

The Neuroprotective Properties of Natural Astaxanthin

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Introduction

A famous TV commercial several years ago in the USA ended with the saying, “A mind is a terrible thing to waste.” We agree. When you think about it, the brain is the centerpiece for most of what goes on in our bodies; it’s the control center for vital processes that transpire throughout the entire body. Keeping the brain healthy as we get older is critical to our well-being during the aging process. And as we’ve seen from the huge increase in the incidence of Alzheimer’s disease and other cognitive ailments associated with aging over the last few decades, maintaining good brain health is emerging as a principal health issue of the 21st century.

As with many other organs in our bodies, there are two primary enemies of the brain that can wear it down over time and decrease performance: Inflammation and oxidation. Levels of both inflammatory cytokines and oxidants are found in every person’s body; however, in today’s world we are subject to factors that cause much higher levels of inflammation and oxidation in our bodies than our ancestors experienced. Chemicals and preservatives in the food we eat, higher levels of stress in today’s society, increased exposure to UV radiation from the sun and many other factors result in our cells being subjected to higher levels of inflammation and oxidation that our grandparents never experienced. The result: Long term systemic inflammation (known as “silent” inflammation) and oxidative imbalance (which cause a host of life-threatening diseases).

The brain is one of the organs most affected by inflammation and oxidation, most likely due to its delicate nature and the extreme importance it extends to other organs and systems throughout the body. What we need as a preventative “brain tonic” as we age is a safe anti-inflammatory and a strong antioxidant, and both of these must be able to cross the blood-brain barrier (a membrane in our heads that protects us by keeping foreign matter away from the brain). Based on research at universities in France and the USA, we know that Astaxanthin can cross the blood-brain barrier and the blood-retinal barrier and get into the brain and eyes to protect them (Grangaud, 1951; Massonet, 1958; Tso & Lam, 1996). And a multitude of additional studies have shown that Astaxanthin is a safe and natural anti-inflammatory as well as the strongest antioxidant known to nature: A perfect combination to keep our brains functioning well against the increased onslaught of inflammation and oxidation in today’s world.

Natural Astaxanthin is perhaps the very best nutrient for anyone over the age of forty to take on a daily basis for a variety of reasons; one of the most important bases from which this statement becomes clear is Astaxanthin’s excellent potential as a neuroprotectant. There have been approximately fifty medical research studies—in-vitro experiments, pre-clinical animal trials as well as double-blind, placebo-controlled human clinical studies that make a clear case for Astaxanthin as a “Brain Health Supplement.” In this review, we’ll first look at Astaxanthin’s ability to protect our cells and DNA; then we’ll examine the research on Astaxanthin’s antioxidant and anti-inflammatory activities. Next, we’ll examine each of the human clinical trials indicating neuroprotective benefits from Astaxanthin use plus a brief examination of some of the most important pre-clinical trials that further validate the human research in this area. We’ll wrap up our review with a short recap of the related field of human eye health research on Astaxanthin and finally, we’ll end with a very important comparison of Natural and Synthetic sources of Astaxanthin, pointing out the vast and disturbing differences between them.

Protection of our Cells by Astaxanthin

The most obvious ways that Astaxanthin protects our brain cells are through its antioxidant and anti-inflammatory activity as we mentioned above. These two properties are at the very root of all the health benefits that Astaxanthin bestows on consumers. But there are also many studies on two very important components of our cells showing that Astaxanthin has a protective effect: These two components are DNA and the mitochondria.

Prevention of DNA Damage. DNA is the main constituent of chromosomes in all living organisms. It carries genetic information which makes us who we are. Damage to DNA has profound implications to our cells; in fact, when DNA is damaged, it can have grave effects up to and including development of a cancerous cell line (Moorhead, et al, 2005). A supplement that can help prevent DNA damage is certainly a powerful preventive medicine to keep our brains and bodies functioning well and to help us live long, healthy lives.

For our discussion of how Natural Astaxanthin can prevent DNA damage, we'll start by examining the work of Dr. Boon Chew from Washington State University in the USA. Dr. Chew and his long-time collaborator Dr. Jean Soon Park have been studying carotenoids for decades and have found that Astaxanthin is the most health-giving molecule in the carotenoid family. They hold a patent on preventing DNA damage from oxidation through the use of Astaxanthin. As amazing as this may seem based on general recommended daily dosages ranging from 4mg to 12mg per day for adults, the findings from their research show that using only 2mg of Natural Astaxanthin each day over four weeks can reduce DNA damage by approximately 40% (Chew and Park, 2006). This is really a phenomenal result—in only one month and at an incredibly low dosage level of only 2mg per day, Natural Astaxanthin can effectively prevent DNA damage by close to half.

In addition to their patent, Drs. Chew and Park published a randomized, double-blind, placebo-controlled human clinical trial in 2010 that outlines the effects of 2mg of Natural Astaxanthin supplementation on several parameters including oxidative stress, inflammation, immune response as well as DNA damage. This study concluded that “dietary Astaxanthin decreases a DNA damage biomarker and acute phase protein, and enhances immune response in young healthy females” (Park, et al, 2010). Corroborating the human research, Drs. Chew and Park had previously demonstrated these findings in dogs and rodents (Chew, et al, 2011; Chew, et al, 1999).

