

# **Astaxanthin & Cardiovascular Health**

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# Table of Contents

|   |    |
|---|----|
| Introduction.....   | 3  |
| Natural Control of Silent Inflammation.....   | 4  |
| Astaxanthin’s Anti-Inflammatory Mechanisms of Action.....   | 4  |
| Differences Between Astaxanthin and Anti-Inflammatory Drugs.....  | 5  |
| Human Clinical Research Shows Astaxanthin’s Effects on C-Reactive Protein....                                       | 5  |
| Combatting Cholesterol with Astaxanthin.....  | 7  |
| Human Clinical Trials Show Astaxanthin Improves Blood Lipid Profiles.....   | 7  |
| Astaxanthin Can Also Inhibit Oxidation of Cholesterol.....  | 7  |
| Other Ways Astaxanthin Can Help our Hearts.....   | 9  |
| Blood Pressure.....   | 9  |
| Increasing Blood Flow.....  | 9  |
| Heart Damage After Exercise.....  | 9  |
| Heart Damage After Heart Attack.....  | 10 |
| “Powerful Means to Prevent Myocardial Injury”.....  | 10 |
| Harvard Medical School Study Shows that Astaxanthin Could Have<br>Prevented the Heart Attacks Caused by Vioxx®..... | 10 |
| Summary.....  | 10 |
| Animal Research Verifies the Clinical Trials.....   | 12 |
| The World’s Strongest <i>and Highest Quality</i> Antioxidant.....   | 13 |
| Quantitative Differences between Astaxanthin and Other Antioxidants.....  | 14 |
| Differences Between <i>Natural</i> Astaxanthin and <i>Synthetic</i> .....   | 18 |
| Qualitative Differences between Astaxanthin and Other Antioxidants.....   | 19 |
| Conclusion.....   | 22 |
| References.....   | 23 |

## **Introduction**

For many years, cholesterol levels were viewed as the #1 predictor for developing cardiovascular disease. During the last twenty years of the previous century, controlling cholesterol levels became the mantra of cardiologists around the world. To this day, most medical doctors still go to great lengths to keep their patients' bad cholesterol (LDL) and triglyceride levels in what they consider a healthy zone. The amount of prescriptions written every year for statin drugs to control cholesterol levels is absolutely staggering. In fact, Pfizer's statin drug Lipitor® is far and away the best-selling drug of all time.

Yet a few years ago, the American Heart Association made headlines by saying that testing C-reactive protein levels (abbreviated as CRP) may be a better indicator of potential heart disease than testing cholesterol levels. CRP is a marker in the blood for systemic inflammation (also known as "silent" inflammation). Researchers have been discovering a lot of frightening things about silent inflammation; in fact, they've connected long-term high levels of silent inflammation to a host of life-threatening diseases above and beyond just heart disease. Silent inflammation has been linked as a root cause of maladies such as cancer, diabetes, Alzheimer's, ulcers, asthma and Parkinson's to name just a few.

The leading cause of death in the developed world is cardiovascular disease, followed closely by cancer. Controlling silent inflammation is critical in preventing both of these killers from affecting us in order to live a long, healthy life. Since the research on which the American Heart Association based its claim about CRP was published, testing CRP has become almost the equal of testing LDL as the way that doctors judge a patient's cardiovascular disease risk. It seems that testing a patient's CRP level has become the "new age" assessment for impending heart disease while testing cholesterol levels is now viewed by many as the "old school" key indicator. So which one is more accurate? Who should we believe?

The answer is that both silent inflammation and high levels of cholesterol play a part in cardiovascular disease. So it is certain that if there were a drug that could reduce both CRP and LDL, it would be an absolute blockbuster. However, many consumers don't like to take prescription drugs because they worry about the side effects; the fact that there are so many of these consumers is a leading reason that the nutritional supplement industry has grown so robustly over the last few decades. So what we really need is a natural supplement that has no side effects or contraindications that can combat both CRP and cholesterol levels to help keep us free from cardiovascular disease. Well, according to several human clinical trials, it appears that Natural Astaxanthin may be just what our bodies' need as a preventive measure against cardiovascular disease. Natural Astaxanthin has been clinically validated to reduce CRP, LDL and triglycerides and to increase HDL (good cholesterol). And amazingly, it's not only good for our hearts because of its effects on CRP and cholesterol levels; some pioneering research has shown that Natural Astaxanthin may have other properties that can also lead to good cardiovascular health. Perhaps a new saying is appropriate: "An Astaxanthin capsule each day can keep the cardiologist away."

# **Natural Control of Silent Inflammation**

There have been a few clinical trials showing that Natural Astaxanthin helps people lower their CRP levels and thus, control silent inflammation. In addition to these clinical trials, there have been a host of in-vitro and animal studies proving that Astaxanthin has a multi-pronged approach to control inflammation. These trials definitively established the mechanism of action by which Astaxanthin decreases inflammation levels in human plasma as measured by CRP. Amazingly, Astaxanthin works on six different inflammatory markers in the bloodstream as compared to over-the-counter and prescription anti-inflammatories which generally work on just one.

We'll begin this section by examining these broad-spectrum mechanisms against inflammation. Next, we'll look at the human clinical trials that validate Astaxanthin's positive effect in controlling CRP.

