

Astaxanthin and risk of cardiovascular diseases: a meta-analysis of epidemiological evidence

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Abstract

Background: The purpose of this study was to analyze and evaluate the effect of astaxanthin on clinical indicators related to cardiovascular disease.

Methods: Fives databases include PUBMED, CNKI, WEIPU, WAN FANG and ClinicalTrials were searched up to January 31, 2022, and the random-effects model was used to calculate the summary risk. A total of 14 epidemiological studies were included in this meta-analysis.

Results: The overall study showed no significant dose-response association of astaxanthin (AST) with diastolic blood pressure, DBP (weighted mean difference, WND:-0.186, 95%confidence interval, CI:-0.374 to 0.002, $P=0.052$) and body mass index, BMI (WND:0.095, 95%CI: -0.164 to 0.354, $P=0.473$).However, the results revealed that astaxanthin can significantly reduce the concentrations of total cholesterol (WND:-0.310, 95% CI:-0.541 to -0.168, $P=0.000$), the concentrations of low-density lipoprotein cholesterol, LDL-C (WND: -0.207, 95% CI: -0.396 to -0.019, $P=0.031$), the concentrations of triglyceride (WND:-0.603, 95% CI:-1.028 to -0.179, $P=0.005$), the concentrations of glucose (WND: -0.353, 95% CI:-0.596 to -0.110, $P=0.004$) and systolic blood pressure, SBP(WND:-0.258, 95% CI:-0.495 to -0.021, $P=0.033$). Moreover, astaxanthin could increase the concentrations of high-density lipoprotein cholesterol, HDL-C (WND: -0.294, 95% CI:-0.515 to -0.072, $P=0.009$).

Conclusions: This meta-analysis indicates that astaxanthin has a protection role on the cardiovascular system. Further studies need to be conducted to verify the findings.

Background

Astaxanthin belongs to a xanthophyll carotenoid, and it was known as the miracle of red(3,3'-dihydroxy- β , β -carotene-4,4'-dione). There are five sources of astaxanthin, including yeast, algae, crops, crustaceans, bacteria and protozoans [1]. Astaxanthin was firstly discovered in lobsters in 1938 and was initially used for the only pigmentation in aquaculture [2]. Astaxanthin has unique chemical properties. It is composed of a series of conjugated double bonds, violet ketone ring, hydroxyl (OH) and keto (C=O). These unique structures can neutralize and scavenge free radicals inside and outside the cell membrane. Astaxanthin has both hydrophilic and hydrophobic groups, which can cross the whole-cell membrane to protect the inside and outside the cell. The molecular structure of astaxanthin ensures the unparalleled penetration of astaxanthin, which penetrates the blood-brain barrier, skins and all organs [2-4]. Astaxanthin act as a safeguard against oxidative and inflammatory damage by various mechanisms. Astaxanthin promotes the dissociation and nuclear translocation of nuclear erythroid 2-related factor, Nrf2 through activating the signaling pathways of PI3K/Akt and extracellular signal-regulated kinase, ERK, which contributes to increased expression of Nrf2-regulated enzymes that resist oxidative stress. Astaxanthin negatively regulates the Sp1/NR1 signaling pathway, alleviating the production of intracellular reactive oxygen species, ROS and oxidative stress. In addition, through restraining I κ B- α degradation and NF- κ B nuclear translocation, astaxanthin inhibits the expression of inflammatory molecules interleukin-6 (IL-6), cell adhesion molecules-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1). Astaxanthin also suppresses the nuclear expression of NF- κ B and reduces downstream production of pro-inflammatory cytokines by restoring physiological levels of SHP-1 [23,24,33,34]. Thus, astaxanthin plays a vital role in anti-inflammation and anti-oxidation. Astaxanthin can resist diseases caused by oxidative stress such as metabolic syndromes, neurodegenerative diseases, cardiovascular diseases, inflammatory diseases and age-related diseases.

