and attenuation of oxidative stress. Mol Med Rep. 2016;13(1):973-9. doi: 10.3892/mmr.2015.4615, PMID 26648531.
8. Sharma K, Sharma D, Sharma M, Sharma N, Bidve P, Prajapati N, *et al.* Astaxanthin ameliorates behavioral and biochemical alterations *in vitro* and *in vivo* model of neuropathic pain. Neurosci Lett. 2018;674:162-70. doi: 10.1016/j.neulet.2018.03.030, PMID 29559419.
9. Kang H, Kim H. Astaxanthin and β-carotene in Helicobacter pylori-induced Gastric Inflammation: A Mini-review on Action Mechanisms. J Cancer Prev. 2017;22(2):57-61. doi: 10.15430/JCP.2017.22.2.57, PMID 28698858.
10. Lauver DA, Driscoll EM, Lucchesi BR. Disodium disuccinate astaxanthin prevents carotid artery rethrombosis and *ex vivo* platelet activation. Pharmacology. 2008;82(1):67-73. doi: 10.1159/000132085, PMID 18477858.
11. Cakir E, Cakir U, Tayman C, Turkmenoglu TT, Gonel A, Turan IO. Favorable effects of astaxanthin on brain damage due to ischemia-reperfusion injury. Comb Chem High Throughput Screen. 2020;23(3):214-24. doi: 10.2174/1386207323666200219121600, PMID 32072893.
12. Gao F, Zhao Y, Zhang B, Xiao C, Sun Z, Gao Y, *et al.* Mitochondrial targeted astaxanthin liposomes for myocardial ischemia-reperfusion injury based on oxidative stress. J Biomater Appl. 2022;37(2):303-14. doi: 10.1177/08853282221087102, PMID 35403475.
13. Relief EF, Range P. Astaxanthin reduces hypertension. AstaReal Com.
14. Yanai H, Ito K, Yoshida H, Tada N. Antihypertensive effects of astaxanthin. Integr Blood Press Control. 2008;1:1-3. doi: 10.2147/ibpc.s4094, PMID 21949609.
15. Shin W, *et al.* GW. Clin Nutr Suppl. 2010;PP208 EFFECTS OF HAEMATOCOCCUS ASTAXANTHIN, AN ANTIOXIDANT, ON OXIDATIVE STRESS IN YOUNG OVERWEIGHT ADULTS.
16. Asker D, Awad TS, Beppu T, Ueda K. Screening and profiling of natural ketocarotenoids from environmental aquatic bacterial isolates. Food Chem. 2018;253:247-54. doi: 10.1016/j.foodchem.2018.01.066, PMID 29502828.
17. Yao K, Zhang R, Liu X, *et al.* Studies on anti-lipid peroxidation activity of different stereoisomeric astaxanthin. J Chin Inst Food Sci Technol. 2018;18(10):86-94.
18. Bao MH, Li JM, Zhou QL, Li GY, Zeng J, Zhao J, *et al.* Effects of miR590 on oxLDLinduced endothelial cell apoptosis: roles of p53 and NFκB. Mol Med Rep. 2016;13(1):867-73. doi: 10.3892/mmr.2015.4606, PMID 26648441.
19. Xu BF, Liu R, Huang CX, He BS, Li GY, Sun HS, *et al.* Identification of key genes in ruptured atherosclerotic plaques by weighted gene correlation network analysis. Sci Rep. 2020;10(1):10847. doi: 10.1038/s41598-020-67114-2, PMID 32616722.
20. Ke J, Li K, Ke T, Zhong X, Zheng Q, Wang Y, *et al.* Association of sedentary time and carotid atherosclerotic plaques in patients with type 2 diabetes. J Diabetes. 2022;14(1):64-72. doi: 10.1111/1753-0407.13242, PMID 34989161.
21. Choi HD, Youn YK, Shin WG. Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects. Plant Foods Hum Nutr. 2011;66(4):363-9. doi: 10.1007/s11130-011-0258-9, PMID 21964877.
