



The effects of astaxanthin supplementation on liver enzyme levels

A systematic review and meta-analysis

Hoda Arefpour¹, Niloufar Rasaei^{2,3}, Mohammad Reza Amini^{4,1} , Marieh Salavatizadeh⁵, Mohtaram Hashemi⁶, Maede Makhtoomi^{7,8}, Mahdi Hajiaqaei⁹, Mohammad Gholizadeh⁵, Moein Askarpour¹⁰, and Azita Hekmatdoost⁵

- ¹ Student Research Committee, Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition & Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran
- ² Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Iran
- ³ Network of Interdisciplinarity in Neonates and Infants (NINI), Universal Scientific Education and Research Network (USERN), Tehran, Iran
- ⁴ Nutrition and Food Security Research Center, Isfahan University of Medical Sciences, Iran
- ⁵ Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Science, Tehran, Iran
- ⁶ Student Research Committee, Semnan University of Medical Sciences, Iran
- ⁷ Student Research Committee, Shiraz University of Medical Science, Iran
- ⁸ Health Policy Research Center, Institute of Health, Shiraz University of Medical Science, Iran
- ⁹ Department of Physiology, Faculty of Medicine, Tehran University of Medical Sciences (TUMS), Iran
- ¹⁰ Student Research Committee, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Iran

Abstract: According to previous studies, astaxanthin exerts various biological effects due to its anti-inflammatory and antioxidant capabilities; however, its effects on liver enzymes have not yet been well elucidated. Therefore, we conducted a meta-analysis to assess astaxanthin's effects on liver enzymes. A systematic literature search was conducted using scientific databases including PubMed, Scopus, Web of Science, the Cochrane databases, and Google Scholar up to February 2023 to find relevant randomized controlled trials (RCTs) examining the effects of astaxanthin supplementation on alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP). A random-effects model was used for the estimation of the pooled weighted mean difference (WMD). Overall, we included five trials involving 196 subjects. The duration of the intervention was between 4 and 48 weeks, and the dose was between 6 and 12 mg/day. ALT levels increased in the intervention group compared to the control group following astaxanthin supplementation (WMD: 1.92 U/L, 95% CI: 0.16 to 3.68, $P=0.03$), whereas supplementation with astaxanthin had a non-significant effect on AST (WMD: 0.72 U/L, 95% CI: -0.85 to 2.29, $P=0.36$), GGT (WMD: 0.48 U/L, 95% CI: -2.71 to 3.67, $P=0.76$), and ALP levels (WMD: 2.85 U/L, 95% CI: -7.94 to 13.63, $P=0.60$) compared to the placebo group. Our data showed that astaxanthin supplementation increases ALT concentrations in adults without affecting the levels of other liver enzymes. Further long-term and well-designed RCTs are necessary to assess and confirm these findings.

Keywords: astaxanthin, aspartate aminotransferase, alanine aminotransferase, meta-analysis

Introduction

Astaxanthin belongs to a group of carotenoids that are oxidized [1, 2, 3]. It is a natural compound found in various sources such as algae, fish and birds [1]. It is a red, lipophilic pigment that is part of the xanthophyll family and closely

related to β -carotene, lutein, and zeaxanthin [4]. Astaxanthin, a naturally occurring C40 carotenoid, is linked to various biological functions primarily related to its antioxidant and anti-inflammatory properties. Astaxanthin is different from other antioxidants because it has the highest oxygen radical absorbance capacity (ORAC), which is 100–500

