

# Astaxanthin in Liver Health and Disease: A Potential Therapeutic Agent

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**Abstract:** Astaxanthin is a carotenoid derived from oxygen-containing non-vitamin A sources and is mainly obtained from marine organisms. Studies have demonstrated that astaxanthin is a natural antioxidant product and it is widely used in the fields of medicine, health-care products and cosmetics. Studies have shown that astaxanthin has important preventive and therapeutic effects on liver fibrosis, non-alcoholic fatty liver, liver cancer, drug and ischemia-induced liver injury, and its mechanism is related to antioxidant and anti-inflammatory activities, and the regulation of multiple signaling pathways. In this review, we discuss the latest data on astaxanthin in the prevention and treatment of liver diseases. An understanding of the structure, source and mechanism of action of astaxanthin in the body would not only provide a theoretical basis for its clinical application but could also have important significance in screening and improving related compounds for the treatment of liver diseases.

**Keywords:** astaxanthin, liver diseases, antioxidants, inflammation, anticancer

## Introduction

Astaxanthin (3, 3'-dihydroxy- $\beta$ ,  $\beta'$ -carotene-4, 4'-dione, ASX) is a non-vitamin A pro-carotenoid, and has attracted considerable attention from the scientific community due to its antioxidant effect which is 10 times higher than that of  $\beta$ -carotene and 100 times stronger than that of vitamin E.<sup>1</sup> Astaxanthin exists widely in nature, mainly in the form of fatty acid esters. Numerous studies have shown that astaxanthin has many biological activities, such as antioxidant, anti-aging, and anti-cancer effects, immunity enhancement, free radical scavenging and it plays an active role in human nutrition and health.<sup>2-4</sup>

## Sources of Astaxanthin

Astaxanthin is produced in two ways: chemical synthesis and biological extraction. Chemical synthesis refers to the preparation of astaxanthin from carotene. Although the synthetic products were cheaper, it is less stable, less absorbable and less safe than natural astaxanthin and has not been legal used in the human diet by the FDA regulation.<sup>5-7</sup> Abundant seawater resources produce high-yield marine animals and plants, which provide favorable conditions for the extraction of astaxanthin.<sup>8</sup> On the one hand, astaxanthin can be extracted and recovered from aquatic wastes by enzymatic hydrolysis and the acid-base method, which can not only increase economic benefits, but also reduce environmental pollution, and realize low-carbon and efficient utilization of marine by-products. However, the cost of extraction is high, which is

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unsuitable for large-scale production. On the other hand, yeasts including *Phaffia rhodozyma*, *Rhodotorula glutinosa*, *Rhodotorula cerevisiae* and *Rhodotorula oceanica* produce astaxanthin. Colonies of *Phaffia rhodozyma* are red due to the production of carotenoids such as astaxanthin, and the average content of astaxanthin is 0.40%.<sup>9,10</sup> It is noteworthy that many types of marine algae can synthesize astaxanthin, such as snow algae, chlamydia, naked algae, and cyanobacteria. The highest yield was obtained from *Haematococcus pluvialis*, which can reach 1.5–3.0%. The accumulation rate and total production in this species are higher than those in other green algae, and it is recognized as the best biological source of natural astaxanthin.<sup>11,12</sup>