While the research of Drs. Chew and Park is excellent and clearly demonstrates Astaxanthin's prevention of DNA damage, one wonders how much damage could be prevented over a longer period of time than just one month as Astaxanthin accumulates throughout the cells in our bodies. It would be very interesting to see how Astaxanthin combats DNA damage at a dosage level toward the 12mg per day upper end of the recommended range and for a period of several months. We suspect that the effect would be much more pronounced than the 40% result that was found at 2mg per day for one month.

Supporting Pre-Clinical DNA Research. In addition to the human research done by Drs. Chew and Park, a flurry of pre-clinical studies has been performed related to DNA damage over the last ten years. Here are some of the most exciting ones:

- Astaxanthin shows a neuroprotective effect in rat retinal cells and aids against oxidative stress, glutamate stress and DNA damage (Yamagishi and Aihara, 2014)
- Astaxanthin enhances a DNA repair enzyme and is a novel candidate for cancer prevention (Kavitha, et al, 2013)
- Astaxanthin improves oxidative stress markers and an indicator of oxidative DNA damage in mouse cells and may be developed as an antioxidant drug to treat diabetic retinopathy (Dong, et al, 2013)
- Astaxanthin modulates age-associated mitochondrial dysfunction in dogs which is attributed to alleviating oxidative damage to cellular DNA and protein (Park, et al, 2013)
- Astaxanthin reduces DNA damage in rat liver cells (Turkez, et al, 2014)
- Astaxanthin may protect against oxidative impairment and DNA damage (Zhao, et al, 2011)
- Astaxanthin improves oxidative stress and DNA damage in rats (Tripathi and Jena 2010)
- Astaxanthin protects retinal cells against oxidative stress and reduces an indicator of DNA damage in mice (Nakajima, et al, 2008)
- Astaxanthin inhibits cytotoxic and genotoxic effects and restores DNA damage in mouse cells (Tripathi and Jena, 2008)
- Astaxanthin protects against DNA damage in human neuroblastoma cells (Santocono, et al, 2007)
- Astaxanthin reduces DNA damage in UVA-irradiated cells (Santocono, et al, 2006)

Astaxanthin's Effects on the Mitochondria: Mitochondria are commonly known as the “powerhouse of the cell.” To put it simply, mitochondria are responsible for energy production in our cells. There is already a great deal of research on how Astaxanthin can protect and benefit the mitochondria (which is probably why it is so effective at increasing energy levels and boosting strength and endurance in human clinical trials). We'll review some of the most relevant studies related to the mitochondria here:

- In a study done at University of Pittsburgh's School of Medicine, Astaxanthin protected against mitochondrial dysfunction and reactive oxygen species in a mouse model of Parkinson's disease and also in-vitro (Lee, et al, 2011).
- In perhaps the earliest study on Astaxanthin's effects on the mitochondria, Japanese researchers at Kochi Medical School found that Astaxanthin protects the mitochondria of rats better than a-tocopherol (Kurashige, et al, 1990).
- In a study done at Washington State University under the auspices of the famous carotenoid researcher Boon Chew, PhD, Astaxanthin prevented age-related mitochondrial dysfunction in dogs (Park, et al, 2013).
- Astaxanthin extended the lifespan of *C. elegans* (a model organism used in longevity studies) by protecting the mitochondria and the nucleus of the cells (Yazaki, et al, 2011).
- Astaxanthin can protect mitochondria that are subjected to oxidative stress. This study's abstract summarized the study very well:

“Mitochondria combine the production of energy with an efficient chain of reduction-oxidation (redox) reactions but also with the unavoidable production of reactive oxygen species. Oxidative stress leading to mitochondrial dysfunction is a critical factor in many diseases, such as cancer and neurodegeneration and lifestyle-related diseases. Effective antioxidants thus offer great therapeutic promise...Astaxanthin at nanomolar concentrations was effective in maintaining mitochondria in a reduced state. Additionally, Astaxanthin improved the ability of mitochondria to remain in a reduced state under oxidative challenge. Taken together, these results suggest that Astaxanthin is effective in improving mitochondrial function through retaining mitochondria in a reduced state” (Wolf, et al, 2009).

- Astaxanthin was found capable of protecting the mitochondrial membrane and preventing DNA damage and cell-death in-vitro in a university study done in Taiwan (Chan, et al, 2009).
- Cells subjected to heat stress in-vitro were protected by Astaxanthin, which the researchers attributed to Astaxanthin’s positive effect on the mitochondria (Kuroki, et al, 2013).
- In different studies on Astaxanthin’s effects on the mitochondria, it was found to be effective in benefiting various organs in different ways. The organs positively affected include:
 - Liver (Ma, et al, 2011; Song, et al, 2011).
 - Kidneys (Manabe, et al, 2008)
 - Heart (Nakao, et al, 2010)
 - Brain and central nervous system (Liu and Osawa, 2009; Liu, et al, 2009; Lu, et al, 2010)

The World's Strongest & Highest Quality Natural Antioxidant

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 comparing with vitamin antioxidants such as Vitamin C and Vitamin E, Astaxanthin has been shown to be as high as 550X to 6000X stronger.

