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Metabolic dysfunction-associated steatotic liver disease: mechanisms, oxidative stress, and the therapeutic potential of garcinol and astaxanthin

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most prevalent chronic liver disease worldwide, affecting nearly one in three adults. Strongly associated with obesity, insulin resistance, and dyslipidemia, MASLD increases the risk of hepatic fibrosis, liver dysfunction, and systemic metabolic complications. Despite its growing prevalence, effective pharmacological therapies remain limited. Natural bioactive compounds with antioxidant, anti-inflammatory, and lipid metabolism-modulating properties are widely studied and gaining popularity for their potential hepatoprotective effects.

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This review provides an overview of the pathophysiology of MASLD, highlighting its metabolic and oxidative stress-related mechanisms, and explores the potential benefits of garcinol (GAR) and astaxanthin (AX), two natural bioactive compounds that may support liver. Based on the literature review of *in vivo* studies, it can be concluded that the administration of GAR and AX to animals with induced liver steatosis exerted hepatoprotective effects. The hepatoprotective impact was evident in their inhibitory action on oxidative stress, inflammation, and fibrosis in the liver, as well as in supporting lipid metabolism. In some studies, GAR and AX were also administered in combination with other hepatoprotective compounds, such as vitamin E and curcuminoids.
Although evidence supports their individual benefits, the therapeutic potential of combining GAR and AX in MASLD remains unexplored. Consequently, based on the available studies, it is not possible to evaluate their combined effects. Further research is needed to determine their mechanisms of interaction, optimal dosages, and clinical relevance. We believe that their combination may offer additional benefits and provide new perspectives on natural bioactive compounds-based interventions for liver protection.

KEYWORDS: MASLD / garcinol / astaxanthin / oxidative stress / hepatoprotective effect / inflammation

Introduction

In June 2023, with the publication of the multi-society Delphi consensus on the new fatty liver disease nomenclature in the *Hepatology*, the term metabolic dysfunction-associated steatotic liver disease (MASLD) was officially introduced, replacing non-alcoholic fatty liver disease (NAFLD) [Rinella *et al*. 2023a]. Earlier in 2020, the first step toward this change was taken when Eslam et al. proposed replacing NAFLD with a term: metabolic dysfunction-associated fatty liver disease (MAFLD). Unlike NAFLD, which required the exclusion of other causes, MAFLD was defined based on positive diagnostic criteria [Eslam *et al*. 2020ab]. One of the concerns raised regarding the MAFLD diagnostic criteria was that it excluded a significant subset of NAFLD patients who are lean with a normal BMI [De *et al*. 2024]. The introduction of MASLD as a new term was the final step in a decades-long process of better understanding fatty liver disease. Previously, it was diagnosed mainly by ruling out alcohol consumption and was labeled with the potentially stigmatizing term "fatty." Now, it is recognized as a metabolic disorder [Rinella *et al*. 2023a].

MASLD is a global pandemic and the most common liver disease, affecting about 25-30% of the general population worldwide [Svobodová *et al*. 2025]. The diagnostic criteria for MASLD require the presence of confirmed hepatic steatosis (histology, imaging, or blood-based biomarkers), in conjunction with the exclusion of other causes of liver steatosis and at least one cardiometabolic risk factor. The defined cardiometabolic risk factors are presented in Table 1 [Rinella *et al*. 2023a].

This complex and heterogeneous disease encompasses a wide spectrum of liver abnormalities, differing in severity of damage and fibrosis progression. Metabolic dysfunction-associated steatotic liver (MASL) is identified by a combination of macrovesicular and microvesicular fat accumulation in the liver, affecting at least

Table 1. Cardiometabolic Risk Factors in the Definition of MASLD based on: Rinella, Lazarus *et al*. [2023]

Metabolic Risk Factor	Adult Criteria
Overweight or obesity	BMI ≥25 kg/m² or waist circumference: ≥94 cm (males), ≥80 cm (females)
Prediabetes or type 2 diabetes	Fasting glucose ≥100 mg/dl or 2-hour plasma glucose (2h-PG) after OGTT ≥140 mg/dl or HbA1c ≥5.7% or diagnosed type 2 diabetes mellitus **or** type 2 diabetes mellitus treatment
Blood pressure	≥130/85 mmHg or treatment for hypertension
Plasma triglycerides	≥150 mg/dl or lipid-lowering treatment
HDL-cholesterol	≤40 mg/dl (males), ≤50 mg/dl (females) or lipid-lowering treatment

5% of hepatocytes, potentially accompanied by mild inflammation; however, the likelihood of it advancing to cirrhosis or liver failure is minimal. In 10-20% of cases, this hepatic steatosis progresses steatohepatitis (MASH), which is marked by the same level of fat accumulation (≥5% of hepatocytes), but also includes inflammation and damage to hepatocytes (ballooning), with or without fibrosis. MASH carries a higher risk of progressing to cirrhosis, liver failure, and, in rare instances, hepatocellular carcinoma. Notably, cirrhosis is the most common reason for liver transplantation [Rinella *et al*. 2023b, Svobodová *et al.* 2025].

The development of MASLD is strongly linked to metabolic syndrome. Patients with MASLD frequently exhibit characteristics of metabolic syndrome including obesity, type 2 diabetes, insulin resistance, hypertension, and dyslipidemia [Chalasani *et al.* 2018]. The exact pathogenesis of MASLD remains unclear. Early research suggested that insulin resistance and hepatic steatosis, driven by an excess of fatty acids, represent the initial stage of liver dysfunction - commonly referred to as the "first hit". Over time, oxidative stress and lipid peroxidation contribute to hepatocyte damage, inflammation, fibrosis, and other pathological changes, forming what was originally described as the "second hit". Currently, the "multiple-hit" hypothesis is considered more likely. According to this understanding, the pathogenesis of MASLD involves a broader range of contributing factors, including lipid accumulation, lipotoxicity, endoplasmic reticulum stress, and oxidative stress [Buzzetti *et al.* 2016, Friedman *et al*. 2018, Guo *et al*. 2022].

A key aspect of MASLD prevention and treatment is lifestyle modifications focusing on weight loss as well as modifying diet composition [Finer 2022, Kaylan and Paul 2024]. For a long time, there were no approved treatments or drugs for patients with MASLD or MASH [Rong *et al*. 2022]. In February 2024, Resmetirom, an oral, liver-directed, thyroid hormone receptor β-selective agonist, was approved by the Food and Drug Administration for the treatment of MASH [Harrison *et al*. 2024]. Since MASLD can progress to MASH, early intervention is crucial to stop MASLD progression. Given the role of diet in MASLD, the search for natural bioactive compounds that could counteract disease progression or mitigate its severity remains highly relevant, even with the availability of Resmetirom.