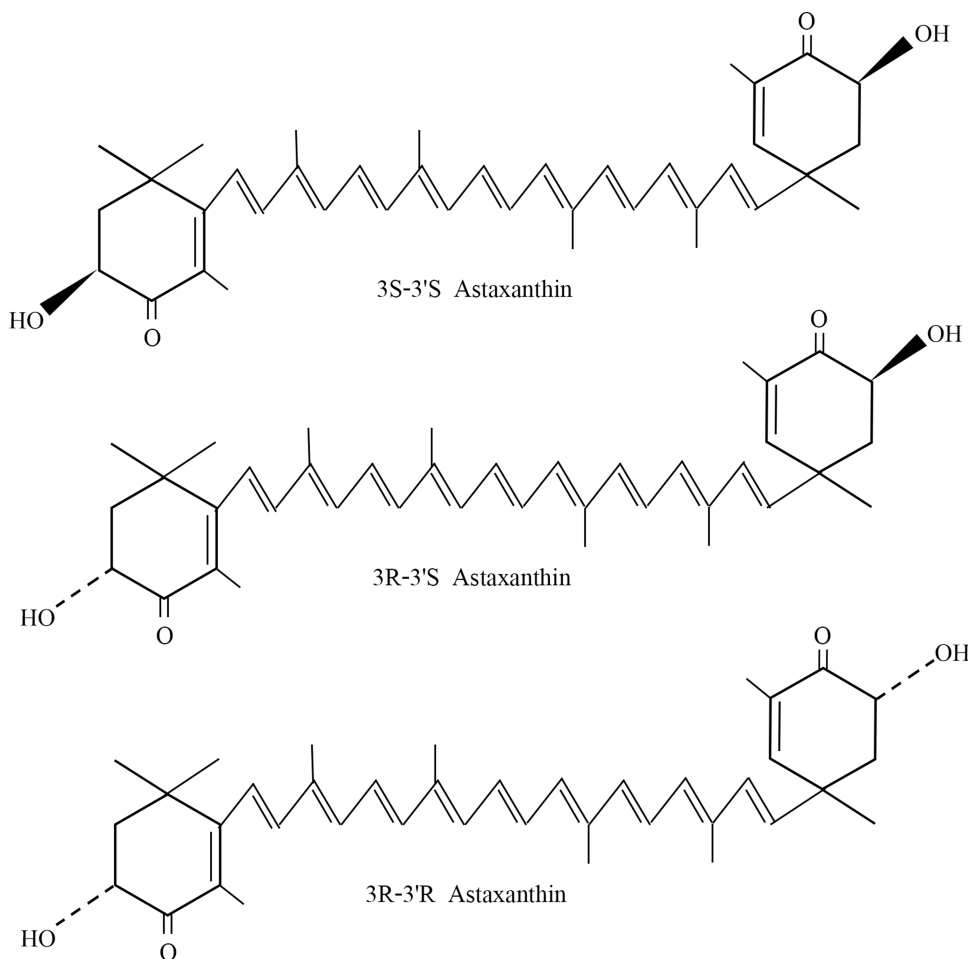
### Structure of Astaxanthin

The molecular formula of astaxanthin is  $C_{40}H_{52}O_4$ . Its melting point is approximately 224°C and it is insoluble in water. Astaxanthin is fat soluble and is soluble in most organic solvents such as chloroform, acetone, ethanol and ether.<sup>13</sup>

The chemical structure of astaxanthin is a six-membered ring consisting of four isoprene units linked by conjugated double bonds and two isoprene units at both ends. This double bond structure determines its color and biological function due to its absorptivity. Astaxanthin can produce three optical isomers (3S, 3'S, 3R, 3'R and 3R, 3'R) due to the presence of two chiral carbon atoms (R or S conformations). Natural astaxanthin exists mainly in the form of 3S, 3'S or 3R, 3'R in organisms (Figure 1). In addition, there is a hydroxyl group in the end ring structure, which can form esters with fatty acids; thus, enabling the natural extract of astaxanthin to have stronger antioxidant activity.<sup>14</sup>

### Biological Safety of Astaxanthin

Astaxanthin is widely used in various fields due to its many biological activities; thus, its safety is a concern. As early as 1997, astaxanthin was proved to be non-genotoxic.<sup>15</sup> In subsequent studies, Stewart and colleagues confirmed that the highest dose of 6000 mg/kg/d did not



**Figure 1** Three stereoisomers of astaxanthin.

lead to acute death in rats.<sup>16</sup> Katsumata and Vega found no observed adverse effect for astaxanthin was at least 1000 mg/kg/d for 13 weeks in rats.<sup>17,18</sup> Edwards et al analyzed clinical experimental data, summarized the genetic toxicity of astaxanthin and its carcinogenicity in rats, and showed no carcinogenicity in the rat life cycle.<sup>19</sup> In addition, there are several studies that prove that astaxanthin is liposoluble. Although it can cause pigmentation of animal skin, astaxanthin of over treatment concentration has no adverse effect on platelet, coagulation and fibrinolysis.<sup>20,21</sup> In 2009, Satoh conducted a safety study of astaxanthin in 127 adults taking 20 mg astaxanthin daily for 4 weeks, and found no organ damage.<sup>22</sup> In addition, different concentrations of astaxanthin also improved the blood lipid level and skin condition of healthy people, but no significant side effects were found.<sup>23–25</sup> The above results indicate that astaxanthin is safe with no genetic toxicity or carcinogenicity observed in acute and chronic experiments.