times higher than that of α -tocopherol. It also has 10 times more free radical inhibitory activity than related antioxidants like α -tocopherol, α -carotene, β -carotene, lutein, and lycopene [5]. Astaxanthin can lower the levels of harmful oxygen molecules, swelling, scarring, and cell death [6, 7, 8]. Moreover, astaxanthin possesses the capability to exert an influence on cellular signaling cascades. In particular, it keeps the redox-sensitive transcription factors nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor kappa B (NF- κ B) under control. Nrf2 and NF- κ B are both involved in oxidative stress and inflammation, respectively [9, 10]. It also regulates the immune system and metabolic processes [11, 12, 13]. It has beneficial impacts on different types of liver damage, such as scarring, fat accumulation, cancer, and drug toxicity [13, 14]. Liver disease causes millions of deaths and disabilities worldwide every year. Approximately 2 million people die from liver disease annually; half of them die because of cirrhosis and half of them due to hepatitis and hepatocellular carcinoma [15, 16]. Cirrhosis is the 11th and liver cancer is the 16th most common cause of death in the world [16]. Depending on the type of liver disease, it has different impacts on liver enzymes [13, 17, 18]. Liver enzymes are proteins that catalyze chemical reactions in the liver [19]. Common liver enzymes include aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) [20, 21, 22]. Rising liver enzymes indicate a hepatocellular damage, resulting in the release of the cellular enzymes into the bloodstream [23, 24]. Therefore, it is extremely important to detect, monitor, and manage it as soon as possible. Given the scarcity of research and data on the effects of astaxanthin supplementation on liver enzymes, we aimed to do this meta-analysis on available data to elucidate these effects.

Methods

The current research was conducted based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The present study was registered at PROSPERO (CRD42023428043).

Search strategy

A systematic literature search was conducted using scientific databases including PubMed, Scopus, Web of Science, the Cochrane databases, and Google Scholar from inception up to February 2023 to find relevant randomized controlled trials (RCTs) examining the effects of astaxanthin supplementation on liver enzyme levels. The PICOS

(Participant, Intervention, Comparison/Control, Outcome, study design) search framework was used to construct search terms and strategies [25]: participant (adults ≥ 18 years old), intervention (astaxanthin), comparator (placebo), outcome (AST, ALT, GGT, and ALP), and study design (parallel and cross-over clinical trial). The following Medical Subject Heading (MeSH) and non-MESH terms were applied for the literature search: (astaxanthin OR astaxanthine OR E-astaxanthin) AND ("liver enzymes" OR "liver enzyme" OR "Liver function" OR ALT OR "alanine aminotransferase" OR "alanine transaminase" OR "serum glutamic-pyruvic transaminase" OR SGPT OR AST OR "aspartate transaminase" OR "aspartate aminotransferases" OR SGOT OR "Alkaline phosphatase" OR ALP OR GGT OR gamma-Glutamyltransferase) AND (intervention OR RCT OR randomized OR randomly OR placebo OR random OR assignment OR trials OR trial). The included articles' reference lists were manually checked for new publications. There was no time or linguistic restriction.

Study selection

We included studies that met the following criteria: (1) RCTs (parallel or crossover), (2) investigated the effects of astaxanthin supplementation on AST, ALT, GGT, and ALP, (3) used the oral intake of astaxanthin, (4) carried out in adult individuals (≥ 18 years old), (5) published liver enzyme means and standard deviations for the intervention and control groups, or offered any additional effect sizes that allowed for the derivation of those estimations. Studies with additional eligible arms were considered separate studies. Cross-sectional, cohort, case-control, in vitro, animal studies, review articles, conference abstracts, and RCTs without a control group were excluded. Studies that were performed on children or adolescents, or those in which astaxanthin was prescribed in combination with other treatments, were also excluded. The titles and abstracts were evaluated by two impartial reviewers (MRA and HA) in accordance with the requirements for eligibility. Any disagreements were resolved through discussion.

