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# Effects of α- and β-Carotene on Liver Diseases Improvement: A Systematic Review

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**Abstract:** Objectives: Chronic liver disease (CLD) has become a major disease that threatens human health. Oxidative stress (OS) is a major contributor to the deterioration of CLD. α- and β-carotene, naturally occurring micronutrients with biological activities such as anti-oxidant, anti-inflammatory and anti-cancer, have been used to defend against or treat CLD. This systematic review aims to explore the role of α- and β-carotene in the prevention and treatment of CLD. Methods: A comprehensive literature search was undertaken on PubMed, EMBASE, Web of Science and CNKI databases from 1993 to 2021, with a deadline of January 2023, and 16 studies were ultimately included in this review. Result: β-carotene supplementation significantly reduced liver fibrosis (SMD = 39.78, 95% CI [−55.55, −24.01]), while gender and obesity status showed no statistical difference. Dietary α-carotene intake was not associated with a reduced risk of non-alcoholic fatty liver disease (NAFLD) (SMD = 1.09, 95% CI [0.82, 1.36]). However, the serum carotene measurement group with carotenoid supplementation (MD = −5.79; 95% CI [−109.58, 98.00]) was a trend toward improvement of liver disease. Conclusions: Dietary intake of β-carotene tends to reduce the risk of liver disease, while dietary α-carotene intake was not associated with a reduced risk of liver cancer and NAFLD in obese populations, which inspired us to develop fresh concepts for modifying meals for various populations.

**Keywords:** α-carotene; β-carotene; chronic liver disease; non-alcoholic fatty liver disease; literature review

## 1. Introduction

Chronic liver disease (CLD) is one of the major global health threats, killing more than 2 million individuals each year [1]. The potential etiology of CLD differs by area, with viral infections being the main culprit in low- and middle-income countries, whereas alcohol and obesity are frequently linked to CLD in Western industrialized nations [2–4]. CLD is a major cause of morbidity and mortality globally, the World Health Organization estimates that approximately 47,000 deaths from liver cancer occur each year in the European Union [5]. Currently, CLD, the third leading cause of death in the UK, is diagnosed late when therapies are ineffective [6]. The Chronic Liver Disease Foundation (CLDF) presented at the HBV Epidemiology Workshop that the overall prevalence of chronic HBV infection in the United States is estimated to be 1.59 million [7].

The same is occurring in the Asia-Pacific region. China may have more than 447 million individuals who suffer from CLD [8]. India has a high prevalence of CLD, particularly among middle-aged males, cirrhosis caused almost 220,000 deaths in 2017 [9]. Alcohol, narcotics, viral hepatitis, metabolic disorders, and autoimmune mechanisms activate hepatic stellate cells that undergo trans-differentiation to become myofibroblasts, the liver's primary extracellular matrix producing cells, resulting in the genesis of liver fibrosis. Chronic fibrosis that is not treated can progress to CLD, cirrhosis, and its consequences [10]. CLD presents phenotypic differences according to clinical features and pathogens including non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver (AFL), drug-induced liver injury (DILI), metabolic associated fatty liver disease (MAFLD) and hepatocellular carcinoma (HCC) [11]. There is no specific drug available for the treatment of CLD, therefore lifestyle interventions (promoting Mediterranean diet), bariatric surgery, pharmacological treatments (e.g., vitamin E, pioglitazone) and liver transplantation have become the main treatment modalities for CLD [12]. CLD not only endangers public health but also places heavier economic strain on families and society, the number of hospitalizations related to CLD has tripled between 2005 and 2014 [13]. To reduce the clinical and economic burden of CLD, analysis of the pathogenesis of CLD and the development of targeted target drugs have become promising strategies for liver preservation.

Oxidative Stress (OS) is considered a stress response triggered by CLD development and hepatocellular carcinoma [14]. OS and free radicals induce activation and proliferation of hepatic stellate cells in injured liver, leading to the progression of CLD [15]. Defending against OS in the early stages of the disease may thus be an essential concept in CLD defense.

Carotenoids are natural micronutrients with reported antioxidant, anti-inflammatory, and potential anti-proliferative properties. Preclinical studies suggest a protective role in fatty liver disease, although clinical evidence remains limited [16,17]. Carotenoids regulate gene expression and protein translation in intracellular signaling networks through their antioxidant, lipid-lowering, anti-inflammatory, anti-fibrotic and insulin-sensitizing properties [16,18]. α- and β-carotene are the main types of carotenoids. β-carotene, the most abundant provitamin A carotenoid in yellow-green fruits and vegetables, has shown chemopreventive potential in preclinical models. Worth noting is that α-carotene also acts as a vitamin A precursor and a strong antioxidant, preventing lipid oxidation and scavenging free radicals [19]. Observational studies have associated higher α-carotene intake or serum levels with a lower risk of gastric, liver, and lung cancers, as well as certain chronic conditions such as diabetes and cardiovascular disease [20–24].