The aim of this review was to present the current state of knowledge on the pathophysiological mechanisms of MASLD and to assess the potential hepatoprotective effects of natural bioactive compounds - garcinol (GAR) and astaxanthin (AX). The authors also aimed to identify research gaps, particularly in the context of their possible synergistic application.

Material and methods

A structured literature review was conducted to identify relevant studies examining the hepatoprotective effects of garcinol and astaxanthin in the context of MASLD. The online scientific literature databases ScienceDirect, Scopus, ProQuest, and PubMed were queried using combinations of the following search terms: "MASLD", "NAFLD", "NASH", "garcinol", "astaxanthin", "oxidative stress", "inflammation", "lipid metabolism", and "hepatoprotection". The search was limited to original research and review articles in English, focusing on *in vivo* studies investigating the effects of garcinol or astaxanthin in animal models of hepatic steatosis. Publications without full-text availability or those unrelated to MASLD were excluded. All eligible full-text articles were reviewed manually. Summary tables were prepared based on experimental model, dose, route of administration, and observed hepatoprotective effects.

Results and discussion

Understanding role of lipid metabolism imbalance in MASLD

Free fatty acids (FFAs) sources. Lipid metabolism imbalance is one of the primary factors contributing to MASLD. Hepatic steatosis develops when the balance between fat synthesis and breakdown is disrupted, exceeding the liver's metabolic capacity [Chen *et al*. 2019].

More than half of the free fatty acids (FFAs) that accumulate in the liver originate from peripheral lipolysis or the pool of non-esterified fatty acids [Arab *et al.* 2018]. Notably, the breakdown of triglycerides is regulated by insulin signaling in white adipose tissue (WAT). As mentioned earlier, patients with MASLD often have insulin resistance, characterized by reduced insulin sensitivity and impaired glucose uptake in peripheral tissues. This leads to uncontrolled lipolysis in WAT, resulting in an excessive influx of FFAs into the liver. The surplus of FFAs contributes to the formation of ectopic lipid deposits and the development of MASLD [Samuel and Shulman 2018, Syed-Abdul 2024].

The second major source of FFAs in the liver is de novo lipogenesis (DNL), a process in which hepatocytes convert excess dietary glucose and fructose into fatty acids [Friedman *et al*. 2018, Heeren and Scheja 2021, Syed-Abdul 2024]. Insulin resistance also enhanced DNL [Lee *et al*. 2023]. Hyperglycemia and hyperinsulinemia activate

carbohydrate response element-binding protein and sterol regulatory element-binding protein 1c (SREBP1c) in hepatocytes. Under conditions of chronic energy surplus and prolonged hyperinsulinemia these lipogenic transcription factors remain persistently active [Syed-Abdul 2024]. This activation enhances the expression of several lipogenic enzymes like acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), promoting the hepatic synthesis of FFAs from glucose [Samuel and Shulman 2018].

Hepatic lipid accumulation results also from diet pattern. Firstly, a high-fat diet can lead to obesity, insulin resistance, and liver steatosis with mild inflammation and fibrosis. Secondly, excessive sugar intake, particularly fructose has been shown to upregulate gene expressions associated with liver fibrosis, inflammation, endoplasmic reticulum (ER) stress, and adipocyte apoptosis. Both animal models and human studies indicate that fructose undergoes selective hepatic metabolism [Basaranoglu *et al*. 2013]. Fructose metabolite, along with other intermediates, as previously described, activates several key regulators of lipid metabolism, which subsequently influence SREBP-1c and ACC, leading to enhanced DNL [Jensen *et al.* 2018, Yu *et al*. 2021]. Moreover, fructose inhibits β-oxidation of fatty acids. Increased DNL and impaired β-oxidation are attributed to the distinct metabolic processing of fructose by fructokinase. This pathway leads to a reduction in ATP levels, accompanied by nucleotide turnover and uric acid production. The prooxidative and proinflammatory properties of uric acid contribute to increased intestinal permeability and endotoxemia, further exacerbating hepatic lipogenesis [Yu *et al.* 2021].

FFAs metabolism in liver. Hepatic FFAs primarily follow two metabolic pathways: mitochondrial β-oxidation or esterification into triglycerides [Arab *et al.* 2018]. Triglycerides are the predominant lipid species stored in lipid droplets within fatty liver, and their accumulation is considered a protective mechanism that shields hepatocytes from lipotoxic damage. Another key adaptation in fatty liver is the increased secretion of triglycerides in the form of very low-density lipoproteins, which can contribute to hypertriglyceridemia [Friedman *et al*. 2018, Samuel and Shulman 2018]. Moreover, excess FFAs can be also utilized as precursors for the formation of lipotoxic molecules, such as ceramides, diacylglycerols, and lysophosphatidylcholine. These compounds contribute to metabolic stress, inflammation, and ultimately cell death [Chen *et al*. 2019, Friedman *et al*. 2018]. When the concentration of lipotoxic substances in hepatocytes surpasses their capacity for transport and detoxification, liver cell injury intensifies, and the disease advances to a more severe stage. Overload the fatty acid oxidation pathways in hepatocytes leads to mitochondrial dysfunction, excessive production of reactive oxygen species (ROS), and the induction of ER stress, autophagy, lipoapoptosis, and inflammatory responses [Rada *et al.* 2020].

Oxidative stress in MASLD

Oxidative stress is considered a major contributor to liver injury and disease progression in MASLD within the framework of the "multiple-hits" theory. The nuclear factor erythroid 2-related factor 2 (Nrf2) plays a crucial role in oxidative stress

regulation by promoting the expression of phase 2 antioxidant and detoxifying enzymes i.e. superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), along with other protective proteins. Under normal physiological conditions, ROS levels are regulated to maintain balance, with excess free radicals being neutralized by antioxidant enzymes. However, disruption of this equilibrium between the antioxidant defense system and oxidative processes can lead to an overproduction of ROS. These reactive molecules and other free radicals can interfere with cellular function by influencing transcription factors and redox-sensitive signaling pathways [Friedman *et al*. 2018, Kasprzak-Drozd *et al*. 2024, Mignini *et al*. 2024]. When ROS reach high concentrations, they induce oxidative damage to key cellular macromolecules, including DNA, lipids, and proteins, leading to their accumulation in a damaged state and ultimately resulting in liver injury. Mitochondrial dysfunction, ER stress, and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activation are the primary mechanisms that account for increased generation of ROS such as $O_2^{\bullet -}$, H_2O_2, malondialdehyde (MDA), and 4-hydroxy-2-nonenal in excess lipid accumulation in the liver [Chen *et al*. 2020].

In response to MASLD, mitochondrial function adapts primarily by downregulating the electron transport chain while maintaining or even increasing the capacity for mitochondrial β-oxidation. This shift promotes excessive ROS production in various electron transport chain components upstream of cytochrome c oxidase. However, non-electron transport chain pathways, particularly fatty acid β-oxidation, appear to be even more significant contributors to ROS production in hepatic metabolic disorders [Cao and Kaufman 2014, Mignini *et al.* 2024].

