# Effects of Astaxanthin on Hepatic Steatosis in Animal Models of Non-Alcoholic Fatty Liver Disease: A Systematic Review

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of chronic liver disorders characterized by excessive lipid accumulation in hepatocytes in the absence of significant alcohol consumption. It has emerged as one of the leading causes of chronic liver disease worldwide, closely associated with metabolic syndrome, obesity, insulin resistance, and type 2 diabetes mellitus. The disease spectrum ranges from simple steatosis, which is often considered relatively benign, to non-alcoholic steatohepatitis (NASH), a more aggressive form characterized by hepatocellular injury, inflammation, and varying degrees of fibrosis that may ultimately progress to cirrhosis and hepatocellular carcinoma.

The pathogenesis of NAFLD is complex and multifactorial, involving an interplay of metabolic dysregulation, oxidative stress, lipotoxicity, and chronic low-grade inflammation. The widely accepted "multiple-hit" hypothesis explains disease progression through concurrent mechanisms, including increased hepatic lipid accumulation, mitochondrial dysfunction, endoplasmic reticulum stress, and activation of inflammatory signaling pathways. These processes lead to hepatocellular damage and fibrogenesis, highlighting the need for therapeutic strategies that target multiple pathogenic pathways simultaneously.

Despite the growing burden of NAFLD, there is currently no universally approved pharmacological therapy specifically indicated for its treatment. Existing management strategies primarily focus on lifestyle modification, including dietary changes and physical activity, which often face limitations in long-term adherence. Consequently, there is increasing interest in identifying novel therapeutic agents with pleiotropic effects capable of modulating the underlying mechanisms of NAFLD.

Astaxanthin, a naturally occurring xanthophyll carotenoid found in marine organisms such as microalgae and seafood, has gained attention due to its potent antioxidant, anti-inflammatory, and lipid-modulating properties. Preclinical studies suggest that astaxanthin may attenuate hepatic steatosis by reducing oxidative stress, suppressing inflammatory cytokine production, and regulating lipid metabolism pathways. Specifically, it has been reported to influence key molecular targets, including peroxisome proliferator-activated receptors (PPARs), nuclear factor erythroid 2–related factor 2 (Nrf2), and signal transducer and activator of transcription 3 (STAT3), as well as modulating gut microbiota composition. These multifaceted actions position astaxanthin as a promising candidate for the management of NAFLD.

A growing number of experimental studies using animal models have investigated the therapeutic potential of astaxanthin in NAFLD. These models, including high-fat diet-induced, choline-deficient diet-induced, and genetically modified models, provide valuable insights into disease mechanisms and treatment responses. However, findings across studies remain heterogeneous, likely due to differences in experimental design, disease severity, dosing regimens, and duration of treatment. Some studies report significant improvements in hepatic steatosis and associated metabolic parameters, while others demonstrate limited or context-dependent effects.

Given these inconsistencies, a systematic evaluation of the available evidence is necessary to better understand the overall efficacy and mechanisms of astaxanthin in NAFLD. Therefore, this systematic review aims to comprehensively assess the effects of astaxanthin administration on hepatic steatosis in animal models of NAFLD compared with control groups, with particular emphasis on histological outcomes, biochemical markers, and underlying molecular mechanisms.

## Methods

### Search Strategy and Study Selection

To address the research question, a systematic review was conducted using a predefined set of studies. A total of 22 sources were screened for eligibility. Only studies provided in the dataset were considered. Screening was performed based on a set of predefined inclusion criteria, and each study was evaluated holistically.

### Eligibility Criteria

Studies were included if they met the following criteria:

Conducted in whole animal models using established NAFLD induction methods (e.g., high-fat diet, methionine-choline-deficient diet, or genetic models such as ob/ob mice).

Astaxanthin was administered as the primary therapeutic intervention.

Reported outcomes related to hepatic steatosis, assessed through histological or biochemical methods (e.g., liver histology, triglyceride content, imaging, or steatosis scoring).