Yet, as we'll examine below, it is not only that Astaxanthin is so much stronger than other antioxidants that makes it unique; Astaxanthin also has four remarkable qualitative properties that demonstrate its superiority over other antioxidants. When taking together both its quantitative and qualitative properties, it quickly becomes crystal clear that Astaxanthin is the best antioxidant we can take to supplement our diets and would provide anyone with a healthy dose of preventative antioxidant protection.

Quantitative Differences Between Astaxanthin and Other Antioxidants: As far back as the 1940's, scientists had discovered the antioxidant abilities of carotenoids and had isolated Astaxanthin as being extremely potent. 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).

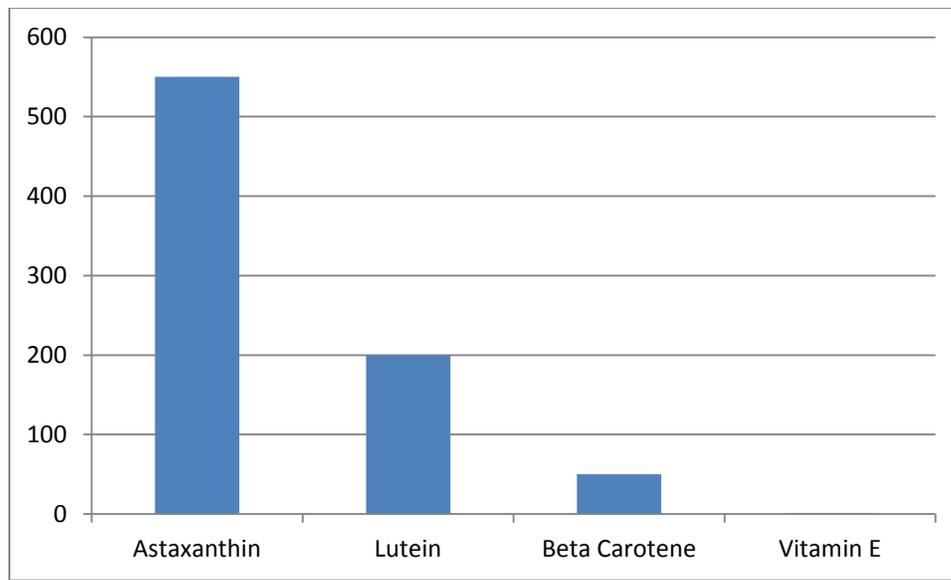
By the 1990's, Astaxanthin's powerful antioxidant activity was becoming widely accepted. A paper published in Japan in 1991 set the platform for the flurry of research that would follow:

“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 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)

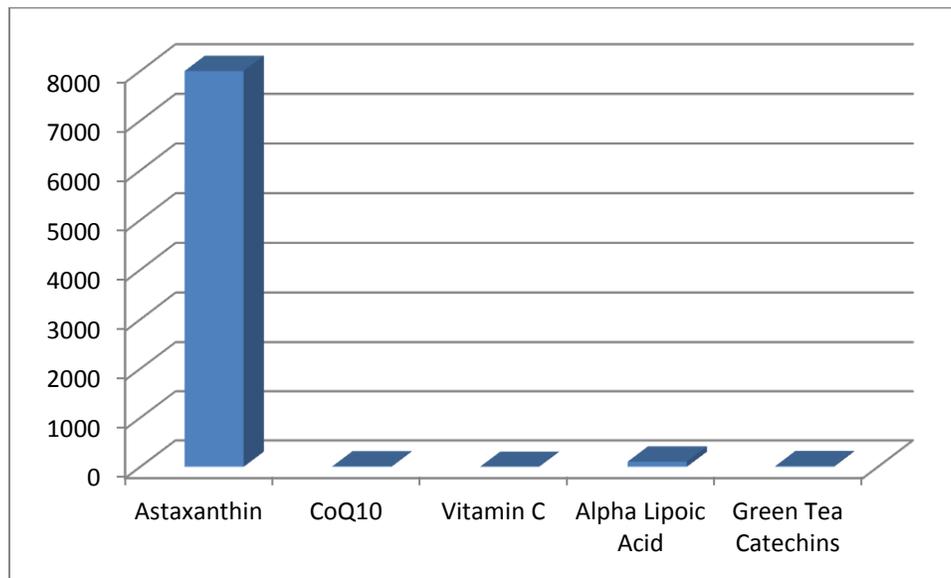
In singlet oxygen elimination, results of this study found Astaxanthin to be:

- 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 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:

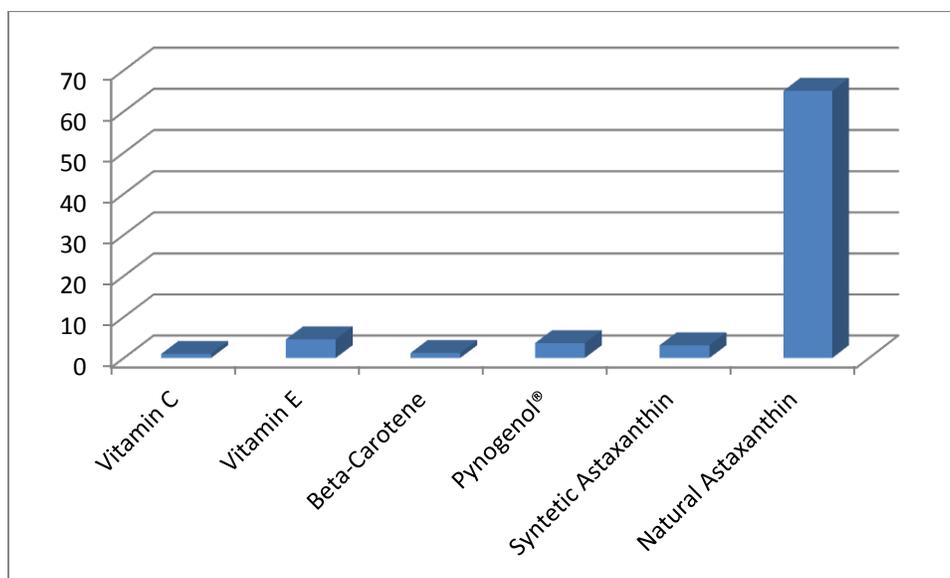
- 8000 times more potent than Vitamin C
- 800 times more potent than CoQ10
- 550 times more potent than Green Tea Catechins
- 75 times more potent than Alpha Lipoic Acid (Nishida, et al, 2007)

The last antioxidant research we'll review here 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.

When comparing antioxidants, it is very important to analyze them head-to-head and to test them in different experiments. A single test of, for example, 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 types of 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 and his co-author Dr. Gerald Cysewski 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, 2013)

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

- ✓ It proved the consistency of Astaxanthin's superior antioxidant strength regardless of how it is analyzed.
- ✓ It quantitatively proved that Astaxanthin is much stronger than other antioxidants that were claiming to be extremely powerful at that time such as Pycnogenol®.
- ✓ It showed how incredibly different *Natural* Astaxanthin is from *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, Dr. Miki's original estimate of 100X 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."

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 on its own 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 lipid 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 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.

- 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 cannot help protect our eyes and brains. Even carotenoid antioxidants that are closely related to Astaxanthin such as beta-carotene and lycopene cannot get through these barriers that are present to protect our most vital organs from foreign matter and contaminants. Since our brains are the control center for everything we think and do, an antioxidant that cannot protect the brain seems to be of little value to us. Fortunately, as we mentioned earlier, 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 brains and eyes of rats (Grangaud, 1951; 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. 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 “Highest Quality Natural Antioxidant;” however, with four important, documented advantages over more commonplace antioxidants, we feel it’s perfectly warranted and that Astaxanthin has earned this title. Coupled with its broad spectrum anti-inflammatory properties, it becomes clear that Astaxanthin is unquestionably the most useful antioxidant to consume as a dietary supplement and is highly recommended for everyone over the age of 40 as a preventative brain & eye health supplement.

A Safe & Natural Broad-Spectrum Anti-Inflammatory

It is difficult to say whether Astaxanthin's anti-inflammatory properties or its antioxidant power is more important with regards to protecting our brains and eyes; both create benefits that can help prevent many of the maladies of these organs associated with aging. Fortunately Astaxanthin is quite capable in both respects, leading to a variety of distinct advantages for anyone approaching middle age or beyond.

Astaxanthin works as an anti-inflammatory through multiple pathways. The various mechanisms of action for Astaxanthin as an anti-inflammatory have been demonstrated in several studies (Lee, et al, 2003; Ohgami, et al, 2003; Choi, et al, 2008; Kishimoto, et al, 2010). This research has consistently shown that Astaxanthin works on a variety of different causes of inflammation. In fact, there is evidence that it works on six different inflammatory markers, but that it works in a gentle, broad-spectrum manner. This is in distinct contrast to anti-inflammatory drugs such as Celebrex® and Vioxx® as well as over-the-counter anti-inflammatories such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs including Tylenol®, Motrin®, Alleve®, etc.) and aspirin, all of which target a single inflammatory marker, but in an intense manner. Inflammatory markers gently reduced by Astaxanthin include:

- Prostaglandin E-2
- Interleukin 1b
- Interleukin 6
- Tumor Necrosis Factor-A
- Nitric Oxide
- Cox 1 & 2 enzymes (Lee, et al, 2003; Ohgami, et al, 2003; Choi, et al, 2008; Kishimoto, et al, 2010)

Natural Astaxanthin has never been documented 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, prescription anti-inflammatory drugs as well as over-the-counter anti-inflammatories all have serious side effects. 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 consumers, 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. 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 show effects; 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 without any side effects.

In addition to several human clinical trials, two consumer surveys have validated Natural Astaxanthin's ability to combat painful inflammatory conditions. In fact, one of these consumer surveys asked users to compare Natural Astaxanthin's anti-inflammatory effects to prescription and OTC anti-inflammatories and found that Natural Astaxanthin has similar results to those non-natural drugs:

- A survey of people with joint, muscle or tendon pain found that:
 - 84% had positive results from using Natural Astaxanthin
 - 83% experienced less pain
 - 60% had increased mobility
 - When asked how Natural Astaxanthin's effects compared to other anti-inflammatories found in the drug store:
 - 75% said that Natural Astaxanthin works the same or better than over-the-counter pain medications such as aspirin, Tylenol, Alleve or Motrin
 - 64% said that Natural Astaxanthin works the same or better than prescription anti-inflammatories such as Celebrex or Vioxx (Capelli, et al, 2008).
- In a consumer survey of 247 Natural Astaxanthin users, “over 80% of those reporting back pain and symptoms from osteoarthritis or rheumatoid arthritis reported an improvement from Astaxanthin supplementation. Astaxanthin supplementation was also reported to improve symptoms of asthma and enlarged prostate. All of these conditions have an inflammation component which is closely tied to oxidative damage” (Guerin, et al, 2002).