Cardiovascular disease is the leading cause of death in the world. At present, the research that astaxanthin affects cardiovascular disease has been increasing [5-8]. However, there are some controversies about the conclusions. Since meta-analysis can systematically evaluate and summarize the results of multiple studies on the same subject, a meta-analysis was presented to assess the efficacy of astaxanthin on cardiovascular diseases in epidemiological studies. This meta-analysis of epidemiological studies powerful revealed that significant reductions in cardiovascular system disease were associated with astaxanthin intake. The astaxanthin remarkably reduces blood lipid concentration, plasma glucose concentration and blood pressure.

Methods

Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statements checklist, PUBMED, CNKI, WEIPU, WANFANG and ClinicalTrials were searched from inception to January 31, 2022. Furthermore, the online search of published literatures were conducted through PubMed using the MeSH (Medical Subject Headings) term and additional grey literature. The search terms keywords were as follows: (astaxanthin or AST 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 by hand.

Study selection

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

The exclusion criteria were as follows: (1) repetitive articles or just titles, abstracts; (2) systematic review, meta-analysis, case reports; (3) letters, and conference data; (4) animal or cell experiments; (5) no control group.

Data extraction

Information was extracted independently by two investigators. The disagreements were adjudicated by the third investigator. Each eligible study was reviewed and extracted as follows: 1) the first author; 2) the year of publication; 3) country; 4) age; 5) sex; 6) the daily dosage of the astaxanthin groups and control groups; 7) the number of participants in the astaxanthin groups and control groups; 8) the means and standard deviations of total cholesterol concentration, HDL-C, LDL-C, triglyceride concentration, plasma glucose concentration, diastolic pressure, systolic pressure and body mass index (BMI); 9) the follow-up time for cohort studies.

Quality assessment

Using the Cochrane Collaboration tool to assess the quality of each study. The evaluation content mainly included: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. The low risk of bias, high risk of bias and unknown risk of bias were evaluated. The evaluative results were divided into three levels, including low risk, high risk and unclear. In the overall analysis of multiple studies, the majority of the information from low risk of preference was called "low risk of bias"; most of the information from unknown risk of preference was considered as "unclear risk of bias"; the proportion of data from studies which are high risk of preference and sufficiently affect the interpretation of results was known as "High risk of bias". The quality evaluation was executed independently by two authors, and the different opinions were decided by a third author.

Statistical analysis

All statistical analyses were conducted by the Comprehensive Meta-Analysis Software, version v. 2.0. As a more conservative estimate, the random-effects model was used to calculate the summary risk. Forest plots described WMD and 95%CI for the effect of astaxanthin in detail. Heterogeneity among studies was estimated through calculating the Q-statistic and I^2 value. The change of I^2 value is due to heterogeneity. The Q-statistic and I^2 value describes the percent of different studies due to heterogeneity rather than chance, of which 0% declares no observed heterogeneity, with 25% regarded as low, 50% as moderate, and 75% as high [9]. If a p -value <0.05 indicated the presence of significant heterogeneity, sensitivity analysis is needed for further exploration. The sensitivity analysis evaluated whether the combined estimates could have been a substantial impact by a single study, each study was excluded one by one, and the investigation based on the remaining studies through forest plot. Publication bias was explored through funnel plots in the studies which were selected for research, and the methods of Begg's test and Egger's test evaluated further whether publication bias exists (there was no publication bias if the funnel plot was symmetric), provided a p -value <0.05 indicated the presence of potential publication bias. The means of trim and fill analysis was used to examine the effects of possibly missing studies. A correlation coefficient (R) was assumed as 0.5 [10].

Results

Characteristics of Eligible Studies

Literature search

A total of 8964 publications was collected from the four databases, of which 1058 were reviewed through titles and, or abstracts, 958 articles were excluded because they were titles, abstracts, meta-analyses, case reports, systematic reviews and irrelevant articles. 100 full-text articles

were screened, and 36 articles fulfilled the inclusion criteria. Finally, 13 studies were selected for the meta-analysis, and the reasons for excluding 23 studies from the remaining articles were as follows: 19 studies combined astaxanthin with other drugs, 4 studies hadn't control group. The flow diagram is shown in Figure 1.