**Astaxanthin's Anti-Inflammatory Mechanisms of Action:** Back in 2003, scientists working concurrently but independently in Japan and Korea were honing in on Astaxanthin's broad-spectrum mechanisms of action for combatting inflammation. Although they were not corresponding or sharing information, and even though they used very different paths to get there, both groups of researchers arrived at similar conclusions. This was the start, but other studies since then have further substantiated the early findings. Below is a summary of some of the most significant research in this area:

- **First Study Proving the Mechanism of Action:** Researchers at Japan's Hokkaido Graduate School of Medicine were the first to prove Astaxanthin's multiple mechanisms for controlling inflammation. They did their research in test tubes and also in rats, focusing on the rats' eyes. They found that Astaxanthin reduced three key causes of inflammation: Nitric oxide (NO), tumor necrosis factor alpha (TNF-a) and prostaglandin E-2 (PGE-2) (Ohgami, et al, 2003).
- **Second Mechanism of Action Study:** Later the same year, Korean researchers working independently found similar results to the Ohgami study in vitro and ex-vivo. In harmony with the Ohgami results, they found that Astaxanthin suppresses the inflammatory mediators nitric oxide, prostaglandin E-2 and tumor necrosis factor alpha. But they also demonstrated Astaxanthin's positive effects on three other inflammatory markers: Interleukin 1B, COX-2 enzyme and nuclear factor kappa-B (Lee, et al 2003).
- **Further Validation:** Several years later, scientists from Korea University further validated the earlier results finding broad-spectrum anti-inflammatory activity (Choi, et al, 2008).
- **Inhibition of Mast Cells:** Mast cells are the key initiators of inflammation. Research at Kyoto University showed an inhibitory effect of Astaxanthin in rats' mast cells (Sakai, et al, 2009).
- **"Remarkable" Results:** Japanese researchers referred to Astaxanthin's anti-inflammatory activity as "remarkable" and found a statistically significant

reduction in the six different inflammatory markers they tested (Kishimoto, et al, 2010).

- In the most recent study in this area, Astaxanthin was found to be effective at protecting against UV-induced inflammation in a broad-spectrum manner. In fact, cell death that is frequently caused by UV exposure was significantly decreased in the Astaxanthin-treated cells (Yoshihisa, et al, 2014).

**Differences Between Astaxanthin and Anti-Inflammatory Drugs.** The research cited above has consistently shown that Astaxanthin works on a variety of different causes of inflammation. This is in distinct contrast to anti-inflammatory drugs such as Celebrex® and Vioxx® as well as over-the-counter anti-inflammatories such as NSAIDs (Tylenol®, Motrin®, Alleve®, etc.) and aspirin which generally target a single inflammatory marker, but in an intense manner. These drugs work so intensely on a single inflammatory marker that they throw our systems out of whack. This leads to the huge downside of the OTC and prescription anti-inflammatories—they all have serious side effects.

Natural Astaxanthin has never been shown to have any side effect or contraindication in hundreds of medical research studies as well as over 15 years of commercial consumer use. There are countless safety studies such as acute toxicity and chronic toxicity studies showing that Natural Astaxanthin is completely safe and has absolutely no adverse side effects or contraindications (Capelli and Cysewski, 2014). Meanwhile, the side effects of the drugs can completely outweigh the benefits derived; over-the-counter anti-inflammatory NSAIDs such as Tylenol, Motrin and Alleve can all cause serious liver problems, while aspirin can harm the stomach lining and cause ulcers. The prescription drugs such as Vioxx and Celebrex are even more dangerous; Vioxx was taken off the market several years ago after causing an increase in heart disease and premature death in many users, while Celebrex remains on the market albeit with extensive warnings about its potential for adverse cardiovascular events.

Natural Astaxanthin is completely different from these other drugs. For painful conditions, it takes significantly longer to work; but it has no side effects. The prescription and over-the-counter drugs can work the same day to combat pain, while Astaxanthin usually takes at least two and up to six or eight weeks to work; but once it starts working, users report that Natural Astaxanthin has the same positive effects on painful inflammatory conditions as the anti-inflammatory drugs. But once again we stress—without side effects.

**Human Clinical Research Shows Astaxanthin's Effects on C-Reactive Protein:** As we mentioned above, the key marker used by doctors to measure how much silent inflammation is occurring in a person's body is called C-reactive protein (CRP). To date, there have been three human clinical trials demonstrating that Natural Astaxanthin can help reduce CRP levels:

- A double-blind, placebo controlled human clinical trial was done to test Natural Astaxanthin's effect on CRP levels in healthy volunteers. The subjects took either 12mg per day of Natural Astaxanthin or a placebo for eight weeks. CRP levels were measured before and after the eight week supplementation period. Results were very good—in only eight weeks people taking Astaxanthin reduced their CRP levels by over 20%; meanwhile, people taking placebo saw a slight increase in their CRP levels (Spiller, et al, 2006a).
- In the second clinical trial, a company experimenting with Natural Astaxanthin production back in 2006 publicized a human clinical trial on patients with CRP levels that were high enough to place them in a high risk category. The patients took Natural Astaxanthin or placebo for three months, after which their CRP levels were again measured. Nearly half of the people taking Astaxanthin fell out of the high risk category while none of those taking placebo did (Mera, 2006).
- Finally, a team of researchers from Washington State University led by long-time carotenoid researcher Boon Chew, PhD did a multi-faceted study on Natural Astaxanthin primarily to test its effect on the human immune response. They used young women in this randomized, double-blind and placebo-controlled study. They measured immune markers as well as DNA damage, oxidative stress levels and CRP. The results were positive on all markers. In fact, at a dose of only 2mg per day they found a statistically significant decrease in CRP levels after eight weeks of supplementation (Park, et al, 2010).

What the exact dosage indicated for reducing CRP should be remains unresolved. The first study used a very high dose of 12mg per day and showed good results; while the last study only used 2mg per day and still yielded statistically significant results. We hope to see research establishing dose-dependence in humans in the future; however, in the meantime, we feel that a dose of 4mg – 8mg per day is sufficient for persons with elevated CRP levels.

## **Combating Cholesterol with Astaxanthin**

There are currently well over forty published medical research studies outlining Astaxanthin's cardioprotective properties. These properties may help people prevent heart disease and may also help people with heart disease to minimize their risk of a heart attack or stroke. The main focus of this research has been on Natural Astaxanthin's ability to improve blood lipid profiles by decreasing low density lipoprotein (LDL or bad cholesterol) and triglycerides, and by increasing high density lipoprotein (HDL or good cholesterol). The first study in this area was done in rats; it demonstrated that Astaxanthin raised HDL (good cholesterol) (Murillo, E, 1992). A further study tested both Astaxanthin and Vitamin E in rabbits that had high cholesterol. This research found that both supplements, particularly Astaxanthin, improved plaque stability in the arteries. All the rabbits that ingested Astaxanthin were classified as "early plaques," as compared to the rabbits ingesting Vitamin E and also the control group in which none of the rabbits could be classified as "early plaques" (Li, et al, 2004). A third animal study was done in rats. This study showed that Astaxanthin increased HDL while decreasing both triglycerides and non-esterified fatty acids in the blood (Hussein, et al, 2006).