Data extraction

Two separate researchers (MRA and HA) extracted data using a standardized data collection form. The following data were extracted from each eligible RCT: name of the first author, publication year, study location, design, subjects' characteristics (mean age, body mass index (BMI), and sex), the health status of participants, sample size, the dosage of astaxanthin, duration of intervention, comparator group, and mean changes and their standard deviation (SDs) of liver enzymes for the intervention and control

Table 1. Risk of bias for randomized controlled trials, assessed according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 1)

Publications	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Other source of bias
1. Chen (2017)	L	U	L	L	U	L	L
2. Coombes (2016)	L	L	L	L	U	L	L
3. Nakagawa (a) (2011)	L	U	L	L	U	L	H
4. Saito (2012)	L	U	L	L	U	L	H
5. Sekikawa (2023)	L	L	L	L	U	L	L

groups. If needed, we contacted the associated author to obtain any missing information.

Quality assessment

The risk of bias for each included study was determined using the Cochrane quality assessment tool [26]. The tool consists of seven domains, including inadequate outcome data, other sources of bias, participants, and staff members' blinding, allocation concealment, reporting bias, and randomized sequence creation. Methodological defects affecting the findings of the research resulted in a "high risk" score for each domain, while a "low risk" score was given to each defect-free domain (Table 1). If the information was not sufficient to determine the impact, an "unclear risk" was considered for the domain. The total risk of bias estimation is as follows: Low; if all domains had "low risk", (2) Moderate; if one or more domains had "unclear risk", and (3) High; if one or more domains had "high risk" [27]. Two impartial reviewers (MRA and HA) independently assessed the possibility of bias.

Statistical analysis

To estimate the mean difference in changes as the effect size, mean differences $\pm$ SDs of ALT, AST, GGT, and ALP in the intervention and control groups were applied. The following formula was used to convert the standard error of the mean (SEM) to SD when the study reported SEM in place of SD: $SD = SEM \times \sqrt{n}$, where "n" is the number of individuals in each group. If the study presented medians and an interquartile range, mean and SD values were calculated using $SD = \text{interquartile range} / 1.35$ (symmetrical data distribution) [28]. When mean and SD were not presented by studies, we estimated them using the following formula [29] in which the correlation coefficient (R) was considered 0.8: $SD_{\text{difference}} = \text{Square Root} [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2 \times R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$. A random-effects model (developed by Der Simonian and Laird) was used for the estimation of pooled weighted mean difference (WMD) and 95% confidence interval (CI) since it

can take into account both within and between-study heterogeneity [30]. I^2 statistic and Cochrane's Q test were used to determine the heterogeneity among studies. The I^2 values $>50\%$ or $P < 0.05$ were regarded as significant between-study heterogeneity [31, 32]. By deleting each study separately and recalculating the pooled analysis, sensitivity analysis was carried out to assess the impact of each study on the overall effect size. Egger's regression test and Begg's rank correlation test were all used to look into the possibility of publication bias [33]. STATA, version 14 (Stata Corp, College Station) was used to perform statistical analysis. P-values less than 0.05 were considered statistically significant.

Results

Study selection

In the first stage of the systematic search, 1617 and 2 papers were identified from online databases and hand searching, respectively. After removing duplicated studies, 918 remaining ones were screened based on title and abstract evaluation, which resulted in the exclusion of 905 records due to animal research ($n=150$), review design ($n=220$), and no relevant or original data ($n=535$). Therefore, 13 potentially relevant articles were included in the full-text review. Out of the 13 studies, six were excluded because they were irrelevant. Two RCTs that were conducted on subjects younger than 18 years were also excluded [34, 35]. Finally, five eligible articles [36, 37, 38, 39, 40] were included in the current systematic review and meta-analysis. The flow chart provided in Figure 1 indicates the selection process.