Study characteristics

The Study characteristics show in Table 1. They were all prospective cohort studies. Eight studies were conducted in Asia (Korea, n=1; Japan, n=5; Iran, n=1; China, n=4), one study was conducted in Europe (Finland, n=1), and one study was conducted in America (Canada, n=1). The other information of the included studies was age range, sex, astaxanthin dose, placebo dose and follow-up period.

Quality assessment

The results of the quality assessment with Cochrane criteria are summarized in Table 3. The quality about the included studies was varied, 46 items of information were low-risk bias, and 43 items of information were unclear bias risk. Only 1 item was high-risk bias, but it didn't affect our findings. Therefore, the included articles were high-quality studies.

Blood lipid

Thirteen studies on the relationship between astaxanthin and the concentration of cholesterol were shown in Figure 2.1. The astaxanthin could remarkably recover the plasma concentration of total cholesterol (WMD: -0.310, 95%CI: -0.541 to -0.168, $P = 0.000$, $Z = -4.294$); HDL-C (WMD: -0.294, 95%CI: -0.515 to -0.072, $P = 0.009$, $Z = 2.594$); LDL-C (WMD: -0.207, 95%CI: -0.396 to -0.019, $P = 0.031$, $Z = -2.153$); triglyceride (WMD: -0.603, 95%CI: -1.028 to -0.179, $P = 0.005$, $Z = -2.787$). The analyses for total cholesterol, HDL-C and LDL-C showed in Table 2 that the heterogeneity was not statistically significant (Total cholesterol: $I^2 = 0.000$, $Q = 13.598$, $P = 0.755$; HDL-C: $I^2 = 37.794$, $Q = 27.329$, $P = 0.053$; LDL-C: $I^2 = 0.000$, $Q = 3.210$, $P = 0.999$). However, there were publication biases of total cholesterol, HDL-C and LDL-C in Table 2. (Total cholesterol: $p_{Begg} = 0.008$, $p_{Egger} = 0.024$; HDL-C: $p_{Begg} = 0.014$, $p_{Egger} = 0.083$; LDL-C: $p_{Begg} = 0.002$, $p_{Egger} = 0.008$). According to the trim and fill analysis, these studies were filled in the right of the mean to make the funnel symmetrical, and the adjusted estimated effect based on the random-effects model, the result emerged the adjusted values was consistent with the observed values in Figure 5. (Total cholesterol: lower limit -0.451 to upper limit -0.168, $Q = 13.598$; HDL-C: lower limit 0.07178 to upper limit 0.51532, $Q = 27.329$; LDL-C: lower limit -0.39587 to upper limit 0.01854, $Q = 3.210$). In analyses for Triglyceride, no publication bias was detected (Triglyceride: $p_{Begg} = 0.06250$, $p_{Egger} = 0.20944$). There was significant heterogeneity (Triglyceride: $I^2 = 84.083$, $Q = 87.956$, $P = 0.000$). They were shown in Table 2. To determine whether the comprehensive assessments would have been markedly affected by single research, the sensitivity analysis was conducted. The results in Figure 3 showed that substantial heterogeneity was not observed in this analysis (all of $P\text{-Value} > 0.00$).

Plasma glucose

Four studies focused on the effect of astaxanthin on plasma glucose concentrations, as shown in Figure 2.2. The results suggested that astaxanthin significantly reduced the blood glucose of patients (WMD: -0.353, 95%CI: -0.596 to -0.110, $P = 0.004$, $Z = -2.848$). The meta-analysis in Table 2 suggested that the heterogeneity was not statistically significant ($I^2 = 20.991$, $Q = 6.328$, $P = 0.276$). These result indicated evidence of no publication bias ($p_{Begg} = 0.42549$, $p_{Egger} = 0.24654$).