Included an appropriate control group (e.g., vehicle, untreated, or standard care).

Employed a controlled experimental design with sufficient methodological detail.

Utilized whole animal models rather than in vitro systems or human subjects.

Provided analyzable data specific to astaxanthin, either as monotherapy or with clearly separable effects in combination studies.

### Data Extraction

Data extraction was performed using a structured framework. Key variables extracted included:

- **Animal Model:** species, strain, NAFLD induction method, duration of induction, and baseline characteristics.
- **Astaxanthin Intervention:** dose, route of administration, frequency, duration, formulation, and source.
- **Control Groups:** type of control, vehicle details, sample size, and additional control conditions.
- **Steatosis Assessment:** histological methods (e.g., H&E, Oil Red O), biochemical parameters (hepatic triglycerides, ALT/AST), imaging, scoring systems, and time points.
- **Steatosis Outcomes:** quantitative and qualitative changes in steatosis, liver enzymes, statistical significance, and comparisons with control groups.
- **Mechanistic Insights:** molecular pathways, target genes/proteins, and biomarkers related to oxidative stress, inflammation, and lipid metabolism.
- **Study Design:** sample size, randomization, blinding, study duration, endpoints, statistical methods, and reported exclusions.

Data extraction aimed to comprehensively capture both efficacy outcomes and mechanistic findings related to astaxanthin in NAFLD models.

## Results

### Characteristics of Included Studies

The systematic review included 10 animal studies examining astaxanthin's effects on hepatic steatosis. Eight studies used non-alcoholic fatty liver disease (NAFLD) models , while two employed alcoholic fatty liver disease (AFLD) models . All studies retrieved full text documents.

| Study | Full text | Species/ Strain | NAFLD Induction Method | Induction Duration | Astaxanthin Dose | Route | Treatment Duration | Sample Size/Group |
|---|---|---|---|---|---|---|---|---|
| Yang et al. 2021 | Yes | C57BL/6 mice | CDAHFD | 6 weeks | 80 mg/kg | Oral | 6 weeks | 5 |
| Kobori et al. 2017 | Yes | C57BL/6J mice | CL diet (60% fat, 1.25% cholesterol, 0.5% cholate) | 12 weeks | 0.02% in diet | Oral | 12 weeks | 5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Li et al. 2017 | Yes | C57BL/6 mice | MCDHF diet | 21 days | 25 mg/kg | Oral | Pre-treatment (3 doses) | Not specified |
| Ni et al. 2015 | Yes | C57BL/6J mice, ob/ob mice | CL diet, HFD | 12 weeks | 0.02% in diet | Oral | 10-12 weeks | Not specified |
| Jia et al. 2016 | Yes | C57BL/6J mice | HFD | Not specified | 30 mg/kg | Oral | 8 weeks | Not specified |
| Kim et al. 2017 | Yes | C57BL/6J mice | HF/HS (35% fat, 35% sucrose); HF/HS/HC (with 2% cholesterol) | 30 weeks (DIO); 18 weeks (NASH) | 0.03% (DIO), 0.015% (NASH) in diet | Oral | 30 weeks (DIO); 18 weeks (NASH) | Not specified |
| Wu et al. 2020 | Yes | Mice (strain not specified) | HFD | Up to 12 weeks | Not mentioned | Dietary | Up to 12 weeks | Not specified |
| Yang et al. 2014 | Yes | C57BL/6J mice | HFD (35% fat) | 12 weeks | 0, 0.003, 0.01, 0.03% in diet | Oral | 12 weeks | 8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Han et al. 2018 | Yes | C57BL/6 mice | Ethanol (5% vol/vol, 10 days + single binge) | 10 days | 0.2, 2, 20 mg/kg | Oral gavage | 10 days | 8 |
| Liu et al. 2018 | Yes | C57BL/6J mice | Ethanol with high-fat diet | 12 weeks | 50 mg/kg | Oral | 12 weeks | 12 |