ER stress has also been linked to MASLD. In prolonged ER stress, an adaptive signaling cascade, known as the unfolded protein response, is initiated to restore ER equilibrium. It enhance expression of proteins oxidoreductin 1 and protein disulfide isomerase which taking part also in ROS production [Lebeaupin *et al.* 2018]. Prolonged ER stress increases ROS generation also by upregulating the activity of enhancer-binding protein homologous protein. ER stress is also involved in the reduction of antioxidant mechanisms, such as downregulation of Nrf2 and depletion of glutathione (GSH) [Cao and Kaufman 2014]. Some findings indicate that ER plays a role in both the development of hepatic steatosis and the progression of MASH. Disrupted ER homeostasis has been observed in the livers of patients with MALSD, suggesting a strong association between ER stress and this disease [Flamment *et al.* 2010, Gentile *et al*. 2011, Puri *et al.* 2008].

Alterations in NADPH oxidase activity is also connected to MALSD. Some evidence indicates that it may contribute to ROS production during liver fibrosis, being important in hepatic stellate cells and hepatocyte apoptosis [Crosas-Molist and Fabregat 2015].

The excessive generation of ROS affects insulin sensitivity, leading to the induction or exacerbation of insulin resistance, as well as the expression and activity of key enzymes involved in lipid metabolism. Furthermore, interactions between redox

signaling and innate immune pathways create a complex regulatory network that influences inflammatory responses. Therefore, ROS contribute to MASLD progression through a combination of widespread oxidative damage and disruptions in redox signaling [Forrester *et al*. 2018, Masarone *et al.* 2018, van der Vliet *et al.* 2018].

Natural bioactive compounds in MASLD prevention

Natural bioactive compounds are small molecules found in various plant parts and foods that exert a range of biological effects by modulating metabolic pathways. Several of them, however, originate from animal sources [Dixit *et al*. 2023]. Natural bioactive compounds may exhibit antioxidant, anti-inflammatory, and other therapeutic effects [Tewari *et al.* 2017, Mozos *et al*. 2018, 2021, Silva Figueiredo *et al.* 2018, Yeung *et al.* 2018, 2019, 2022, 2023, 2021ab, 2020ab, Wang *et al*. 2018, 2020, Li *et al*. 2021, Copra *et al.* 2022, Noce *et al*. 2021], contributing to their potential in MASLD prevention and management. Due to their diverse origins, they possess strikingly diverse chemical structures and biological activities. They can be primary or secondary metabolites or food components, such as polyphenols (e.g., resveratrol, curcumin, GAR), and carotenoids (e.g., AX) - Noce *et al*. [2021], Silva Figueiredo *et al*. [2018].

Many natural products contain a wide range of bioactive compounds with significant hepatoprotective effects. Increasing evidence suggests that specific nutraceuticals such as omega-3 fatty acids, silymarin, berberine, coenzyme Q10, curcumin, resveratrol, green tea extract, artichoke extract, and vitamin E, each exerting hepatoprotective, antioxidant, anti-inflammatory, insulin-sensitizing, or lipid-lowering effects, may contribute to the improvement of liver steatosis and enzyme levels, and may help delay the progression of non-alcoholic fatty liver disease [Lee *et al*. 2023, Rizzo *et al.* 2023]. According to a bibliometric study published in 2023, resveratrol and curcumin were most frequently mentioned in the context of MASLD [Yeung *et al.* 2023].

Resveratrol. Resveratrol is a polyphenol found in wine, grapes, berries, tomatoes, and nuts. Resveratrol was described in field of reducing hepatic fat accumulation. It also activates SOD, GPx, and CAT, increases the activity of various nuclear transcription factors, such as Nrf2, activator protein-1, and sirtuin 1, and enhances non-enzymatic antioxidants, including GSH [Ławiński *et al.* 2025, Yeung *et al*. 2019, 2024] thereby potentially mitigating the negative effects of ER stress in MASLD. Resveratrol indirectly induces autophagy through both mTOR-dependent and TFEB-dependent pathways, involving key signaling cascades such as AMPK/SIRT1/Nrf2[1], ERK/p38MAPK[2], and PTEN/Akt[3]. These pathways contribute to the regulation of oxidative stress by enhancing the production of antioxidant molecules and upregulating the expression of related genes [Kasprzak-Drozd *et al*. 2024].

[1] AMPK - AMP-Activated Protein Kinase; SIRT1 - Sirtuin 1.
[2] ERK - Extracellular Signal-Regulated Kinase; p38MAPK - p38 Mitogen-Activated Protein Kinase.
[3] PTEN - Phosphatase and Tensin Homolog; Akt - Protein Kinase B.

Curcumin/curcuminoids. Second mentioned - curcumin is one of three curcuminoids present in rhizomes next to demethoxycurcumin, and bisdemethoxycurcumin. It has been extensively studied for its antioxidant, anti-inflammatory, anti-carcinogenic, and antibacterial properties [Matin *et al.* 2025]. Curcuminoids significantly enhance mitochondrial health by promoting mitochondrial biogenesis and function and inhibiting oxidative stress in WAT, and the liver. The hepatoprotective activity of curcuminoids is reported to be mediated by the reduction of oxidative stress and the attenuation of nuclear factor kappa B (NF-κB)-mediated proinflammatory activity. This effect is likely achieved through the activation of phase 2 detoxifying and antioxidant enzymes, such as heme oxygenase-1 and NADPH quinone oxidoreductase-1, as well as the Nrf2/Keap1/ARE[4] pathway, which plays a crucial role in counteracting oxidative stress, and suppressing NF-κB-driven inflammation. Curcuminoids also decreased MDA levels in isolated hepatic mitochondria and reduced ROS levels in liver cells. Additionally, by boosting mitochondrial function, they help mitigate insulin resistance, enhance fatty acid oxidation, and prevent liver steatosis [Kim *et al*. 2024, Majeed *et al*. 2020a, Pandey *et al.* 2023].

Curcuminoids activity was also examined in combinatorial regimen. Majeed *et al*. [2020] examined the hepaprotective effects of *Curcuma longa* extract standardized to contain 95% w/w of Curcuminoids and 20% w/w of GAR from *Garcinia indica* in an animal model of MASH. Curcuminoids were chosen due to their potent anti-inflammatory properties. GAR was selected for its potential to reduce steatosis, as it has been reported that GAR exhibit anti-adipogenic activity by alleviating ER stress and promoting adipocyte browning. Conducted research's results show a reduction in steatosis, hepatocyte ballooning, inflammation, fibrosis, and the number of hepatic stellate cells. Alterations in antioxidant markers were observed, including reductions in both non-enzymatic (GSH) and enzymatic antioxidants (GPx and SOD) with significantly decreased protein levels of tumor necrosis factor α (TNF-α) and NF-κB. The authors conclude that the findings indicate the combinatorial regimen may serve as a beneficial supplement in slowing the progression of liver steatosis to inflammation and fibrosis in MASH [Majeed *et al.* 2020a].