Study characteristics

The range of publication years for the included studies was between 2011 and 2023. The characteristics of these articles are reported in Table 2. The studies consisted of 196 subjects in both intervention and control groups. All of the

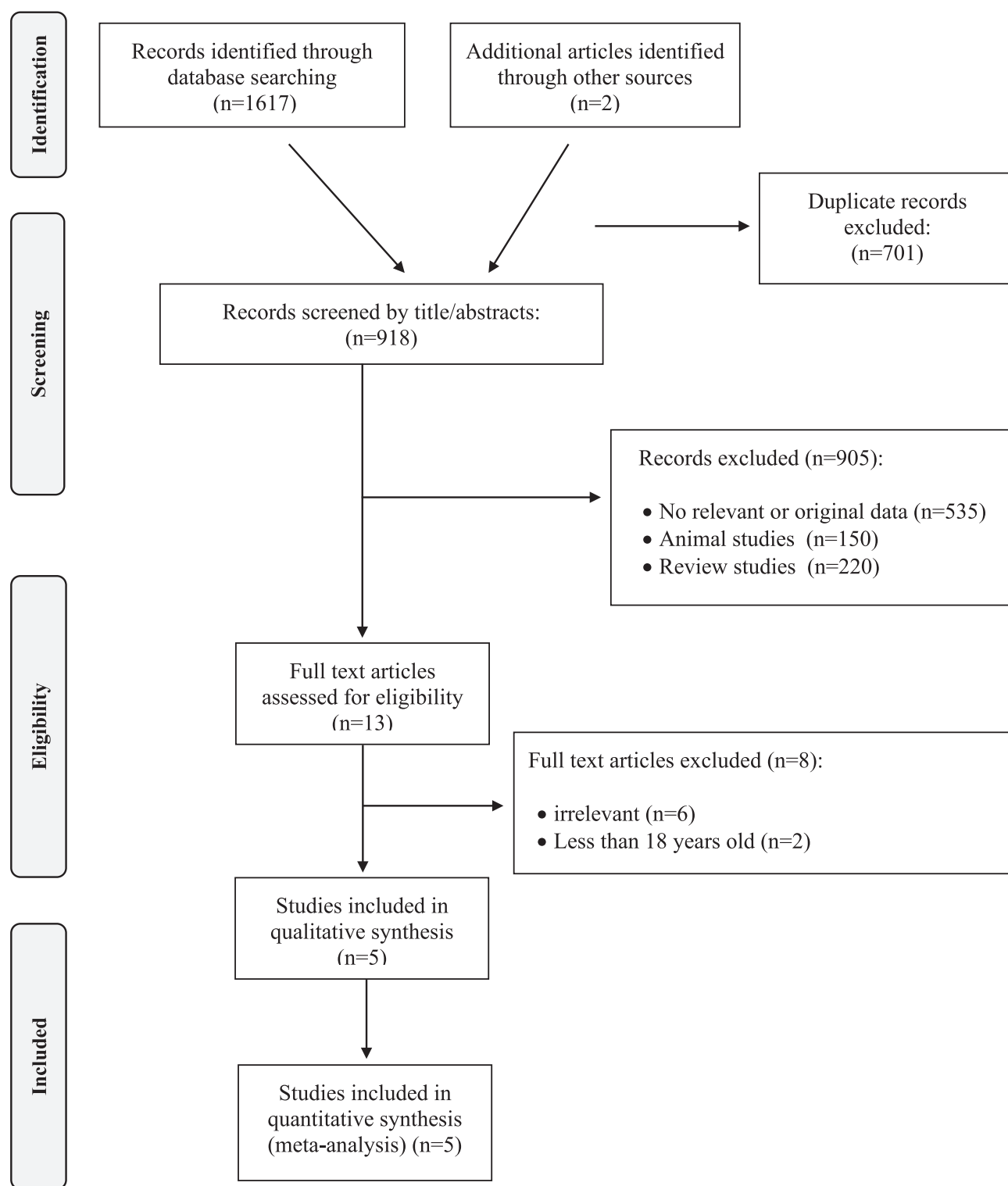


Figure 1. Flow chart of the number of studies identified and selected into the meta-analysis.