Clinical and epidemiological studies have suggested associations between α- and β-carotene exposure and liver disease risk modulation, although findings remain inconsistent. However, the results of the current study could not yield uniform results. To better understand the role of and -carotene against liver diseases caused by various etiologies and to objectively assess the ameliorative effects of and -carotene on liver diseases, this meta-analysis will examine the relationship between and -carotene on the improvement of NAFLD, AFL, oxidative liver injury, liver fibrosis, and HCC.

## 2. Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [25]. The study protocol is registered on PROSPERO under reference number: CRD42023421029 and can be accessed at: https://www.crd.york.ac.uk/prospero/#recordDetails, accessed on 15 August 2023.

### *2.1. Search Strategy*

We performed a systematic search for published articles in PubMed, EMBASE, Web of Science and CNKI as well as literature tracing methods between 1993 and 2021, with a search deadline of January 3, 2023. The main keywords for the relevant searches included: α-carotene AND β- carotene AND liver disease (Hepatopathy OR Liver Complaint). In addition, the reference lists of reviews, meta-analyses and other relevant publications were hand-searched in case articles were missed.

### *2.2. Inclusion and Exclusion Criteria*

Inclusion in the original study according to the following inclusion criteria: (1) HBV, HCV infection, excessive alcohol consumption, malnutrition, chronic hypoxia, cholestasis, etc.; (2) HCC, oxidative liver injury, liver fibrosis, NAFLD, alcoholic cirrhosis related indicators abnormal or any one indicator more than 2 times higher than normal; (3) exploring the association of dietary or serum alpha and beta-carotene with CLD risk; (4) observational studies, cohort or case-control studies (5) Subjects provide informed consent, and the procedure of gaining informed consent must adhere to applicable national rules.

Exclusion criteria include (1) exclusion of studies with incomplete data that could not be used for statistical analysis; (2) exclusion of literature of a non-thesis nature such as reviews, letters, commentaries, etc.; (3) duplicate publications or data from the same population used in multiple studies, only the most recent study or the one with the most complete or highest quality information was included and all the rest were excluded; (4) other disease studies; (5) other vitamin supplementation studies.

### *2.3. Quality Assessment*

The following information were extracted independently from the included literature: first author's name, year of publication, type of liver disease, type of study, sample size, type of carotenoid intake, type of nutrient, relevant variables, objects and literature score. The Newcastle-Ottawa Scale (NOS), a case-control study quality evaluation standard recommended by the Agency for Healthcare Research and Quality (AHRQ), was used to assess the methodological quality of the included studies, and studies with scores greater than or equal to 6 were included in the Meta-analysis. If differences of opinion arose during the literature data extraction process and quality evaluation, group discussions were conducted to obtain consensus.

### *2.4. Data Processing and Statistical Analysis*

Meta-analysis was performed using R4.2.1 software. Summary estimates were obtained using a random-effects model and studies were weighted based on an estimate of mean difference. The effect size was expressed as standardize mean difference (SMD) and 95% CI. The heterogeneity tests were applied based on the chi-square Q test and $I^2$ statistic [26]. If the heterogeneity test was statistically different ($p < 0.05$ or $I^2 > 50\%$), the random effects model was chosen to calculate the combined effect values. Otherwise, the fixed effects model was chosen to combine the data ($p > 0.05$ and $I^2 < 50\%$), and the results of the Meta-analysis were presented in forest plots. Subgroup analyses were performed to determine the cause of heterogeneity and the robustness of the pooled effect estimate, where subgroup analyses were performed on the type of liver disease, gender and obesity of the study.

The standardized mean difference (SMD) was used as the effect size to pool results across studies with different outcome scales. A random-effects model was applied if significant heterogeneity was present ($I^2 > 50\%$); otherwise, a fixed-effects model was used. Heterogeneity was assessed using the Q test and $I^2$ statistic.

## 3. Results

### *3.1. Screening Process for Eligible Literature*

Relevant literature was searched in four major English databases according to the search strategy: 1605 articles were initially retrieved (PubMed (751), Embase (510), Web of Science (260) and CNKI (84)). Duplicates were removed from 563 papers, leaving 1042 papers, 468 articles that did not fit the title were excluded, and the remaining 574 were excluded from 558 (175 letters/editorial/comments; 143 case series/report; 125 reviews; 94 cannot extract data; 21 duplicated populations) and included 16 eligible papers [27–42]. The flow chart of -the selected literature is shown in Figure 1.

