The Most Versatile Nutrient for Eye Health: Natural Astaxanthin

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Introduction

Two young scientists working toward their doctorates in France way back in the 1940's were really on to something. And they were clearly way ahead of their time. Before almost any scientist in the world had ever heard of "Astaxanthin," Renee Massonet and Rene Grangaud had already discovered how protective Astaxanthin is for the eyes. The work they started in the 1940's was completed and published in the 1950's as their doctoral theses, earning them their PhD's and great respect from their peers in France.

Then something strange happened. The research community somehow forgot about Astaxanthin for eye health. In fact, the scientific community pretty much completely forgot about Astaxanthin as a nutrient for improving health for almost 30 years. Amazingly, it was so completely forgotten that in 1996, a professor and ophthalmologist at the University of Illinois, Dr. Mark Tso, MD, was able to get a patent on the use of Astaxanthin for eye and central nervous system diseases and damage! (As anyone who's familiar with patents knows, they're supposed to be granted based on a new, previously undiscovered invention.) How could Dr. Tso get a patent on Astaxanthin for eye disease when Massonet and Grangaud had discovered its potential in this area over 40 years earlier? Frankly, this just shows how completely forgotten Astaxanthin had become.

Since the early pioneers of Astaxanthin research Massonet and Grangaud uncovered the incredible potential of this nutritional gem and Dr. Tso's subsequent patent, a great deal of research has been completed on Astaxanthin showing a variety of health benefits. One of the greatest and most clinically validated of these areas of investigation is Astaxanthin's protective properties for the eyes. In human clinical research, Astaxanthin has shown potential to:

- Improve visual acuity (the ability to see fine detail)
- Treat or prevent asthenopia (eye fatigue)
- Reduce blurred vision
- Increase accommodation amplitude (the adjustment in the lens that allows it to focus)
- Prevent eye strain
- Reduce eye soreness
- Prevent eye dryness
- Improve depth perception
- Prevent diplopia (double vision)
- Increase blood flow to the retina and to the vascular layer of the eye
- Increase blood flow velocity to the eyes

Many other nutrients have claimed to be the top supplement for eye health. Even other carotenoids in the same family such as lutein and zeaxanthin have garnered a reputation as fantastic eye health supplements. There is no doubt that these are excellent supplements for people concerned with keeping their eyes healthy. Yet, as you'll discover as you read through this paper, unlike many antioxidants (and even carotenoid cousins of Astaxanthin from the same family), Astaxanthin can cross the blood-brain barrier and get into the brain; once in the brain, it can then cross the blood-retinal barrier and get into the eyes. When it reaches the eyes,

Astaxanthin can really shine and provide protection like no other nutrient. Astaxanthin is far and away the world's strongest and highest quality natural antioxidant; plus, Astaxanthin also has anti-inflammatory properties which can help eyes to continue functioning well as they age. These facts make Astaxanthin the top choice among nutrients for eye health, besting even its fellow carotenoids lutein and zeaxanthin.

In order to fully understand Astaxanthin's potential to protect our eyes, we'll begin this paper by looking at Astaxanthin's strength and qualities as an antioxidant; then we'll delve into Astaxanthin's anti-inflammatory mechanisms and activity; next, we'll review the human clinical research which validates Astaxanthin's benefits for the eyes; and finally, we'll briefly look at some of the supporting pre-clinical research in the area of eye health.

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

Quantitative Differences Between Astaxanthin and Other Antioxidants

As we mentioned above, researchers in France in the late 1940's began to understand that Astaxanthin serves as an outstanding protectant for the eyes. The first published paper on Astaxanthin was also done in France just a few years before Massonet and Grangaud began their eye health research; it classified Astaxanthin as a strong antioxidant. This study looked at both Astaxanthin and beta-carotene and found that they are powerful antioxidants, with Astaxanthin being the stronger of the two (Herisset, A., 1946). Then the long dark ages of Astaxanthin research began.