Blood pressure

Six studies investigated the role of astaxanthin in controlling blood pressure, as shown in Figure 2.3. The results didn't show the potential role of astaxanthin in DBP (WMD: -0.186, 95%CI: -0.374 to 0.002, $P = 0.052$, $Z = -1.943$), while astaxanthin was significant for reducing SBP (WMD: -0.236, 95%CI: -0.425 to -0.048, $P = 0.014$, $Z = -2.460$). No significant publication bias was observed in this analysis (DBP: $p_{Begg} = 0.105$, $p_{Egger} = 0.103$; SBP: $p_{Begg} = 0.266$, $p_{Egger} = 0.216$). The heterogeneity wasn't significant in this study (DBP: $I^2 = 0.000$, $Q = 1.235$, $p = 0.996$; SBP: $I^2 = 0.000$, $Q = 3.636$, $p = 0.888$). These were shown in Table 2.

BMI

As shown in Figure 2.4, five studies evaluated the association between astaxanthin and body mass index. The results indicated the null effect of astaxanthin on BMI (WMD: 0.095, 95%CI: -0.164 to 0.354, $p = 0.473$). Heterogeneity was not found in the analysis ($I^2 = 0.000$, $Q = 0.592$, $P =$

0.999). However, the publication bias existed in Table 2 ($p_{\text{Begg}}=0.013$, $p_{\text{Egger}} = 0.042$). Then, the trim and fill analysis were implemented, and the adjusted estimated effect was based on the random-effects model. The result in Figure 5 emerged that the adjusted values were consistent with the observed values (BMI: lower limit -0.164 to upper limit 0.354, $Q = 0.592$).

Discussion

A total of 13 studies were included to assess the impact of astaxanthin on cardiovascular disease in this meta-analysis. This report proved that astaxanthin had a significant influence on cardiovascular disease. The intake of astaxanthin significantly reduce the concentrations of total cholesterol, the concentrations of LDL-C, the concentrations of triglyceride, the concentrations of glucose and systolic blood pressure, and significantly increase the concentrations of HDL-C. In the study by Chen YQ et al, male spontaneously hypertensive rats (SHRs) were intragastric injected 200 mg/kg astaxanthin once a day, The untreated groups were gavaged with equivalent normal saline. After 11 weeks, SHRs suffered from gradually elevated blood pressure rising to 185/124 mmHg, the SBP and DBP of ATX-treated SHRs were reduced to 153/100 mmHg [35]. Kumar R et al. received 50 mg/kg astaxanthin orally with gavage and served as test group for astaxanthin, The total cholesterol in experimental group is significantly decreased compared to the control group, and HDL-C is significantly increased [21]. Meanwhile, the atherosclerotic lesions were significantly reduced compared with the control group [21]. The research findings by Birudaraju D, et al. showed that active group subjects (Contains astaxanthin) could improve the endothelial function and reduce SBP at 4 weeks [20].

Nevertheless, the previous meta-analysis didn't indicate a significant effect of astaxanthin supplementation on plasma lipid profile[10]. The reasons for inconsistency may be different retrieval times, different retrieval database or different sample size. In the sensitivity analysis, the effect size was relatively stable, and removing any individual study didn't affect the overall results. In HDL-C studies, the potential heterogeneity was statistically significant. However, sensitivity analysis indicated that there were no significant fluctuations. The main reasons are as followings: (1) Chen DF et al. only used women as subjects [17]; (2) The subjects were all men in the research by Guang Yang et al. [14]; (3) Two studies (Mashhadi NS,2018; Chen DF, 2015) didn't specify the daily dose of astaxanthin [5,14]. These factors partly affected the level of heterogeneity to a certain degree. Thus, excluding one study could reduce heterogeneity.

