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Astaxanthin as a Potential Protector of Liver Function: A Review

Jui-Tung Chen[a, c], Kazuhiko Kotani[b]

Abstract

Protecting against liver damage, such as non-alcoholic fatty liver disease, is currently considered to be important for the prevention of adverse conditions, such as cardiovascular and cancerous diseases. Liver damage often occurs in relation to oxidative stress with metabolic disorders, including cellular lipid accumulation. Astaxanthin (3,3′-dihydroxy-β,β-carotene-4,4′dione), a xanthophyll carotenoid, is a candidate for liver protection. Here, we briefly review astaxanthin as a potential protector against liver damage. In particular, studies have reported antioxidative effects of astaxanthin in liver tissues. Astaxanthin treatment is also reported to improve hyperlipidemia, which indirectly induces the antioxidative effects of astaxanthin on liver pathologies. Furthermore, astaxanthin may alleviate liver damage independent of its antioxidative effects. Of note, there are still insufficient human data to observe the effect of astaxanthin treatment on liver function in clinical conditions. More studies investigating the relevance of astaxanthin on liver protection are necessary.

Keywords: Antioxidant; Alanine aminotransferase; Aspartate aminotransferase; γ-glutamyltransferase; Liver function; Oxidative stress; Reactive oxygen species

The Importance of Liver Protection for Human Health

The liver is pivotal to lipid and glucose metabolism [1]. Recently, the importance of liver function has been widely recognized in the context of non-viral liver pathologies, such as non-alcoholic fatty liver disease (NAFLD), which are prevalent and are known to lead to cardiovascular and cancerous diseases [2-10]. Such liver pathologies, including NAFLD, typically lead to conditions of oxidative stress with lipid accumulation in liver tissues [1-4].

In general, NAFLD is clinically diagnosed by an increase in blood liver enzymes (i.e., aspartate aminotransferase (AST), alanine transaminase (ALT), and γ-glutamyltransferase (γ-GT)), following the exclusion of other causes of increased liver enzymes (i.e., hepatitis viruses) [10-12]. However, it is important to consider that liver pathologies can be silent and asymptomatic among subjectively healthy individuals [4, 13]; therefore, methods of liver protection while the liver is still relatively healthy are required.

A candidate method for liver protection is the use of natural supplementation. Astaxanthin (3,3′-dihydroxy-β,β-carotene-4,4′dione, $C_{40}H_{52}O_4$), a xanthophyll carotenoid that is found in various microorganisms and marine animals, is one of the candidate supplements for liver protection because of its antioxidative activity and other functions [14]. Of note, animal studies have reported the effects of astaxanthin treatment on liver damage [15-17]. Here, we briefly review the potential for astaxanthin as a protector against liver pathologies.

Potential Mechanisms of Astaxanthin for Liver Protection

Antioxidative effects

Astaxanthin is well documented to have antioxidative activity as a scavenger of free radicals and a quencher of reactive oxygen species (ROS), thereby protecting native molecules (e.g., fatty acids) and cell membranes from oxidation [18-20]. The antioxidative activity of astaxanthin on cells is greater than that of β-carotene, vitamin C, vitamin E, lutein, lycopene, and other catechins [14, 19, 21]. In fact, the antioxidative activity of astaxanthin has been shown to be 100- to 500-fold greater than α-tocopherol and 5- to 15-fold greater than other carotenoids [21]. Of importance, astaxanthin is reported to accumulate in rat liver, and its bioactivities are functional in liver tissues as well as blood [22].

The development of fatty liver and liver stenosis is multifactorial, but oxidative stress is closely involved in the pathogenesis [23, 24]. Lipid accumulation, insulin resistance, ROS, and lipid oxidation products in the liver interact and enhance

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[a]Jui-Tung Chen Clinic, Tokyo, Japan
[b]Division of Community and Family Medicine, Jichi Medical University, Tochigi, Japan
[c]Corresponding Author: Jui-Tung Chen, J.T. Chen Clinic, 2-13-5 Akasaka, Akasaka-Kaikan B1F, Minato-Ku, Tokyo 107-0052, Japan.
Email: chin-cl@jcom.zaq.ne.jp

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the formation of liver damage [23]. Astaxanthin has been shown to inhibit the level of lipid peroxidation, as measured by thiobarbituric acid reactive substances, and increase the level of cellular antioxidants, as measured by glutathione and superoxide dismutase, in rat liver tissues treated with carbon tetrachloride [15]. Astaxanthin also inhibits the conversion of xanthine dehydrogenase to xanthine oxidase and the protein carbonyl level in rat liver tissues following ischemia-reperfusion injury (a severe oxidative condition) [16]. Astaxanthin has also been shown to induce expression of nuclear factor-erythroid 2-related factor 2 mRNA and its downstream antioxidant-related genes in the mouse liver [17].