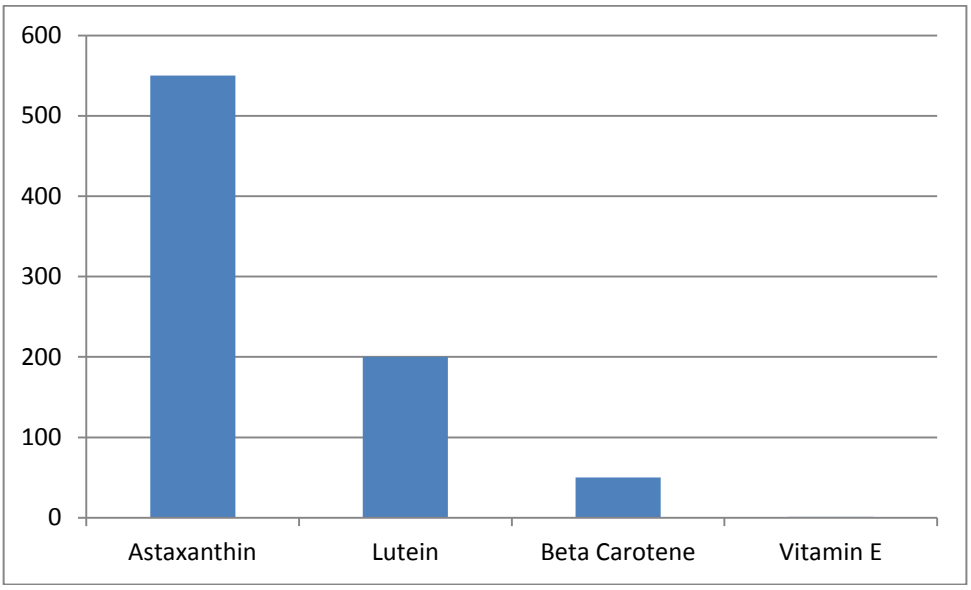
Finally, in the early 1990's research on Astaxanthin started becoming significantly more prevalent. At the same time a professor and medical doctor from University of Minnesota's School of Medicine named Dr. Jyonouchi, MD began discovering that Astaxanthin can positively affect the immune response, a Japanese researcher named Dr. Miki was finding out how powerful Astaxanthin is as an antioxidant. His paper, published 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 alpha-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.



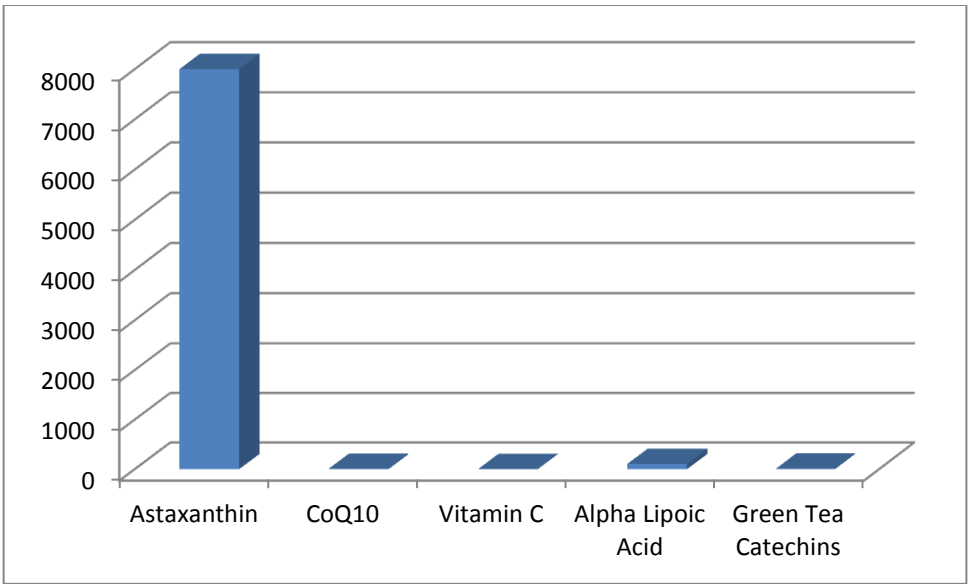
Singlet Oxygen Elimination (Shimidzu, Goto, Miki, 1996)

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)