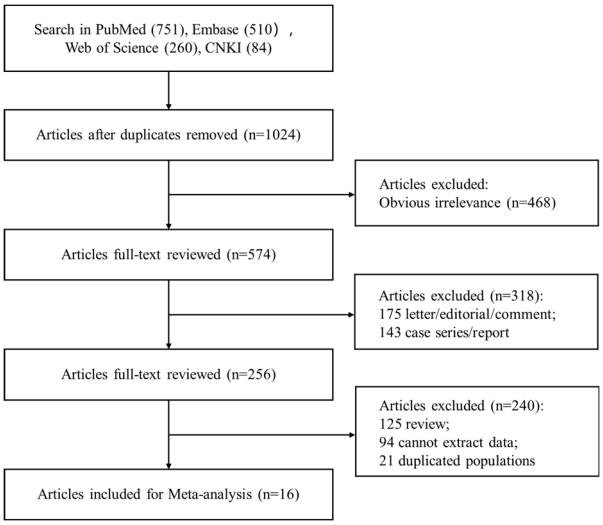


**Figure 1.** Literature search and study selection.

### *3.2. Characteristics of Included Studies*

The years of publication of the included studies were between 1993–2021, the regions studied were mainly the United States, China, Italy, Japan, Ethiopia, Brazil, Turkey, India, and Egypt. Combining Tables 1 and 2, the overall quality of the literature is relatively high. Tables 1 and 2 show the 16 included studies, including human (n = 9) and rat (n = 7), involving a total of 14,967 sample size data (6047 experimental groups and 8920 control groups), containing human (n = 14,769) and rat (n = 198), including alcoholic cirrhosis (n = 102), HCC (n = 342), liver fibrosis (n = 93), oxidative liver injury (n = 13,649) and NAFLD (n = 781). The main nutrients studied were α-carotene and β-carotene. The covariates of the included studies mainly included age, γ-tocopherol, α-tocopherol, cholesterol, and total bilirubin. For human studies, all participants provided informed consent in accordance with the ethical standards of the Declaration of Helsinki. For animal studies, all experimental procedures were approved by the Institutional Animal Care and Use Committee and complied with national guidelines for laboratory animal welfare.

**Table 1.** Characteristics of the human samples included in the study.

| Study | Year | Type of Hepatopathy | Type of Study | Sample Size | Diet/Serum | Nutrient Type | Adjustment for Covariates | Score * | Research Object |
|---|---|---|---|---|---|---|---|---|---|
| Leo M. A. | 1993 | Alcoholic Cirrhosis | Case-control study | 11/40 | Diet | α-carotene β-carotene | γ-Tocopherol, α-Tocopherol, Cholesterol, Bilirubin, Albumin | 8 | Human |
| Pan W. H. | 1993 | Hepatocellular Carcinoma | Case-control study | 59/101 | Diet | α-carotene | Age, Body mass index, Ethnicity, Occupation, Education, Alcohol consumption, Smoking, | 9 | Human |
| Ahmed S | 1994 | Alcoholic Cirrhosis | Case-control study | 17/34 | Diet | α-carotene β-carotene | Vitamin E, Albumin,TG, Cholesterol Alcohol intake, Age, Days from Last Drink, Cholesterol, | 9 | Human |
| Rocchi E. | 1997 | Hepatocellular Carcinoma | Case-control study | 27/11 | Diet | α-carotene | ALP, Total Bilirubin, Albumin, Cryptoxanthin, Lycopene, γ-Tocopherol, α-Tocopherol | 6 | Human |
| Yadav D. | 2002 | Liver Fibrosis | Case-control study | 3/18 | Serum | α-carotene | Albumin, Prothrombin, Bilirubin, Cholesterol, Triglycerides, γGT, Alkaline Phosphate, Iron, TIBC, Ferritin, α-Fetoprotein | 8 | Human |
| Constance E. R. | 2003 | Oxidative Liver Damage | Case-control study | 5558/8047 | Serum | α-carotene | Age, Route of transmission, Genotype, WBC, Hct, Total Bilirubin, Albumin, Transferrin saturation, γ-Tocopherol, α-Tocopherol, Lutein, Cryptoxanthin, Lycopene, MDA | 9 | Human |
| Nishino H. | 2007 | Hepatocellular Carcinoma | Case-control study | 46/46 | Diet | α-carotene β-carotene | Saturation, Iron, Vitamin C Concentration, Vitamin E, Selenium, β-cryptoxanthin, Lutein/Zeaxanthin, Lycopene, Obesity, Waist-to-hip Ratio, Diagnosed Age, Observation Period, Lycopene, Induction | 9 | Human |
| Chaves G. V. | 2008 | Non-alcoholic Fatty Liver Disease | Cohort study | 91/54 | Serum | β-carotene | Weight, BMI, WC, HC, RWH, GGT, Total Bilirubin, Albumin, PTTs, Cholesterol, Triglycerides, HDL, LDL, VLDL, Glucose, Basal insulin, HOMA-IR | 7 | Human |
| Kimura M. | 2020 | Non-alcoholic Fatty Liver Disease | Case-control study | 128/478 | Diet | α-carotene β-carotene | Age, Female, BMI, BFP, Diabetes, Dyslipidemia, Hypertension, Current Smoker, Habitual Exerciser, Energy, Cryptoxanthin, Alcohol, Hepatic Steatosis, Platelet Count, Albumin, GGT, Total Bilirubin, Glucose, HbA1c, Insulin, HOMA-IR, Total Cholesterol, HDL cholesterol, LDL cholesterol, Triglyceride, FFA, APRI, Lutein, Zeaxanthin | 8 | Human |

*: NOS Score (The Newcastle-Ottawa Scale).