The molecular and cellular mechanisms of astaxanthin in cardiovascular disease are as follows: 1. Since its chemical structure, astaxanthin has both polar region and nonpolar groups of the molecule, it takes on a transmembrane alignment on biofilms and protects cell membranes against RONS and oxidative damage; 2. A series of conjugated bonds in the central non-polar region of astaxanthin makes the molecule to transport free radicals along its own carbon chain. Then removes them from the inside of the cell. finally, the free radicals are neutralized by other antioxidants located outside the cell membrane; 3. Astaxanthin neutralizes peroxynitrite, then inhibits lipid peroxidation and LDL oxidation; 4. Astaxanthin can reduces production of superoxide anion radicals released by NADPH oxidase and increases NO. Thus, astaxanthin appear to delay the progression of cardiovascular diseases [33]. Free radicals are highly reactive, which can trigger lipid peroxidation, destroy the primary groups and lead to genetic mutations. Then, they damage the sugar chains of cell membrane and cause the cell autolysis, change protein conformation and cause protein function loss. Finally, normal physiological activities are affected [18]. Astaxanthin has a role of antioxidant activities by quenching singlet oxygen and scavenging radicals to terminate chain reactions [19]. Therefore, This meta-analysis reconfirms the conclusion that astaxanthin has a protective effect on the cardiovascular system. Moreover, no serious adverse effects of astaxanthin consumption have been reported in animals and humans, even at the high dose of 45 mg/d [15,22,25,26,27]. These results support the safety of astaxanthin for future clinical studies.

Study strengths and limitations

Similar to all studies, several limitations existed in this meta-analysis. Firstly, the included studies and sample size is smaller (a total of 13 included articles with 694 cases). When the number of the studies is smaller than 10 in analysis, the power of the publication bias test is declined, and the combined results are unstable [16]. Secondly, the confounding factors should be adjusted, including age, sex, environmental factors, lifestyle and the dose of medicine. To move forward in the research project of astaxanthin on the cardiovascular system, the literature will be collected and the data will be updated in time in the future. The animal experiments will be conducted to analyze the effect of astaxanthin on the cardiovascular system.

Conclusion

This is a meta-analysis to comprehensively assess the effect of astaxanthin on the risk of cardiovascular disease. The study is an update on previous research reports. The results showed that astaxanthin could significantly reduce the concentration of blood sugar, concentration of blood lipid and blood pressure, and the analysis suggested that astaxanthin supplementation plays an essential role in preventing cardiovascular disease. In summary, the updated literature analysis in this study further verified that astaxanthin had a protective effect on cardiovascular system.

Declarations

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Authors' contributions

GXZ and DL designed the study and revised the manuscript. LZ, KRR, MRL, HR and QPY searched the literature, MWY and YHQ analyzed the data and summarized the results. All authors passed on the final version of the manuscript.

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All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have declared that they have no competing interests. This meta-analysis was written independently.

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Tables

Table 1

the Characteristics of included studies.

First author, year	Country	Age	Sex(Male/Female)	Astaxanthin dose (mg/day)	Placebo dose (mg/day)	Follow-up (day)
⁸ Choi HD,2011	Korea	20-55	23/4	20	20	84
²⁹ Iwamoto T,2000	Japan	20-36	—	1.8	0	14
²⁹ Iwamoto T,2000	Japan	20-36	—	3.6	0	14
²⁹ Iwamoto T,2000	Japan	20-36	—	14.4	0	14
²⁹ Iwamoto T,2000	Japan	20-36	—	21.6	0	14
³⁰ Karppi J,2007	Finland	19-33	—	8	8	90
¹¹ Yoshida H,2011	Japan	20-65	41/20	18	0	84
¹¹ Yoshida H,2011	Japan	20-65	41/20	12	0	84
¹¹ Yoshida H,2011	Japan	20-65	41/20	6	0	84
¹³ Chen JT,2016	Japan	46-56	0/29	12	12	90
¹² Mashhadi NS,2018	Iran	30-60	17/27	—	—	56
¹⁴ Yang G,2015	China	17-23	16/0	9	9	28
⁷ Chen DF,2015	China	38-54	60/47	3.72	0	45
¹⁵ Peng L,2011	China	45-65	53/62	40	0	90
²⁸ Michiyuki S,2012	Japan	26-50	5/15	12	12	28
³¹ Kiyotaka N,2011	Japan	50-63	10/10	6	6	84
³¹ Kiyotaka N,2011	Japan	51-62	10/10	12	12	84
²² Zhu XB,2020	China	37-64	57/63	9	9	90
³² Macdermid JC,2012	Canada	29-74	18/45	4	4	42
³² Macdermid JC,2012	Canada	29-74	18/45	4	4	84

Table 2

The basis for Basis for heterogeneity and publication bias.