**Human Clinical Trials Show Astaxanthin Improves Blood Lipid Profiles.** But it's not only animals' cholesterol profiles that may benefit from ingesting Astaxanthin. A placebo-controlled human clinical study on 61 volunteers with mild hyperlipidemia showed benefits for improving blood lipid profiles and also for increasing adiponectin in the serum. Doses were varied at 6mg, 12mg and 18mg per day over a 12-week supplementation period. Blood lipid improvements were seen in significantly increased levels of HDL (good) cholesterol and significantly decreased triglyceride levels (Yoshida, et al, 2008).

In a human clinical trial done in Eastern Europe, researchers took men with high cholesterol and supplemented them with 4 mg of Astaxanthin per day for one month. The average decrease in cholesterol levels was excellent in just one month: Subjects supplementing with Astaxanthin showed an average decrease of triglycerides of 24% and an average decrease in total cholesterol and of LDL of 17% (Trimeks, 2003).

**Astaxanthin Can Also Inhibit Oxidation of Cholesterol.** Many researchers believe that the oxidation of cholesterol in our bodies is more damaging than simply having a high level of cholesterol. Oxidized cholesterol can attach to the walls of our veins and arteries and clog them, thus reducing critical blood flow and leading to heart disease.

A clinical trial in Japan found a very promising effect on LDL (bad cholesterol) both in test tubes and in human volunteers. The in-vitro test showed that Astaxanthin dose-dependently prolonged the oxidation lag time of LDL. The test was then repeated in humans at doses as low as 1.8 mg per day and as high as 21.6 mg per day for fourteen days. This study found that all four doses positively affected LDL oxidation lag time—at

1.8 mg per day it was 5% longer; at 3.6 mg it was 26% longer; at 14.4 mg it was 42% longer; and at the highest dose of 21.6 mg, the upward trend stopped and the lag time was only 31% longer. This suggests that the optimum dose is significantly less than 21.6 mg per day. The researchers concluded that consumption of Astaxanthin “inhibits LDL oxidation and possibly therefore contributes to the prevention of atherosclerosis” (Iwamoto, et al, 2000; Capelli and Cysewski, 2014).

Another study in this area showed excellent results as well. This randomized double-blind study was done on healthy, young men in Finland at the Research Institute of Public Health to test the effect of Astaxanthin on lipid peroxidation. Subjects in the treatment group were given 8mg of Natural Astaxanthin each day for three months. At the end of the study, the researchers found that Natural Astaxanthin significantly reduced the levels of two hydroxy fatty acids in the subjects’ blood plasma (Karppi, et al, 2007).

In-vitro research done in 2008 verified these two human clinical studies. Researchers in Italy tested Astaxanthin against three other carotenoids—lutein, beta-carotene and canthaxanthin—and found that Astaxanthin was the very best of all the carotenoids tested in inhibiting cholesterol oxidation (Palozza, et al, 2008).



## **Other Ways Astaxanthin Can Help our Hearts**

**Blood Pressure.** Another potential benefit for cardiovascular health may be Astaxanthin's ability to decrease blood pressure. To date, research has only been conducted as pre-clinical animal trials in rodents, but the results look promising. A group of researchers in Japan have done three separate experiments on rats with high blood pressure. In the first study, the researchers discovered that supplementation with Astaxanthin for fourteen days resulted in a significant decrease in blood pressure for the hypertensive rats, while rats with normal blood pressure levels showed no decrease. They also showed that stroke-prone rats that were fed Astaxanthin for five weeks had a delayed incidence of stroke and also decreased blood pressure. In another area researched in this study, mice with poor blood flow to the brain improved their memory when fed Astaxanthin; basically, the treatment mice proved to be smarter after being fed Astaxanthin. The study concluded, "These results indicate that Astaxanthin can exert beneficial effects in protection against hypertension and stroke and in improving memory in vascular dementia" (Hussein, et al, 2005a).

The second study in this series again examined the effect of Astaxanthin on hypertensive rats, but with an aim of also finding Astaxanthin's mechanism of action for reducing high blood pressure. They found that Astaxanthin's mechanism for decreasing high blood pressure may be due to its modulating effect on nitric oxide. Nitric oxide is a causative factor for inflammation. So at the same time Astaxanthin is controlling inflammation through its modulation of nitric oxide, it is also controlling blood pressure. This study went on to examine the hearts of the rats after contractions were induced with a variety of substances. The constrictive effects of these introduced substances were improved by Astaxanthin, demonstrating that it may help reduce the consequences of a heart attack. The conclusion was that Astaxanthin may help with blood fluidity in hypertension, and that it may restore the vascular tone (Hussein, et al, 2005b; Capelli and Cysewski, 2014).

**Increasing Blood Flow.** In a human clinical study related to blood pressure improvement, researchers gave human volunteers a dosage of 6 mg of Astaxanthin per day. This study only lasted for ten days, yet at the end of the ten day period, a significant improvement in blood flow was found in the treatment group (Miyawaki, H, 2005). Blood flow improvement can have a positive effect on different conditions related to cardiovascular health, including blood pressure as well as prevention of atherosclerosis.

**Heart Damage After Exercise.** In a very interesting study done on mice at the Kyoto University of Medicine in Japan, researchers had mice run on a treadmill until they were exhausted. The treatment group was fed Astaxanthin while the control group was not. At the end of the study, the scientists measured heart damage in both groups and found that the mice fed Astaxanthin had significantly less heart damage. They examined the mice's hearts and found that Astaxanthin had concentrated there, providing its

antioxidant and anti-inflammatory activity to prevent damage to the heart and cardiovascular system (Aoi, et al, 2003).