While the properties of curcuminoids, particularly curcumin, are well established, the second component studied by the authors - GAR - deserves closer attention.

Garcinol (GAR). GAR (Fig. 1) is a crystalline polyisoprenylated benzophenone belonging to polyphenols, derived mainly from *Garcinia indica* [Schobert and Biersack 2019, Wang *et al*. 2023]. It is an evergreen tropical tree belonging to the *Clusiaceae* (mangosteen) family and is commonly known as a kokum. It is distributed across tropical regions of Asian and Africa [Lim *et al*. 2021, Ranveer and Sahoo 2017]. All parts of this plant-including the leaves, bark, seeds, and fruit-rind have a long history of use in Indian Ayurveda [Ranveer and Sahoo 2017]. Fruits contain 1.5% GAR with a molecular weight of 602.8 g/mol. GAR is a fat-soluble pigment [Majeed

[4] Keap1 - Kelch-like ECH-Associated Protein 1; ARE - Antioxidant Response Element.

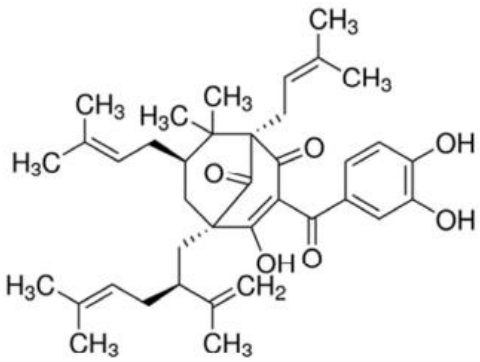

Fig. 1. Chemical structure of garcinol.

et al. 2020b, Ranveer and Sahoo 2017]. It is obtained through extraction, followed by chromatographic purification and/or crystallization for optimal refinement [Schobert and Biersack 2019, Wang *et al*. 2023].

GAR by virtue of its phenolic hydroxyl groups as well as a β-diketone moiety demonstrates significant antioxidant activity effectively scavenging free radicals and superoxide anions [Lim *et al*. 2021]. C57BL/6 male mice fed a Western diet and supplemented with a GAR-enriched fraction (85.98% w/w GAR) exhibited increased GSH levels, enhanced CAT and SOD activity, and reduced MDA concentrations in tissues, indicating improved antioxidant defense. Additionally, GAR improved lipid profiles by increasing high-density lipoprotein (HDL) levels and lowering triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL), while also reducing inflammatory markers such as interleukin-6 (IL-6). Notably, GAR supplementation led to a decrease in atherogenic indices, including the Atherogenic Index of Plasma, Cardiac Risk Ratio, and Atherogenic Coefficient, which are commonly used to assess cardiovascular risk. [Barve 2021].

GAR treatment in BALB/c male mice with LPS/D-Gal[5]-induced hepatic injury significantly reduced serum alanine transaminase (ALT) and aspartate transaminase (AST) levels, improved histological alterations in liver tissue, and decreased MDA content in liver homogenates. Additionally, it suppressed NF-κB activation, a key regulator of the inflammatory response, and downregulated the expression of apoptotic markers, including caspase-3, caspase-8, and caspase-9 [Jing *et al.* 2014]. The anti-inflammatory properties of GAR were further confirmed by a literature review published seven years later. According to the authors, GAR exerts anti-inflammatory effects by modulating multiple signaling pathways, influencing molecular interactions, and regulating gene expression associated with inflammation. It modulates arachidonic acid metabolism, suppresses NF-κB activation, and inhibits cyclooxygenase-2 expression by disrupting lipopolysaccharide binding to toll-like

[5] LPS - Lipopolysaccharide; D-Gal - D-Galactosamine.

receptors and inhibiting the synthesis of inducible nitric oxide synthase [Lim *et al.* 2021]. Its anti-inflammatory effects were also demonstrated in a diabetic wound model using C57BL/6 male mice, as well as in an *in vitro* study on human umbilical vein endothelial cells exposed to a high-glucose environment. In these models, GAR suppressed the PI3K/Akt/NF-κB[6] pathway, leading to a reduction in inflammatory cytokine secretion by macrophages [Li *et al*. 2025].

In another study using a high-fat diet-induced mouse model, GAR downregulated genes involved in DNL, while reducing TC, TG, LDL, insulin, and fasting glucose levels. Additionally, GAR lowered ALT and AST levels, indicating improved liver function. Moreover, it enhanced the expression of occludin, claudins, and zonula occludens-1, which play a crucial role in maintaining the integrity of sinusoidal vessels, thereby preventing the uncontrolled passage of toxins and pro-inflammatory factors into the liver parenchyma. [Basumatary *et al.* 2024].

In another *in vivo* study, GAR reduced apoptosis, necrotic liver areas, and histone H3 acetylation, leading to decreased liver damage and improved survival in C57BL/6 male mice with acute liver failure [Ferriero *et al*. 2018]. In another study, the administration of GAR at concentrations of 0.1% and 0.5% with a HFD was evaluated in C57BL/6 mice. The results demonstrated that GAR effectively mitigated liver steatosis, inflammatory infiltration, and ballooning degeneration in a dose-dependent manner. Additionally, GAR reduced body weight, TG, TC, ALT, LDL, adipocyte size, and WAT mass. These findings suggest that GAR may play a protective role against hepatic alterations [Lee *et al*. 2019].

An *in vitro* study demonstrated that GAR inhibits the proliferation, adipogenesis, and adipocyte-related inflammatory response in both preadipocytes and mature adipocytes. Furthermore, GAR has been shown to upregulate the gene expression of adiponectin while downregulating the expression of leptin, resistin, and FAS during 3T3-L1 adipocyte differentiation [Hsu *et al.* 2012].

GAR has been also recognized for its anti-obesity effects by alleviating ER stress and promoting adipocyte browning. Mice receiving Livinol™ remained lean despite the HFD and exhibited a dose-dependent reduction in visceral fat accumulation. Histological analysis further confirmed a reduction in adipocyte size in the perigonadal adipose tissue of treated animals. Additionally, GAR extract alleviated ER stress in adipose tissues by downregulating the expression of X-Box Binding Protein 1; Glucose-Regulated Protein 78; Activating Transcription Factor 6. Furthermore, GAR supplementation reduced the transcription of genes involved in adipogenesis (Peroxisome Proliferator-Activated Receptor Γ (PPARγ); CCAAT/Enhancer-Binding Protein A, Adipocyte Protein 2 and FAS) while upregulating markers associated with thermogenesis and mitochondrial activity (Uncoupling Protein 1, Peroxisome Proliferator-Activated Receptor Γ Coactivator 1-A, PR Domain Containing 16; Bone Morphogenetic Protein 17). GAR decreased phosphorylation of Protein Kinase

[6] Phosphoinositide 3-Kinase.