	Point estimate (95%CI)	Heterogeneity			Publication bias	
		I ²	Q	P	Begg	Egger
Total cholesterol	-0.310(-0.451,-0.168)	0.000	13.598	0.755	0.00789	0.02386
HDL-C	0.294(0.072,0.151)	37.794	27.329	0.053	0.01401	0.08278
LDL-C	-0.207(-0.396,-0.019)	0.000	3.210	0.999	0.00240	0.00779
Triglyceride	-0.603(-1.028,-0.179)	84.083	87.956	0.000	0.06250	0.20944
Glucose	-0.353(-0.596,-0.110)	20.991	6.328	0.276	0.42549	0.24654
SBP	-0.236(-0.425,-0.048)	0.000	3.636	0.888	0.26581	0.21568
DBP	-0.186(-0.374,0.002)	0.000	1.235	0.996	0.10545	0.10254
BMI	0.095(-0.164,0.354)	0.000	0.592	0.999	0.01298	0.04178

Table 3

Cochrane criteria as the evaluation criteria for the quality assessment.

Notice: "√" express the 'Low risk' of bias, "X" as the 'High risk' of bias, "-" as the 'Unclear risk' of bias.

First author year	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Low risk	High risk	Unclear risk
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias			
⁸ Choi HD,2011	√	-	√	-	√	-	√	4	0	3
²⁹ Iwamoto T,2000	-	-	-	-	-	-	√	1	0	6
³⁰ Karppi J,2007	√	√	√	-	√	-	√	5	0	2
¹¹ Yoshida H,2011	√	-	√	-	√	-	√	4	0	3
¹³ Chen JT,2016	√	-	√	-	-	-	X	2	1	4
¹² Mashhadi NS,2018	√	-	√	-	√	-	√	4	0	3
¹⁴ Yang G,2015	√	√	-	-	√	-	√	4	0	3
⁷ Chen DF,2015	X	√	√	-	√	-	√	4	1	2
¹⁵ Peng L,2011	√	√	-	-	√	-	√	3	0	4
²⁸ Michiyuki S,2012	√	√	√	-	-	-	√	4	0	3
³¹ Kiyotaka N,2011	√	√	√	-	-	-	√	4	0	3
²² Zhu XB,2020	√	-	-	-	-	-	√	2	0	5
³² Macdermid JC,2012	√	√	√	√	-	-	√	5	0	2

Figures

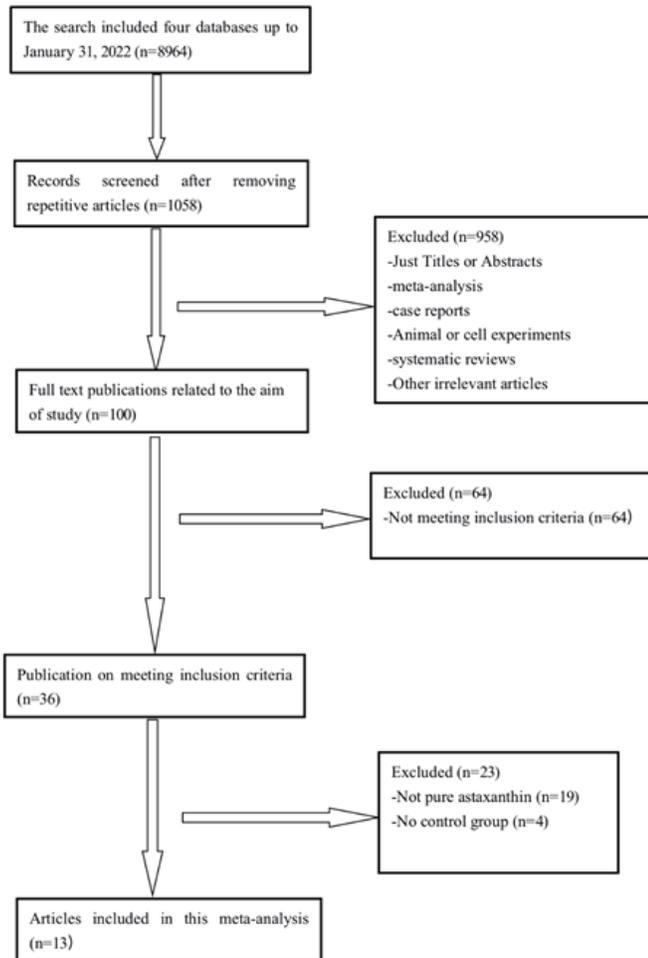
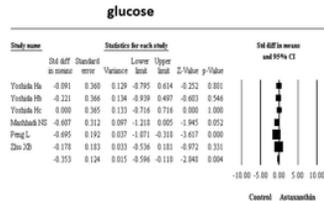
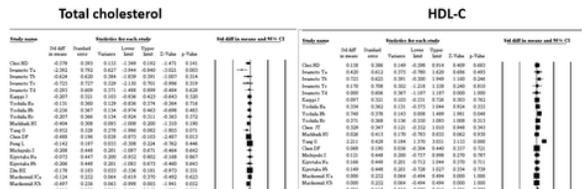