## Pharmacokinetics of Astaxanthin

Whether astaxanthin can exert its biological activity after ingestion depends on its absorption rate, which may be related to its existing form and the level of enzymes in the gastrointestinal tract.<sup>26</sup> Ranga and Parker believe that adding lipid to the diet can improve the bioavailability of astaxanthin.<sup>7,27</sup> The peak value of astaxanthin in blood taken 30 minutes after a meal is 2.4–3.0 times higher than that taken before a meal, which may be due to stimulation of liver bile secretion and cholesterol lipase after oral administration, which accelerates the hydrolysis and absorption of astaxanthin ester. Fukami and colleagues synthesized astaxanthin monoester and diester for administration in a rat model. The results showed that the bioavailability of astaxanthin monoester was higher than that of the diester, and the maximum metabolic concentration of astaxanthin monoester in the liver was three times as high as that in serum.<sup>28</sup> The above results show that composition of the fatty acid chain of astaxanthin is closely related to its bioavailability, but this specific relationship requires further clarification.

## Biological Activity of Astaxanthin

Studies have shown that most carotenes have anti-aging, free radical scavenging, antioxidant and anti-cancer effects, and have been widely used in the fields of medicine, food, cosmetics and feed.<sup>1,29</sup> Astaxanthin is an effective natural antioxidant and has shown excellent biological

functions in many fields of life science.<sup>6</sup> Firstly, astaxanthin is the only carotenoid to penetrate the blood-brain and retinal barriers. It is frequently used as an antioxidant to treat brain injury and cardiovascular diseases, and has been extensively studied in clinical practice.<sup>4,30</sup> In addition, astaxanthin has shown anti-cancer effects in many cancers, including liver cancer, colon cancer, bladder cancer, oral cancer and leukemia.<sup>3,31–33</sup> In addition, many animal experiments have proved that astaxanthin plays an important role in regulating sugar metabolism, improving immunity and improving motor function<sup>5</sup> (Figure 2). As the largest digestive gland in the human body, the liver not only undertakes the metabolism and transformation of nutrients in the body, but also participates in the defense and immunity of the body, coagulation factor synthesis and other physiological processes. The effects and mechanisms of astaxanthin on liver diseases, such as non-alcoholic fatty liver disease (NAFLD), liver fibrosis, hepatitis and hepatocellular carcinoma, are summarized.

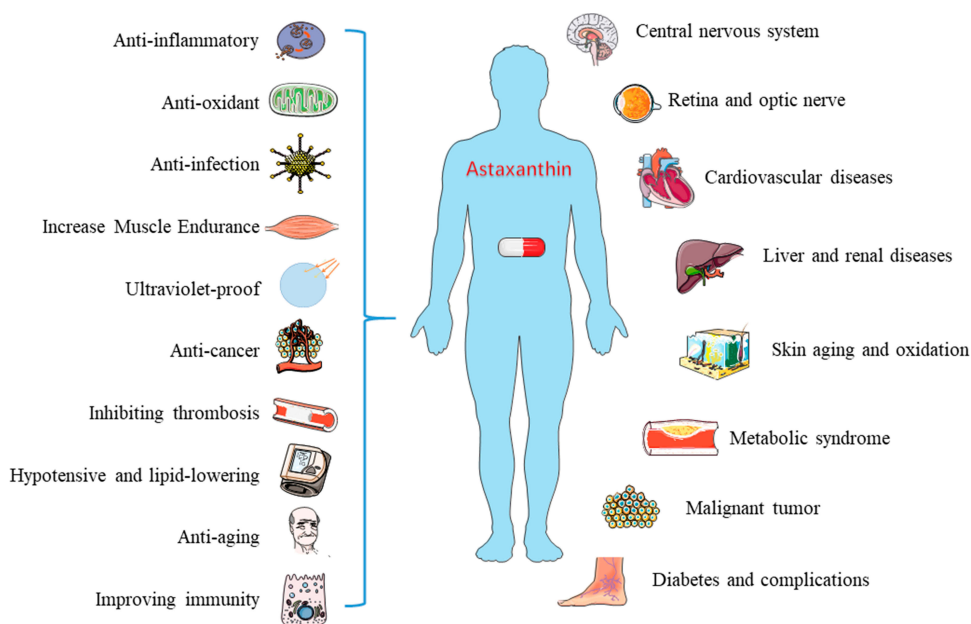
## The Role of Astaxanthin in Liver Diseases

