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The Impact of Astaxanthin Supplementation on the Lipid Profile

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Abstract

Astaxanthin (AST) is a carotenoid renowned for its strong antioxidant properties and its role as a pigment in various aquatic organisms. Initially isolated from lobster and subsequently characterized in detail, AST has garnered significant interest in recent years within the research, pharmaceutical, cosmetic, and supplement industries. This review aims to synthesize current literature on the impact of astaxanthin supplementation on lipid profiles, specifically focusing on low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol

(HDL-C), and triglycerides. Evidence suggests that AST effectively prolongs the oxidation lag time of LDL, thereby mitigating the risk of atherosclerosis and cardiovascular diseases through its antioxidative mechanisms. The effects of AST on HDL-C levels are less consistent, with some studies reporting modest increases while others show no significant changes. Similarly, the influence of AST on triglyceride levels remains inconclusive, with studies presenting mixed outcomes ranging from significant reductions to negligible effects. AST is characterized by a high safety profile and favorable bioavailability, which is influenced by its source and isomeric composition. Despite these promising findings, many existing studies are limited by small sample sizes, heterogeneous participant groups, and varied dosing regimens, which impede the ability to draw definitive conclusions. Consequently, there is a need for larger, well-standardized clinical trials to accurately assess the efficacy and safety of astaxanthin as a therapeutic agent for lipid modulation and the prevention of metabolic disorders. Future research should focus on robust methodological designs and standardized supplementation protocols to clarify AST's role in managing dyslipidemia and enhancing cardiovascular health.

Keywords: astaxanthin, lipid profile, LDL cholesterol, HDL cholesterol, triglycerides, antioxidant, safety, bioavailability

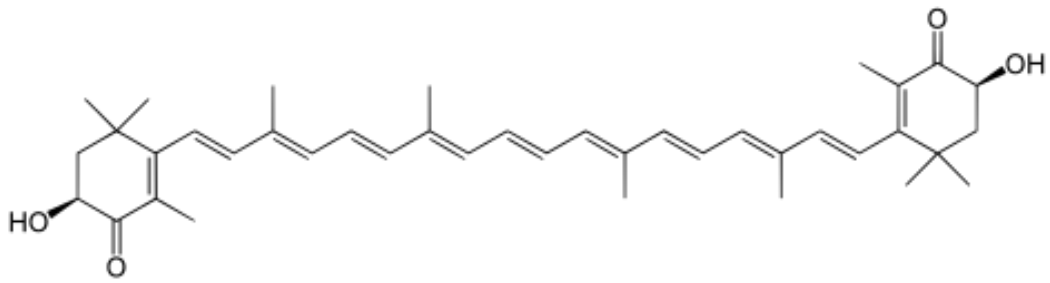
Introduction

Astaxanthin (AST) is a substance classified as a carotenoid. It was first isolated from lobster by Richard Willstätter, a German Nobel laureate known for his research on chlorophyll. However, astaxanthin was described in more detail many years later by another German Nobel laureate, Richard Kuhn, in 1939, who was known for his work on carotene. Only in recent years has this compound regained the attention of researchers as well as the pharmaceutical, cosmetic, and supplement industries.

Astaxanthin is a xanthophyll, a pigment responsible for the reddish-pink coloration of various aquatic organisms such as salmon, shrimp, crabs, and lobsters. [1] However, its function as a pigment is not its only action – astaxanthin exhibits impressive biological properties, making it one of the most powerful antioxidants found in nature. Studies indicate that AST may have up to 65 times stronger antioxidant effects than vitamin C and up to 14 times stronger than vitamin E [2]. Its antioxidant properties are also significantly stronger compared to beta-carotene, lutein, and zeaxanthin [1]

Oxidative stress, generated by factors such as UV radiation, prolonged stress, or tobacco smoke, can damage the internal structures of cells. Astaxanthin has a unique chemical structure, with a long polyene chain and additional hydroxyl and ketone groups at each end, which contribute to its high antioxidant potential [3]. These structural features allow it to neutralize free radicals effectively. The primary mechanism by which free radicals involved in oxidative stress damage cells is their impact on DNA and the oxidation of critical biological compounds. Excessive oxidative stress can lead to cell apoptosis. AST, due to its long

polyene chain, can donate free electrons and stabilize reactive molecules before they damage cellular structures. Its chemical structure, containing hydroxyl and ketone groups, gives it amphipathic properties, allowing it toact effectively in both aqueous and lipid environments in the body. [4]