**Table 2.** Characteristics of the animal samples included in the study.

| Study | Year | Type of Hepatopathy | Type of Study | Sample Size | Diet/Serum | Nutrient Type | Adjustment for Covariates | Score * | Research Object |
|---|---|---|---|---|---|---|---|---|---|
| Wamutu S. | 2008 | Oxidative Liver Damage | Case-control study | 16/16 | Serum | β-carotene | GGT, Total Bilirubin, Scores for Necrosis, Steatosis | 6 | Rats |
| Nigar V. | 2010 | Oxidative Liver Damage | Case-control study | 6/6 | Serum | β-carotene | Damage, MDA, SOD, CAT, GP-x | 8 | Rats |
| Bokang | 2012 | Hepatocellular Carcinoma | Case-control study | 30/10 | Diet | β-carotene | Tumour weight, Tumour size, Inhibition Rate, NK, IL-2, TNF-α, WBC, TP, ALB, ALP | 9 | Rats |
| Naik M. M. | 2013 | Hepatocellular Carcinoma | Case-control study | 8/4 | Serum | β-carotene | ALP, Total Bilirubin, Total Protein | 7 | Rats |
| Farouk K. E. | 2020 | Liver Fibrosis | Case-control study | 24/8 | Diet | β-carotene | Diameter, Thickness, Weight Variation, Friability, Disintegration, Bilirubin, Albumin, TNF-α, IL-6, TGF-β | 9 | Rats |
| Hussein A. | 2020 | Non-alcoholic Fatty Liver Disease | Case-control study | 18/12 | Diet | β-carotene | Casein, Oil, Salt, Cellulose, Fat, Fructose, Sucrose, Starch, Thiamine, Riboflavin, Niacin, Pyridoxine, Folic,γ-Tocopherol, α-Tocopherol, Creatinine, Urea | 9 | Rats |
| Farouk K. E. | 2021 | Liver Fibrosis | Case-control study | 32/8 | Serum | β-carotene | Bilirubin, Albumin, Catalase | 9 | Rats |

*: NOS Score (The Newcastle-Ottawa Scale).

### *3.3. Association between Dietary Intake of β-Carotene and Improved Liver Disease*

Seven papers examined the effect of β-carotene supplementation on liver disease (Figure 2A). Change in alanine aminotransferase (ALT) as a biomarker of liver disease improvement. Meta-analysis was performed on the ALT index of samples with or without β-carotene use. The results (MD = −22.35; 95% CI [−51.04, 6.35]) showed that ALT levels in the group with dietary intake of β-carotene were lower than in the group without β-carotene intake, but the difference between the two groups was not significantly different ($p < 0.01$; $I^2 = 99\%$, random-effects model).

To further analyze the relationship between dietary intake of β-carotene and improvement of liver disease, the group without β-carotene intake was set up as a control group here with subgroup analysis according to the type of liver disease, gender and obesity status.

Type of liver disease (Figure 2B). Where AC represents alcoholic cirrhosis, HC represents hepatocellular carcinoma, NAFLD represents non-alcoholic fatty liver disease, and LF represents liver fibrosis. The ALT index was lower in the group consuming β-carotene than in the group not consuming β-carotene in all groups. For AC (SMD = −3.07, 95% CI [−7.81, 1.66]), for HC (SMD = −2.19, 95% CI [−7.13, 2.75]), for NAFLD (SMD = −1.35, 95% CI [−6.37, 3.68]), but this showed that the ALT indexes were not significant between the three liver diseases and control group. In contrast, the LF showed there was a significant difference between the means (SMD = −39.78, 95% CI [−55.55, −24.01]). Dietary intake of β-carotene showed a significant improvement in ALT index across liver disease types ($p < 0.01$), and dietary intake of β-carotene had a better improvement in LF ($p < 0.0001$).

Gender (Figure 2C). Subgroup analysis revealed that β-carotene exhibited a decrease in ALT trend in both males (SMD = −6.45, 95% CI [−16.17, 3.28]) and females (SMD = −1.78, 95% CI [−7.54, 3.99]), but the difference in ALT with the control group was not significant across gender conditions.

Obesity condition (Figure 2D). Subgroup analysis revealed that β-carotene exhibited a decrease in ALT trend in both non-obesity (SMD = −2.55, 95% CI [−5.37, 0.27]) and obesity (SMD = −13.09, 95% CI [−37.11, 10.93]), but the difference between ALT with or without obesity and control group was not significant.