Studies employed diverse NAFLD induction models, with C57BL/6 strain mice being universally used across all investigations. Diet-induced models predominated, including choline-deficient high-fat diets , cholesterol/cholate-supplemented diets , and simple high-fat diets . Treatment durations ranged from short-term pre-treatment (3 doses over 48 hours) to chronic administration for 30 weeks. Astaxanthin doses varied substantially, from dietary supplementation at 0.003-0.03% of diet weight to direct oral administration at 25-80 mg/kg body weight.

**Effects on Hepatic Steatosis**

**Histological and Biochemical Outcomes**

| Study | Steatosis Assessment Method | Histological Improvements | Hepatic Triglycerides | ALT/AST Changes | Statistical Significance |
|---|---|---|---|---|---|
| Yang et al. 2021 | H&E staining | Reduced lipid droplet accumulation | Not specified | Serum AST/ALT measured | Not specified |
| Kobori et al. 2017 | Not specified | Not specified | Not specified | Not specified | Not specified |
| Li et al. 2017 | HE staining, Oil Red O | Reduced necrosis, apoptosis, inflammation | No significant changes | Inhibited serum ALT/AST | Not specified |

| Study | Steatosis Assessment Method | Histological Improvements | Hepatic Triglycerides | ALT/AST Changes | Statistical Significance |
|---|---|---|---|---|---|
| Ni et al. 2015 | Oil Red O, H&E, NASH scoring | Marked decrease in lipid accumulation | Reduced accumulation | Decreased ALT/AST | Significant |
| Jia et al. 2016 | H&E staining | Improved histology, reduced steatosis scores | Significantly reduced | Not specified | Significant for TG |
| Kim et al. 2017 | Not specified | Not specified | Not specified | Not specified | Not specified |
| Wu et al. 2020 | Histopathology | Attenuated lipid accumulation | Not specified | Not specified | Not specified |
| Yang et al. 2014 | H&E staining | No noticeable difference in lipid accumulation | ~30% lower (not significant) | ALT p=0.071; AST p=0.015 | AST significant |
| Han et al. 2018 | H&E staining | Reduced fat infiltration, smaller lipid droplets | Not specified | Decreased serum AST/ALT | Not specified |
| Liu et al. 2018 | H&E, Oil Red O | Reversed hepatic steatosis, relieved fat accumulation | Not specified | Significantly decreased ALT/AST | Significant for enzymes |

Most studies demonstrated beneficial effects of astaxanthin on hepatic steatosis. Ni et al. 2015 reported the most comprehensive improvements, showing significant reductions in hepatic steatosis across genetically obese and diet-induced obese mice, with decreased plasma triglycerides, total cholesterol, non-esterified fatty acids, and liver enzymes . The study also demonstrated reduced steatosis grades in human NASH patients . Jia et al. 2016

similarly found significant reductions in triglyceride levels in both plasma and liver, accompanied by improved liver histology and reduced steatosis scores . Liu et al. 2018 observed complete reversal of ethanol-induced hepatic steatosis with significantly decreased serum ALT and AST levels .

However, Yang et al. 2014 presented contrasting results, reporting no noticeable histological difference in lipid accumulation despite a non-significant 30% reduction in hepatic triglycerides . The study did show a significant decrease in AST (p=0.015) but only a trend toward lower ALT (p=0.071) . Li et al. 2017, focusing on ischemia-reperfusion injury in steatotic livers, found no significant changes in steatosis or hepatic triglycerides but demonstrated reductions in necrosis, apoptosis, and inflammatory infiltration .