RNA-like Endoplasmic Reticulum Kinase, Inositol-Requiring Enzyme 1, and spliced X-Box Binding Protein 1, indicating a significant protective effect against ER stress [Majeed *et al.* 2020b]**.**

Based on the cited in vivo studies (Tab. 2), GAR has demonstrated anti-inflammatory, antioxidant, hepatoprotective, and metabolic regulatory properties. It mitigates oxidative stress by enhancing antioxidant defenses and reducing lipid peroxidation markers. Its hepatoprotective effects are linked to the reduction of inflammation, apoptosis, fibrosis, and histological damage, as well as the regulation

Table 2. Summary of *in vivo* study on GAR

Study	In vivo study model	Form	Dose and route	Effect
Jing *et al.* [2014]	LPS induced hepatic injury in D-Gal-sensitized BALB/c mice male	GAR (Sigma)	2.5, 5.0, 10 mg/kg/day dissolved in olive oil *i.p.*	↓ALT; ↓AST; ↓MDA; ↓p65(K310) of NF-κB; ↓histological alterations; ↓caspase-3, caspase-8, caspase-9
Ferriero *et al*. [2018]	CD95-antybody or α-amanitin or acetaminophen induced hepatic injury C57BL/6 mice male	GAR (Ezno Life Sciences)	20 mg/kg/day *i.p.*	↓liver damage = ↓necrotic liver areas, ↓acetylated H3, ↓apoptosis; ↑survival
Lee *et al*. [2019]	C57BL/6 mice male 13 weeks of HFD (50% energy as fat)	GAR (East Windsor)	HFD with 0.1% or 0.5% GAR *ad libitum*	↓BW; ↓TG; ↓TC; ↓ALT; LDL; ↓HDL**; ↓adipocyte size; ↓WAT; ↓ballooning; ↓steatosis; ↓INF infiltration ** only 0,5%
Majeed *et al*. [2020b]	C57/BL6 mice 16 weeks of HFD (50 kcal/day)	Livinol™, stand. for 20% w/w of GAR	Livinol: 5, 10, 20, and 40 mg/kg/day = GAR: 1, 2, 4, and 8 mg/kg/day with HFD	↓BW; ↓adipocyte size; ↓visceral fat accumulation; ↓TG; ↓TC; ↓LDL; ↓VLDL; ↑HDL; ↓Glc; ↓ALT; ↓AST; ↓transcription of PPARγ, c/EBPα, AP2, FAS; ↑UPC1, PGC1α, PRDM16, BMP17; ↑phos. AMPK; ↓ER stress (XBP-1, GRp78, ATF6)
Barve [2021]	C57/BL6 mice male 15-22 g 16 weeks of WD	GAR (Cayman Chemical Company)	25, 50, and 100 mg/kg/day with western diet	↓BW; ↑HDL; ↓TG; ↓TC; ↓LDL; ↓AIP, CRR, AC; ↓IL-6; ↓MDA; ↑GSH; ↑CAT; ↑SOD
Basumatary *et al*. [2024]	C57BL/6 mice male 12 weeks of HFD (45% energy as fat)	GAR (Sigma)	50, 100, 150 mg/kg/day with HFD	↓BW; ↓Glc; ↓OGTT; ↓TG; ↓TC; ↓LDL; ↓ALT; ↓AST; ↓INS; ↓expression of Pck1, Acc1, Acc2, FAS; ↓intercellular gaps; ↑expression of occludin, claudins, zonula occludens-1
Li *et al*. [2025]	Induced diabetic C57BL/6 mice male	GAR (MedChem Express)	Dermal application around created wound	↓PI3K/Akt/NF-κB pathway

AC - atherogenic coefficient; Acc1 - Acetyl-CoA Carboxylase 1; Acc2 - Acetyl-CoA Carboxylase 2;Acetylated H3 - Acetylated Histone H3; AIP - atherogenic index of plasma; ALT - alanine transaminase; AP2 - Adipocyte Protein 2; AST - aspartate transaminase; ATF6 - Activating Transcription Factor 6; BMP17 - Bone Morphogenetic Protein 17; BW - body weight; caspase 3 - cysteine-aspartic acid protease 3; caspase 8 - cysteine-aspartic acid protease 8; caspase 9 - cysteine-aspartic acid protease 9; CAT - catalase; C/EBPα - CCAAT/Enhancer-Binding Protein A; CRR - cardiac risk ratio; D-Gal - D-galactosamine; ER - endoplasmic reticulum; FAS - fatty acid synthase; GAR – garcinol; GRP78 - Glucose-Regulated Protein 78; GSH - glutathione; Glc - Glucose level; HDL - high-density lipoprotein; HFD - high-fat diet; IL-6 - inerleukin-6; INF - inflammatory; INS - insulin level; i.p. - intraperitoneal; LDL - low-density lipoprotein; LPS - lipopolysaccharide; MDA - malondialdehyde; OGGT - oral glucose tolerance test; SGOT - serum glutamic-oxaloacetic; p65(K310) of NF-κB - Nuclear Factor Kappa B p65 subunit acetylated at lysine 310; Pck1 - Phosphoenolpyruvate Carboxykinase 1; PGC1α - Peroxisome Proliferator-Activated Receptor Γ Coactivator 1 A; Phos. AMPK - Phosphorylated AMP-Activated Protein Kinase; PPARγ - peroxisome proliferator-activated receptor γ; PRDM16 - PR Domain Containing 16; SGPT - serum pyruvic transaminase; SOD - superoxide dismutase; TG - triglycerides; TC- total cholesterol; UCP1 - Uncoupling Protein 1; WAT - white adipose tissue; WD - western diet (21% milk powder, 34% sucrose, 0.2% cholesterol, 20% vanaspati ghee, 10% pork) XBP-1 - X-Box Binding Protein 1.

of lipid metabolism, including lowering TC, TG, and LDL levels and improving atherogenic indices. Additionally, GAR supports hepatic function and strengthens liver barrier integrity by upregulating tight junction proteins. It also alleviates ER stress and promotes adipocyte browning, suggesting a potential role in metabolic regulation and obesity prevention.

Since GAR combined with curcuminoids has shown beneficial effects, it raises the question of whether other combinations could also provide hepatoprotective properties. Given its multifaceted effects in MASLD AX, which is regarded as the best antioxidant among carotenoid could be a promising candidate for such a combination [Radice *et al*. 2021].