Figure 1

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.



2.2

Figure 2

2.1. Forest plots detailing weighted mean difference (WMD) and 95% confidence intervals (95%CI) for the effect of astaxanthin on Blood lipid. The horizontal axis scale of the invalid line vertical line is 0.00, and each horizontal line is the 95% confidence interval. The length of the horizontal line expresses the size of the confidence interval, The size of each box reflects the study's weight in the analysis. The p value < 0.1 indicated the existence of heterogeneity among studies.

2.2. Forest plots detailing weighted mean difference (WMD) and 95% confidence intervals (95%CI) for the effect of astaxanthin on glucose.

2.3. Forest plots detailing weighted mean difference (WMD) and 95% confidence intervals (95%CI) for the effect of astaxanthin on Blood pressure

2.4. Forest plots detailing weighted mean difference (WMD) and 95% confidence intervals (95%CI) for the effect of astaxanthin on BMI

Triglyceride

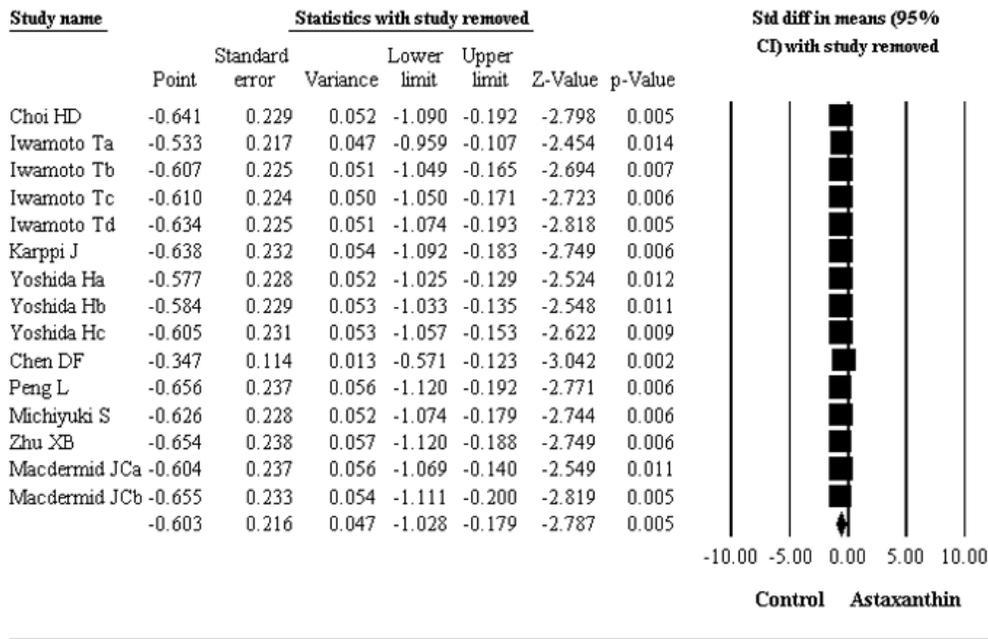


Figure 3

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.