studies were double-blinded RCTs with a parallel design. Except for one study [39] conducted on females, other studies [36, 37, 38, 40] were carried out on both sexes. The participants of all studies were adult individuals aged ≥ 18

years. One study was from Australia [38], while others were done on the Japanese population. Four studies reported the BMI of the participants, which was between 21.6 and 27.6. The duration of the intervention varied from 4 to 48 weeks

Table 2. Demographic characteristics of the included studies

First author (year)	Location	Study design	Health status	Sex	Sample size	Duration (week)	Mean age (year)	Baseline BMI (kg/m ²)	Intervention group	Comparator group	Outcome
1. Chen (2017)	Japan	RCT, double-blind, parallel	Healthy	Female	29	12	51.5	21.6	12 mg/day astaxanthin	Placebo	ALT/AST/GGT
2. Coombes (2016)	Australia	RCT, double-blind, parallel	Renal transplant recipients	Both	58	48	49.9	26.9	12 mg/day astaxanthin	Placebo	ALT/AST/GGT/ALP
3. Nakagawa (a) (2011)	Japan	RCT, double-blind, parallel	Healthy	Both	15	12	56.4	27.5	6 mg/day astaxanthin	Placebo	ALT/AST/GGT/ALP
4. Nakagawa (b) (2011)	Japan	RCT, double-blind, parallel	Healthy	Both	15	12	56.3	27.6	12 mg/day astaxanthin	Placebo	ALT/AST/GGT/ALP
5. Saito (2012)	Japan	RCT, double-blind, parallel	Healthy	Both	20	4	38.5	NA	12 mg/day astaxanthin	Placebo	ALT/AST/GGT/ALP
6. Sekikawa (2023)	Japan	RCT, double-blind, parallel	Healthy	Both	59	6	39.1	NA	9 mg/day astaxanthin	Placebo	ALT/AST/GGT/ALP

Abbreviations. RCT = randomized controlled trial; BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; ALP = alkaline phosphatase.

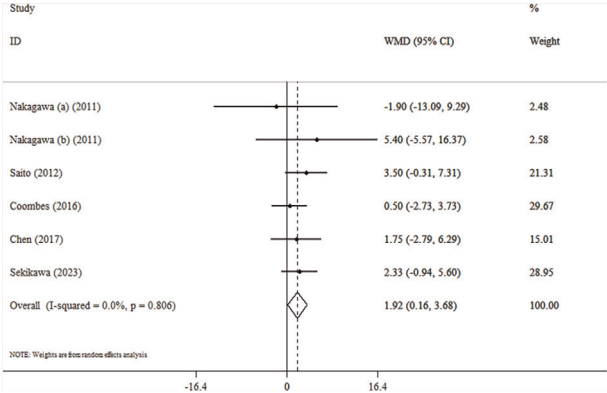


Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of astaxanthin on alanine transaminase.

among the included articles. In terms of health status, four RCTs recruited healthy subjects; however, the investigation of Coombes et al. [38] was conducted on renal transplant recipients. In contrast to the Sekikawa et al. study [40] in which 9 mg/day of astaxanthin was prescribed, in other studies, the dosage of astaxanthin for intervention groups was 12 mg/day. Nakagawa et al.'s investigation [36] had two types of intervention doses (6 and 12 mg/day), which is the reason for the two arms in this research. Three RCTs [38, 39, 40] had moderate quality, in which one or more domains had an unclear risk of bias. Two studies [36, 37] could be considered low quality since one of them was at high risk of bias.

The effect of astaxanthin on ALT

Combining six effect sizes from five studies [36, 37, 38, 39, 40] revealed that ALT levels increased in the intervention group compared to the control group following astaxanthin supplementation (WMD: 1.92, 95% CI: 0.16 to 3.68 U/L, P=0.03) (Figure 2). No significant heterogeneity was found between studies investigating the impact of supplementation with astaxanthin on ALT concentrations ($I^2=0\%$, P=0.80). The sensitivity analysis revealed that the overall impact of astaxanthin supplementation on ALT levels was unaffected by the deletion of any particular study (Supplementary Figure 1 in ESM 1). In addition, according to the results of Egger's regression test, no evidence of publication bias was found (P=0.93).