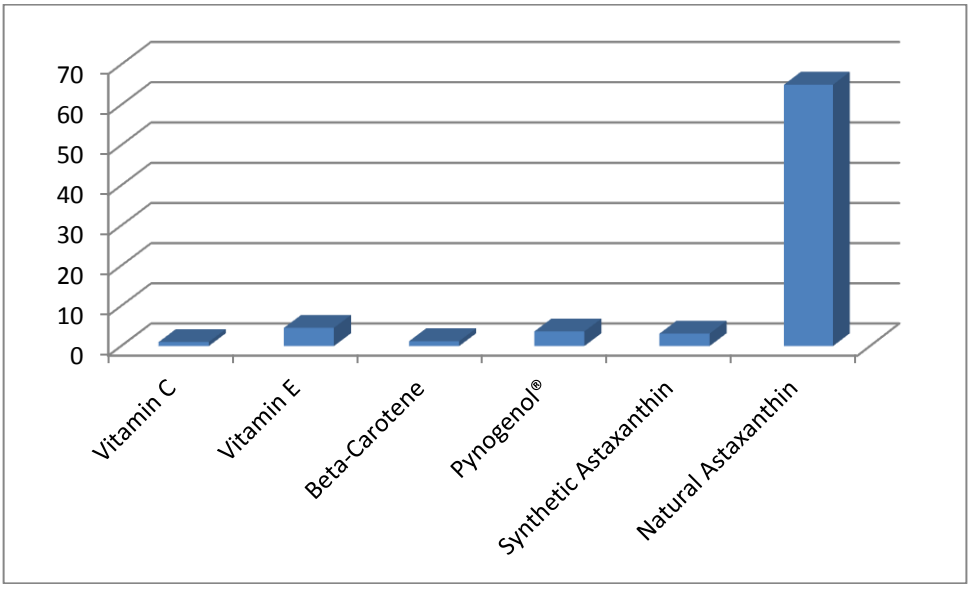
As you can see from the chart above, none of the other antioxidants were even remotely close to Astaxanthin's capacity to eliminate harmful singlet oxygen. The closest of the four was alpha lipoic acid, yet Astaxanthin was still 75 times more potent. Results showed that Astaxanthin is:

- 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)

As you can see, 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 1991would 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 Dr. Bagchi's 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, 2013).
- **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 very relevant fact to our discussion in this paper: 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 damaging oxidants and inflammation. 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.

A Safe and Natural Broad Spectrum Anti-Inflammatory

The medically-accepted test for systemic or "silent" inflammation in our bodies is a blood test of C-reactive protein (CRP) levels. Excessive silent inflammation in our bodies is now considered, along with oxidation, to be the root cause of a host of life-threatening diseases. For example, the American Heart Association now warns that CRP levels are a better indicator of heart disease than cholesterol levels.

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).

Further human clinical research validating Astaxanthin's anti-inflammatory properties above and beyond the CRP studies has been done showing that Natural Astaxanthin can ameliorate many painful conditions caused by inflammation such as rheumatoid arthritis, carpal tunnel syndrome (repetitive stress injury), tendonitis and even joint & muscle soreness due to heavy exercise (Capelli and Cysewski, 2014). However, since our primary objective in this paper is to discuss Astaxanthin's benefits for the eyes, we will leave a discussion of these inflammatory pain trials to another paper. Instead, we'll begin this section by examining Astaxanthin's broad-spectrum mechanisms of action against inflammation, and finish by looking 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 reduces 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, 2006).
- 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).

The exact dosage indicated for reducing CRP 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.

The Most Versatile Nutrient for the Eyes: Natural Astaxanthin

As anyone who is 50 or older knows, the eyes change with age. Many people who never required corrective lenses as children or in their 20's and 30's find themselves going to the optometrist for a pair of reading glasses in their mid-40's. And as people get older, many serious issues such as age-related macular degeneration, cataracts and glaucoma become increasingly prevalent. What we need as an ounce of prevention for our aging eyes and brains is a combination supplement: A strong antioxidant and broad spectrum anti-inflammatory that can get through the blood-brain barrier and enter the brain. Then, once in the brain, it must be able to get through the blood-retinal barrier to bring its antioxidant and anti-inflammatory protection to the eyes.