To summarize, it appears from these consumer surveys that Natural Astaxanthin works about as well as prescription and OTC anti-inflammatories. It does, however, take considerably longer to work. But the critical distinction is that Natural Astaxanthin has never been reported to have any side effects or contraindications—it is completely safe and natural—while OTC pain pills and prescription anti-inflammatories all have serious side effects under certain conditions, some that can end up killing you (Capelli and Cysewski, 2014). So the crucial decision is left up to the consumer: Do you want fast results that may end up seriously hurting you, or would you rather wait about a month for the same results and be safe and healthy?

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:

1. First Study Proving 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).
2. 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 (IL-1b), COX-2 enzyme and nuclear factor kappa-B (Lee, et al 2003).
3. Further Validation: Several years later, scientists from Korea University further validated the earlier results finding broad-spectrum anti-inflammatory activity (Choi, et al, 2008).
4. "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 tested (Kishimoto, et al, 2010).
5. 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).
6. 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).

There have been several human clinical trials showing that Astaxanthin reduces pain in joints, tendons and muscles in groups of patients suffering from chronic conditions as well as in healthy men doing intense exercise (Capelli and Cysewski, 2014). For more information on this research, please contact us at support@bggworld.com

Human Research Reveals Astaxanthin's Neuroprotective Properties

As we pointed out in the Introduction, the incidence of age-related neurological problems is one of the fastest growing health issues facing the world's aging population. In fact, with the possible exceptions of skin cancer and diabetes, we have seen the incidence of maladies affecting the brain increase quicker than any other ailment over the last few decades. Certainly, a preventive food supplement that is safe and natural that could help prevent age-related neurological issues would be a logical recommendation for everyone who is approaching middle age. Fortunately, according to some great research over the last few years, it appears that we may have found just that in Natural Astaxanthin. There have been many pre-clinical studies on how Astaxanthin can support the brain, eyes and central nervous system. In fact, animal research in this area began in the late 1940's in France and was published as doctoral theses by two scientists who were certainly way ahead of their time (Grangaud, 1951; Massonet, 1958). With regards to human research, let's look at three of the recent studies showing benefits for our brains. (All three of these human clinical trials were done in Japan, a country that has embraced Natural Astaxanthin as an outstanding preventative supplement for several years already.)

Age-Related Decline in Cognitive and Psychomotor Functions. The first study involved elderly subjects with age-related forgetfulness. After first establishing safety at dosages ranging from 4mg per day up to 20mg per day in a general pool of healthy adult volunteers, the researchers then focused on the older subjects who were experiencing forgetfulness due to their advanced age. These patients were given a *Haematococcus pluvialis* algae extract equivalent to 12mg of pure Astaxanthin per day over the course of 12 weeks.

No abnormalities were observed in the subject pool during supplementation. Promising results were found related to Astaxanthin's neuroprotective activity. The researchers' conclusion was that "efficacy for age-related decline in cognitive and psychomotor function was suggested" (Satoh, 2009). This promising result in a population of people with the very common condition associated with aging of forgetfulness was very promising, and led to the following study (in which the lead researcher from this first study, Dr. Satoh, also took part).

Improvement in Marker of Dementia. The second study was a state-of-the-art research project: A randomized, double-blind and placebo-controlled clinical trial in human volunteers. This study tested a key marker for dementia: Phospholipid hydroperoxides. "Phospholipid hydroperoxides accumulate abnormally in the erythrocytes of dementia patients, and dietary xanthophylls (polar carotenoids such as Astaxanthin) are hypothesized to prevent their accumulation (Nakagawa, et al, 2011).

The researchers randomly separated 30 subjects into three groups: Group A was supplemented with 6mg per day of Astaxanthin; Group B was supplemented with 12mg per day of Astaxanthin; and Group C was given a placebo. The supplementation period lasted 12 weeks.

At the end of the trial, as expected, the subjects in both Group A and Group B who had supplemented with Astaxanthin were found to have higher erythrocyte Astaxanthin concentrations than the placebo group. Of clinical interest, after 12 weeks at either 6 mg or 12 mg daily Astaxanthin dosages, subjects were found to have decreased levels of phospholipid hydroperoxides in their erythrocytes as well as improved erythrocyte antioxidant status. The Astaxanthin groups were also found to have somewhat lower phospholipid hydroperoxide levels in their plasma. The study concluded: “These results suggest that Astaxanthin supplementation results in improved erythrocyte antioxidant status and decreased phospholipid hydroperoxide levels, which may contribute to the prevention of dementia” (Nakagawa, et al, 2011).

Improvement in Cognitive Function in Elderly Subjects. The most recent human study related to brain health incorporated a larger subject pool than the first two studies. (This clinical trial also involved the lead researcher from the first study, Dr. Satoh.) Once again, this was a state-of-the-art study: Randomized, double-blind, and placebo-controlled.