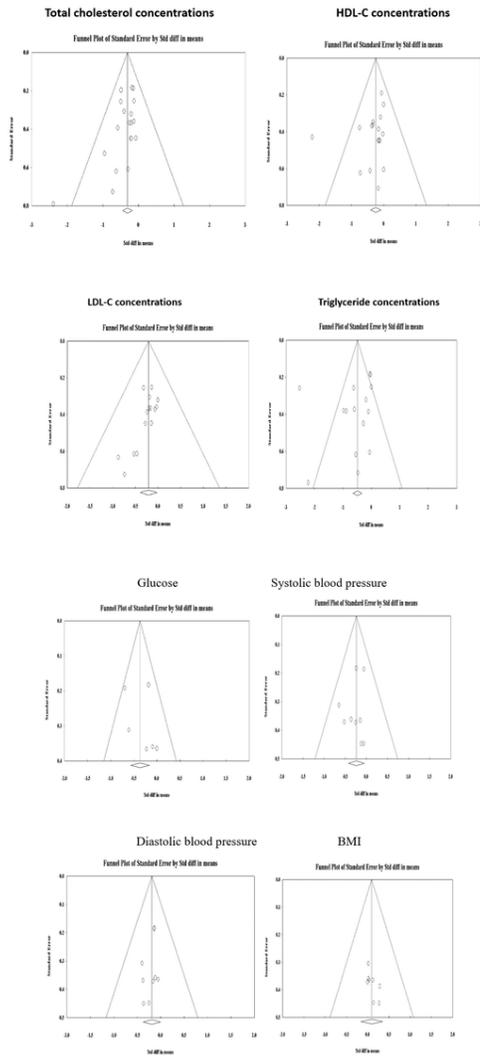


Figure 4
 Funnel plots detailing publication bias about lipid profile in the studies selected for analysis. Circles represent observed published studies.

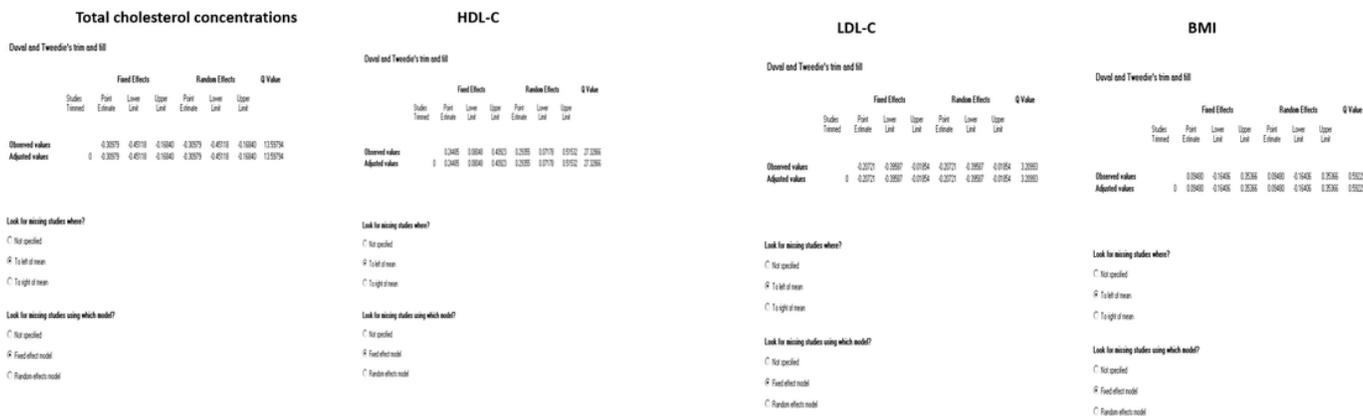


Figure 5

Trim and fill method was used to impute for potentially missing studies and adjust the analysis for the effects of publication bias.