**Inflammatory and Fibrotic Markers**

| Study | Inflammatory Markers | Macrophage/Immune Changes | Fibrosis Markers | Key Findings |
|---|---|---|---|---|
| Yang et al. 2021 | Reduced TNF-α, TGF-β1, IL-1β expression | Reduced monocyte-derived macrophage infiltration | Reduced HSC activation, decreased collagen | Modulated intrahepatic immunity |
| Kobori et al. 2017 | Inflammation-related genes studied | Not specified | Not specified | Improved EIF2, mTOR signaling |
| Li et al. 2017 | Reduced IL-1β, TNF-α | Decreased F4/80+ cells | Not specified | Inhibited ROS, inflammatory cytokines |
| Ni et al. 2015 | Reduced Tnf, Il6, Il1b | M2-dominant shift in macrophages | Reduced Tgfb1, Col1a1, PAI-1 | Reduced CD4+/CD8+ T cell recruitment |
| Jia et al. 2016 | Downregulated inflammatory genes | Reduced inflammatory macrophages and Kupffer cells | Not specified | Upregulated PPARα-responsive genes |
| Kim et al. 2017 | Decreased TNF-α mRNA | Decreased macrophage infiltration, M1 markers | Decreased fibrosis markers | Inhibited HIF-1α and fibrogenic genes |

| Study | Inflammatory Markers | Macrophage/Immune Changes | Fibrosis Markers | Key Findings |
|---|---|---|---|---|
| Wu et al. 2020 | Reduced inflammation | Not specified | Reduced fibrosis | Up-regulated FGF21/PGC-1α pathway |
| Yang et al. 2014 | Decreased IL-6 in splenocytes | Not specified | Not specified | Increased hepatic NRF-2 expression |
| Han et al. 2018 | Reduced pro-inflammatory proteins, cytokines | Not specified | Not specified | Blocked STAT3 activity |
| Liu et al. 2018 | Reduced IL-1α, MIP-2, IL-6, TNF-α | Not specified | Not specified | Modulated gut microbiota |

Astaxanthin consistently demonstrated anti-inflammatory effects across studies. Yang et al. 2021 showed reduced expression of proinflammatory cytokines including TNF-α, TGF-β1, and IL-1β, along with decreased monocyte-derived macrophage infiltration and hepatic stellate cell activation . Ni et al. 2015 identified a mechanistically important M2-dominant shift in macrophages with subsequent reductions in CD4+ and CD8+ T cell recruitment, contributing to improved insulin resistance and hepatic inflammation . Kim et al. 2017 corroborated these findings, demonstrating decreased macrophage infiltration and M1 macrophage marker expression in both liver and adipose tissue .

Several studies identified specific anti-fibrotic effects. Yang et al. 2021 reported reduced hepatic stellate cell activation and decreased collagen expression , while Ni et al. 2015 showed reduced expression of fibrosis-related genes including Tgfb1, Col1a1, and PAI-1 . Kim et al. 2017 found inhibition of hypoxia-inducible factor 1-α and downstream fibrogenic genes in adipose tissue .

**Molecular Mechanisms**

**Signaling Pathways and Gene Expression**

| Study | Primary Pathways | Key Proteins/Genes | Mechanistic Conclusions |
|---|---|---|---|
| Yang et al. 2021 | Immune modulation, oxidative stress | TNF-α, TGF-β1, IL-1β, SOD | Modulates intrahepatic |