**Heart Damage After Heart Attack.** Another study done with rats showed a similar effect. This study was done at the Medical College of Wisconsin. Rats in the treatment group were fed Astaxanthin before having a heart attack. After the study, the hearts of both the control and treatment groups were examined. The researchers found significantly less damage and a reduced area of infarction caused by the heart attack in mice that were fed Astaxanthin (Gross and Lockwood, 2004).

**“Powerful Means to Prevent Myocardial Injury.”** A group of researchers from Hawaii are trying to launch an injectable delivery system for Astaxanthin into a patented prescription drug for cardiovascular patients. They have done several studies on Astaxanthin. One of these studies was done in dogs and some others in rats. The results were very positive in both species: “These results suggest that Cardax [the trademarked name for their Astaxanthin product] has marked cardioprotective properties in both rodents and canines. Thus, Cardax may be a novel and powerful new means to prevent myocardial [inner heart muscle tissue] injury” (Gross and Lockwood, 2003; Gross and Lockwood, 2005).

**Harvard Medical School Study Shows that Astaxanthin Could Have Prevented the Heart Attacks Caused by Vioxx®:** A study led by a scientist at the prestigious Harvard Medical School tested Astaxanthin’s influence against the negative side effects of Vioxx®. Vioxx is a prescription anti-inflammatory that can have a horrible side effect of causing deaths from cardiovascular disease and heart attacks. This study states that the dangerous cardiovascular effects that may be caused by Vioxx are related to its action of increasing the susceptibility of LDL and cellular membrane lipids to oxidation, which contributes to plaque instability and thrombus formation (formation of blood clots in the arteries). This study demonstrated that Vioxx is a pro-oxidant. Fortunately, Astaxanthin, as a powerful antioxidant, completely negated the pro-oxidant effect of Vioxx. The study states, “Remarkably, Astaxanthin was able to completely inhibit the adverse effects of Vioxx on lipid peroxidation...We have now demonstrated a pharmacologic approach to block the pro-oxidant effects of Vioxx using a high lipophilic chain-breaking antioxidant, Astaxanthin” (Mason, et al, 2006; Capelli and Cysewski, 2014). If Merck (the pharmaceutical company that manufactured Vioxx) had only combined their Vioxx drug with a little Astaxanthin, they could have saved themselves \$5 billion in lawsuit settlements. And more importantly, they could have prevented the unnecessary deaths that Vioxx caused.

**Summary.** The research being done on Astaxanthin in the area of cardiovascular health is extremely promising. Several human clinical trials demonstrate that Natural Astaxanthin can improve blood lipid profiles, improve lipid peroxidation of cholesterol,

and increase blood flow. And perhaps the most amazing study of all in this area is the Harvard study showing that Astaxanthin negates the pro-oxidant effects of Vioxx and could have prevented Vioxx users from succumbing to heart attacks. This research, along with the studies showing Astaxanthin's positive effects on the key marker of silent inflammation clearly demonstrate that Astaxanthin may have a very beneficial effect on our cardiovascular systems.

## **Animal Research Verifies the Clinical Trials**

There are approximately forty different pre-clinical trials that further validate the research done in humans. Let's briefly review a few of the key studies done in mammals:

- Astaxanthin prevents clogging of cerebral blood vessels in rats with high blood pressure (Sasaki, et al, 2011).
- Astaxanthin reduces blood pressure and improves cardiovascular parameters in rats with high blood pressure (Monroy-Ruiz, et al, 2011).
- Astaxanthin exhibits cardioprotective properties in rabbits with high cholesterol levels (Riccioni, et al, 2012).
- Astaxanthin lowers cholesterol and reduces atherosclerosis in mice (Ryu, et al, 2012).
- Astaxanthin reduces the risk of clogged arteries in dogs (Lauver, et al, 2008).
- Astaxanthin supplementation provides significant cardioprotection in rats (Gross, et al, 2006).
- Astaxanthin prevents damage from stroke in rabbits (Lauver, et al, 2005).
- Astaxanthin demonstrates potential against obesity and metabolic syndrome (a leading cause of heart disease) in obese mice fed a high-fat diet (Ikeuchi, et al, 2007).
- Astaxanthin shows various cardioprotective properties in rats such as inhibition of stroke, anti-hypertension, and inhibition of vascular contraction (Hiroshi, et al, 2006).
- Astaxanthin is more effective than other carotenoids at preserving membrane structure and antioxidant activity during lipid peroxidation (McNulty, et al, 2008).

## **The World's Strongest & Highest Quality Natural Antioxidant**

The study about Astaxanthin and Vioxx we talked about above is a perfect segue to our final discussion about Astaxanthin's potential in cardiovascular health. Vioxx caused heart attacks because it became a pro-oxidant. That means that it caused increased oxidation in the patients who used it, and this high level of oxidation caused heart disease. Most likely, the heart disease that ensued from Vioxx's pro-oxidative properties was causing cholesterol to oxidize in the patients' blood vessels. This oxidized cholesterol can easily attach itself to the blood vessel walls and block blood flow to the heart. While the theory that Vioxx specifically caused blockage of arteries remains unproven, it is evident that Vioxx caused users to die from heart disease.

The fact that Astaxanthin can never become a pro-oxidant is extremely relevant to our discussion of its effects on cardiovascular health; and as you'll see below, this is just one of Astaxanthin's four distinct qualitative properties that make it the world's highest quality antioxidant. These properties, coupled with the fact that Astaxanthin has proven time and time again to be the most powerful natural antioxidant available, provide the final element through which Astaxanthin may help keep us free from cardiovascular disease.

Many experts have said that oxidation in our bodies is the "evil twin" of silent inflammation. We can't feel it happening, yet over time it can ravage our cells and lead to the major diseases that kill us, heart disease and cancer. We discussed two human clinical studies above that show Astaxanthin's antioxidant benefit for our cardiovascular system in action: Astaxanthin decreased LDL oxidation (Iwamoto, et al, 2000) and reduced the levels of two hydroxy fatty acids in blood plasma (Karppi, et al, 2007). Now, let's look at how Astaxanthin stacks up as an antioxidant from both a quantitative and qualitative perspective.