The subjects were healthy people who were either middle age or elderly who complained of age-related forgetfulness. The number of subjects was impressive: A total of 96 people were randomly assigned to take either placebo, 6mg of Natural Astaxanthin per day, or 12mg of Natural Astaxanthin per day. The study duration was twelve weeks; however, several tests were performed on the subjects every four weeks during the study. The tests included blood work, urine screens, somatometry, as well as cognitive tests such as the Groton Maze Learning Test and CogHealth.

In this study, the 12mg dose appeared to work somewhat better than the 6mg dose. Improvements in the CogHealth battery score improved in the 12mg group after 12 weeks. Improvements were noted earlier in the Groton Maze Learning Test in both Astaxanthin groups (as compared to the placebo group). The authors concluded, “The results suggested that Astaxanthin-rich *Haematococcus pluvialis* extract improves cognitive function in healthy aged individuals” (Katagiri, et al, 2012).

Further Substantiation in Pre-Clinical Research

Besides the three brain health studies described above in humans, there are almost fifty pre-clinical trials in animals and in-vitro that further substantiate the human research. There are far too many to cover in any degree of depth in a review of this nature, so we'll look at a few of the most relevant studies in some level of detail and then summarize results from several others in a single sentence.

Back in 2009, two researchers from Japan's Nagoya University hypothesized that, since Astaxanthin is a powerful antioxidant that can cross the blood-brain barrier, it should protect neuronal cells against oxidation. They treated neuronal cells with two different oxidative agents and measured the results without Astaxanthin and again with a pre-treatment of Astaxanthin. Significant protection was found in the cells pre-treated with Astaxanthin. "The neuroprotective effect of Astaxanthin is suggested to be dependent upon its antioxidant potential and mitochondria protection; therefore, it is strongly suggested that treatment with Astaxanthin may be effective for oxidative stress-associated neurodegeneration and a potential candidate for natural brain food" (Liu and Osawa, 2009).

The Chinese Academy of Sciences found excellent results for memory improvement in mice fed Astaxanthin. They fed mice Natural Astaxanthin for thirty days and tested them in a water maze and also in finding a safe place on an insulated platform. The mice were separated into four different groups—three with different dosage levels of Astaxanthin and one as a control that was given a placebo. The mice fed Astaxanthin at each level remembered the platform as a safe place, while the mice given the placebo forgot the original location. The summary stated: "These results indicate that *Haematococcus pluvialis* powder is associated with dose-dependent memory improvement and that a low dosage of algal powder is really good for improving memory" (Zhang, et al, 2007).

At University of Pittsburgh's School of Medicine in Pennsylvania, USA, a group of scientists tested Astaxanthin's therapeutic potential in a mouse model of Parkinson's disease as well as in-vitro. In both cases, positive results emerged. In-vitro, Astaxanthin inhibited the production of intracellular reactive oxygen species and reduced cytotoxicity in human neuroblastoma cells. In the Parkinson's mouse model, Astaxanthin protected against neuronal cell death. "These data indicate that Astaxanthin may provide a valuable therapeutic strategy for the treatment of progressive neurodegenerative disease such as Parkinson's disease" (Lee, et al, 2011).

The potential for therapeutic benefits in the brain are not limited to Parkinson's disease; two studies found prospective benefits for Astaxanthin in the treatment of Alzheimer's disease as well. In 2010, scientists at Hungkuang University in Taiwan found that Astaxanthin can protect neurons in several different ways including suppressing approximately 75% of reactive oxygen species and inhibiting or completely eliminating different inflammatory markers. "Conclusively, Astaxanthin may have merit to be used as a very potential neuron protectant and an anti-early-stage Alzheimer's disease adjuvant therapy" (Chang, et al, 2010). Last year, a different group of researchers also concluded that Astaxanthin may be useful for the treatment of neurodegenerative

diseases like Alzheimer's after showing a variety of positive effects such as resistance to brain cell death (Wen, et al, 2015).

Autism is a neurological condition that is increasing very quickly over the last few decades. A study in 2015 created a model of human autism in mice. They theorized that prenatal treatment with Astaxanthin might improve autistic behavioral activities in mice when autistic-like conditions are created. The finding was very promising; they concluded that "Astaxanthin improves the impaired behavior in an animal model of autism presumably by its antioxidant activity" (Al-Amin, et al, 2015).

Earlier this year, a study was done in rodents to test Astaxanthin's anti-inflammatory activity in mice. The aim of this study was to see if Astaxanthin may be a treatment for depression in humans. The researchers point out that inflammation and increased cytokine levels are associated with depression-like symptoms and neuropsychological disturbances in humans. Using two different physical tests and introducing lipopolysaccharides to induce inflammation, they discovered that Astaxanthin can reverse prolongation of immobility caused by these stimuli and also decrease the incidence of pro-inflammatory cytokines (Jiang, et al, 2016).

In a mouse study also done earlier this year, Astaxanthin showed potential benefits for traumatic brain injury. Mice were subjected to traumatic brain injury and subsequently treated with Astaxanthin. Twenty-four hours later, different neurological metrics were measured; Astaxanthin was found to dose-dependently improve these metrics indicating that it may have neuroprotective properties when administered after traumatic brain injury (Zhang, et al, 2016).