As noted above, Astaxanthin is a very strong antioxidant and also has anti-inflammatory properties (Shimidzu, et al, 1996; Nishida, et al, 2007; Ohgami, et al, 2003; Lee, et al, 2003). There is substantial evidence that most diseases associated with the eyes and brain are the result of oxidation and/or inflammation. Silent inflammation, free radicals and singlet oxygen can manifest in the eyes as numerous diseases including retinal arterial occlusion, venous occlusion, macular degeneration, glaucoma, cataract, diabetic retinopathy, and more. Free radicals and singlet oxygen oxidize the polyunsaturated fatty acids in the retina which leads to functional impairment of the retinal cell membranes, causing temporary and permanent damage to the retinal cells. Once the retina is damaged, it cannot be replaced. Antioxidants and anti-inflammatories that can reach the inner eye by crossing the blood retinal barrier are essential because they protect the eye from these damaging conditions (Tso and Lam, 1996).

Which brings us back to where we started this paper—the 1940's, when researchers from France theorized, and then confirmed that Astaxanthin crosses the blood retinal barrier and acts as a strong retinal protectant. In 1948, Grangaud and Massonet published their first in a series of papers that reported the remarkable properties of Astaxanthin in the eye (Grangaud, 1951; Massonet, 1958; Capelli and Cysewski, 2014). Since then, a great deal of research has led to an abundant variety of potential benefits for the eyes from supplementing with Natural Astaxanthin:

- Improve visual acuity (the ability to see fine detail)
- Treat or prevent asthenopia (eye fatigue)
- Reduce blurred vision
- Increase accommodation amplitude (the adjustment in the lens that allows it to focus)
- Prevent eye strain
- Reduce eye soreness
- Prevent eye dryness
- Improve depth perception
- Prevent diplopia (double vision)
- Increase blood flow to the retina and to the vascular layer of the eye
- Increase blood flow velocity to the eyes

There are many human clinical trials that indicate these potential eye health benefits; let's examine some of the best human trials that have shown Natural Astaxanthin's diverse positive effects on the eyes.

Eye Fatigue and Eye Accommodation

Some remarkable research has surfaced over the last fifteen years about how Astaxanthin can help our eyes in today's world. Two of the most interesting areas of this research have been in conditions known as eye fatigue and eye accommodation:

- **Eye fatigue** (which is known medically as "Asthenopia") is becoming more prevalent due to extensive use of computers and other visual display terminals. This can manifest as eye strain, blurring and diplopia (a disorder of vision in which two images of a single object are seen because of unequal action of the eye muscles – also called double vision).
- **Eye accommodation** is a critical function of the eyes. This is the process by which the eye changes optical power to focus on a particular object as the viewing distance varies.

An extensive series of human clinical trials have shown that Natural Astaxanthin has positive benefits for both of these conditions and their accompanying symptoms. All of these studies have taken place in Japan where researchers as well as nutritional supplement companies have embraced Astaxanthin much more so than in most other countries. These clinical trials have clearly established a critical mass of evidence indicating that Natural Astaxanthin is the most diverse nutrient yet discovered to support eye health.

- ✓ The first study in this area was a state-of-the-art investigation—a randomized, double blind, placebo-controlled human clinical trial. After four weeks of supplementation with 5 mg of Astaxanthin per day (extracted from Haematococcus algae meal) the authors reported a 46% reduction in the number of eye strain subjects. They also found higher accommodation amplitude (the adjustment in the lens of the eye that allows it to focus) in subjects who used visual display terminals (Nagaki, 2002).

- ✓ The next study we'll look at examined Natural Astaxanthin's effects on eye fatigue. This study tested two different dosage levels. Results showed positive effects at 4 mg per day, but found a better result at 12 mg per day (Nakamura, 2004). This study showed that the optimum dose was above 4mg per day, but there was no conclusion as to whether the optimum would be 12mg or somewhat higher or lower. (Note: Much of the research since then has centered on 6mg per day as the optimum dose for eye health.)