Astaxanthin has been used in the prevention and treatment of a variety of systemic diseases in vivo due to its various biological activities. In recent years, researchers have confirmed that astaxanthin plays an important role in preventing acute liver injury, alleviating insulin resistance and NAFLD, liver fibrosis and liver cancer.<sup>34</sup>

### Liver Fibrosis

Liver fibrosis is a key link in the deterioration of chronic liver diseases such as viral hepatitis and fatty liver. Without effective intervention, 75–80% of these diseases can develop into cirrhosis, which seriously endangers human health.<sup>35,36</sup> The synthesis of extracellular matrix (ECM) induced by activation of hepatic stellate cells (HSCs) and the transformation of myofibroblasts (MFs) are the key factors in hepatic fibrosis. The reversibility of these factors also provides an important research target for the reversal of hepatic fibrosis. The mechanism of liver fibrosis is complex, involving the regulation of histopathology, cytology, cytokines and their molecular levels.<sup>37</sup> Studies have confirmed that astaxanthin plays an anti-fibrotic role via its antioxidant, apoptotic, lipid peroxidation and autophagy activities.

Yang et al demonstrated that astaxanthin inhibited the activation of resting HSCs and restored the resting state of



**Figure 2** Biological activity of astaxanthin and its function in relevant diseases.

activated HSCs in mice. Astaxanthin also decreased reactive oxygen species (ROS) production and increased the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), the main transcription factor in endogenous antioxidant defense.<sup>38</sup> Therefore, the protective effect of astaxanthin on hepatic fibrosis may be attributed to its enhanced antioxidant capacity. Islam and colleagues subsequently demonstrated that astaxanthin could restore the activity of catalase (CAT) and superoxide dismutase (SOD) in rats with carbon tetrachloride (CCl<sub>4</sub>)-induced liver fibrosis, and prevent liver fibrosis induced by CCL4 by inhibiting lipid peroxidation and stimulating the cell antioxidant system.<sup>39</sup>

The transforming growth factor (TGF)- $\beta$ /Smads pathway is a key pathway in the induction of ECM formation during hepatic fibrosis. Astaxanthin has been shown to inhibit ECM formation through the TGF- $\beta$ 1/Smad3 pathway in the human HSC cell line LX-2.<sup>40</sup> There are many downstream influencing factors, and apoptosis and autophagy are two programmed cell death pathways directly related to the survival status of HSCs in hepatic fibrosis. On the one hand, astaxanthin can induce apoptosis of LX-2 cells by regulating mir-29b, which mainly inhibits Bcl-2 and increases the expression levels of Bax and Caspase-3, thus playing a role in preventing liver fibrosis.<sup>41</sup> On the other hand, astaxanthin significantly improved liver fibrosis induced by CCL4 and bile duct ligation (BDL) in mice. It can also reduce the expression

of TGF- $\beta$ 1 and autophagy by inhibiting the level of nuclear factor (NF)- $\kappa$ B, which inhibits the activation of HSCs and the formation of ECM.<sup>42</sup> Its effectiveness is related to the release of energy by autophagy through lipid droplet degradation, thus providing favorable conditions for the activation of HSCs.<sup>43</sup> In addition, histone acetylation, as an epigenetic model, participates in the activation of HSCs and liver fibrosis.<sup>44</sup> The level of histone deacetylase 9 (HDAC9) in primary biliary cirrhosis of the liver was significantly higher than that in normal liver, and other liver pathologies showed high expression of HDAC9. Accordingly, Yang et al found that the level of HDAC9 in primary activated HSCs increased significantly, while HDAC9 knockout in LX-2 cells decreased the expression of the fibrosis gene induced by TGF- $\beta$ 1. It was proved that astaxanthin significantly inhibited the activation of HSCs by down-regulating the expression of HDAC9. HDAC3 and HDAC4 may also participate in the inhibition of HSCs activation by astaxanthin.<sup>45</sup>

The use of astaxanthin is often limited due to its lack of stability and water solubility. Wu and colleagues prepared Astaxanthin-Han aggregates (AHAna) by adding astaxanthin to hydrophilic hyaluronan nanoparticles (HAn) and used these aggregates in rat models of liver fibrosis with good results.<sup>46</sup> In addition, Chiu and Pan et al used liposomes to encapsulate astaxanthin, achieving improved stability.<sup>14,47</sup> In conclusion, astaxanthin has significant

anti-fibrosis effects, but the mechanism requires further investigation.

## Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) refers to a clinicopathological syndrome characterized by excessive fat deposition in hepatocytes, excluding alcohol and other specific liver-damaging factors, and mainly includes non-alcoholic steatohepatitis (NASH). NAFLD is an important metabolic syndrome, which, can increase mortality in obese and diabetic patients.<sup>48</sup> At present, the pathogenesis of NAFLD is complex, and is related to many factors, such as insulin resistance, oxidative stress, inflammatory mediators and cytokines. At present, there are no effective targeted drugs for the treatment of NAFLD, and treatment includes diet therapy and lifestyle adjustment, liver protection and lipid lowering, and insulin sensitization.<sup>49,50</sup> Astaxanthin has a wide range of effects, and may play an effective role in preventing the pathogenesis of NAFLD from many aspects.

In 2007, Ikeuchi et al studied the effect of astaxanthin supplementation on obese mice fed a high fat diet. The results showed that astaxanthin inhibited the increase in body weight and adipose tissue caused by the high fat diet. In addition, astaxanthin also reduced liver weight and liver triglyceride, plasma triglyceride and total cholesterol levels.<sup>51</sup> These results indicate that astaxanthin may play an important role in improving lipid metabolism and lays the foundation for future research on the treatment of NAFLD.

The release of inflammatory factors is crucial in the pathogenesis of NAFLD. Ni et al found that astaxanthin significantly reduced M1 macrophages and increased M2 macrophages, reduced liver recruitment of CD4<sup>+</sup> and CD8<sup>+</sup> and inhibited inflammation in NAFLD. Compared with vitamin E, astaxanthin reduced lipid accumulation, improved insulin signal transduction and inhibited pro-inflammatory signal transduction more effectively by inhibiting the activation of Jun N-terminal kinase (JNK)/p38 mitogen-activated protein kinase (MAPK) and NF- $\kappa$ B pathways.<sup>52</sup> Similarly, Kim demonstrated that astaxanthin reduced macrophage infiltration and the expression of macrophage markers in mice, inhibited inflammation and fibrosis in liver and adipose tissue, and enhanced the ability of skeletal muscle to oxidize mitochondrial fatty acids in obese mice.<sup>53</sup>

Peroxisome proliferator-activated receptors (PPARs) play an important role in the regulation of inflammation.

Activated PPAR- $\alpha$  has become a key target in NAFLD as it can improve fatty acid transport, metabolism, oxidation and inhibit liver fat accumulation. In addition, activation of PPAR- $\gamma$  can also regulate gene expression related to lipid synthesis and promote fatty acid storage.<sup>54,55</sup> Overexpression of PPAR- $\gamma$  can induce lipid accumulation in the liver. Kobori et al used DNA microarray to analyze gene expression in the liver of mice fed astaxanthin. It was found that astaxanthin inhibited PPARs. Screening drugs for liver PPARs and their related molecular functions in mice provided a new therapeutic basis for NAFLD.<sup>56</sup> Jia et al confirmed the above findings in animal models. Astaxanthin was administered orally to mice fed a high-fat diet for 8 weeks. It was found that astaxanthin improved liver lipid accumulation induced by a high-fat diet, reduced triglyceride levels in the liver, and decreased the number of inflammatory macrophages and Kupffer cells. These changes were attributed to the regulation of PPARs by astaxanthin. Astaxanthin activates PPAR- $\alpha$  and inhibits the expression of PPAR- $\gamma$  and the levels of interleukin-6 and tumor necrosis factor- $\alpha$  in the liver, inhibits inflammation and reduces fat synthesis in the liver. In addition, astaxanthin also causes autophagy of hepatocytes by inhibiting the AKT-mTOR pathway and decomposes lipid droplets stored in the liver.<sup>57</sup> Compared with N-Acetyl-L-cysteine (NAC) and vitamin C (VC), astaxanthin effectively reduced intracellular lipid deposition.<sup>58</sup>

In addition, astaxanthin also significantly inhibited the expression of fatty acid synthase and acetyl coenzyme A carboxylase, increased SOD, CAT, GPX activity and glutathione (GSH) in the liver, and significantly reduced lipid peroxidation in the liver.<sup>59</sup> Yang et al demonstrated that astaxanthin significantly reduced the accumulation of TAG in apolipoprotein E knockout mice, and increased the expression of Nrf2 and its target genes (including SOD 1 and glutathione peroxidase 1). This is very important for the endogenous antioxidant mechanism.<sup>60,61</sup> Compared with the standard NAFLD antioxidant vitamin E, astaxanthin not only inhibits the expression of lipid-producing genes but also improves the level of liver enzymes; vitamin E only reduces blood lipids.