Diabetes adversely affects many organs in the body including the brain. It causes inflammation and a condition that has been described as accelerated brain aging. "Neurons in the hippocampal and cortical functional regions are more susceptible to damage induced by hyperglycemia, which can result in severe spatial learning and memory impairment" (Zhou, et al, 2015). Research published last year on diabetic mice given Astaxanthin found excellent results for cognitive function. Neuronal survival was tested; in addition, the diabetic mice were put through a water maze test. Mice fed Astaxanthin had significantly increased neuronal survival. In the water maze test, Astaxanthin helped the mice improve in three different measurable ways—by increasing the distance, enhancing the time spent in the target quadrant, and by decreasing latency. "Overall, the present study implied that Astaxanthin can improve cognition by protecting neurons against inflammation injury" (Zhou, et al, 2015). This study is particularly relevant since it not only measured survival rates of neuron cells, but also tangibly measured improvements in cognitive abilities. Other studies by different research teams found related results in diabetic rats. The first study showed that Astaxanthin improved results in the water maze test, reduced blood glucose levels, reduced inflammation and oxidative stress levels, and protected brain cells (Xu, et al, 2015). Another study demonstrated that Astaxanthin reduces diabetes type-2 associated cognitive decline in rats (Li, et al, 2016).

Aluminum chloride is a chemical used to induce neurodegenerative diseases when researching brain health in animals. A study published this year took mice and separated them into four different groups—one was fed only aluminum chloride; the next was fed aluminum chloride and Astaxanthin; the third was fed only Astaxanthin; and finally, the control group was fed

distilled water. Two behavioral tests were done on all groups, plus oxidative stress markers were measured in the mice's brains. The group fed only aluminum chloride showed poor spatial memory performance and exhibited signs of anxiety, while examination of their blood revealed deterioration of oxidative stress markers in their brains. Conversely, the mice fed Astaxanthin along with aluminum chloride showed improved spatial memory and locomotor activity, while their brains had less oxidative stress markers (Al-Amin, et al, 2016).

Other carotenoids also are potential neuroprotectants, but it appears that Astaxanthin may be the most potent based on a 2013 study where three different carotenoids were tested head-to-head. This study tested beta-carotene, canthaxanthin and Astaxanthin against a variety of harmful molecules in rat neural cells to determine the relative strength in protecting against cell death and eliminating free radicals. First, the antioxidant status of the three different carotenoids was tested with Astaxanthin coming out the strongest. In analyzing the different metrics measured, the researchers pointed out that Astaxanthin protected cells in four different ways and declared: "Our results conclusively show that Astaxanthin has merit as a potential neuron protectant" (Chang, et al, 2013).

As noted previously, with almost fifty pre-clinical trials showing potential neuroprotective properties for Astaxanthin, due to space constraints we will only cite a portion of the published literature in this review. In order to give a more fully-rounded view of this research supporting the human clinical trials, we will summarize in a single sentence several more of the most relevant studies from which our Readers can pursue additional investigation if desired:

- Astaxanthin improves early brain injury in rats by inducing antioxidant and detoxifying enzymes (Wu, et al, 2014).
- Reiterating an earlier study, Astaxanthin reduced brain cell death in rats fed a substance to induce brain damage (Wang, et al, 2016).
- Astaxanthin protects brain cells from the damaging effects of alcohol and may be effective for preventing neurotoxicity associated with excessive alcohol consumption (Yan, et al, 2016).
- Astaxanthin has shown various potential cardiovascular benefits (Capelli and Cysewski, 2014). In a study on rats, Astaxanthin was specifically shown to imbue neurovascular protection in rats (Zhang, et al, 2015).
- Ischemic brain injury is the result of blocked blood flow to the brain; corroborating the above study, an earlier rat trial shows that Astaxanthin reduced ischemic brain injury when the rats were injected with Astaxanthin before the blockage occurred (Shen, et al, 2009).
- Neuron loss due to epilepsy was reduced by Astaxanthin in the hippocampus of rats (Lu, et al, 2015).
- Both rats and rabbits were protected from early brain injury and showed less oxidative stress when ingesting Astaxanthin (Zhang, et al, 2014).
- A university study in Brazil showed that Astaxanthin dose-dependently reduced cortical spreading depression in rats subjected to chronic alcohol consumption (Abadie-Guedes, et al, 2008).

- In a later study, the same lead researcher found that Astaxanthin helps protect both young and old rats against the impairing effect of ethanol (Abadie-Guedes, et al, 2012).
- Astaxanthin helped improve spatial memory and increase the genesis of neuron cells in mice (Yook, et al, 2016).
- Astaxanthin shows anti-hypertensive and neuroprotective effects in rats (Hussein, et al, 2005).
- Researchers at the Federal University of Sao Paulo in Brazil found that Astaxanthin limits oxidative insult in the forebrain of rats (Mattei, et al, 2011).
- Finally, scientists at the Gifu Pharmaceutical University in Japan found that Astaxanthin supplementation leads to anti-anxiety effects in mice (Nishioka, et al, 2011).