In liver fibrosis, as characterized by the excessive deposition of extracellular matrix [25, 26], oxidative stress stimulates hepatic Kupffer cells to secrete fibrogenic cytokines such as transforming growth factor β1 (TGF-β1), which is considered to be the most critical molecule in the fibrotic process [27-29]. Astaxanthin inhibited cellular ROS levels induced by TGF-β1 in an experimental membrane model [20]. Astaxanthin is expected to inhibit the expression of TGF-β1 by nuclear factor-κB (NF-κB, a major mediator of inflammation) [30], because astaxanthin could inhibit the level of NF-κB [31].

Of interest, there have been a few studies of clinical conditions in humans to observe the effects of astaxanthin treatment on oxidative stress markers [32-34]. A double-blind randomized controlled trial in Finnish men (astaxanthin, 8 mg/day, 3 months (n = 20) versus placebo (n = 20)) reported that astaxanthin treatment significantly reduced plasma lipid peroxidation markers, including 12-hydroxy fatty acids (by 36%) and 15-hydroxy fatty acids (by 60%) [32]. A double-blind randomized controlled trial in obese Korean adults (astaxanthin, 5 mg/day, 3 weeks (n = 12) versus 20 mg/day (n = 11)) reported that astaxanthin treatment in the respective doses significantly and similarly reduced blood oxidative stress markers, such as malondialdehyde (by 34.6% and 35.2%) and isoprostanes (by 64.9% and 64.7%), and improved antioxidant markers, such as superoxide dismutase (by 193% and 194%) and total antioxidant capacity (by 121% and 125%) [33]. Another double-blind randomized controlled trial (astaxanthin, 0, 2 versus 8 mg/day, 8 weeks (n = 14 in each dose group)) reported that astaxanthin treatment significantly reduced circulating 8-hydroxy-2′-deoxyguanosine (8-OHdG, an oxidative DNA marker) in both the 2 and 8 mg dose groups, while no significant change in 8-isoprostane (a lipid peroxidation marker) was observed [34]. These human studies demonstrated favorable effects of astaxanthin treatment on oxidative stress; however, the effects in liver are speculation.

Indirect antioxidative and/or independent effects

Multiple factors (e.g., lipid disorders) are involved in liver damage. These induce oxidative stress reactions and, vice versa, oxidative stress can worsen these conditions. In this sense, the factors are believed to have independent and/or indirect antioxidative effects of astaxanthin on liver damage.

Lipid accumulation in liver tissues due to fatty acid flux to liver from the gut and blood dyslipidemic conditions can contribute to liver damage [8]. Astaxanthin was reported to reduce the expression of lipogenic and lipid-uptake genes in mice, and this might be independent of the influence of fatty acid oxidation-related genes in the liver [8]. Astaxanthin also reduced both hepatic and blood triglyceride (TG) and cholesterol levels in mice [35]. Of note, a randomized placebo-controlled clinical trial in mild hyperlipidemic human subjects (astaxanthin, 0, 6, 12 versus 18 mg/day, 3 months (n = 15 in each of the first three groups and n = 16 in the latter group)) reported treatment with 12 and 18 mg/day both significantly reduced blood TG levels and treatment with 6 and 12 mg both significantly increased blood high-density lipoprotein cholesterol levels [36].

Liver energy metabolism is related to lipid accumulation and oxidative stress formation [37, 38]. A mitochondrial membrane potential on hepatocytes is, thus, a point of interest. An experimental study reported that the effect of astaxanthin on liver is not via the ROS pathway but via an H^+-transferring function, and this can improve mitochondrial function [37].

Given its physiological role in regulating lipid and glucose metabolism in liver [39], peroxisome proliferator-activated receptors (PPARs) in hepatocytes are also of interest. In general, PPAR-α activation normalizes lipid metabolism by reducing TG concentrations through the modulation of target gene expression, and PPAR-γ activation improves cellular insulin resistance [39]. An experimental study reported that astaxanthin significantly reduced lipid accumulation in lipid-loaded hepatocytes by activating PPAR-α, but inhibited PPAR-γ transactivation [40].

Effects of astaxanthin on liver function: the need for human studies

Thus, we briefly described the possibility of the protective action of astaxanthin against liver pathologies. However, it is crucial to note that there is a paucity of "human studies" to investigate the effects of astaxanthin treatment on liver function in the clinical setting. Two animal studies have investigated the level of ALT, a clinically well-used marker specific to liver function, was examined under astaxanthin treatment [16, 17]; one study showed that astaxanthin significantly reduced blood ALT levels in mice [17], but in another study, astaxanthin did not change the ALT levels in rats following ischemia-reperfusion injury [16]. Before astaxanthin is confirmed as protective to liver, accumulation of data from such human studies is needed.

Conclusions

The present review described astaxanthin as a potential protector against liver pathologies. However, the use of astaxanthin in liver protection, with subsequent prevention of the development cardiovascular and cancerous diseases, has yet to be determined. Further studies, particularly human studies, are warranted.

Conflicts of Interest

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