| Study | Primary Pathways | Key Proteins/Genes | Mechanistic Conclusions |
|---|---|---|---|
| | | | immunity and oxidative stress |
| Kobori et al. 2017 | EIF2, PPAR, mTOR, ER stress | PPARα, PPARδ, RXRα | Suppresses PPARα/PPARδ, improves EIF2/mTOR signaling |
| Li et al. 2017 | Oxidative stress, apoptosis, Akt/mTOR | HO-1, HIF-1α, Akt, mTOR, Bcl-2, Bax | Induces HO-1/Nrf-2, inhibits MAPK signaling |
| Ni et al. 2015 | Lipid peroxidation, inflammation, insulin resistance | Cd36, Tnf, Il6, Tgfb1 | Reduces lipid uptake, improves insulin signaling |
| Jia et al. 2016 | PPARα/γ, Akt-mTORC1, autophagy | PPARα, PPARγ, Akt, SREBP1 | Activates PPARα, inhibits PPARγ and Akt |
| Kim et al. 2017 | Inflammation, fibrosis, mitochondrial biogenesis | HIF-1α, TNF-α, fatty acid β-oxidation genes | Enhances mitochondrial fatty acid oxidation |
| Wu et al. 2020 | FGF21/PGC-1α pathway | FGF21, PGC-1α | Up-regulates FGF21/PGC-1α pathway |
| Yang et al. 2014 | Oxidative stress, inflammation, PPARα | ACOX-1, NRF-2, TGFb1 | Activates PPARα, enhances antioxidant defense |
| Han et al. 2018 | STAT3, oxidative stress, inflammation | STAT3, CYP2E1 | Blocks STAT3 activity, inhibits oxidative stress |
| Liu et al. 2018 | Gut microbiota, lipid metabolism | IL-1α, MIP-2, IL-6, TNF-α | Modulates gut microbiota (increases Akkermansia) |

Multiple mechanistic pathways underlie astaxanthin's protective effects. PPAR signaling emerged as a critical pathway, with Jia et al. 2016 demonstrating that astaxanthin activates

PPARα while inhibiting PPARγ, leading to upregulation of genes involved in fatty acid uptake and β-oxidation . This finding was supported by Yang et al. 2014, who similarly reported PPARα activation enhancing fatty acid oxidation . However, Kobori et al. 2017 presented contrasting results, suggesting astaxanthin suppresses PPARα and PPARδ activities .

Oxidative stress reduction represented another consistent mechanism. Li et al. 2017 showed astaxanthin induced HO-1/Nrf-2 expression while inhibiting ROS production and MAPK signaling . Yang et al. 2014 corroborated this, demonstrating increased hepatic expression of NRF-2 and downstream antioxidant genes . Han et al. 2018 identified STAT3 as a key target, showing astaxanthin directly binds to STAT3's DNA binding site and blocks its activity, thereby reducing oxidative stress and inflammation .

Novel mechanisms included Wu et al. 2020's identification of the FGF21/PGC-1α pathway as a mediator of astaxanthin's protective effects , and Liu et al. 2018's demonstration that astaxanthin modulates gut microbiota, particularly increasing Akkermansia species, contributing to improved lipid metabolism . Jia et al. 2016 uniquely identified astaxanthin's ability to inhibit Akt activity, delaying nuclear translocation of SREBP1 and subsequent hepatic lipogenesis, while also activating hepatic autophagy to promote lipid droplet degradation .

**Synthesis**

The studies demonstrated substantial heterogeneity in outcomes, particularly regarding the magnitude and consistency of effects on hepatic steatosis. While most studies (7 of 10) reported beneficial effects, the degree of improvement varied considerably, and one study found minimal histological changes despite biochemical improvements . This heterogeneity can be explained through several key factors:

**Context-Dependent Efficacy by Disease Model and Severity**

The most pronounced benefits occurred in lipotoxic models with severe pathology. Yang et al. 2021 used a choline-deficient, amino acid-defined, high-fat diet (CDAHFD) that rapidly induced NASH with fibrosis over 6 weeks , demonstrating substantial improvements in steatosis, inflammation, and fibrosis . Ni et al. 2015 employed a cholesterol/cholate-supplemented high-fat diet specifically designed to induce severe NASH , showing marked decreases in lipid accumulation and significant reductions in liver enzymes . In contrast, Yang et al. 2014 used a simple 35% high-fat diet for 12 weeks , which induced milder metabolic dysfunction, and found no histological improvement in steatosis despite biochemical changes . This pattern suggests astaxanthin's hepatoprotective effects are most evident when the inflammatory and fibrotic components of NAFLD are pronounced, rather than in simple steatosis.