Astaxanthin has been tested head-to-head in many experiments on antioxidant strength against several other carotenoids and antioxidants; it has consistently come out as the very strongest of all natural antioxidants in these tests regardless of the type of test. For example, whether examining free radical elimination or singlet oxygen quenching, Astaxanthin's power as an antioxidant comes out far beyond the capacity of other antioxidants. This is really amazing when you think about it, since many of the antioxidants Astaxanthin has been tested against are closely related molecules in the carotenoid family. Yet Astaxanthin usually comes out superior by at least a power of ten. And when compared with vitamin antioxidants such as Vitamin C and Vitamin E, Astaxanthin has been shown to be as high as 550X to 6000X stronger!

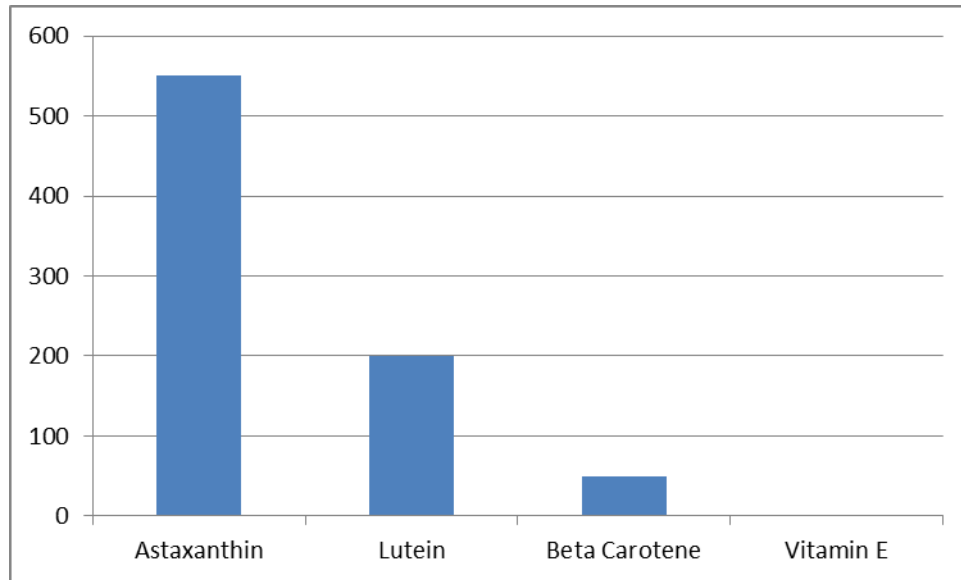
**Quantitative Differences Between Astaxanthin and Other Antioxidants.** As far back as the 1940's, scientists had discovered the antioxidant abilities of carotenoids and had identified Astaxanthin as being extremely potent in this respect. Research in France in 1946 found that Astaxanthin and beta-carotene were both powerful antioxidants, with Astaxanthin being the stronger of the two (Herisset, A., 1946). Pioneering researchers in the area of eye health discovered Astaxanthin's superior antioxidant protection for the eyes shortly afterward (Grangaud, 1951; Massonet, 1958).

By the 1990's, Astaxanthin's superior antioxidant activity was becoming widely accepted. A paper published in Japan in 1991 set the platform for a flurry of research that would follow:

“Astaxanthin, one of the dominant carotenoids in marine animals, showed both a strong quenching effect against singlet oxygen and a strong scavenging effect against free radicals. These effects are considered to be defense mechanisms in the animals for attacking these active oxygen species. The activities of Astaxanthin are approximately 10 times stronger than those of other carotenoids that were tested, namely zeaxanthin, lutein, tunaxanthin, canthaxanthin and beta-carotene, and 100 times greater than a-tocopherol. Astaxanthin also showed strong activity as an inhibitor of lipid peroxidation mediated by these active forms of oxygen. From these results, Astaxanthin has the properties of a ‘Super Vitamin E’ (Miki, et al, 1991).

Dr. Miki must have been extremely impressed to call Astaxanthin a “Super Vitamin E;” during that period in the early 1990's, Vitamin E was considered by many to be about the most beneficial nutrient for both topical application and internal consumption. However, in finding that Astaxanthin was 10 times stronger as an antioxidant than its carotenoid cousins and 100 times stronger than Vitamin E, he must have felt that it deserved such a venerable title.

Many other experiments have been done since Dr. Miki's, all with the same results—Astaxanthin remains the most powerful natural antioxidant found to date. The volume of studies is far too great to review in their totality in a paper of this scope, so we will look at a few of the most important studies which will enable our Readers to get a general idea of Astaxanthin's superior antioxidant strength. The first study we'll examine was also done in the 1990's and also in Japan. This study focused on singlet oxygen quenching. It pitted Astaxanthin against several other antioxidants including carotenoids such as lutein and beta carotene, and it also tested Astaxanthin against Vitamin E. The results were heavily favored toward Astaxanthin; lutein got within the same realm as Astaxanthin in this particular test, but beta carotene and particularly Vitamin E were far weaker than Astaxanthin.