22. Iwamoto T, Hosoda K, Hirano R, Kurata H, Matsumoto A, Miki W, *et al.* Inhibition of low-density lipoprotein oxidation by astaxanthin. J Atheroscler Thromb. 2000;7(4):216-22. doi: 10.5551/jat1994.7.216, PMID 11521685.
23. Yoshida H, Yanai H, Ito K, Tomono Y, Koikeda T, Tsukahara H, *et al.* Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. Atherosclerosis. 2010;209(2):520-3. doi: 10.1016/j.atherosclerosis.2009.10.012, PMID 19892350.
24. Ciaraldi TP, Boeder SC, Mudaliar SR, Giovannetti ER, Henry RR, Pettus JH. Astaxanthin, a natural antioxidant, lowers cholesterol and markers of cardiovascular risk in individuals with prediabetes and dyslipidemia. Diabetes Obes Metab. 2023;25(7):1985-94. doi: 10.1111/dom.15070, PMID 36999233.
25. Mashhadi NS. Astaxanthin improves glucose metabolism and reduces blood pressure in patients with type 2 diabetes mellitus. Asian J Clin Nutr. 2018;27(2):341-6.
26. Chen JT, Kotani K. Effects of astaxanthin on liver and leukocyte parameters in healthy climacteric women: preliminary data. J Med Food. 2017;20(7):724-5. doi: 10.1089/jmf.2016.3819, PMID 28692413.
27. Nakagawa K, Kiko T, Miyazawa T, Carpentero Burdeos G, Kimura F, Satoh A, *et al.* Antioxidant effect of astaxanthin on phospholipid peroxidation in human erythrocytes. Br J Nutr. 2011;105(11):1563-71. doi: 10.1017/S0007114510005398, PMID 21276280.
28. Saito M, Yoshida K, Saito W, Fujiya A, Ohgami K, Kitaichi N, *et al.* Astaxanthin increases choroidal blood flow velocity. Graefes Arch Clin Exp Ophthalmol. 2012;250(2):239-45. doi: 10.1007/s00417-011-1843-1, PMID 22072378.
29. Wu H, Niu H, Shao A, Wu C, Dixon BJ, Zhang J, *et al.* Astaxanthin as a potential neuroprotective agent for neurological diseases. Mar Drugs. 2015;13(9):5750-66. doi: 10.3390/md13095750, PMID 26378548.
30. Landon R, Gueguen V, Petite H, Letourneur D, Pavon-Djavid G, Anagnostou F. Impact of astaxanthin on diabetes pathogenesis and chronic complications. Mar Drugs. 2020;18(7):357. doi: 10.3390/md18070357, PMID 32660119.
31. Pereira CP, Souza AC, Vasconcelos AR, *et al.* Antioxidant and antiinflammatory mechanisms of action of astaxanthin in cardiovascular diseases [review]. Int J Mol Med. 2020;1.
32. Xue Y, Sun C, Hao Q, Cheng J. Astaxanthin ameliorates cardiomyocyte apoptosis after coronary microembolization by inhibiting oxidative stress via Nrf2/HO-1 pathway in rats. Naunyn Schmiedebergs Arch Pharmacol. 2019;392(3):341-8. doi: 10.1007/s00210-018-1595-0, PMID 30506291.
33. Xia Y, Huang CX, Li GY, Chen KH, Han L, Tang L, *et al.* Meta-analysis of the association between MBOAT7 rs641738, TM6SF2 rs58542926 and nonalcoholic fatty liver disease

susceptibility. Clin Res Hepatol Gastroenterol. 2019;43(5):533-41. doi: 10.1016/j.clinre .2019.01.008, PMID 30824369.

34. Tang L, Li J, Bao M, Xiang J, Chen Y, Wang Y. Genetic association between HER2 and ESR2 polymorphisms and ovarian cancer: a meta-analysis. Onco Targets Ther. 2018;Volume(11):. doi: 10.2147/OTT.S149428.