Astaxanthin (AX). AX is a xanthophyll carotenoid with a purplish-red color that is widely found in microorganisms and marine organisms, including prawns, crabs, salmon, and the green microalga *Haematococcus pluvialis*. Among these, *H. pluvialis*, a freshwater species belonging to the *Chlamydomonadaceae* family, is recognized as the primary natural source of AX [Nguyen-Le *et al.* 2023]. Its molar mass is 596,841 g/mol, and its chemical structure is 3,3′-dihydroxy-4,4′-diketo-β,β′-carotene (Fig. 2).

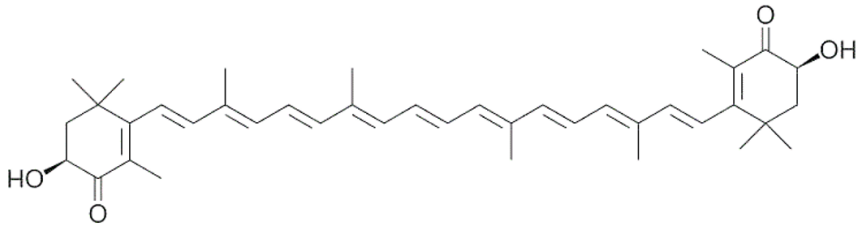

Fig. 2. Chemical structure of astaxanthin.

AX enhances cellular permeability, allowing it to effectively neutralize ROS and free radicals [Cicero *et al*. 2018, Nishida *et al*. 2023]. Due to its exceptional antioxidant potency, AX is estimated to be 500 times stronger than vitamin E, 100 times more effective than α-tocopherol, and 10 times more active than other carotenoids, such as lutein, β-carotene, and zeaxanthin [Chen and Kotani 2016].

AX exhibits a distinct metabolic pathway compared to other carotenoids. It is absorbed in the intestinal mucosa via passive diffusion and transported to the liver through both the lymphatic and circulatory systems, enclosed in chylomicrons. A key distinction between AX and other carotenoids lies in their lipoprotein transport mechanisms after hepatic metabolism. While most carotenoids are predominantly carried in LDL, AX is evenly distributed between LDL and HDL, suggesting a potentially broader role in lipid metabolism and antioxidant defense [Radice *et al*. 2021].

AX has been the subject of numerous *in vivo* studies investigating its hepatoprotective properties. In an *in vivo* study, C57BL/6J mice fed an HFD supplemented with 0.03% of AX for 12 weeks exhibited lower plasma TG, and AST

levels compared to the control group. Additionally, the expression of genes involved in lipogenesis, fatty acid β-oxidation, cholesterol metabolism, and antioxidant defense was measured. A significant increase in the mRNA abundance of lipogenic genes, such as FAS and diglyceride acyltransferase 2 was observed in AX-supplemented mice. Moreover, AX supplementation led to a notable upregulation of acyl-CoA oxidase 1, a key enzyme in the peroxisomal fatty acid β-oxidation. Moreover, genes involved in cholesterol metabolism, such as 3-hydroxy-3-methylglutaryl-CoA reductase and low-density lipoprotein receptor, were significantly upregulated in AX-supplemented mice. Furthermore, the expression of transforming growth factor-β1 (TGF-β1), a potent profibrogenic cytokine, was significantly increased in AX-treated mice. In addition, AX upregulated the expression of key antioxidant genes, including NRF-2, glutamate-cysteine ligase modifier subunit, SOD-1, and GPx-1, suggesting enhanced hepatic antioxidant capacity. Notably, IL-6 expression was also elevated, suggesting a potential role of AX in modulating inflammatory responses [Yang *et al*. 2014].

Jia *et al*. [2016] supplemented male C57BL/6J mice fed a high-fat diet (45% fat) with 6 and 30 mg/kg/ day of AX for 8 weeks. The results demonstrated that AX reduced TG level in both plasma and liver as well as hepatic steatosis, epididymal WAT mass, and adipocyte size. These effects were mediated through activation of peroxisome proliferator-activated receptor α (PPARα), a key regulator of fatty acid oxidation, and inhibition of PPARγ, which promotes adipogenesis, leading to enhanced fatty acid oxidation and hepatic autophagy. Additionally, AX upregulated the expression of acyl-CoA oxidase 1 and carnitine palmitoyltransferase 1, which facilitate mitochondrial uptake of long-chain fatty acids for β-oxidation. It also increased lipoprotein lipase, responsible for hydrolyzing triglycerides in lipoproteins and promoting fatty acid uptake, as well as uncoupling protein 2, a mitochondrial protein that limits fat accumulation. AX also led to the downregulation of pro-inflammatory cytokines, including TNF-α and IL-6. Additionally, AX modulated liver X receptor α, a nuclear receptor involved in cholesterol and lipid metabolism, and decreased phosphorylation of SREBP-1, a transcription factor that regulates fatty acid and triglyceride synthesis, further contributing to lipid homeostasis [Jia *et al.* 2016].

In another study using a similar in vivo model, AX supplementation at 0.25%, 0.5%, and 0.75% dose-dependently reduced lipid droplet formation, and lowered TG, AST, eWAT, and adipocyte size, as reported in previously cited study. AX also attenuated TC, LDL and body weight. Furthermore, AX increased not only SOD, but also GSH, CAT, and total antioxidant capacity. Additionally AX decreased malondialdehyde MDA levels, a marker of lipid peroxidation [Wang *et al*. 2022]. Another study examined the effects of oral AX supplementation at 30 mg/kg in female Swiss mice fed an HFD (60% fat) for 16 weeks, followed by an eight-week withdrawal period. The results demonstrated that despite a significant increase in body weight, AX decreased TC, TG, LDL, and AST levels, as well as attenuated hepatic steatosis and decreased the lipid droplets ratio, similar to previously cited studies, in which no weight gain was observed [Nguyen-Le *et al.* 2023].

Yang *et al.* [2021] demonstrated that AX supplementation at 80 mg/kg/day in C57BL/6 mice fed an HFD for 6 weeks effectively mitigated the progression of MASH and liver fibrosis by regulating hepatic immune responses, inflammation, and oxidative stress. AX treatment reduced monocyte-derived macrophage infiltration in the liver, suppressed hepatic stellate cell activation, and diminished oxidative stress and hepatocyte death. These effects were accompanied by a downregulation of hepatic pro-inflammatory cytokine gene expression, including TNF-α, TGF-β1, and interleukin-1β (IL-1β). Moreover, AX supplementation decreased the expression of fibrotic markers such as collagen type I α1, type IV α1, and α-smooth muscle actin, indicating its potential role in preventing liver fibrosis [Yang *et al.* 2021].

The influence of AX on hepatic mRNA expression of macrophage polarization and fibrosis markers was also observed in another study after 18 weeks of supplementation at 0.015% in diet in male C57BL/6 mice fed a high-fat, high-sucrose, and choline-deficient diet with 2% of cholesterol. AX treatment shifted macrophage polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype. This immunomodulatory effect was accompanied by a reduction in liver fibrosis markers, including collagen type I α1, lumican, and tenascin C, as well as decreased expression of TGF-β1. These molecular changes coincided with a reduction in plasma TC, TG, and glucose levels [Kim *et al.* 2017].