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The main natural source of astaxanthin is the microalgae *Haematococcus pluvialis*, which produce this compound as a protective response to various environmental stressors, such as intense UV radiation, nutrient depletion, and changes in salinity [5]. It has the highest capacity to accumulate astaxanthin, reaching up to 4–5% of the cell's dry weight [6]. In marine ecosystems, astaxanthin's biological significance is not limited to these algae; for instance, it accumulates in creatures like salmon, krill, and crustaceans. In salmon specifically, this carotenoid confers protection against oxidative stress, offering support during their demanding, long-distance migratory journeys [7]. However, the dietary intake of astaxanthin through commonly consumed seafood, like salmon or shrimp, remains relatively low compared to the concentrated levels available directly from microalgal sources [8].

From a chemical standpoint, astaxanthin's exceptional stability underpins its robust antioxidant properties. Its amphipathic nature allows it to integrate effectively into cell membranes, positioning itself in both hydrophobic and hydrophilic layers. This unique orientation enables astaxanthin to interact with a wide range of reactive oxygen species, effectively neutralizing oxidative damage across different cellular compartments. By protecting critical organelles, such as mitochondria, astaxanthin helps maintain cellular integrity and contributes to overall metabolic homeostasis.

In recent years, a growing body of literature has expanded our understanding of astaxanthin's potential health benefits beyond its well-documented antioxidant capabilities. Research now explores how this compound may influence inflammatory pathways, improve lipid profiles, enhance insulin sensitivity, and even slow aspects of the aging process. Such findings are of increasing interest as metabolic syndrome is characterized by a cluster of risk factors like elevated blood pressure, dyslipidemia, insulin resistance, and central adiposity continues to affect an ever-larger segment of the global population. Identifying efficacious strategies for prevention and intervention is paramount, and astaxanthin's multifaceted biological actions position it as a promising candidate for future therapeutic development.

By exploring astaxanthin's full potential in addressing metabolic challenges and supporting human health, researchers can lay the groundwork for new applications in preventive medicine and nutrition. As we refine our understanding of the molecular mechanisms

underlying its effects, we may uncover more precise interventions for optimizing metabolic health, reducing the burden of chronic diseases, and enhancing overall quality of life.

Astaxanthin Supplementation and LDL-C

Hyperlipidemia is characterized by elevated total cholesterol and/or LDL-C levels, which is a major risk factor for atherosclerosis and cardiovascular diseases. Dyslipidemia refers to abnormalities in the levels of lipid fractions or lipoproteins, such as hypercholesterolemia, atherogenic dyslipidemia, or hypertriglyceridemia. Excess LDL-C is one of the types of dyslipidemia.

According to WHO guidelines, hypercholesterolemia is diagnosed when LDL-C levels are >=190 mg/dl or LDL levels are >=115 mg/dl in healthy individuals or exceed recommended values for those at cardiovascular risk. Dyslipidemia is diagnosed when >=1 abnormality in the lipid profile is present: LDL-C >=190 mg/dl, LDL >=115 mg/dl, TG >=150 mg/dl, HDL <40 mg/dl in men, and <45 mg/dl in women [9].

Epidemiological analyses from the WOBASZ II study indicate that in 2013-2014, hypercholesterolemia occurred in 70.3% of men and 64.3% of women in a representative sample of Polish adults, making it the most common metabolic disorder in Poland [10]

LDL is a low-density lipoprotein and the primary carrier of cholesterol in the bloodstream, responsible for transporting cholesterol from the liver to peripheral cells and tissues [20]. The leading class of drugs effectively reducing LDL levels in serum are statins, which act as HMG-CoA reductase inhibitors [21]. Statins exhibit pleiotropic effects, including improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, anti-inflammatory effects, and stabilization of atherosclerotic plaques [22]. By inhibiting cholesterol synthesis in the liver, statins increase the expression of LDL receptors and accelerate the clearance of these particles from the bloodstream [23]. Despite their high efficacy in lowering LDL and reducing cardiovascular risk, statins do not guarantee the achievement of target LDL values for every risk group, and some patients experience intolerance. Thus, new and alternative methods for influencing the lipid profile are being sought. PCSK9 inhibitors, which lead to a more intensive reduction in LDL [24] and ezetimibe, which limits intestinal cholesterol absorption [25], have joined the gold standard. Additionally, there is ongoing research into naturally derived substances that could support or complement conventional therapy.