In clinical trials, a prospective, randomized, double-blind study confirmed the effect of astaxanthin on oxidative stress in overweight and obese adults in Korea. Twenty-three adults with a body mass index >25.0 kg/m<sup>2</sup> were enrolled in this study and randomly divided into two dosage groups: astaxanthin 5 mg or 20 mg once a day for 3 weeks. The results showed that the oxidative stress

markers, malondialdehyde (MDA), isoprostane (ISP), SOD and total antioxidant capacity (TAC) were significantly improved.<sup>62</sup> In view of these beneficial effects, astaxanthin should be further evaluated as a new and promising treatment for NAFLD.

## Liver Cancer

Hepatocellular carcinoma (HCC) accounts for 70–90% of primary liver cancer, and the complex pathogenesis and genetic polymorphisms restrict the development of HCC therapy and seriously endanger human health. In recent years, although progress has been made in clinical research of HCC, the mechanism of invasion and metastasis is still not fully clear. The development of HCC is closely related to many signaling pathways, such as MAPK, PI3K/Akt/mTOR, JAK/STAT, Wnt/ $\beta$ -catenin, NrF2/ARE and VEGF.<sup>63,64</sup> Astaxanthin has been shown to play an important role in cancer prevention, inhibition of cell proliferation and metastasis, promotion of cell apoptosis and enhancement of immunity.<sup>3</sup>

As early as the 1990s, Gradelet et al discovered that astaxanthin inhibited the occurrence and development of HCC by inhibiting the binding of aflatoxin B1 (AFB1) to liver DNA and plasma albumin in the AFB1-induced hepatoma model.<sup>65</sup> In 2010, Tripathi confirmed that astaxanthin reduced the number and area of liver cancer lesions in rats by regulating the NrF2/ARE pathway in early cyclophosphamide-induced liver tumors, and played an important role in preventing the occurrence and development of liver cancer.<sup>66</sup> Song and Li proved that astaxanthin promoted mitochondrial apoptosis of CBRH-7919 mouse hepatoma cells and human LM3 and SMMC-7721 hepatoma cells in a concentration-dependent manner. The mechanism was related to JAK1/STAT3, NF- $\kappa$ B P65 and Wnt/ $\beta$ -catenin. In addition, astaxanthin may also regulate nucleoside diphosphate kinase (NPK) nm-23, which is conducive for the correct assembly of cytoskeleton and signal transfer of T protein, thus inhibiting the occurrence of liver tumors.<sup>33,67,68</sup> Consistent with the above results, Shao et al demonstrated that astaxanthin inhibited cell proliferation and promoted cell apoptosis *in vitro* and *in vivo*, and that astaxanthin mainly blocked the cell cycle in G2 phase.<sup>69</sup> Abnormal lipid metabolism is an important feature in the occurrence and development of malignant tumors and obesity is more likely to cause tumors. Fatty acid synthase, which regulates lipid metabolism, has been demonstrated to be elevated in a variety of cancer models.<sup>70</sup> Ohno et al studied the fatty acid synthase

(FASN) regulation of astaxanthin in a mouse model. It was found that astaxanthin improved the level of serum adiponectin and significantly reduced reactive oxygen metabolites/biological antioxidant potential ratio, thus playing a role in liver tumors of obese individuals.<sup>71</sup>

As mentioned above, animal experiments have demonstrated the preventive and therapeutic effects of astaxanthin on many types of tumors, and its mechanism has been investigated. It has been found that astaxanthin may be related to a variety of signaling pathways, but its specific mechanism is still unclear and requires further study.