The Related Study of Astaxanthin for Eye Health

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, much more serious ocular issues such as age-related macular degeneration, cataracts and glaucoma become increasingly prevalent. Similar to the case with aging brains, what we need as an ounce of prevention for our aging eyes 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. Fortunately, Astaxanthin has exhibited these abilities in university and private research which began over 60 years ago in Europe and has continued since then, primarily in the USA and Japan (Grangaud, 1951; Massonet, 1958; Tso and Lam, 1996; Capelli and Cysewski, 2014). There are several human clinical trials that validate a variety of 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, Eye Accommodation and Eye Strain. 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). 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 all of these conditions.

An early study in this area was done in Japan. It was a state-of-the-art study—a double blind, placebo-controlled human clinical study. 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 tested two different dosage levels of Natural Astaxanthin for eye fatigue. 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. (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 and 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 showed that three

separate visual parameters were found to have statistically significant benefits from Astaxanthin supplementation. This study established an optimum daily dose for eye fatigue of at least 6 mg per day (Nitta, 2005). A study the following year corroborated these results. This study 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 preventative as well as a therapeutic potential for Astaxanthin for eye conditions such as strain and accommodation.

This preventative role is 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 were subjected to heavy visual stimuli to induce eye fatigue, and it was found that the treatment group recovered more quickly. This clearly indicates that Natural Astaxanthin may serve not only to treat eye fatigue in those that already suffer from it, but also to prevent eye fatigue from occurring in healthy people (Takahashi and Kajita, 2005).

Other Human Research. A study was done in Japan with subjects comprised of twenty year old, healthy men. The treatment group was 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).

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 next study we'll review showed a different benefit for using Natural Astaxanthin related to blood flow. This double-blind, placebo-controlled 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 and can also increase the speed at which the blood is flowing to the eyes.

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, 2005; Nagaki, 2006; Capelli and Cysewski, 2014).

Differences Between *Natural Astaxanthin* and *Synthetic*

It is extremely important to understand the vast differences between Natural and Synthetic Astaxanthin since this distant synthetically-produced cousin of Natural Astaxanthin is now being falsely promoted in the supplement industry as “Nature Identical.” Synthetic Astaxanthin has been used for many years in the animal feed industry, primarily to pigment the flesh of farm-raised salmon. 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.

A critical finding of a landmark series of head-to-head antioxidant experiments is the clear superiority of Natural Astaxanthin to Synthetic Astaxanthin in antioxidant strength. In both university research at Creighton University under the auspices of acclaimed antioxidant researcher Debasis Bagchi, PhD as well as in independent laboratory testing at Brunswick Laboratories, Natural Astaxanthin extracted from microalgae was found to be a minimum of 20X stronger in antioxidant strength than Synthetic Astaxanthin produced from petrochemicals (Capelli, et al, 2013).

Briefly, the primary differences between Natural and Synthetic Astaxanthin 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. (This is an overriding concern due to serious safety issues with related synthetic carotenoids beta-carotene and canthaxanthin.)
- **Efficacy:** Amazingly and perhaps most importantly, Synthetic Astaxanthin has never been shown to have any health benefit in human clinical research. It is completely untested and may turn out to 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.

- **Antioxidant Strength:** To expand on what we mentioned above, Natural Astaxanthin is 20X stronger than Synthetic Astaxanthin as an antioxidant in scavenging free radicals. In another antioxidant head-to-head comparison, it was shown that Natural Astaxanthin is over 50X stronger than Synthetic Astaxanthin in singlet oxygen quenching.
- **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 (Capelli, et al, 2013).

With this brief analysis of these distant Astaxanthin cousins, we quickly see that Synthetic Astaxanthin is far inferior to Natural Astaxanthin. It is comparatively weak as an antioxidant, and even more frighteningly, it has never been tested for safety or for health benefits in humans. Regardless of how Synthetic Astaxanthin is marketed, it is clear that it is absolutely not “Nature Identical.”

Conclusion

Three human clinical trials backed up by almost fifty supporting pre-clinical experiments indicate that Astaxanthin may be among the very best nutrients for people concerned with protecting their brains. Two of the human studies showed promising results for age-related decline in cognitive function. Furthermore, there is also indication of improved psychomotor function through Astaxanthin supplementation as well as an ability to lower a key marker for dementia. Many animal trials, mostly in rodents, corroborate these results and go even further to show a host of other potential preventative traits for the brain from Astaxanthin use.

Why is this true? On a cellular level, Astaxanthin can protect our cells extremely efficiently and through different pathways. A great deal of research has been done showing benefits of Astaxanthin specific to key parts of our cells. It can prevent damage in DNA and protect the mitochondria, two valuable characteristics of this fascinating molecule. It is recognized as the world's strongest natural antioxidant, and it has also been shown to be a safe and effective natural anti-inflammatory. Its documented ability to cross the blood-brain barrier allows Astaxanthin's antioxidant and anti-inflammatory properties to reach our bodies' command center—the brain. It has similarly been documented to reach the eyes by crossing the blood-retinal barrier and has been shown to have a variety of potential eye health benefits in many human clinical trials.

Astaxanthin's multi-pronged approach of neutralizing oxidation, reducing inflammation, preventing DNA damage and protecting the mitochondria means that Natural Astaxanthin may help combat many of the problems associated with aging brains and eyes. It is for this reason that we highly recommend the preventative use of 6mg – 12mg per day of Natural Astaxanthin for all people over the age of 40.

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