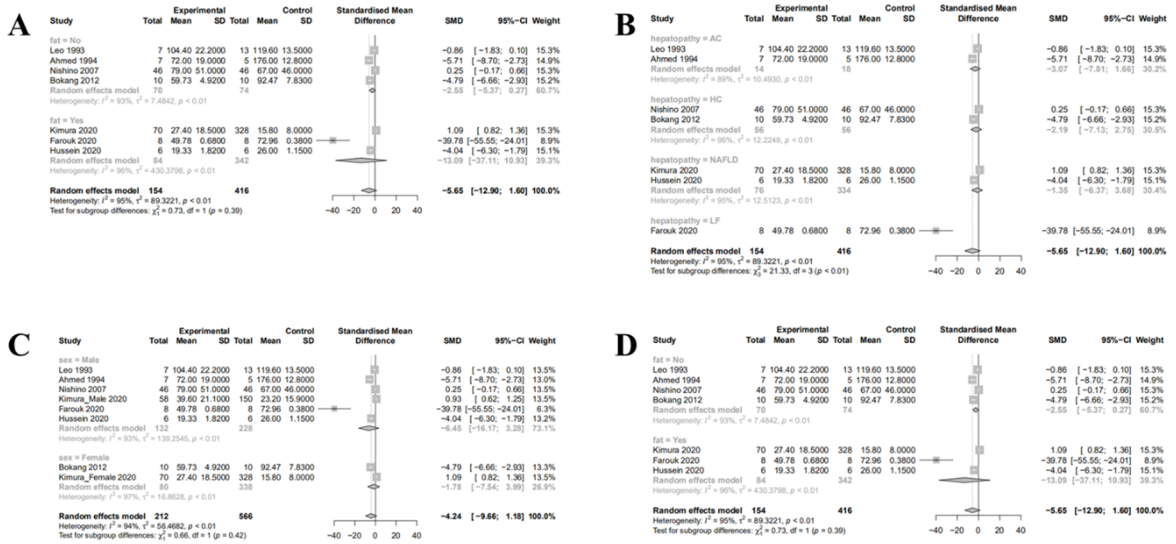


**Figure 2.** Forest plots of studies investigating the effects of dietary intake of β-carotene on liver disease and subgroup analysis. (**A**) β-carotene and liver disease improvement; (**B**) β-carotene and liver disease type association analysis; (**C**) β-carotene and gender association analysis; (**D**) β-carotene and obesity status association analysis.

### *3.4. Association between Dietary Intake of α-Carotene and Improved Liver Disease*

Six papers examined the effect of α-carotene supplementation on liver disease (Figure 3A). Change in ALT as a biomarker of liver disease improvement. Meta-analysis was performed on the ALT index of samples with or without α-carotene use. The results (MD = 9.88; 95% CI [−44.41, 64.16]) showed that ALT levels in the group with dietary intake of α-carotene were higher than in the group without α-carotene intake, but the difference between the two groups was not significantly different ($p < 0.01$; $I^2 = 99\%$, random-effects model).

To further analyze the relationship between dietary intake of α-carotene and improvement of liver disease, the group without α-carotene intake was set up as a control group here with subgroup analysis according to the type of liver disease, gender and obesity status.

Type of liver disease (Figure 3B). Where AC represents alcoholic cirrhosis, HC represents hepatocellular carcinoma, NAFLD represents non-alcoholic fatty liver disease. For AC (SMD = −3.07, 95% CI [−7.81, 1.66]), there was a trend for α-carotene to reduce ALT, but the difference was not significant with the control group. For HC (SMD = 2.12, 95% CI [−0.77, 5.02]), there was a trend for α-carotene to elevate ALT, but the difference with the control group was not significant. For NAFLD (SMD = 1.09, 95% CI [0.82, 1.36]), there was a trend for α-carotene to significantly elevate ALT index in NAFLD samples ($p < 0.0001$).

Gender (Figure 3C). For males (SMD = −1.04, 95% CI [−3.59, 1.51]), there was a tendency for α-carotene to decrease ALT, but the difference with the control group was not significant. For females (SMD = 2.39, 95% CI [−0.16, 4.94]), there was a tendency for α-carotene to elevate ALT, but the difference with the control group was not statistically significant.

Obesity condition (Figure 3D). For the non-obesity (SMD = −0.17, 95% CI [−4.41, 4.08]), the difference with the control group was not significant. For obesity (SMD = 1.13, 95% CI [0.92, 1.34]), the results showed a tendency for α-carotene to elevate ALT and a significant difference with the control group. As seen in the subgroup analysis of obesity status, the heterogeneity of the non-obese group as well as the total studies implies that the studies included in this Meta-analysis (whether the participants were obese or not) may be a source of heterogeneity.