Astaxanthin, the subject of this discussion, has been shown in studies to have antioxidant effects, inhibiting lipid peroxidation and the oxidation of LDL [27]. LDL oxidation involves modification of LDL particles by reactive oxygen species [25] Oxidized LDL are more atherogenic—they promote the formation of atherosclerotic plaques, endothelial cell activation, monocyte infiltration, and foam cell formation, all of which contribute to the development of atherosclerosis [26].

In a study evaluating the impact of astaxanthin on LDL oxidation in both in vitro and ex vivo conditions, it was shown that astaxanthin significantly prolonged LDL oxidation lag time in both settings. In vitro, the oxidation lag times increased in a dose-dependent manner: 31.5, 45.4, and 65.0 minutes for 12.5, 25.0, and 50.0 μg/ml, respectively, compared to 19.9 minutes in the control group. Ex vivo, volunteers who took astaxanthin for 14 days at doses of 1.8, 3.6, 14.4, and 21.6 mg per day experienced increases in LDL oxidation lag time of 5.0%, 26.2%, 42.3%, and 30.7%, respectively, while no changes were observed in the control group [28].

By reducing inflammation, astaxanthin may indirectly support beneficial changes in LDL metabolism. It inhibits the expression of pro-inflammatory cytokines and promotes the production of anti-inflammatory cytokines, thereby facilitating more effective LDL clearance from the bloodstream and protecting the endothelium [29].

In a study using an apolipoprotein E-deficient mouse model to assess the impact of astaxanthin on experimental atherosclerosis, astaxanthin was shown to reduce plasma lipid levels. Mice fed a high-fat diet supplemented with 0.03% astaxanthin for 4 weeks had lower plasma total cholesterol and triglyceride levels than control mice. Astaxanthin increased the levels of LDL receptor, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, and sterol regulatory element-binding protein 2 (SREBP-2) in the liver, which may be responsible for its hypocholesterolemic effects [30].

Effects of Astaxanthin on HDL-C

HDL is a high-density lipoprotein responsible for reverse cholesterol transport, meaning it transports cholesterol from peripheral tissues and blood vessel walls to the liver, where it is metabolized and excreted from the body. HDL also has anti-inflammatory and antioxidant properties, which help protect blood vessels and support endothelial function.

Historically, researchers have explored various avenues to raise HDL levels or enhance its functionality, given the well-documented benefits of HDL on human health. Niacin (vitamin B3) was once considered one of the most effective agents for increasing HDL levels—sometimes by as much as 20–30% [5]. However, large-scale randomized clinical trials such as AIM-HIGH and HPS2-THRIVE failed to demonstrate clear cardiovascular benefits from niacin therapy, underscoring the complexity of HDL biology [6,7]. Other approaches have included the use of fibrates—PPAR-α agonists primarily aimed at lowering triglycerides. Although fibrates can modestly raise HDL and improve the overall lipid profile, their impact on HDL tends to be less pronounced than their triglyceride-lowering effect [8]. Inhibitors of cholesteryl ester transfer protein (CETP) were also investigated for boosting HDL levels. Although these agents can significantly elevate HDL concentrations, multiple large trials did not show a meaningful reduction in cardiovascular events, once again suggesting that simply increasing HDL levels does not fully capture its cardioprotective properties [9,10]. Furthermore, safety concerns and non-cardiovascular effects have limited the widespread adoption of CETP inhibitors.

Given the limitations and uncertainties surrounding currently available HDL-targeted therapies, there is a growing interest in alternative or adjunctive methods that might help improve HDL levels or enhance its functionality. Astaxanthin has attracted attention not only

for its potent antioxidant properties but also for its potential influence on the lipid profile. The theoretical rationale for astaxanthin's effects on HDL partially overlaps with the mechanisms proposed for its impact on triglycerides. By modulating lipid metabolism through pathways involving PPAR, adiponectin, and the expression of inflammatory cytokines [11], astaxanthin may foster a more favorable inflammatory and oxidative environment—potentially helping to maintain or even improve both serum HDL levels and its functional capacity.

Preliminary experimental research and early clinical trials have yielded mixed findings on astaxanthin's potential to favorably modify HDL levels. Some initial human studies on astaxanthin supplementation suggested a slight increase in HDL levels, particularly at doses ranging from 6 to 18 mg/day over several weeks. For example, in the same 2010 study by Yoshida et al. that evaluated the effect of AST on triglycerides, the authors also noted a statistically significant increase in HDL levels at higher doses (12 and 18 mg/day) [19]. This observation aligns with the theoretical assumption that improving underlying metabolic and inflammatory conditions can support higher HDL levels. Another randomized, placebo-controlled trial conducted by Choi et al. (2011), which focused on the antioxidant properties of astaxanthin, reported slight improvements in various lipid parameters, including HDL. However, these changes were often subtle and not always statistically significant [12].