The effect of astaxanthin on AST

All studies included in the present meta-analysis had complete data in this respect. Supplementation with astaxanthin had a non-significant effect on AST levels (WMD: 0.72, 95% CI: -0.85 to 2.29 U/L, P=0.36) based on our analysis of

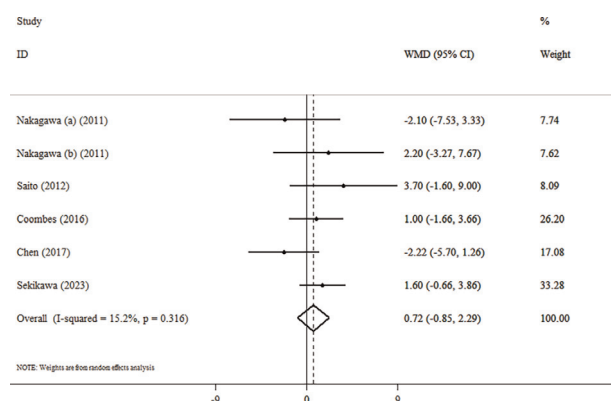


Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of astaxanthin on aspartate transaminase.

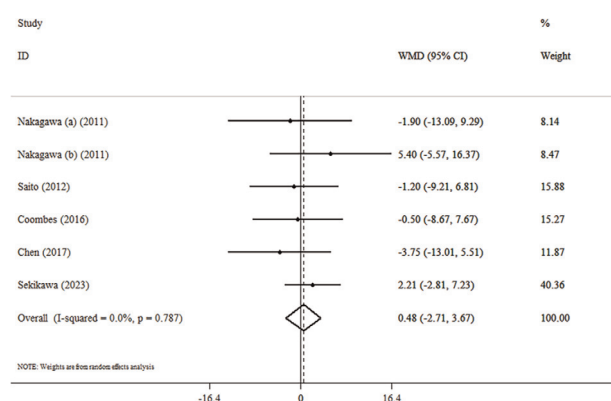


Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of astaxanthin on gamma-glutamyl transferase.

6 arms of RCTs [36, 37, 38, 39, 40] when compared to the placebo group (Figure 3). Non-significant heterogeneity was seen between studies ($I^2=15.2\%$, $P=0.31$). Sensitivity analysis showed that the overall effect of supplementation on AST concentrations was not dependent on any single study (Supplementary Figure 2 in ESM 1). Moreover, Egger's regression test rejected the presence of publication bias ($P=0.81$).

The effect of astaxanthin on GGT

The influence of astaxanthin supplementation on GGT was evaluated in 6 arms of 5 RCTs [36, 37, 38, 39, 40]. The pooled mean difference showed a non-significant effect on GGT in comparison to the control group (WMD: 0.48, 95% CI: -2.71 to 3.67 U/L, $P=0.76$) (Figure 4). Between-study heterogeneity was also non-significant ($I^2=0\%$, $P=0.78$). Sensitivity analysis indicated that after removing any single study from the meta-analysis, overall estimates were not changed (Supplementary Figure 3 in ESM 1). Also,

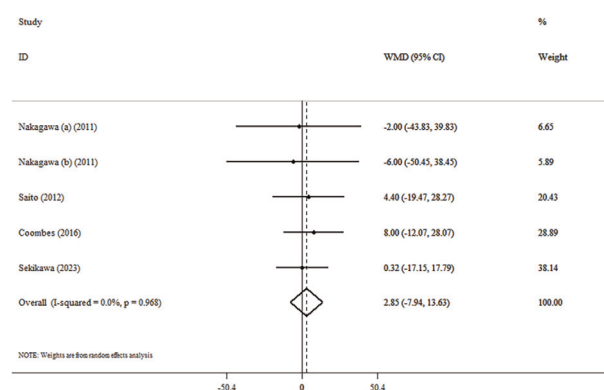


Figure 5. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of astaxanthin on alkaline phosphatase.

no evidence of publication bias was seen based on the results of Egger's regression test ($P=0.46$).