35. Ursoniu S, Sahebkar A, Serban MC, Banach M. Lipid profile and glucose changes after supplementation with astaxanthin: a systematic review and meta-analysis of randomized controlled trials. Arch Med Sci. 2015;11(2):253-66. doi: 10.5114/aoms.20 15.50960, PMID 25995739.
36. Kishimoto Y, Yoshida H, Kondo K. Potential anti-atherosclerotic properties of astaxanthin. Mar Drugs. 2016;14(2):35. doi: 10.3390/md14020035, PMID 26861359.
37. Chen D, Wang F, Jiang S, *et al.* Advances in chemical and biosynthetic research of astaxanthin. Food Ind Sci Technol. 2021;42(21):9.
38. Peng L, Zhao P, Li B, *et al.* Antioxidant effects and impact on human health of astaxanthin. Chin J Food Hyg. 2011;23(4):313-6.
39. Zhu XB, Wu J, Yu LD, *et al.* Experimental study on antioxidant function of astaxanthin in human body. Sci Technol Inf. 2020;12:206-8, 211.
40. Ling W, Yu-Yu Z, Xiao-Juan Y. The value of food antigen-specific IgE in predicting the risk of food allergy in children with atopic dermatitis. Food Nutr China. 2019.
41. Niu T, Zhou J, Wang F, Xuan R, Chen J, Wu W, *et al.* Safety assessment of astaxanthin from Haematococcus pluvialis: acute toxicity, genotoxicity, distribution and repeat-dose toxicity studies in gestation mice. Regul Toxicol Pharmacol. 2020;115:104695. doi: 10 .1016/j.yrtph.2020.104695, PMID 32512118.
42. Kajita M, Kato T, Yoshimoto T, *et al.* Study on the safety of high dose administration of astaxanthin. Folia Jpn Ophthalmol Clin. 2010.
43. Karppi J, Rissanen TH, Nyyssönen K, Kaikkonen J, Olsson AG, Voutilainen S, *et al.* Effects of astaxanthin supplementation on lipid peroxidation. Int J Vitam Nutr Res. 2007;77(1):3-11. doi: 10.1024/0300-9831.77.1.3, PMID 17685090.
44. Yang G, Wu LJ. Effects of astaxanthin on antioxidant indexes and serum lipid metabolites in exercises. Contemp Sports Technol. 2015;10:14.
45. Chen DF, Wang HY, Zhang CT, *et al.* Study on the function of astaxanthin capsule in lowering blood lipid in hyperlipidemia. Henan J Prev Med. 2015;22(12):1435-7.
46. Joy C, MacDermid E, *et al.* A blinded placebo-controlled randomized trial on the use of astaxanthin as an adjunct to splinting in the treatment of carpal tunnel syndrome. Hand. 2012.
47. Rad NR, Movahedian A, Feizi A, Aminorroaya A, Aarabi MH. Antioxidant effects of astaxanthin and metformin combined therapy in type 2 diabetes mellitus patients: a randomized double-blind controlled clinical trial. Res Pharm Sci. 2022;17(2):219-30. doi: 10.4103/1735-5362.335179, PMID 35280834.
48. Urakaze M, Kobashi C, Satou Y, Shigeta K, Toshima M, Takagi M, *et al.* The beneficial effects of astaxanthin on glucose metabolism and modified low-density lipoprotein in healthy volunteers and subjects with prediabetes. Nutrients. 2021;13(12):4381. doi: 10.3390/nu13124381, PMID 34959932.
49. Villano I, La Marra M, Allocca S, Ilardi CR, Polito R, Porro C, *et al.* The role of nutraceutical supplements, monacolin K and astaxanthin and diet in blood cholesterol homeostasis in patients with myopathy. Biomolecules. 2022;12(8):1118. doi: 10.3390/biom12081118, PMID 36009012.
50. Sratongfaeng C, Suksumek N, Aksorn N, Chanvorachote P, Meksawan K. Astaxanthin supplementation lowers dietary intake in healthy subjects. Curr Top Nutraceutical Res. 2020;19(1):46-51. doi: 10.37290/ctnr2641-452X.19: 46-51.

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