Such modest improvements could reflect differences in dosing, individual variability, or variations in baseline metabolic parameters among participants.

Despite many promising indications, the evidence remains far from conclusive. Studies examining astaxanthin's impact on HDL face similar limitations to those encountered in research on its effects on triglycerides or LDL. Clinical trials frequently involve relatively small sample sizes, and participants often differ significantly in terms of age, baseline lipid profiles, and metabolic disorders. Moreover, the duration of supplementation and the doses of astaxanthin employed across studies vary widely, making direct comparisons and definitive conclusions challenging. While one study may show a slight HDL increase following astaxanthin supplementation, another may find no significant changes, particularly under different dosing protocols or among populations with distinct metabolic characteristics.

A 2024 metaanalysis [24] attempted to clarify these issues by employing more stringent study selection criteria and accounting for potential confounders. This more recent analysis suggested that astaxanthin might exert a moderate effect on HDL levels under certain conditions, such as among individuals with metabolic syndrome or mild dyslipidemia. Even so, the review emphasized that current evidence is neither robust nor consistently cohesive. As a result, it remains unclear whether astaxanthin can reliably and sustainably raise HDL levels and—most importantly—whether any observed increases translate into meaningful cardiovascular benefits.

Effects of Astaxanthin on Triglycerides

Triglycerides are a fundamental type of lipid in the human body, serving as both an essential energy source and a storage form of fat. Structurally, they consist of a glycerol backbone esterified with three fatty acid molecules, which makes them highly efficient for energy storage due to their high caloric density. Triglycerides are primarily obtained from dietary fats but can also be synthesized endogenously in the liver from carbohydrates through de novo

lipogenesis. Once synthesized or absorbed, triglycerides are transported through the bloodstream in lipoproteins, such as chylomicrons and very-low-density lipoproteins (VLDL), to deliver energy to tissues or to be stored in adipose tissue for future use. Elevated plasma triglyceride levels, known as hypertriglyceridemia, are increasingly recognized as a significant risk factor for cardiovascular diseases and acute pancreatitis accounting for up to 10% of all cases of acute pacreatitis, particularly at extreme levels [12,13] Conversely, low triglyceride levels, though less common, can indicate underlying metabolic or malabsorptive conditions [14]. Understanding the mechanisms regulating triglyceride metabolism, as well as the clinical implications of their dysregulation, is critical for the development of effective prevention and treatment strategies for related disorders.

There are many therapeutic approaches to deal with high triglycerides, but none of them can be considered ideal. The most effective drugs for managing severe hypertriglyceridemia are fibrates. Fibrates, as PPAR-α agonists, are the most potent drugs available for reducing triglyceride levels, and they also significantly increase HDL cholesterol [15]. Their effect on LDL cholesterol varies depending on the patient's lipoprotein phenotype and the specific agent used [16]. They also enhance lipid uptake and catabolism, stimulate hepatic production of apoA-I and apoA-II, the main components of HDL-C, and beneficially modify the size and distribution of lipoprotein subclasses. [15]. Studies shown that "fibrates decrease plasma triglyceride levels by 35% to 50% and increase HDL cholesterol by 10% to 35%"[17].

Now, as we have demonstrated, there is no doubt that these are highly effective drugs. However, with effectiveness in medicine comes certain drawbacks. They are associated with a slightly increased risk of myopathy, cholelithiasis, venous thrombosis and non-cardiovascular mortality in some patients. Generally speaking, they should be avoided in high doses when combined with statins, which are very commonly used in clinical practice. [18]

There is, therefore, a rationale to explore alternative therapies that could enhance or potentially even replace fibrates in clinical practice. At this point, a substance called astaxanthin comes into focus. First, it is worth considering the theoretical basis for why astaxanthin could potentially lower triglyceride levels. It has been demonstrated that, like fibrates, astaxanthin affects adiponectin levels, which are tightly regulated by the PPAR-γ pathway. Due to this influence on adiponectin, astaxanthin not only impacts TG levels but also the overall inflammatory status of the body. This is because adiponectin inhibits the expression of pro-inflammatory cytokines such as TNF-α and IL-6, while enhancing the synthesis of anti-inflammatory cytokines, such as IL-10.