- ✓ Another group of researchers found similar results in their own human clinical study. This double blind study was done to evaluate Astaxanthin's effect on eye fatigue as well as visual accommodation. Forty subjects were divided into placebo and treatment groups, with the treatment group receiving 6 mg of Astaxanthin for four weeks. The results: Three separate visual parameters showed statistically significant benefits from

Astaxanthin supplementation. This study established an optimum daily dose for eye fatigue and accommodation amplitude of at least 6 mg per day (Nitta, 2005).

- ✓ A study the following year corroborated these results. This was a crossover study which concluded that taking 6mg of Natural Astaxanthin per day has the effects of reducing and preventing eye strain and accommodative dysfunction (Iwasaki, et al, 2006). This study was interesting in the sense that it showed both a prophylactic as well as a therapeutic potential for Astaxanthin for eye conditions such as fatigue and accommodation. In other words, besides being able to prevent eye strain and fatigue and improve accommodation, Natural Astaxanthin also shows a capacity to reverse these conditions in people already afflicted with these disorders.

- ✓ Astaxanthin's preventative role was further displayed in a clinical study done on subjects whose eyes were healthy, with no signs of fatigue or strain. Both the treatment and the placebo groups in this study were subjected to heavy visual stimuli to induce eye fatigue, and it was found that the treatment group recovered more quickly. This study and the previous study we cited go one step farther than earlier studies which demonstrated that Natural Astaxanthin may serve to treat eye fatigue in those that already suffer from it: We see from these two studies that Astaxanthin may be useful not only to treat eye fatigue, but also to prevent eye fatigue from occurring in healthy people (Takahashi and Kajita, 2005).

- ✓ Additional studies have shown that 6 mg per day of Natural Astaxanthin supplementation for four weeks can reduce eye soreness, dryness, tiredness and blurred vision (Shiratori, et al, 2005; Nagaki, et al, 2006; Capelli and Cysewski, 2014).

To summarize, the diverse maladies that can come from our modern lifestyles of desk work, computer use and television viewing such as tired, sore eyes that don't focus well and may even reach a level of blurred or double vision may all be prevented or improved by supplementing with Natural Astaxanthin.

Other Human Clinical Research

- ➢ A very different kind of eye study was also done in Japan. This study was done on a subject pool comprised of twenty year old, healthy men. The men were randomly separated into a placebo group or a treatment group who were given 6 mg of Natural Astaxanthin per day for four weeks. Statistically significant improvement was found in two different parameters—visual acuity (the ability to see fine detail) and depth perception. Depth perception in particular saw a remarkable improvement by 46% in the group supplementing with Natural Astaxanthin (Sawaki, et al, 2002).

- ➢ Improvement in visual acuity was found in an older group of subjects as well. This study took 49 healthy volunteers who were over the age of 40 and tested for improvements in

visual function at 2mg per day, 4mg per day, 12mg per day and with a placebo. This study was done over a 28 day period, after which time the groups taking the 4mg and 12mg doses were found to have statistically significant improvements in both visual acuity and accommodation time. No improvements were found in the placebo group nor the group supplementing at 2mg per day (Nakamura, et al, 2004). Once again, this study indicates that the optimal dosage is somewhere between 4mg and 12mg per day.

- It is very important to have sufficient blood flow to the eyes and the retina to ensure they are healthy and functioning properly. A human clinical study examined the ability of Astaxanthin to improve retinal capillary blood flow. Eighteen subjects were given 6 mg per day of Natural Astaxanthin and another eighteen people were given a placebo. After four weeks it was found that the Astaxanthin group had improved retinal capillary blood flow as compared to the placebo group (Yasunori, 2005).

- The final study we'll review in this section showed a different benefit for using Natural Astaxanthin related to blood flow. This double-blind, placebo-controlled study separated healthy volunteers into a placebo group and a group that was given 12mg of Natural Astaxanthin per day for four weeks. The study examined Astaxanthin's effect on blood flow to the vascular layer of the eye. Increased blood flow velocity was found in subjects taking Astaxanthin (Saito, et al, 2012). It appears that Astaxanthin can increase blood flow volume and can also increase the speed at which the blood is flowing to the eyes.