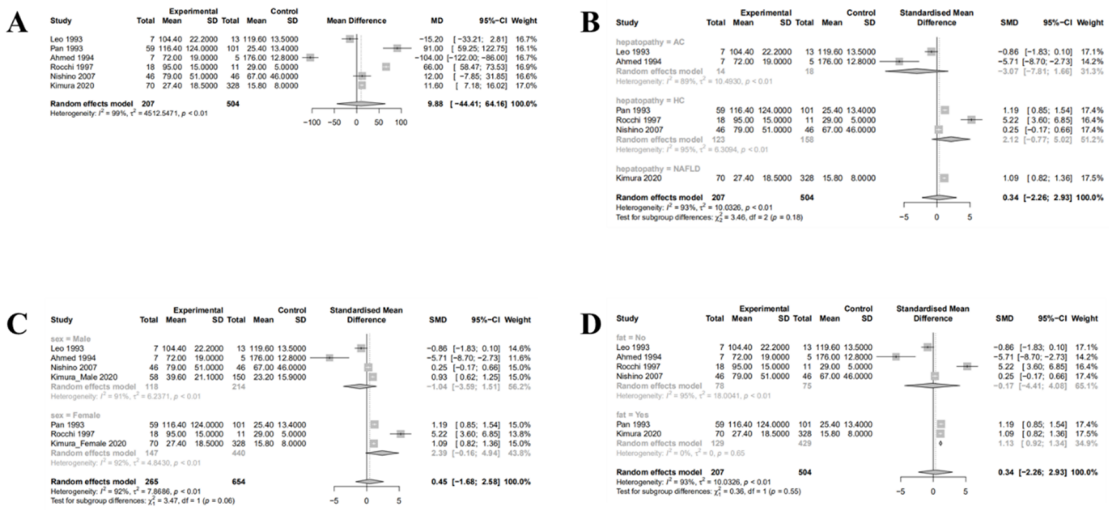


**Figure 3.** Forest plots of studies investigating the effects of dietary intake of α-carotene on liver disease and subgroup analysis. (**A**) α-carotene and improvement of liver disease; (**B**) association analysis between α-carotene and type of liver disease; (**C**) association analysis between α-carotene and gender; (**D**) association analysis between α-carotene and obesity status.

### *3.5. Relationship between Serum Carotenoids and Improved Liver Disease*

A total of 14 data sets from 7 studies were included here. The history of carotenoid supplementation and subgroups of included studies are shown in Table 3. Meta-analysis of serum carotenoid measurement groups with and without a history of carotenoid supplementation, change in ALT as an indicator of improvement in liver disease (Figure 4A). The results (MD = −5.79; 95% CI [−109.58, 98.00]) showed that the serum carotenoid measurement group after carotenoid supplementation had lower ALT levels than the serum carotenoid measurement group without a history of carotenoid supplementation, but not significantly different ($p$ = 0; $I^2$ = 100%, random effects model).

To further analyze the relationship between various types of carotenoids in serum and the improvement of liver disease. Subgroup analysis was performed here according to the type of carotenoids in serum, with the group without a history of carrot supplementation as a control group.

**Table 3.** History of carotenoid supplementation and subgroups.

| Study | Carotene Intake | Control | Experimental |
|---|---|---|---|
| Yadav (2002) | No vitamin supplement | Healthy individuals | CHC patients |
| Constance (2003) | Intramuscular β-carotene injection | Physiological Saline | β-carotene |
| Wamutu (2008) | Unknown | None | People with liver injury |
| Chaves (2008) | Unknown | None | Obese patients |
| Nigar (2010) | Gavage ofβ-carotene | Physiological Saline | β-carotene |
| Naik (2013) | Intraperitoneal injection ofβ-carotene | Physiological Saline | β-carotene |
| Farouk (2021) | *Haematococcus pluvialis* β-carotene | 0.1% Tween 80 water | β-carotene |

A meta-analysis of ALT indicators in the serum carotene measurement group supplemented with various carotenes was carried out (Figure 4B). Where alpha represents serum α-carotene and beta represents serum β-carotene. For serum α-carotene (SMD = −6.54, 95% CI [−18.78, 5.71]), there was a tendency for serum α-carotene to reduce ALT, but the difference was not significant compared to the serum measurement group without carotene supplementation. In response to β-carotene in serum (SMD = −0.45, 95% CI [−9.47, 8.57]), there was a tendency for β-carotene in serum to decrease ALT, but the difference was not significant compared to the serum measurement group without carotene supplementation. Overall, there was a tendency for both serum carotenoids to lower ALT, but there was no significant difference in the effect of either. The results of the above carotenoid Meta-analysis are shown in Table 4.