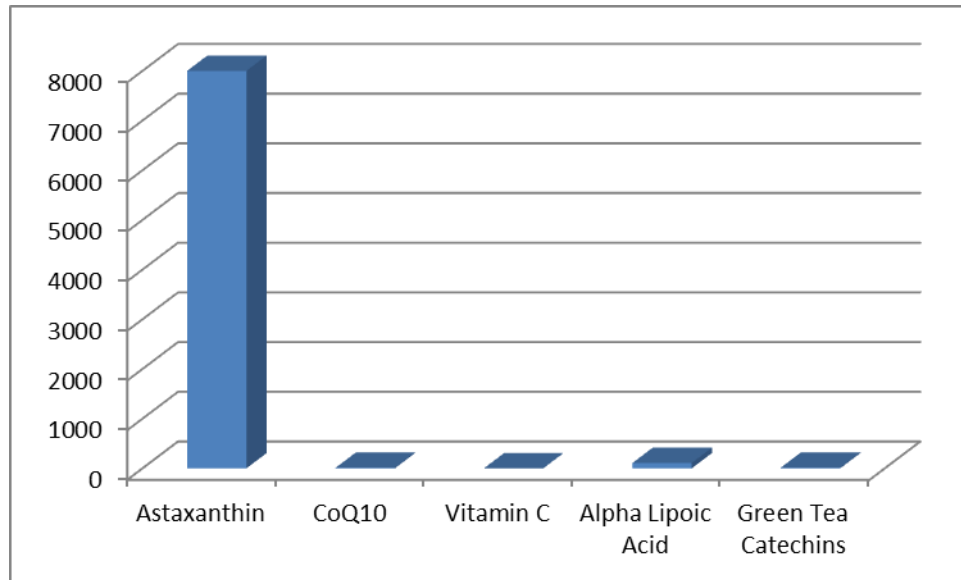
Singlet Oxygen Elimination (Shimidzu, Goto, Miki, 1996)

In singlet oxygen elimination, results of this study found Astaxanthin to be:

- 550 times stronger than Vitamin E
- 11 times stronger than beta-carotene
- 2.75 times stronger than lutein (Shimidzu, et al, 1996)

One of the authors of this study was Dr. Miki, the original researcher who did the oft-times quoted study from 1991 showing Astaxanthin to be phenomenally stronger than other antioxidants and calling it a “Super Vitamin E.” As a great fan of Astaxanthin, Dr. Miki participated in another study of Astaxanthin’s strength against singlet oxygen many years later in 2007. This time they pitted Astaxanthin against a completely different set of antioxidants. The antioxidants evaluated in this study were Coenzyme Q10, green tea catechins, alpha lipoic acid and Vitamin C. The main difference between this study and Dr. Miki’s earlier work is that the results were even more slanted in Astaxanthin’s favor.

Many people consider CoQ10 to be an excellent antioxidant. And among vitamins, Vitamin C is also fairly highly regarded as an antioxidant. Yet when tested against Astaxanthin for their ability to eliminate singlet oxygen, Astaxanthin wasn’t just superior—it was incredibly more potent.



Singlet Oxygen Quenching (Nishida, Yamashita, Miki, 2007)

As you can see from the chart above, none of the other antioxidants were even remotely close to Astaxanthin's capacity to eliminate harmful singlet oxygen. The closest of the four was alpha lipoic acid, yet Astaxanthin was still 75 times more potent. Results showed that Astaxanthin is:

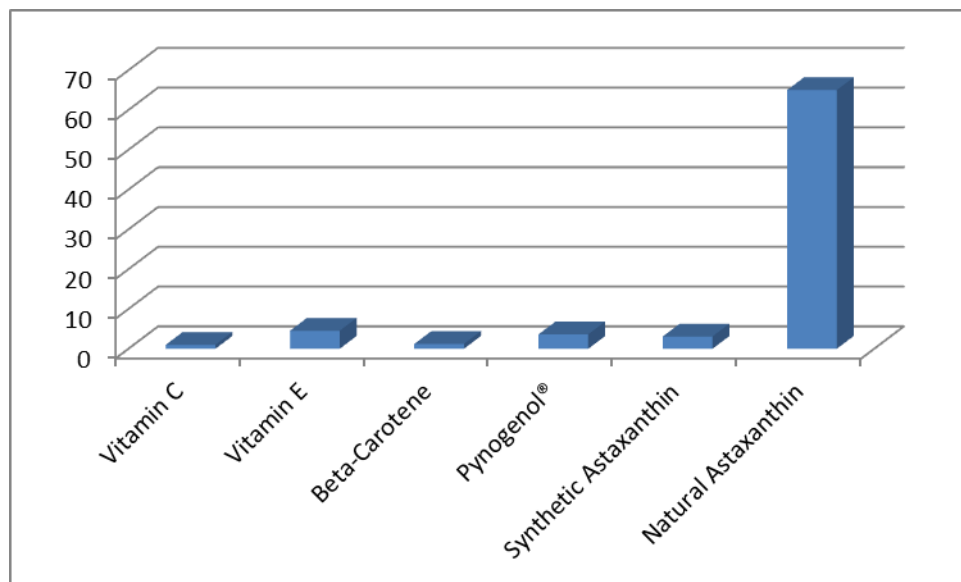
- 6000 times more potent than Vitamin C
- 800 times more potent than CoQ10
- 550 times more potent than Green Tea Catechins
- 75 times more potent than Alpha Lipoic Acid (Nishida, et al, 2007)

The last antioxidant research we'll review in this paper was done at Creighton University by a leading antioxidant and nutritional supplement researcher, Debasis Bagchi, PhD. Professor Bagchi is very well respected in his field with almost 300 publications including several books and hundreds of peer-reviewed studies. Incredibly, Dr. Bagchi's work has been cited by his colleagues over 12,000 times! And relevant to our discussion here, one of Dr. Bagchi's most interesting accomplishments is developing a very effective protocol for testing the free radical scavenging ability of antioxidants.

When comparing antioxidants, it is very important to analyze them head-to-head and to test them in different experiments. For example, a single test of Astaxanthin versus Vitamin E as a singlet oxygen eliminator is not a comprehensive view of the two different molecules' antioxidant capacity. Singlet oxygen are without a doubt extremely harmful to our cells over time, but they are just one of many different oxidants that wreak havoc in our bodies. The research in the 1990's focused primarily on Astaxanthin as a singlet oxygen eliminator, so Dr. Bagchi decided to look at Astaxanthin from a different angle: In a very well designed experiment, he tested Astaxanthin head-to-head against other well-known antioxidants by measuring their ability to scavenge free radicals.