In another in vivo study, AX administration alleviated hepatic damage through the regulation of lipid metabolism, fibrosis, and inflammation, similar to previous findings. However, in contrast to some earlier studies, this research also demonstrated that AX significantly reduced hepatocyte apoptosis, as evidenced by the downregulation of Bcl-2-Associated X Protein and caspase-9 expression. Additionally, AX supplementation suppressed FFA-induced injury in hepatocytes and increased lipid efflux, lipid degradation, and fatty acid oxidation, suggesting enhanced lipid turnover. Furthermore, similar to previous studies, AX lowered serum TG, ALT, AST levels, while reducing hepatic steatosis, adipocyte size, and inflammatory cell infiltration. Additionally, it downregulated inflammatory markers such as TNF-α and IL-1β. Importantly, this study identified a novel mechanism of AX action by upregulating fibroblast growth factor 21 and PPARγ coactivator-1 α, which are key regulators of mitochondrial function and energy metabolism. This mitochondrial effect was associated with the reduction of inducible nitric oxide synthase expression, which plays a role in oxidative stress and inflammation [Wu *et al.* 2020].

It was also observed that AX decreased the number of TUNEL-positive cells, indicative of apoptotic cells identified by DNA fragmentation, as well as F4/80-positive cells, a marker for macrophage infiltration, and 4-HNE-positive cells, which reflect lipid peroxidation and oxidative stress. Additionally, in contrast to previous studies that focused on diet-induced liver damage, this study examined the effects of AX in a model of ischemia-reperfusion injury in mice fed a methionine- and choline-deficient high-fat diet. AX supplementation at 5 mg/kg, administered three times within 48

hours, 24 hours, and 40 minutes before ischemia-reperfusion injury, significantly lowered serum ALT and AST levels, indicating its hepatoprotective role. Similar to previous findings, AX downregulated the expression of inflammatory cytokines, including TNF-α and IL-1β, while enhancing antioxidant defense mechanisms. Specifically, AX increased heme oxygenase-1, hypoxia-inducible factor 1-α, and NrF-2, key regulators of oxidative stress response. Furthermore, AX treatment reduced ROS levels in Kupffer cells and enhanced phosphorylation of AKT and mTOR, suggesting a role in promoting cell survival and reducing apoptosis [Li *et al*. 2017].

AX has also been studied in combination with other compounds. In in vivo study, the combined effects of flaxseed oil (FO) and AX on hepatic lipid metabolism and oxidative stress were evaluated in male Sprague-Dawley rats fed a 20% fat diet. Similar to findings for AX alone, this combination significantly reduced hepatic steatosis, TG, and TC levels. Notably, FO + AX supplementation downregulated the expression of SREBP-1 and 3-hydroxy-3-methylglutaryl-CoA reductase, consistent with results observed for AX alone. Additionally, the combination enhanced the activation of PPARα, similarly to what was reported for AX alone. Beyond lipid regulation, FO + AX also inhibited FAS and acetyl-CoA carboxylase, while upregulating carnitine palmoitoyltransferase 1 and acyl-CoA oxidase 1 further reinforcing its role in promoting β-oxidation. Additionally, this combination enhanced hepatic antioxidant defenses, as evidenced by increased activity of SOD, CAT, GPx, and GSH levels, similar as AX alone [Xu *et al*. 2017].

Another study examined the effects of AX and vitamin E. Both compounds effectively enhanced the expression of genes linked to eukaryotic initiation factor-2α signaling, which is typically suppressed in MASH due to ER stress in the liver. Additionally, AX was predicted to inhibit the activity of ligand-dependent nuclear receptors, specifically PPARα and PPARδ, thereby influencing associated molecular pathways. However, unlike vitamin E, AX did not enhance the expression of genes involved in mitochondrial function [Kobori *et al.* 2017].

The effects of AX were compared with vitamin E in a study investigating its potential in the prevention and treatment of diet-induced MASH in mice. Both AX and vitamin E improved hepatic steatosis and plasma TG, TC, and non-esterified fatty acids levels. However, AX demonstrated more pronounced effects in reducing hepatic steatosis, improving glucose tolerance, and increasing insulin sensitivity. While both compounds had an impact on lipid metabolism, AX was more effective in modulating immune responses, shifting macrophage polarization from the pro-inflammatory M1 type to the anti-inflammatory M2 type, and reducing liver inflammation. Furthermore, AX showed greater effectiveness in downregulating fibrotic markers, including TGF-β1 and collagen type I α1. AX exhibited more significant results in regulating SREBP1c, Liver X receptor α, and fibrosis-related markers [Ni *et al*. 2015].

Based on the cited *in vivo* studies (Tab. 3), it may be concluded, that AX exerts hepatoprotective effects by reducing oxidative stress, inflammation, and fibrosis while supporting lipid metabolism. It enhances the antioxidant defense system,