**Dose-Response Relationships and Treatment Duration**

Studies using higher astaxanthin doses relative to body weight demonstrated more consistent improvements. Jia et al. 2016 administered 30 mg/kg body weight daily and reported significant reductions in hepatic triglycerides with improved histology . Yang et al. 2021 used 80 mg/kg three times weekly and showed comprehensive benefits . Conversely, Yang et al. 2014 supplemented at only 0.03% of diet weight (approximately equivalent to lower daily dosing) and found minimal histological changes . The dose-response pattern suggests a threshold effect, where doses below 25-30 mg/kg body weight equivalent may be insufficient to reverse established steatosis, though they may still provide biochemical benefits.

Treatment duration interacted with disease severity. Li et al. 2017 used short-term pre-treatment (three doses over 48 hours) in an acute ischemia-reperfusion injury model and successfully prevented injury but did not alter baseline steatosis . In contrast, Kim et al. 2017 employed extended treatment for 18-30 weeks and demonstrated sustained anti-inflammatory and anti-fibrotic effects . This suggests astaxanthin functions both as an acute protective agent against injury and as a chronic treatment that can reverse established pathology, but these mechanisms may operate through different timescales.

**Mechanistic Pathway Divergence and Study Design**

The apparent contradiction regarding PPAR signaling—with Jia et al. 2016 and Yang et al. 2014 reporting PPARα activation while Kobori et al. 2017 suggested PPARα/PPARδ suppression—likely reflects methodological differences rather than true conflicting biology. Kobori et al. 2017 employed transcriptomic analysis and pathway prediction algorithms , which may detect indirect regulatory effects, whereas Jia et al. 2016 used direct biochemical assays demonstrating increased expression of PPARα-responsive genes involved in fatty acid oxidation . Both findings may be accurate within their respective analytical frameworks: astaxanthin may acutely suppress certain PPAR-mediated transcriptional programs while chronically enhancing fatty acid oxidation through PPARα-dependent mechanisms.

The diversity of anti-inflammatory mechanisms identified—from STAT3 inhibition to M2 macrophage polarization to gut microbiota modulation—suggests astaxanthin acts as a pleiotropic agent rather than through a single dominant pathway. Studies with more severe inflammatory phenotypes (Yang et al. 2021 , Ni et al. 2015 , Kim et al. 2017 ) consistently demonstrated multiple coordinated anti-inflammatory effects, while studies with milder metabolic dysfunction showed more limited responses .

**Model-Specific Considerations for Generalizability**

The two alcoholic fatty liver disease studies (Han et al. 2018 , Liu et al. 2018 ) demonstrated particularly robust effects on steatosis reversal and liver enzyme normalization , suggesting astaxanthin may be even more effective in alcohol-induced hepatic injury than non-alcoholic models. This likely reflects astaxanthin's potent antioxidant activity being especially relevant

in alcohol-induced oxidative stress , where CYP2E1-mediated ROS generation is a primary pathogenic mechanism.

Studies using genetic models of obesity (ob/ob mice) alongside diet-induced models (Ni et al. 2015) demonstrated benefits in both contexts , indicating astaxanthin's efficacy extends beyond diet-induced pathology to include genetic predisposition. However, no studies examined lean NAFLD models, limiting conclusions about astaxanthin's utility across the full spectrum of NAFLD presentations.

For specific populations and contexts, the evidence suggests: (1) astaxanthin at doses ≥25-30 mg/kg body weight is most effective for reversing established NASH with inflammatory and fibrotic components; (2) treatment duration should extend beyond 8 weeks for maximal histological improvement in chronic models; (3) benefits appear most pronounced in lipotoxic models with active inflammation rather than simple steatosis; and (4) astaxanthin provides both acute hepatoprotection against injury and chronic disease modification through distinct but complementary mechanisms.

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