While this research was originally done in 2001, Dr. Bagchi had great foresight and decided to test both Natural Astaxanthin and Synthetic Astaxanthin in this study even though Synthetic Astaxanthin was not available at the time as a human nutritional supplement. He pitted the natural and synthetic versions of Astaxanthin against Vitamin E, Vitamin C, beta-carotene, and he also included the trademarked supplement Pycnogenol® in the mix as it was claiming to be an extremely powerful antioxidant in its marketing literature. Although this was a completely different way to measure antioxidant strength from the earlier Miki studies, and this set of antioxidants included two completely new molecules—Synthetic Astaxanthin and Pycnogenol®—Natural Astaxanthin again came out the undisputed champion with antioxidant strength ranging from 14X greater than Vitamin E to 65X greater than Vitamin C.



Free Radical Elimination (Capelli, Bagchi, Cysewski, 2013)

Natural Astaxanthin was again far more potent than all other antioxidants. The results showed that, in free radical quenching, Natural Astaxanthin is:

- 14X stronger than Vitamin E
- 18X stronger than Pycnogenol®
- 21X stronger than Synthetic Astaxanthin
- 54X stronger than Beta-Carotene
- 65X stronger than Vitamin C (Capelli, et al, 2013a)

This university-based research led by one of the world's leading experts in the field accomplished three very important things:

- ✓ It proved the consistency of Astaxanthin's superior antioxidant strength regardless

- of how it is tested against other antioxidants.
- ✓ It quantitatively proved that Astaxanthin is much stronger than other antioxidants that were claiming to be extremely powerful such as Pycnogenol®.
  - ✓ It showed how incredibly different and more potent *Natural* Astaxanthin is than *Synthetic* Astaxanthin.

We see by the relationship between Astaxanthin and Vitamin E in the studies cited above how important it is to use more than one method of measuring antioxidant strength. In the singlet oxygen experiments in the 1990's, Astaxanthin was proven to be 550X stronger than Vitamin E. Yet, when Dr. Bagchi tested the two as free radical scavengers in 2001, Astaxanthin was shown to be 14X stronger. While 14X is still quite impressive, it is a far cry from 550X. So the question comes up as to which number is accurate. The answer is that both of these numbers are accurate, and Astaxanthin is 14 times better than Vitamin E in eliminating free radicals and 550 times better than Vitamin E in specifically eliminating singlet oxygen. It would be impossible to accurately give an exact number when comparing the two in "antioxidant strength," but if we had to pick a number, Dr. Miki's original estimate that Astaxanthin is 100X stronger than Vitamin E back in 1991 would probably be just about right. Which may be why Dr. Miki simplified things and started calling Astaxanthin a "Super Vitamin E."

**Differences Between *Natural* Astaxanthin and *Synthetic*.** A critical finding of this study is the clear superiority of Natural Astaxanthin to its distant relative Synthetic Astaxanthin in antioxidant strength. While a full review of the vast differences between these two molecules would be too comprehensive for this paper, it is important that our Readers understand that these are two completely distinct molecules. In fact, other than sharing the same chemical formula, they are almost exact opposites in all other respects. The primary differences between the two are:

- **Shape:** The Natural Astaxanthin molecule's stereochemistry is unique (it is shaped differently than the Synthetic Astaxanthin molecule).
- **Esterification:** Natural Astaxanthin is 95% esterified (it has a fatty acid molecule attached to either one or both ends of the molecule). Synthetic Astaxanthin is exclusively "free" Astaxanthin and does not have fatty acid molecules attached to it.
- **Synergy:** Natural Astaxanthin from *Haematococcus pluvialis* microalgae comes complexed in nature with supporting carotenoids. There are consistently small amounts of other antioxidant carotenoids such as lutein, beta-carotene and canthaxanthin ranging from 3% - 15% of the total carotenoid fraction which may provide a synergistic effect when ingested. Synthetic Astaxanthin does not contain supporting carotenoids.
- **Source:** Synthetic Astaxanthin is synthesized from petrochemicals in an elaborate process. Natural Astaxanthin is extracted from natural *Haematococcus pluvialis* microalgae.
- **Safety:** Natural Astaxanthin has an extensive portfolio of human safety studies and a history of over 15 years of safe use as a commercially-sold nutritional

supplement. Synthetic Astaxanthin has never been directly tested in humans for safety. (As we'll review in the next section, this is an overriding concern due to serious safety issues with related synthetic carotenoids beta-carotene and canthaxanthin.)

- **Antioxidant Strength:** As noted above, Natural Astaxanthin is 20X stronger than Synthetic Astaxanthin as an antioxidant in scavenging free radicals. Another antioxidant head-to-head comparison has shown that Natural Astaxanthin is over 50X stronger than Synthetic Astaxanthin in singlet oxygen quenching (Capelli, et al, 2013a).
- **Efficacy:** Amazingly, Synthetic Astaxanthin has never been shown to have any health benefit in human clinical research. It is completely untested and may not have any health benefit at all (which leads to the logical question as to why the company that released it to the human nutritional supplement market made this groundless decision). Meanwhile, Natural Astaxanthin has been shown to have diverse health benefits in approximately 100 different positive human clinical trials.
- **Dosage:** In the event that Synthetic Astaxanthin is ultimately proven safe for long-range human consumption, dosages would logically be a minimum of 20 times greater than corresponding dosages of Natural Astaxanthin due to its vastly inferior antioxidant profile. This high dosage requirement would most likely put Synthetic Astaxanthin out of reach economically for most consumers.