## Alcoholic Liver Disease

Liver is the main organ in drug metabolism, and some drugs are metabolized only in hepatocytes. Therefore, the intake of toxic substances can easily lead to accumulation and damage of hepatocytes. Alcoholic hepatitis is mainly caused by direct or indirect inflammation, oxidative stress, enterogenous endotoxin, inflammatory mediators and nutritional imbalance during the metabolism of ethanol and its derivatives.<sup>72,73</sup> Studies have shown that astaxanthin can alleviate liver steatosis and inflammation caused by ethanol.<sup>74</sup> In addition, the levels of ROS, pro-inflammatory proteins and related inflammatory factors were also significantly decreased in liver tissue in the drug group, which may be related to negative phosphorylation of STAT3.<sup>75</sup> Besides inhibiting oxidative stress and inflammation to prevent alcohol-induced liver damage, astaxanthin can also regulate intestinal flora and may play a potential therapeutic role in alcoholic liver disease-induced bacterial diseases.<sup>76</sup> Similarly, liposomal encapsulation of astaxanthin exerted rapid and direct effects against repeated alcohol-induced liver disease and could boost recovery from liver injuries caused by long-term alcohol intake.<sup>77</sup>

## Drug-Induced Liver Injury

Astaxanthin has also been shown to be effective in other drug-induced liver injury. Turkez demonstrated in cell and animal models that astaxanthin significantly reduced liver injury induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and significantly increased the activity of inhibited antioxidant enzymes.<sup>78,79</sup> In addition, by inhibiting the expression of inflammatory factors such as TNF- $\alpha$  and ROS production, liver injury induced by paracetamol (APAP), concanavalin A (ConA) and lipopolysaccharide (LPS) can be alleviated. The main mechanism of this

**Table I** Summary of Astaxanthin in Liver Diseases

Diseases	Model	Dosage	Duration	Effects	References
Liver Fibrosis	Primary HSCs	25 $\mu$ M	2–4 d	Anti-oxidation	[33]
	Rats	10 mg/kg	2 w	Anti-oxidation	[34]
	Primary HSCs	25 $\mu$ M	12 h 24 h	TGF- $\beta$ /Smads	[35]
	LX-2 cells			ECM formation	
	LX-2 cells	10–40 $\mu$ M	24 h 48 h	Pro-Apoptosis	[36]
	Mice	20–80 mg/kg	8 w	TGF- $\beta$ /Smads Autophagy	[37]
NAFLD	Primary HSCs	25 $\mu$ M	24 h	TGF $\beta$ 1/Smads	[40]
	LX-2 cells			HDAC9	
	Mice	0.02%	10 w	Anti-inflammatory	[46]
	Primary hepatocytes	25–100 $\mu$ M	16 h		
	Mice	0.03%	15–30 w	Anti-inflammatory	[47]
	HepG2 HEK293	6–30 $\mu$ M	12 h	Anti-inflammatory	[51]
	Mice	30 mg/kg	8 w		
	HepG2 cells	10 $\mu$ M	24 h	Anti-inflammatory	[52]
Rats	1 g/kg	10 w	Anti-oxidation	[53]	
Mice	0.03%	12 w	Anti-oxidation	[54,55]	
Adults	5–20 mg	3 w	Anti-oxidation	[56]	
Liver Cancer	AFBI -Rats	300 ppm	5 d	DNA	[59]
	CTX-Rats	25 mg/kg	2w	NrF2	[60]
	CBRH-7919	0–100 $\mu$ M	24 h	JAK I/STAT3	[61,62]
	LM3	0–200 $\mu$ M	0–72 h	NF- $\kappa$ B P65	[27]
	SMMC-7721			Wnt/ $\beta$ -Catenin	
	H22	20–40 $\mu$ M	12–24 h	Apoptosis	[63]
	Mice	2–4 $\mu$ g/kg	7 d	Arrest in G2 phase	
DEN-Mice	200 ppm	20 w	FASN	[65]	
Drug-Induced Liver Injury	Alcoholic-mice	50 mg/kg	10 w	Anti-inflammatory MAPK	[68]
	Alcoholic-mice	0.2–20 mg/kg	10 d	Anti-inflammatory Anti-oxidation	[69]
	Alcoholic-mice	50 mg/kg	12 w	Anti-inflammatory Regulation of intestinal flora	[70]
	APAP-mice	30–60 mg/kg	14 d	Anti-inflammatory Anti-oxidation	[75]
	ConA-mice	20–40 mg/kg	14 d	Anti-inflammatory JNK	[74]
	TCDD-Rats	12.5–25 mg/kg	21 d	Anti-oxidation	[71,72]
	hepatocytes	2.5–10 $\mu$ M	48 h		
LPS-mice	2–10 mg/kg	7 d	Anti-inflammatory Anti-oxidation	[73]	
Liver IR	Rats	5 mg/kg	14 d	Anti-oxidation	[82]
	Mice	30–60 mg/kg	14 d	Anti-oxidation	[83]
	Mice	25 mg/kg	0–48 h	Anti-oxidation	[84]
		10 $\mu$ M	24 h		