Table 3.Summary of *in vivo* study on AX

Study	*In vivo* model	Dose & route	Effect
Yang *et al*. [2014]	C57BL/6J mice, HFD (35% fat), 12 wks	0.003, 0.01 or 0.03 % AX in HFD	In 0.03% AX: ↑eWAT; ↓plasma TG, AST; ↑FAS, ↑DGAT-2; ↑ACOX-1;↑HMGR; ↑LDLR; ↑TGFβ1; ↑NRF-2; ↑SOD-1; ↑GCLm; ↑GPx-1; ↓IL-6;
Ni *et al*. [2015]	C57BL/6J mice, CL or NC diet, 12 wks	0.0067% or 0.02% AX in CL diet; 0.0067% or 0.02% AX in NC	↓steatosis; ↓plasma: TG, TC, NEFA ,ALT, AST; ↓hepatic: TG, TC, NEFA; ↓TBARS; ↑FAT; ↑Glc tolerance; ↑insulin sensitivity; ↓F4/80+ cells; ↓fibrosis; ↓HDXprol.; ↓M1-type; ↑M2-type; ↓T-cells;↓SREBP1c; ↓ LXRα; ↓ChREBP; ↓FAS, ↓SCD1; ↓IL-6, ↓TNFα, ↓IL-1β; ↓TGFβ1, ↓COL1α1, ↓PAI-1;
Jia *et al*. [2016]	C57BL/6J mice, male, HFD (45% fat), 8 wks	6, 30 mg/kg/day AX with HFD	↓steatosis; ↓plasma & hepatic TG; ↓Kupffer cells; ↓macrophage; ↓eWAT; ↓adipocyte size; ↑HDL; ↑PPARα; ↓PPARγ; ↑ACOX-1; ↑CPT-1; ↑LPL; ↑UCP2; ↑LXRα; ↓phos.of SREBP-1; ↑autophagy; ↓plasma & liver TNFα, IL-6;
Li *et al*. [2017]	C57BL/6 mice, MCDHFD	5mg/kg AX 3x for 48 h, 24 h and 40 min. before IRI	↓TUNEL-positive cells; ↓F4/80-positive cells; ↓ALT; ↓AST; ↓ 4-HNE-positive cells; ↓TNFα; ↓IL-1β; ↑HO-1; ↑HIF-1α; ↓ROS in Kupffer cells; ↑ phos. of AKT, mTOR; ↑NRF-2; ↓apoptosis
Kim *et al*. [2017]	C57BL/6 mice, male, HFHS2CD, 18 wks	0.015% AX with diet	↓markers of M1-type; ↑markers M2-type; ↓ F4/80; ↓CD68; ↓TGFβ1; ↓COL1α1;↓ LUM; ↓TNC; ↓TNFα
Kobori *et al*. [2017]	C57BL/6J mice, male, CL diet, 12 wks	0.02% AX in CL diet	↑EIF2α; ↓PPARα; ↓PPARδ
Xu *et al*. [2017]	Male Sprague-Dawley rats, (20% fat diet)	1 g/kg FO + AX - 25, 50, 100% fat	↓steatosis; ↓hepatic TG, TC; ↓SREBP1; ↓HMGR; ↑PPARα; ↓FAS; ↓ACC; ↑ ACOX-1; ↑CPT-1; ↑hepatic SOD, CAT, GPx, GSH; ↓TBRAS
Wu *et al*. [2020]	C57 mice, male, HFD, 10 wks	10, 30, 60 mg/kg/day AX every 2 days by gavage	↓BW; ↓serum TG, ALT, AST; ↓ballooning; ↓infiltration of inflammatory cells; ↓TUNEL-positive cells; ↓steatosis; ↓adipocyte size; ↓TNF-α; ↓IL-1β; ↓iNOS; ↑ PPARα; ↓Bax; ↓caspase 9; ↓COL1α1; ↓TGFβ1; ↑lipid efflux; ↑lipid degradation; ↑fatty oxidation; ↓FFA, Chol. synthesis; ↓SREBP1; ↑FGF21; ↑PGC-1α
Yang *et al*. [2021]	C57BL/6 mice, HFD, 6 wks.	80 mg/kg/day AX with HFD	↓hepatic infiltration; ↓COL1α1, COL4 α1, α-SMA; ↓HSC activation; ↓oxidative stress ↓hepatocyte death; ↓hepatic gene expression of TNF-α, TGF-β1, IL-1β
Wang *et al*. [2022]	C57BL/6 mice, male, HFD, 9 wks	0.25%, 0.5%, 0.75% AX with HFD	↓BW; ↓eWAT; ↓TC; ↓TG; ↓LDL; ↓AST; ↓MDA; ↑GSH; ↑CAT; ↑SOD; ↑T-AOC; ↓lipid droplets ratio; ↓adipocyte size; ↓steatosis
Nguyen-Le *et al*. [2023]	Female Swiss mice, HFD (60% fat), 16 wks	30 mg/kg/day AX with HFD	↑BW; ↓TC; ↓TG; ↓LDL; ↓AST; ↓steatosis; ↓lipid droplets ratio

α-SMA - α-smooth muscle actin; ACC - acetyl-CoA carboxylase; ACOX-1 - acyl-CoA oxidase 1; ALT - alanine transaminase; AST - aspartate transaminase; AX - astaxanthin; Bax - Bcl-2-associated X protein; BW - body weight; CAT - catalase; Caspase 9 - cysteine-aspartic acid protease 9; CD68 - cluster of differentiation 68; Chol. - cholesterol; ChREBP - Carbohydrate response element-binding protein; CL - high-cholesterol, high-cholate, and high-fat; COL1α1 - collagen type I α 1 chain; COL4α1 - collagen type IV α 1 chain; CPT-1 - carnitine palmoitoyltransferase 1; DGAT-2 - diglyceride acyltransferase 2; EIF2α - eukaryotic initiation factor-2; eWAT - epididymal adipose tissue; FAT - fatty acid translocase; FAS - fatty acid synthase; FFA - free fatty acids; FGF21 - fibroblast growth factor 21; FO - flaxseed oil; GCLm - glutamate-cysteine ligase, modifier subunit; Glc - glucose; GPx - glutathione peroxidase; GSH - glutathione; HDL - high-density lipoprotein; HDXprol - hydroxyproline; HFD - high-fat diet; HFHS2CD - 35% fat and 35% sucrose + 2% cholesterol; HIF-1α - hypoxia-inducible factor 1-α; HO-1 - heme oxygenase-1; HMGR - 3-hydroxy-3-methylglutaryl-CoA reductase; HSC - hepatic stellate cell; IL-1β - interleukin-1 β; IL-6 - interleukin-6; iNOS - inducible nitric oxide synthase; INF - inflammation; IRI - ischemia-reperfusion injury; LDL - low-density lipoprotein; LDLR - LDL receptor; LPL - lipoprotein lipase; LUM - lumican; LXRα - Liver X receptor α; M1-type - macrophages type-1; M2-type - macrophages type-2; MCDHFD - methionine, choline-deficient and high-fat diet; MDA - malondialdehyde; NC - normal chow; NEFA - non-esterified fatty acid; NRF-2 - nuclear factor erythroid 2-related factor 2; PAI-1 - plasminogen activator inhibitor-1; PGC-1α - peroxisome proliferator-activated receptor γ coactivator 1-α; phos. - phosphorylation; PPARα/γ - peroxisome proliferator-activated receptor α/γ; ROS - reactive oxygen species; SCD1 - Stearoyl-CoA desaturase; SOD - superoxide dismutase; SREBP1c - sterol regulatory element-binding proteins 1c; T-AOC - total antioxidant capacity; TBARS - thiobarbituric acid reactive substrates; TC - total cholesterol; TG - triglycerides; TGF-β1 - transforming growth factor β 1; TNC - tenascin-C; TNFα - tumor necrosis factor α; UCP2 - uncoupling protein 2.

mitigates inflammatory responses, and regulates immune cell activity. Additionally, AX modulates lipid homeostasis by promoting fatty acid oxidation and improving cholesterol metabolism. Its antifibrotic properties help prevent liver fibrosis by limiting extracellular matrix deposition and hepatic stellate cell activation. These combined effects suggest that AX may contribute to liver health and metabolic regulation.

In conclusion, both GAR and AX exhibit anti-inflammatory, antioxidant, and lipid-regulating properties, which may contribute to liver health. Given their complementary mechanisms of action, it can be hypothesized that their combination may provide enhanced benefits in liver protection and metabolic health. Further studies are needed to explore their potential synergistic effects.

Conflict of interest: The authors declare no conflict of interest.

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