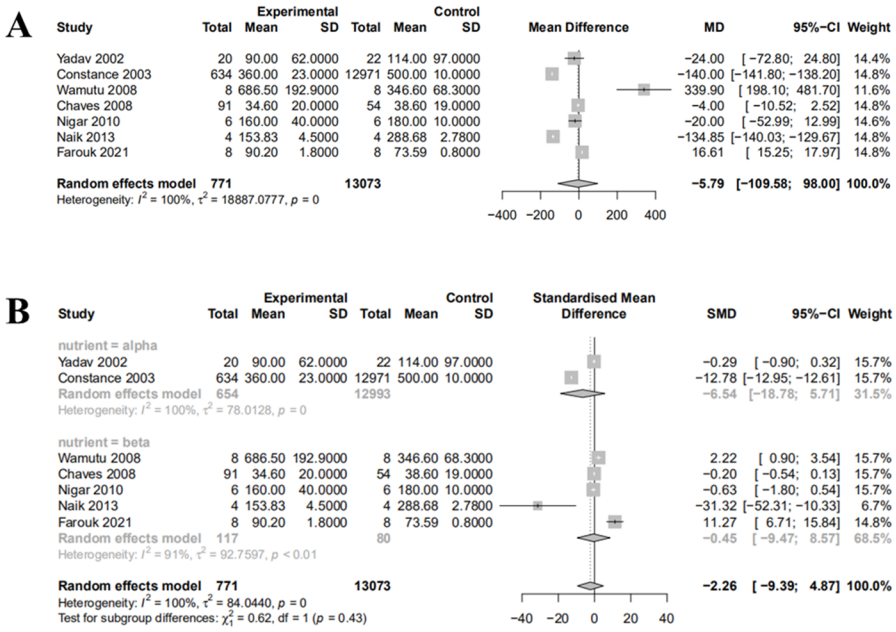


**Figure 4.** Forest plots of studies investigating the effects of carotenoids in serum on liver disease (**A**) Whether to supplement carotenoids (**B**) Subgroup analysis of different carotenoids.

**Table 4.** Results of Meta-analysis of different carotenoids.

| Incontinence Model | Sample Size | | Test of Association | | | Model | Test of Heterogeneity | | |
|---|---|---|---|---|---|---|---|---|---|
| | Carotene | Control | *SMD (95%CI)* | Z | *p* | | *Q* | *p* | $I^2$ (%) |
| β-carotene | 117 | 80 | −0.4512 [−9.4679; 8.5656] | 0.40 | 0.6887 | Random | 2.2 | <0.01 | 91.2 |
| α-carotene | 654 | 12993 | −6.5374 [−18.7825; 5.7076] | −1.46 | 0.1439 | Random | 310.8 | <0.0001 | 99.9 |

### *3.6. GRADE Assessment*

The quality of evidence for the main outcomes was assessed using the GRADE framework. For β-carotene in improving liver fibrosis and α-carotene in exacerbating NAFLD, the overall evidence quality was moderate, downgraded mainly due to high heterogeneity ($I^2$ > 90%) across studies. Other domains, including risk of bias, indirectness, imprecision, and publication bias, showed no serious limitations (Table 5).

**Table 5.** GRADE evidence quality assessment.

| Outcome | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | GRADE Quality |
|---|---|---|---|---|---|---|
| β-carotene for liver fibrosis | No serious limitation | Serious limitation (high heterogeneity, $I^2$ > 90%) | No serious limitation | No serious limitation | Undetected | **Moderate** |
| α-carotene for NAFLD | No serious limitation | Serious limitation (high heterogeneity, $I^2$ > 90%) | No serious limitation | No serious limitation | Undetected | **Moderate** |

## 4. Discussion

The present systematic review and meta-analysis considered the effects of supplementation with α- and β-carotene on liver disease improvement, and represented the most comprehensive synthesis of data from currently available studies of α- and β-carotene adjuvant therapy in patients with liver disease (Table 6). We included reports of 16 eligible studies that pooled clinical studies on dietary and serum α- and β-carotene and liver disease risk. Integrating validated data from 14,967 liver disease cases (102 alcoholic cirrhosis, 342 liver cancer, 93 liver fibrosis, 13,649 oxidative liver injury, 781 nonalcoholic fatty liver). A comprehensive examination was conducted on the safety and efficacy of alpha and beta-carotene adjuvant therapy for liver disease. Subgroup analyses were performed according to type of liver disease, gender, and obesity condition.

The subgroup analyses revealed that dietary intake of α- and β-carotene had different induced trends. Intake of β-carotene tends to improve liver fibrosis significantly, and dietary α-carotene intake was not associated with a reduced risk of liver cancer and NAFLD in obese populations, and obesity status may be a source of heterogeneity in the Meta-analysis of the effect of dietary intake of α-carotene on the improvement of liver disease. However, most current evidence comes from observational studies, in which confounding factors are difficult to fully

exclude. Therefore, the hepatoprotective effects specifically attributable to α-carotene still need confirmation through well-designed interventional trials.

We also focused on trends in the effect of serum carotenoids on liver disease. Case-control studies found a trend toward a lower risk of liver disease for both serum carotenoids and a more pronounced trend toward lower serum α-carotene. Serum carotenoids also have a substantial correlation with other chronic diseases such as diabetes [43,44], hypertension [45], obesity and insulin resistance [46,47], and cardiovascular diseases [48] in addition to liver diseases [49,50], which could be a key research direction in the future. Additionally, there are some therapeutic application possibilities for researching the connection between blood carotenoids and glucolipid metabolism for the management and prevention of metabolic syndrome.