The effect of astaxanthin on ALP

In total, 5 effect sizes from 4 studies [36, 37, 38, 40] were included in the meta-analysis. The analysis's findings showed that, when compared to the control group, astaxanthin supplementation had no discernible impact on ALP levels (WMD: 2.85, 95% CI: -7.94 to 13.63 U/L, $P=0.60$) (Figure 5). Heterogeneity between studies was non-significant in this regard ($I^2=0\%$, $P=0.96$). Analysis of the estimates' sensitivity revealed that no study had a substantial impact on them (Supplementary Figure 4 in ESM 1). No substantial publication bias was also detected according to Egger's regression test ($P=0.40$).

Discussion

The impact of astaxanthin consumption on adults' liver enzyme levels was examined in the current systematic review and meta-analysis. This is the first systematic review and meta-analysis that we are aware of that evaluated the impact of astaxanthin on the levels of hepatic enzymes. This systematic review and meta-analysis of 196 individuals includes five trials with six arms. The results showed that the overall effect of astaxanthin on rising serum ALT was significant. However, no significant effect was observed on other liver enzymes such as AST, ALP, and GGT by using an astaxanthin supplement in adults.

Astaxanthin (3, 3'-dihydroxy- β , β' -carotene-4, 4'-dione, ASX) is a natural compound and a type of antioxidant, non-vitamin A pro-carotenoid, which is usually found in seafood and marine organisms [13]. Fatty acid esters are the most common type of astaxanthin found in nature

[13]. Studies have shown that this compound has various important effects, such as anti-inflammatory, antioxidant, neutralizing free radicals, and controlling the different signaling pathways [13, 41]. Therefore, it can play a role in the prevention and treatment of various liver diseases, including liver injury, liver fibrosis, and liver cancer [14, 42, 43, 44]. However, the results of existing studies have been contradictory, and some studies reported positive effects [40] and some negative effects on the levels of liver enzymes [14, 39] due to the consumption of astaxanthin supplements, while others did not observe any significant effect [36, 38]. For this reason, we conducted the present systematic review and meta-analysis study.

In this systematic review and meta-analysis, no significant effect was observed with astaxanthin consumption on the liver enzymes of AST, ALP, and GGT in adults. Similar to our results, Nakagawa et al. showed that the consumption of 6 or 12 mg/day of astaxanthin for 3 months in thirty middle-aged individuals did not have any significant impact on liver enzyme levels (ALT, AST, ALP, and GGT) [36]. In line with the results of this study, the results of Coombes et al.'s study showed that astaxanthin has no effect on ALT, AST, ALP, and GGT in renal transplant recipients [38]. Sixty-one participants participated in this randomized controlled experiment and were given astaxanthin or placebo orally for 12 months. According to the study's findings, compared to the control group, daily supplementation with 12 mg of astaxanthin for a year had no discernible impact on the hepatic enzymes or other end measures such as oxidative stress and inflammation [38].

The presence of astaxanthin's antioxidant effects has been demonstrated in some animal and human studies to improve immune response, liver function, and the prevention and management of liver diseases [13, 42, 45], though other studies have not supported this claim [38, 39]. The absence of a positive antioxidant effect has often been observed in randomized controlled trials in humans [46, 47], and more effective results have been observed in animal studies [48]. The antioxidant systems of humans and animals have many differences, so there is always doubt about generalizing the results of animal studies to humans [49, 50].