**Qualitative Differences Between Astaxanthin and Other Antioxidants.** Astaxanthin is not only an incredibly powerful antioxidant, it is also a unique antioxidant in terms of how it works in our bodies. There are four distinct ways we can see these qualitative properties. While each of these independently would be a critical differentiator from other antioxidants in terms of health value and efficacy, the four of these taken together form a critical mass of evidence of Astaxanthin's superior qualitative antioxidant properties. Each of these is very impressive, and while hard to pick the most important or least, below we list these qualitative differences in the order of their relative importance in our opinion:

1. **Spans the cell membrane to protect the entire cell:** A general rule of antioxidants is: "Lipid soluble antioxidants protect the lipid (oil) soluble part of our cells, and water soluble antioxidants protect the water soluble part of our cells." So when we ingest Vitamin C which is water soluble, its antioxidant properties are useful in one part of our cells, and when we ingest Vitamin E which is oil soluble, its antioxidant properties are useful in the remaining part of our cells. The shape of the Astaxanthin molecule allows it to span the cell membrane and have one end of the molecule in the oil soluble part of the cell and the other end of the molecule in the water soluble part of the cell. This gives Astaxanthin the distinctive characteristic of being able to protect the entire cell. And Astaxanthin has been found capable of travelling throughout the entire body, into the bloodstream, muscle tissue, skin, as well as the various critical organs (Capelli and Cysewski, 2014). This double feature of being able to get throughout the

body and being able to protect the entire cell makes Astaxanthin a super-effective antioxidant and anti-inflammatory for humans and is most likely the key reason that Astaxanthin is effective for a multitude of different health issues.

- 2. Never a Pro-Oxidant:** A lot of very good antioxidants can, under certain conditions, turn into oxidants and start harming our cells. This is what happened in the famous “Finnish Smokers Study” on beta-carotene published in the prestigious “New England Journal of Medicine” in 1994. This study tested consumption of synthetic beta-carotene, which (like Synthetic Astaxanthin) is completely different from the natural form. Heavy smokers who were smoking on average three packs of cigarettes each day were supplemented with synthetic beta-carotene and found after time to have a slightly higher incidence of cancer. This was amazing to all involved since dozens of epidemiological studies as well as pre-clinical research showed that beta-carotene has cancer-preventative properties (Moorhead, et al, 2005). What was happening was that the beta-carotene was turning into a pro-oxidant in the smokers’ bodies because smoking depleted their Vitamin C levels. In the absence of Vitamin C, the beta-carotene molecules had no supporting antioxidants to pass off the supercharged free radicals caused by smoking, so they “changed teams” and became oxidants. This caused additional cellular damage, which in turn, increased the incidence of cancer (Heinonen and Albanes, 1994). “Without Vitamin C, beta-carotene can catch the destructive energy of a free radical and itself become a damaging molecule. In this situation, beta-carotene has entered a ‘pro-oxidant’ state. If Vitamin C is available this pro-oxidant state will quickly be converted back to an antioxidant state without damage to cells” (Malila, et al, 2006; Capelli and Cysewski, 2014).

Many other excellent antioxidants besides beta-carotene can become pro-oxidants under certain conditions. For example, well-known vitamin antioxidants such as Vitamins C & E, zinc, and even carotenoid antioxidants such as lycopene and zeaxanthin can all become pro-oxidants (Martin, et al, 1999). Fortunately, Astaxanthin can never become a pro-oxidant and cause damage to our cells (Beutner, et al, 2000).

- 3. Crosses the blood-brain barrier and blood-retinal barrier:** A lot of very good antioxidants can’t help protect our eyes and brains. Even carotenoid antioxidants that are closely related to Astaxanthin such as beta-carotene and lycopene can’t get through these barriers that exist to protect our most vital organs from potentially damaging matter. Since our brains are the control center for everything we think and do, an antioxidant that can’t protect the brain seems to be of little value to us. Fortunately, Astaxanthin can get through the blood-brain barrier to protect our brains. When it reaches our brains, it can then travel through the blood-retinal barrier to help protect our eyes. Some of the earliest research on Astaxanthin back in the 1940’s and 1950’s showed Astaxanthin’s ability to get into the eyes of rats (Grangaud, 1951 and Massonet, 1958); meanwhile, many human clinical studies have been completed over the last

several years to confirm Astaxanthin's diverse health benefits for the eyes and brain (Capelli and Cysewski, 2014). And once present in the eyes and brain, it is not only Astaxanthin's antioxidant activity that is working prophylactically, but also its broad spectrum anti-inflammatory properties are providing additional protection to these vital organs. This one-two punch against oxidation and inflammation is exactly what brains and eyes need to stay healthy and function well.

4. **Bonds with muscle tissue:** As we mentioned above, Astaxanthin can get throughout the entire body and into all the critical organs. Of utmost import to athletes and active people, it can also bond with muscle tissue to protect muscles from increased levels of oxidation and inflammation and keep the muscles functioning smoothly.

If Astaxanthin only had one distinct advantage over other antioxidants, it would be unjustified to call it the "World's Highest Quality Natural Antioxidant;" however, with four important, documented advantages over more commonplace antioxidants, we feel it's perfectly warranted: Astaxanthin has earned this venerable title.

## **Conclusion**

Reducing silent inflammation; controlling cholesterol levels; increasing blood flow; reducing oxidation (particularly oxidation of cholesterol in plasma); reducing high blood pressure...these are some of the potential benefits of Natural Astaxanthin in the fight against the developed world's #1 killer: Cardiovascular disease. In all of the examples above (with the one exception being blood pressure), human clinical evidence clearly points to Astaxanthin's benefits for combatting highly prevalent cardiovascular maladies. And in every case listed above (including blood pressure this time), there is substantial pre-clinical evidence that Astaxanthin imbues cardiovascular benefits.

Two human clinical trials have shown that Natural Astaxanthin can increase HDL (good cholesterol) levels and decrease LDL (bad cholesterol) and triglyceride levels. And multiple clinical trials have shown that Astaxanthin can prevent oxidation of cholesterol that is already present in the bloodstream. Coupled with the three human trials that demonstrate how Astaxanthin can reduce CRP (the key marker for silent inflammation) and the wealth of research showing that Astaxanthin is the "World's Strongest and Highest Quality Natural Antioxidant," it becomes crystal clear that Astaxanthin is the supplement of choice for cardiovascular health. University researchers in United States, Japan, China and Europe have all found substantiation indicating the use of Astaxanthin as a preventive cardiovascular tonic. While we are not in any way prescribing Astaxanthin as a drug for heart disease, we feel that the evidence showing potential benefits is significant enough that people concerned with maintaining good cardiovascular health should seriously consider supplementing with 6mg – 8mg of Natural Astaxanthin each day.

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