We also conducted a preliminary analysis of the mechanism of α- and β-carotene prevention and inhibition of liver disease. Stimulation of the body by external factors such as alcohol, diet and drugs disturbs the balance of free radicals in the body leading to a significant increase in lipid peroxidation, activating hepatic stellate cells (HSC) and leading to fibrosis. β-carotene is the predominant carotenoid in the liver [51], as well as the most active vitamin A pro-carotenoid. β-carotene has been reported to have preventive and curative effects on fibrosis, oxidative stress, hepatic steatosis, inflammation and apoptosis [16] in the following ways: (1) promoting the antioxidant system [52–54]; (2) β-carotene prevents HSC activation and hepatocyte inflammation [53,55]; (3) Inhibition of HSC activation and restoration of antioxidant status and retinol-like content of hepatic stellate cells [53]; (4) Reduces the index levels of inflammatory factors and liver function proteins [37,56]. α-Carotene, one of the vitamin A pro-carotenoids, has a positive effect on the prevention of cancer, cardiovascular disease and other diseases [57]. Michiaki et al. compared the effects of α- carotene had a significant inhibitory effect on spontaneous liver carcinogenesis in male mice [58].

There are many advantages of meta-analysis. Firstly, we assessed the association between α- and β-carotene and the risk of liver disease from both dietary intake and serum secondary studies. Secondly, the meta-analysis collected a large number of cases and subjects, which is more valid for assessing the association between α- and β-carotene and the risk of liver disease. Again, we performed a detailed subgroup analysis according to the type of liver disease, gender and obesity. According to GRADE assessment, the evidence supporting β-carotene for liver fibrosis and α-carotene for NAFLD is of moderate quality, requiring further large-scale clinical trials to confirm the findings.

However, there are some limitations to our study. Firstly, the source of heterogeneity in the ameliorative effect of serum carotene on liver disease was also not identified in this Meta-analysis, and more influencing factors could be considered for analysis in subsequent studies. In addition, the dose-relationship between α- and β-carotene and the risk of liver disease was not described and a dose-response meta-analysis was not performed.

**Table 6.** Meta-analysis Summary of analysis results.

| Analysis Object | Analysis Results |
|---|---|
| Dietary intake of β-carotene, subgroup analysis by type of liver disease | No significant difference in liver disease improvement between AFL, HCC and NAFLD intake and non-intake of β-carotene; Intake of β-carotene for liver fibrosis had a significant improvement over non-intake of β-carotene |
| Dietary intake of α-carotene, subgroup analysis by type of liver disease | No significant difference in liver disease improvement between cirrhosis and HCC intake and non-intake of α-carotene; dietary α-carotene intake was not associated with a reduced risk of NAFLD |
| Dietary intake of α-carotene, subgroup analysis by obesity condition | No significant difference in liver disease improvement between the non-obese group intake and non-intake of α-carotene; dietary α-carotene intake was not associated with a reduced risk of HCC and NAFLD in obese populations |
| Effect of dietary intake of β-carotene on liver disease | No significant difference in liver disease improvement between dietary intake and non-intake of β-carotene |
| Dietary intake of β-carotene, subgroup analysis by gender | No significant difference in liver disease improvement between males who intake and non-intake of β-carotene; No significant difference in liver disease improvement between females who intake and non-intake of β-carotene |
| Dietary intake of β-carotene, subgroup analysis by obesity condition | No significant difference in liver disease improvement between the non-obese group who intake and non-intake of β-carotene; No significant difference in liver disease improvement between the obese group who intake and non-intake of β-carotene |
| Effect of dietary intake of α-carotene on liver disease | No significant difference in liver disease improvement between dietary intake and non-intake of α-carotene |
| Dietary intake of α-carotene, subgroup analysis by gender | No significant difference in liver disease improvement between males who intake and non-intake of α-carotene; No significant difference in liver disease improvement between females who intake and non-intake of α-carotene |
| Relationship between serum carotene levels and liver disease after carotenoid enrichment | No significant difference in liver disease improvement between the serum carotenoid measurements group who intake and non-intake of carotenoid |
| Relationship between serum α/β-carotene and liver disease | No significant difference in liver disease improvement between the serum carotenoid measurements group who intake and non-intake of α-carotene; No significant difference in liver disease improvement between the serum carotenoid measurements group who intake and non-intake of β-carotene |

## 5. Conclusions

The comprehensive evaluation of this Meta-analysis revealed that dietary intake of β-carotene, α- and β-carotene detected in the serum showed a trend towards improvement of liver disease. Dietary intake of β-carotene had a significant ameliorative effect on liver fibrosis. Serum α-carotene had a more pronounced tendency to improve liver disease compared to serum β-carotene. Whereas dietary α-carotene intake was not associated with a reduced risk of liver cancer and NAFLD in obese populations. The doses and mechanisms of carotenoid effects on liver disease will need to be confirmed in larger, higher-quality trials or meta-analyses in the future.

## Author Contributions

J.F.: writing—reviewing and editing, validation; L.D. (Lu Dong): data curation, writing—original draft preparation, methodology, visualization, investigation; J.Z.: validation; L.D. (Liping Du): validation; J.W.: conceptualization, funding acquisition, supervision, validation; J.H.: funding acquisition, validation. All authors have read and agreed to the published version of the manuscript.

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## Institutional Review Board Statement

Not applicable.

## Informed Consent Statement

Not applicable.

## Data Availability Statement

Data available on request from the authors.

## Conflicts of Interest

The authors declare no conflict of interest.

## Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used DeepSeek to assist with grammar and language refinement. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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