In contrast to our results, Sekikawa et al. showed that the consumption of 9 mg/day from a diet containing astaxanthin for 6 weeks in healthy individuals caused a significant increase in ALP. Although the levels of this enzyme remained within the normal range after the intervention, this increase was not outside the normal range. Moreover, there was no significant effect on other liver enzyme levels such as ALT, AST, and GGT [40]. Contrary to the results of this study, in a double-blind randomized controlled clinical trial by Chen et al. there was a significant negative association between astaxanthin intake and ALT and AST levels.

This study was done on 14 healthy climacteric women who received 12 mg/day of astaxanthin [39]. A reducing trend was observed in the levels of these two enzymes, while both of them were still within the normal range. However, there was no significant change in the levels of GGT [39]. The levels of oxidative stress markers in the blood and urine, however, did not change much; therefore, the decline in ALT and AST levels cannot be attributed to a reduction in oxidative stress [39]. Additionally, as oxidative stress plays a role in the proper control of liver function, this reduction cannot be linked to an improvement in liver function [51, 52]. In another randomized, double-blind, placebo-controlled trial by Saito and colleagues, a rising trend was observed in ALT and AST with astaxanthin supplementation compared to the placebo group. In this study, 20 healthy volunteers who consumed 12 mg/day of astaxanthin for a month were evaluated. The findings of this study showed that daily supplementation with 12 mg of astaxanthin for 4 weeks resulted in a non-significant tendency to raise AST and ALT levels as well as a non-significant trend to reduce GGT and ALP levels in the astaxanthin-treated group [37].

Due to variations in the dose of the intervention employed, the varied duration of the intervention, or the varied populations studied, there are often no consistent results in different research studies about the influence of astaxanthin supplementation on various liver enzyme levels. In general, the results of this study showed that supplementation with astaxanthin has no effect on albumin, AST, ALP, and GGT, whereas it causes an increase in the levels of ALT. It is noteworthy that only five studies were included in this meta-analysis, and the total sample size was 196 people. Also, four out of five studies were done on healthy people who were not sick and did not have any diseases. Therefore, it is possible that all these issues have an effect on the results obtained in the present systematic review and meta-analysis.

There are several strengths and weaknesses of the present systematic review and meta-analysis study, which are mentioned below. In the present study, there was no limit for the articles included in terms of time or language. All of the included studies were double-blind randomized control trials. This issue reduces the possibility of bias in the present study results. To our knowledge, this is the first systematic review and meta-analysis to examine how astaxanthin ingestion affects adult liver enzymes. Finally, the effects of astaxanthin on ALT, AST, ALP, and GGT were evaluated using a standardized technique. This research has several restrictions. The sample size and number of included studies were limited. The included studies were only from Japan and Australia, so the results cannot be generalized to other populations from other countries. So that more research is necessary in different ethnic populations.

Lastly, in different studies, different methods have been used to evaluate the levels of liver enzymes, which can cause errors and differences in the results obtained.

Conclusion

Astaxanthin supplementation has an increasing influence on ALT concentrations in adults without changing the levels of other liver enzymes, according to a comprehensive review and meta-analysis of five trials. Further long-term and well-designed RCTs are needed to further assess and confirm these results.

Electronic supplementary material

The following electronic supplementary material is available with this article at <https://doi.org/10.1024/0300-9831/a000804>

ESM 1. Supplementary figures 1–4 (PDF).

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

MRA conducted the study. MRA and HA performed data screening and literature searches. MRA gathered data on its own and assessed its caliber. After data interpretation, HA, NR, MS, MH, MG, and MA wrote the paper. AH oversaw the research. All authors have read and approved the final draft.

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ORCID

Mohammad Reza Amini

 <https://orcid.org/0000-0003-0640-2142>

Prof. Azita Hekmatdoost

Department of Clinical Nutrition and Dietetics
Faculty of Nutrition Sciences and Food Technology
National Nutrition and Food Technology Research Institute
Shahid Beheshti University of Medical Science
Tehran, Iran
a.hekmat2000@yahoo.com