**Abbreviations:** DEN, diethylnitrosamine; CTX, cyclophosphamide; APAP, acetaminophen; ConA, concanavalin A; LPS, lipopolysaccharide; AFBI, aflatoxin B1; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

effect may be related to inhibition of the MAPK family and NF- $\kappa$ B pathways.<sup>47,80,81</sup> Therefore, astaxanthin not only effectively inhibits the occurrence and development

of liver fibrosis, NAFLD and liver cancer, but also plays an important role in the prevention of acute drug-induced injury.

## Hepatic Ischemia-Reperfusion

Hepatic ischemia-reperfusion (IR) injury often occurs after hepatectomy, liver transplantation and shock, and can cause serious liver dysfunction.<sup>82</sup> With improvements in economic and living conditions, more patients with end-stage liver disease choose liver transplantation to prolong their lives. Therefore, it is essential to prevent liver IR injury. At present, it is generally believed that such injuries are related to ROS, Kupffer cells, inflammatory cytokines, and ROS are key to inducing such injuries.<sup>83,84</sup> Astaxanthin, a strong antioxidant, has been shown to play an important role in IR of the cardiovascular system, liver and kidney.<sup>84–87</sup>

Curek and colleagues first demonstrated that after 14 days of astaxanthin preconditioning, hepatocyte injury and mitochondrial swelling were lower in IR rats and unprotected groups, and it was shown that astaxanthin significantly inhibited the conversion of xanthine dehydrogenase (XDH) to xanthine oxidase (XO).<sup>88</sup> This suggests that astaxanthin improves hepatic IR injury via its antioxidant effect. Li et al subsequently determined ROS and inflammatory factors in a mouse model of IR after astaxanthin preconditioning to determine the role of astaxanthin in scavenging oxidative stress products, and examined the relevant mechanisms, which may be related to down-regulation of the activity of the MAPK family-related proteins, thus inhibiting apoptosis and autophagy.<sup>89</sup> In addition, the apoptosis of hepatocytes induced by hypoxia can also be inhibited by astaxanthin, which further demonstrates that astaxanthin has a protective effect in hepatic IR injury via antioxidation, and is a safe and effective treatment method.<sup>90</sup> The role of astaxanthin in liver disease is summarized in Table 1.

## Conclusion and Perspectives

Astaxanthin is a secondary carotenoid mainly obtained from marine organisms. Studies have shown that astaxanthin has preventive and therapeutic effects on liver fibrosis, liver tumors, liver ischemia-reperfusion injury, non-alcoholic fatty liver and other related diseases. Astaxanthin not only has strong antioxidant effect, but also can regulate many signal pathways. For example, it reduces JNK and ERK-1 activity to improve liver insulin resistance, inhibits PPAR- $\gamma$  expression to reduce fat synthesis in the liver, down-regulates the expression of TGF- $\beta$ 1/Smad3 to inhibit the activation of HSCs and liver fibrosis, inhibits the JAK/STAT3 and Wnt/ $\beta$ -catenin signaling pathways to inhibit

liver tumors, and inhibits apoptosis and autophagy to protect against liver ischemia-reperfusion injury.

The role of astaxanthin in liver diseases and its related mechanisms were summarized in this study. Astaxanthin can prevent and treat liver diseases by inhibiting inflammation and improving glycolipid metabolism.<sup>91</sup> Therefore, astaxanthin could have widespread application in the prevention and treatment of liver diseases. At present, the tissue distribution, absorption and toxicity of astaxanthin in experimental animals have been fully studied, but in clinical trials, there is a lack of data. Therefore, extensive epidemiological and clinical studies are needed to provide favorable evidence for further application of astaxanthin. In addition, the effective structure of astaxanthin can be further improved, and more stable and effective preparations can be synthesized and added to health medicines and food to benefit human health.

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## Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest.

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