Supporting Pre-Clinical Trials

Finally, extensive research has been done in rodent studies and other animals demonstrating Natural Astaxanthin's positive effects on eye health which help substantiate the human clinical studies cited above. In fact, a US Patent was granted back in the 1990's (currently expired) to scientists from the University of Illinois based on wide-ranging research in rodents for the use of Astaxanthin for eye and brain diseases. This research once again demonstrated that Astaxanthin can cross the blood-brain and blood-retinal barriers. It then went on to show through an extensive series of experiments a multitude of potential preventative and therapeutic benefits for Astaxanthin in the areas of eye and brain health (Tso and Lam, 1996).

In addition to the University of Illinois research, a variety of other animal studies have been performed. Here are some of the most promising of these studies:

1. Cataract research has been performed in three very different animal species: Rats, salmon and chick embryos:
    a. Astaxanthin was successful in preventing the formation of cataracts in rats (Liao, et al, 2009).
    b. In a fascinating study done at Norway's National Institute of Nutrition and Seafood Research, Astaxanthin and Vitamins C & E prevented the formation of

cataracts in salmon while pro-oxidants such as iron, copper and manganese increased the incidence of cataracts Waagbo, et al, 2003).

c. Astaxanthin also protected against the formation of cataracts in chick embryos (Ishikawa, et al, 2015).

2. Astaxanthin protects the vascular layer of the eye in mice and may be a potential therapy for age-related macular degeneration (Izumi-Nagai, et al, 2008).
3. Astaxanthin prevents retinal injury in rats with high ocular blood pressure (Cort, et al, 2010).
4. Astaxanthin inhibits oxidative stress and may be developed as an antioxidant drug to treat diabetic retinopathy (Dong, et al, 2013).
5. Astaxanthin protects retinal cells against oxidative stress in mice and in-vitro (Nakajima, et al, 2008).
6. Astaxanthin protects against eye inflammation in rats (Suzuki, et al, 2006).
7. Astaxanthin protects against ganglion cell death due to various stressors in rat retinal cells (Yamagishi and Aihara, 2014).
8. Astaxanthin protects against light-induced retinal damage in mice (Otsuka, et al, 2013).
9. Astaxanthin protects against oxidative stress and protein degradation in porcine lens cells in-vitro (Wu, et al, 2006).
10. In a topical-use study in the eyes, mice treated with Astaxanthin eye-drops improve their resistance to UV-induced eye damage (Lennikov, et al, 2012).

Please Note: This is a summary of some of the most important studies in relation to Astaxanthin's potential benefits for eye health. For a full list of abstracts from medical research papers, please contact Algae Life Sciences at info@algaelifesciences.com or BGG North America at support@bggworld.com

Conclusion

We've seen that Natural Astaxanthin can get through the blood brain and blood retinal barriers; (in fact, this has been known since the late 1940's). We've seen how powerful Natural Astaxanthin is when compared head-to-head to other antioxidants. And we've identified four key differences between Natural Astaxanthin and other common antioxidants that make it a superior antioxidant qualitatively. We've compared Natural Astaxanthin to anti-inflammatories that you find in a drug store such as NSAIDs, aspirin and prescription drugs like Celebrex and found that Natural Astaxanthin works gently on six different inflammatory markers in our bodies (as compared to the other anti-inflammatories that work intensely on a single inflammatory marker). The result of this safe and natural broad-spectrum anti-inflammatory activity is that Astaxanthin may serve to reduce silent inflammation in our bodies (as well as painful, chronic inflammation) without any of the serious side effects that anti-inflammatory drugs elicit. In addition, we've pointed out that most diseases of the eye are caused by oxidation and inflammation. The logical conclusion derived from all of the above is that Natural Astaxanthin is an excellent nutrient to protect our eyes.

Furthermore, when reviewing the variety and depth of human clinical trials on Astaxanthin and eye health in such diverse areas as eye fatigue, eye accommodation, visual acuity, depth perception and blood flow to the retina, our Readers can begin to understand why we call Natural Astaxanthin "The Most Versatile Nutrient for Eye Health."

After examining all the published literature in the area of eye health, we recommend daily supplementation with 6mg to 8mg of Natural Astaxanthin as a preventative and potentially therapeutic measure to maintain optimum eye health.

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