The first-ever randomized, placebo-controlled human study demonstrating the effects of astaxanthin on serum triglyceride (TG) levels, conducted by H. Yoshida et al. [19], showed that higher doses of astaxanthin (12 mg and 18 mg daily) administered over 12 weeks effectively lowered TG levels in patients with moderate hypertriglyceridemia. While astaxanthin achieved a statistically significant reduction in TG ($p < 0.05$), the correlation with adiponectin levels did not reach the significance threshold ($p < 0.01$). This indicates that astaxanthin may reduce TG through mechanisms independent of adiponectin pathways. Some studies [] suggest that astaxanthin may affect lipid levels through molecular pathways, specifically by reducing the expression of miRNA-222 and miRNA-378, both of which have been associated with elevated serum triglyceride concentrations.

A year later, another research group carried out a similar randomized, placebo-controlled study. After 12 weeks, they found no significant changes in serum TG levels, even though they used a higher daily dose of astaxanthin (20 mg) than the dose administered in the H. Yoshida et al. study.

It becomes evident at this point that the studies appear to contradict one another. A similar impression emerges when we examine meta-analyses of multiple studies on astaxanthin and its impact on triglycerides. A 2015 meta-analysis indicated that AST does not have a significant effect on lowering overall lipid levels, including serum triglycerides. One year later, another meta-analysis approached astaxanthin from a different angle. The researchers considered krill oil, which, as we know, is rich in astaxanthin, and found that supplementing with this oil led to a statistically significant reduction in serum TG levels. However, it is crucial to note that beyond astaxanthin, krill oil is also rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—substances long recognized for their ability to lower serum TG levels. Therefore, we cannot accept the latter study as reliable evidence for the isolated effects of astaxanthin.

The most recent analysis published in 2024 [24] suggests that astaxanthin has a moderate effect on lowering triglyceride levels but also highlights inconsistencies in the body of research surrounding AST.

In light of the presented studies, the relationship between astaxanthin and serum triglycerides remains unresolved, with current evidence leaning toward either no effect or, at best, a moderate triglyceride-lowering potential.

Safety

A substantial body of research supports the high safety profile of natural astaxanthin. A comprehensive review of 87 human trials, including 35 studies administering ≥12 mg/day, found no evidence of adverse health effects. While recommended daily doses vary internationally from 2 to 24 mg, initial guidance by the European Food Safety Authority (EFSA) was based on synthetic astaxanthin studies in rats, which may not reflect the safety of the natural compound [34]. In humans, double-blind, placebo-controlled trials administering natural astaxanthin at doses up to 12 mg/day for several weeks have shown no significant changes in blood pressure, blood biochemistry, liver and kidney function, or markers of oxidative DNA damage [35, 37]. Moreover, even at pharmacologically relevant concentrations, synthetic derivatives did not adversely affect platelet function, coagulation, or fibrinolysis, indicating a favorable safety margin [36, 32]. Animal toxicity studies also confirm the lack of harmful effects at very high doses (up to 1000 mg/kg), with no pathological findings in major organs [38]. Similarly, short-term high-dose supplementation in healthy volunteers (8 mg/day for 8 weeks) caused no hepatic or renal dysfunction [39].

Bioavailability

Astaxanthin’s bioavailability appears influenced by its source and isomeric composition. Studies comparing wild-caught versus farmed salmon each providing similar total astaxanthin content revealed that certain isomers were more readily absorbed, resulting in higher plasma

levels from farmed salmon [40]. In response to emerging data, EFSA updated its opinion in 2019, setting a new acceptable daily intake of 0.2 mg/kg body weight—reflecting greater scientific clarity on both safety and bioavailability [41].

Conclusions and Recommendations

Despite the promising results observed in studies on astaxanthin, several significant limitations must be acknowledged. Many existing studies have been conducted on relatively small and heterogeneous participant groups, introducing variability and restricting the generalizability of their findings. Moreover, variations in study design, particularly in dosing regimens and supplementation durations, have created inconsistencies that complicate direct comparisons between investigations. These differences make it challenging to draw definitive conclusions about the efficacy and safety of astaxanthin, emphasizing the need for larger, well-standardized clinical trials capable of producing more reliable and broadly applicable data. To confirm the beneficial effects of astaxanthin on the lipid profile, future research should focus on robust methodological designs, larger and more diverse populations, and standardized dosing protocols. Incorporating advanced data visualization techniques, such as detailed graphs and comparative charts, could further enhance clarity and accessibility, enabling more intuitive interpretation of results and fostering broader application of the findings in both clinical and scientific contexts.

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